Metadata of the chapter that will be visualized online

Series Title	Current Clinical Psychiatry	
Chapter Title	The Neurobiological Foundations of Psychotherapy *	
Chapter SubTitle		
Copyright Year	2012	
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Keywords (separated by '-')	Adaptive change - emotions - Freud - memory - neurobiology - psychotherapy - thalamocorticostriatal circuits - unconscious	

Chapter 17
The Neurobiological Foundations of Psychotherapy *

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Keywords Adaptive change • Emotions • Freud • Memory • Neurobiology • Psychotherapy • Thalamocorticostriatal circuits • Unconscious

Introduction

Psychotherapy is an interactive process that addresses maladaptive behaviors and mental states through the use of structured communication. Although psychotherapeutic systems and techniques have evolved independently of neurobiological science, there has been a tacit understanding, at least since the days of Freud, that psychotherapy produces its effects by acting on the brain. Modern technology has underscored the importance of this concept, as functional imaging reveals the neural activation patterns associated with behavioral dysfunction, and how these patterns can be modified through psychotherapy.

A fundamental neurobiological principle, namely the existence of species-specific brain architecture, underlies one of psychotherapy's most important properties, which is its generalizability across multiple individuals and disorders. The neural organization that characterizes the human species is the legacy of millions of years of natural selection. It confers upon each person a specialized set of functional capabilities and vulnerabilities. Fuster [1] used the term "phyletic memory" to define the basic neural attributes that are shared by all members of a species. Phyletic memory represents a legacy of success in adapting to the unique demands of the social and physical environments in which a species continuously evolves. It is the basis for human communication and order, and also represents the structural substrate on which psychotherapy operates.

Freud spent a lifetime attempting to define the common functional characteristics of the human mind and realized that any system of psychotherapy must begin with a description of the psychological phenomena that are common to all humans. Although Freud would have liked to link mind and brain, the technology of his time did not permit it. As a result, Freud conceptualized the workings of the mind independently of the brain and strictly on the basis of clinical observations and his interpretation of their meaning. His far-reaching vision of how the mind develops and functions evolved

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R.A. Levy et al. (eds.), *Psychodynamic Psychotherapy Research*, Current Clinical Psychiatry,
DOI 10.1007/978-1-60761-792-1_17,

gradually, organized around an interconnected set of unifying principles that allowed him to make sense of the clinical phenomena manifested by his patients. Eventually, Freudian formulations, and treatment techniques were applied to a wide range of psychiatric disorders, albeit with mixed success. Freud himself believed that his methods were not well suited for the treatment of certain disorders, such as the psychoses. In theory, the effectiveness of psychodynamic psychotherapy should be highest in patients with a relatively intact set of species-specific neural circuits, since its organizing principles were synthesized from clinical work with patients of this type. The reasons for this practical limitation are important to consider.

Information in the brain is processed by collections of circuits whose organization is both genetically and experientially determined. Most of the information contained within the brain exists as some type of neuronal representation. Neurotransmitter levels, blood flow patterns, and other physical permutations can also contain information, but will not be considered here. Representations of information in neurons range from the transient, chemically based changes that support short-term memory, to more durable structural changes in synaptic connections (covered later in this chapter). Each person's repertoire of memories, values, and behavioral responses is contained within that individual's synaptic connections. Within the specialized pathways defined by these connections, both genetic factors and past experience determine how new information is processed in the context of the old.

Psychiatric disorders arise from interactions between genes and environment. Some of the most severe psychiatric illnesses, such as schizophrenia and bipolar disorder, for example, appear to have structural components that may not be amenable to correction through the types of inputs and interactions on which psychotherapy relies. As a result, it may not be productive to focus on experientially derived neural contents in the treatment of these types of disorders, since their primary cause appears to be a genetically based deficit in neural architecture. Despite these considerations, a modified version of the Freudian concept of "psychic determinism" is valid in this context. From a modern perspective, all behaviors, like Freud asserted, have potentially discoverable mental and neural origins. However, while in some cases, the etiology of a behavior is related to previous experiences, in others, it arises solely from genetically determined variations in brain structure.

The neurobiologically informed psychotherapist can leverage an understanding of both mind and brain to adjust interventions to the needs of each patient, maximizing function and adaptability wherever possible, while acknowledging that some aspects of mental dysfunction are beyond the scope of psychotherapy. This chapter will discuss the most important neural targets of psychotherapy and how successful psychotherapeutic treatment modulates the actions of the brain.

Neural Circuitry in the Context of Psychotherapy

General Considerations

Every human being has a core complex of evaluative and behavioral neural functions that promote avoidance of risk and acquisition of reward. Overlaid on these functions is an array of more advanced neural circuits that can temper the pursuit of reward on the basis of experience and learned rules. Basic and advanced circuits operate in parallel, and their behavioral influences often conflict. For example, the sights, smells, and easy access to palatable food at an "all you can eat" restaurant can be powerful inducers of unrestrained eating behavior. On the other hand, health concerns and other cognitive considerations ideally would temper the desire to eat and limit food consumption to an appropriate level. In the best of circumstances, a collaborative synthesis of competing directives is used to guide behavior. Unfortunately, this does not always occur. In fact, many of the behavioral problems that come to the attention of psychotherapists are related to poor modulation of core circuitry by the higher levels of the brain.

In general, volitional actions are driven by perceptions of risk and value. The ability to recognize certain classes of objects and experiences as "rewarding" and others as "punishing" is an important tool for survival. The neurobiological foundation for this ability is the possession of a genetically encoded array of sensory stimuli that are "hardwired" to "feel" either pleasant or unpleasant. This basic core of hardwired sensory phenomena forms the basis for the classification of all other experiences and is a major organizing principle for each individual's subjective reality. Previously, neutral objects and stimuli can acquire value as they become linked to primary sensory phenomena [5]. For example, babies innately like sweet substances and dislike bitter ones. In contrast, many adults come to "like" certain bitter substances, such as coffee and chocolate, because their distinctive flavor becomes associated with the memory of a pleasant internal state that overrides the innate distaste for bitterness. Eventually, every human develops an internal classification of food preferences that expands significantly beyond innately wired "likes and dislikes." This expansion reflects sociocultural influences as well as genetic inputs and subjective experiences. In primates, basic information about primary and secondary reinforcers is processed in the amygdala and orbitofrontal cortex [5]. These regions also play a role in the creation of new secondary reinforcers. In addition, they modulate the autonomic and motivational circuits that generate the emotions and "gut feelings" that arise automatically whenever cues that signal potential reward or punishment are encountered [5]. In a sense, the amygdala and orbitofrontal cortex are the repository of all the rewarding and aversive experiences of a lifetime.

As humans classify environmental objects through experience, they also learn behaviors that obtain objects of value and avoid the rest. Eventually, long chains of causality are created that drive complex behavioral sequences. For example, a person may learn to work hard because work generates money, which in turn facilitates the acquisition of many pleasures. Throughout each person's lifetime, a complex web of linkages is created that ideally defines adaptive behaviors within the individual's milieu. The continuous process of forming and maintaining these linkages is influenced by development, environmental factors, and psychiatric illness. In order to succeed in modern sociocultural settings, the linkages that define adaptive actions must be intact, and cognitively driven behavioral sequences that transcend the simple pursuit of reward must be constantly implemented. This requires situational suppression of the hardwired motivation to pursue potential rewards whenever they become available. In this context, a number of functional circuits that are of special interest to the psychotherapist are discussed later in this chapter. These circuits are important because they participate in the motivation and execution of behavior and, as a result, are crucial targets for psychotherapeutic modulation. These subjects will be covered more extensively in Viamontes [6].

The Neurobiology of Emotions

Emotions are mind–body phenomena that reflect the subjective meaning of experiences, and prepare a person to act effectively within the perceived circumstances. Emotional disturbances are, of course, a primary focus of psychotherapy. Rolls [5] has proposed a powerful, yet concise view of emotions: "The definition of emotions is that [they] are states elicited by rewards and punishers, that is, by instrumental reinforcers."

In other words, emotions are reactions to perceptions of possible risk or reward. Emotions involve special combinations of neurotransmitter, autonomic, and hormonal responses that prepare the brain and body to address what has been perceived. In addition, emotions bias behavior in a specific direction, depending on the nature of the event that triggered them. Each emotion generates a characteristic brain–body state, which gives it a unique experiential framework. Ideally, emotional states are adaptive because they can prepare the body for perceived challenges and motivate behavior that secures a good outcome. On the other hand, emotions can also be maladaptive if they are triggered inappropriately, since under such circumstances, they can inhibit the generation of effective action.

Rolls [5] has stated that the ability of emotions to motivate a general type of response without specifying an exact course of action is one of their most important attributes. While it is advantageous to transmit general information about risks and rewards in the genes, it would be impossible to specify an exact action within an organism's DNA for every possible encounter with potential rewards and punishers. In contrast, it is both feasible and adaptive to encode the motivation to perform general types of actions as a way of linking perception of rewards and punishers with appropriate responses.

Phillips et al. [7] have conceptualized a theoretical framework to explain the neural origin of emotions. They identified three stages in the generation of an emotional response. First, a stimulus is identified and evaluated. Second, an affective state, which can include neuroendocrine and autonomic activation, changes in facial expression, vocalizations, gestures, and specific behavioral responses, is produced in response to the stimulus. As these processes unfold, the individual becomes conscious of the emotional response. Third, the emotion is modulated by cognitive circuits, which consider perceived appropriateness in terms of internalized rules.

This conceptual model has been projected to an anatomical level in light of neuroimaging data [7]. In the anatomical model, actual emotional responses to neurally represented stimuli are generated by a ventral processing system with epicenters in the amygdala, insula, ventral striatum (including the nucleus accumbens), ventral regions of the anterior cingulate gyrus, and ventral prefrontal regions, including the orbitofrontal cortex.

The amygdala is an important early sensor of possible risk and reward. It also coordinates responses to objects and situations that elicit fear, functions in the circuitry that recognizes facial expressions, and modulates the brain's reward system [7]. The insula creates neural representations of a wide range of emotional and autonomic states. These can reach consciousness once represented. The insula participates in neural circuits that generate such diverse phenomena as sadness, pain, anticipatory anxiety, guilt, the affective components of substance withdrawal, and the recall of emotional states [7].

The ventral striatum, and in particular the nucleus accumbens, is an important component of the brain's reward system. It participates in circuits that identify objects of potential value and motivates the organism to pursue them. The anterior cingulate gyrus, through its autonomic and hypothalamic connections, plays an important role in the generation of affective states in response to cognitive representations, and in linking perceived objects with appropriate levels of motivational energy. It also participates in circuits that focus attention on activities likely to yield reward and helps to generate mood-appropriate affective states [7].

The medial orbitofrontal and ventromedial prefrontal cortices are important generators of the autonomic components of emotions. The orbitofrontal cortex receives a comprehensive representation of internal and external sensory perceptions. In addition, it receives projections that convey the amygdala's reactions to the same sensory stimuli. This information is integrated and evaluated, and the result is relayed to the ventromedial prefrontal cortex, which modulates autonomic tone. The orbitofrontal cortex also functions in the top-down modulation of the amygdala, and, together with the ventromedial prefrontal cortex, participates in fear extinction [8].

The dorsal emotional system, which includes the hippocampus, the dorsal anterior cingulate, and the dorsal regions of the prefrontal cortex [7], appears to function in modulating the progression of emotions with respect to contextual cues, memory, and internalized rules. In this context, an imaging study which examined whether rational reappraisal of emotions could result in attenuation of negative emotional states [9] found that reframing emotional events in unemotional terms could significantly reduce affective intensity. The neural correlates of this phenomenon began with activation of the dorsal and ventral regions of the left lateral prefrontal cortex, as well as the dorsomedial prefrontal cortex during the reappraisal procedure. Activation of the right anterior cingulate and right supramarginal gyrus was correlated with success in mitigating negative emotion. The specific neural correlates of successful emotional reappraisal involved increased activation of lateral and medial prefrontal cortices combined with decreased activation of the amygdala and medial orbitofrontal cortex [9].

Emotions play an important role in the integration of conscious and unconscious processes. More specifically, emotions provide a means for unconscious processes to influence conscious behavioral responses. Emotions evolved in parallel with consciousness, since the generation of perceptible body states is neither possible nor useful in organisms without consciousness. The behavior of organisms with limited consciousness is already controlled directly by unconscious mechanisms. Emotions, which strongly demand the attention of consciousness, arose to facilitate continued modulation of behavior by unconscious factors, even in the presence of advanced conscious processes. In humans, emotions can also be generated by conscious processes, even those that are purely intellectual. The many types of body states that can be induced by emotions, which include generalized arousal, preparation of the body for perceived challenges, and increased likelihood of certain types of behaviors, can provide significant adaptive value in the context of conscious actions. Conversely, strong emotions can also be maladaptive, and can hinder the implementation of rationally motivated behavior. Emotional dysfunctions often bring patients to psychotherapy and significantly affect the unfolding psychotherapeutic process.

The Neurobiology of Memory

Memory functions can be divided into two main categories: implicit and explicit (reviewed in [10]). Implicit memory includes the learning of habits and motor skills, various types of reflexive learning, such as operant conditioning, and fear conditioning, a process mediated by the amygdala that links fear responses to previously neutral objects. Explicit memory, which involves the recollection of locations, objects, and events, as well as their verbal descriptions, is mediated by the actions of the hippocampus.

The process of creating and recalling explicit memories can be divided into four distinct steps (reviewed in [10]):

1. Encoding, or the process by which the elements of a new memory are integrated into a coherent neural representation. Encoding binds together the multiple components of a memory, including visual, auditory, olfactory, tactile, and emotional elements, through convergence on a set of dedicated neurons. Encoding in the hippocampus appears to take place in the CA3 region, where single cells that respond to multiple types of inputs can be found [11]. Encoding requires compression of information, as multiple inputs converge onto a smaller number of encoding neurons.
2. Consolidation, or the stabilization of information for long-term retention. Consolidation requires the synthesis of proteins that modify neuronal connectivity. Memories are therefore stabilized through the translation of chemical representations into structural modifications. Consolidation is believed to involve the strengthening of the synaptic connections that bind together the various elements of a memory. Consolidation follows the principle introduced by Donald Hebb to describe how information might be stored in neural networks which states, in simple terms, "neurons that fire together wire together" (reviewed in [10]). Memories are consolidated and stored if they continue to be activated at least intermittently after they are first made.
3. Storage, or the process by which memories are retained over long periods of time. The major difference between consolidation and storage has to do with location. Consolidation of explicit memories takes place within the memory encoding regions of the hippocampal complex. For a time, these regions hold a record of the integrated memory and the "addresses" of the individual memory components (e.g., olfactory, visual, tactile) in the higher cortices. Eventually, if the memory merits permanent storage (through frequent reactivation and perceived importance), recurrent connections from hippocampal regions direct rewiring of higher cortices to represent the memory.

4. Retrieval, or the process by which encoded, consolidated, or stored memories are recalled and possibly recombined with other materials. To retrieve a memory, it is necessary to reactivate the network that represents it [1]. This can be accomplished in a number of ways:
   - Re-experiencing a sensory stimulus that is incorporated in the memory.
   - Re-experiencing another memory whose components overlap with the memory in question.
   - Re-experiencing an internal state or emotion that is incorporated in the memory.
   - Using words as symbolic "pointers" to one of the memory's components.

Memory Representations in the Right and the Left Brain

The storage of memories in the hippocampus is not hemispherically symmetrical. The right hippocampus encodes and retrieves episodic, non-verbal aspects of memory, while the left hippocampus supports the creation of semantic, or verbal memories that involve the encoding of experience into the symbolic representations facilitated by language [10].

Left-brain memory representations are primarily symbolic, since they are based on language. This facilitates logical manipulations of the representations and permits the exploration of complex relationships among them, including intentionality, causality, meaning, and purpose. Right-brain memories, in contrast, are holistic and experiential; recalling them revisits how the experience "felt" in terms of emotions, arousal, autonomic tone, and hormonal release, although usually in a less intense manner. In some cases, the recalled right-brained memories can be uncomfortably realistic, and they are experienced as "flashbacks" and similar symptoms associated with post-traumatic stress disorder (PTSD). A functional imaging study compared brain activity in the recall of traumatic memories between individuals with and without PTSD [12]. Individuals without PTSD activated left brain regions as they recounted traumatic experiences. These included the left superior frontal gyrus, the left anterior cingulate gyrus, the left striatum, left parietal lobe, and left insula. In contrast, individuals with PTSD activated their right brains when they recounted traumatic memories. Specifically, the right posterior cingulate gyrus, the right caudate, right parietal lobe, and right occipital lobe were activated [12]. In these individuals, the right-sided representations had a distinct experiential rather than strictly verbal nature and actually included a visual component in the occipital lobe.

Neural Substrates of Memory

From an anatomical perspective, discrete networks of neural structures support the various types of memory. Implicit memories related to automatic motor sequences are thought to be stored as special programs in the basal ganglia [13]. Simple association of previously neutral objects with natural reinforcers or punishers is accomplished by the circuitry of the amygdala and orbitofrontal cortex [5]. The hippocampus and its associated structures facilitate the storage of spatial, episodic, and semantic memories. More specifically, the right hippocampus functions in the generation of episodic, non-verbal aspects of memory, including the characteristics of physical spaces, while the left hippocampus generates semantic, or verbal memories, that involve the encoding of experience into the powerful symbolic representations facilitated by language [10].

Anatomically, the hippocampus itself is divided into three regions, named cornu Ammonis (CA) 1, 2, and 3. The term "cornu Ammonis" refers to the hippocampus' resemblance to the "horn of Ammon," which is a ram's horn. The hippocampal complex receives most of its inputs at three main regions, the parahippocampal, perirhinal, and entorhinal cortices. The parahippocampal and perirhinal cortices also project to the entorhinal cortex, which therefore contains the widest representation of incoming information within the hippocampal complex. The inputs that converge on the entorhinal cortex include projections from the prefrontal cortex, cingulate gyrus, occipital lobe, superior and inferior temporal gyri, temporal pole, amygdala, and insula [14]. These projections deliver a comprehensive summary of experience, from properties of objects and their value, to perceived risk, associated emotions, and cognitive factors.

The perirhinal cortex is believed to be responsible for "recognition memory" (reviewed in [11]). It receives direct inputs from visual object areas in the inferior temporal cortex. It is also connected with the orbitofrontal cortex, to which it may provide object recognition information that can be used to drive motivational reactions to reinforcers and punishers.

Processed information from the perirhinal cortex projects to the entorhinal cortex as part of the larger information stream just described. From the entorhinal cortex, information flows into the hippocampus itself. Information first arrives at the dentate gyrus via the perforant pathway, the first of three hippocampal fiber arrays. The dentate gyrus contains sparsely connected neurons and is thought to function in the orthogonalization of informational patterns [11]. This process differentiates the arrays of neurons that represent individual data sets as much as possible to enhance later separability and minimize interference. From the dentate gyrus, the information is conveyed to the CA3 region of the hippocampus via the mossy fibers, the second of the main hippocampal fiber systems. CA3 also receives a sparse array of direct inputs from the entorhinal cortex. Encoding, or the binding together of all the elements that comprise a memory, is believed to be accomplished through the convergence of individual inputs from dentate gyrus neurons on a smaller number of "indexing" neurons in CA3, which are highly interconnected [15]. There is a significant amount of compression as information flows from the dentate gyrus into CA3. In the rat, there is almost an order of magnitude more neurons in the dentate gyrus than in CA3, and about 50 mossy fibers converge onto each CA3 neuron [11].

CA3 has also been proposed as the hippocampal component that "completes" previously encountered patterns when only parts of them are perceived [15]. This feature, which is based on the high interconnectivity of CA3 neurons, can have effects of interest to the psychotherapist, since automatic, maladaptive pattern completion could manifest itself as psychopathology. The high level of connection among CA3 neurons is thought to play a critical role in the binding of the multiple sensory, emotional, and cognitive elements that make up each individual memory [11].

From CA3, information flows through the third hippocampal fiber array, the Schaeffer collaterals, to CA1. This area of the hippocampus is believed to facilitate the encoding of spatial information that may be included in a memory [15]. Hippocampal information completes a recurrent loop as it flows from CA1 back to the entorhinal cortices via the subiculum. Information flows are somatotopically mapped, which allows the same entorhinal cells that originated a particular signal to receive the appropriate back projections [11]. From the entorhinal cortex, information spreads to the perirhinal and parahippocampal cortices, and eventually to many of the unimodal and polymodal cortices where the information originated [11].

Long-Term Potentiation

The consolidation and long-term storage of memories is believed to depend on gradual strengthening of the synaptic connections that define each encoded memory. The strengthening of these synaptic connections depends, in turn, on a process called long-term potentiation (LTP), which was originally described by Bliss and Lomo [16]. Whenever neurons in any of the three main hippocampal pathways (perforant pathway, mossy fibers, and Schaeffer collaterals) are stimulated, they become sensitized to subsequent stimulation, and the excitatory postsynaptic potentials in each pathway's information-receiving neurons are increased. In intact animals, the sensitization, which is called long-term potentiation, can last for many days (reviewed in [10]).

Specifically, LTP induction within the hippocampus occurs in the following manner. In the perforant pathway from the entorhinal cortex to the dentate gyrus, activation of NMDA receptors in dentate gyrus cells with subsequent calcium influx plus retrograde excitatory transmission to presynaptic entorhinal cells combine to mediate LTP. In the mossy fiber pathway from dentate gyrus cells to CA3 cells, LTP is mediated by calcium influx into the presynaptic dentate gyrus cells, which is facilitated by repeated firing of these cells. LTP in the mossy fiber pathway is positively modulated by norepinephrine and is not NMDA dependent [10]. LTP induction in the Schaffer collateral pathway from CA3 to CA1 is mediated by NMDA receptor firing in CA1 cells, with subsequent calcium influx and excitatory retrograde transmission. Early phases of LTP increase the possibility of successful synaptic signal transmission without increasing the numbers of synapses or receptors. The activation sequences described previously therefore increase neurotransmission by making it more effective. Presynaptic neurons that have been activated, for example, will reliably release the maximum possible number of neurotransmitter vesicles at each synaptic event, and activated postsynaptic receptors become more sensitive to released neurotransmitter [10]. Later phases of LTP, in contrast, require protein synthesis and feature a greatly increased upper value for the possible strength of neurotransmission across the activated neurons. It is believed that this greatly enhanced level of signal transmission involves the increase of neurotransmitter release sites as well as an increase in postsynaptic receptors [10].

It is widely believed [11, 17] that encoded memories that continue to be triggered for prolonged periods (years) are eventually encoded in extrahippocampal sites. This process permits the recycling of hippocampal space by allowing weak memories to fade, while moving strong, frequently retrieved ones out of the hippocampus. Studies with non-human primates suggest that the transition from short- to long-term encoding of visual memory involves the creation of linkages in region BA 36 of the perirhinal cortex under the guidance of stored hippocampal patterns [17]. Next, through the action of back projections from the perirhinal cortex, linkages among individual memory elements are eventually created in the anterior inferior temporal cortex, which is an important area for visual object representation [17]. It has been hypothesized that this general scheme of interim memory linkage in the entorhinal and perirhinal cortices with subsequent transfer of the links to representational areas of the neocortex may be the general process by which long-term memory storage is accomplished [17].

Memory Processes and Psychopathology

The continuous projection of every modality of sensory and emotional information that is being represented in the brain onto the entorhinal cortex (reviewed in [11]) has interesting consequences. Since not all of the projected information may reach consciousness, it is theoretically possible to encode memories that contain unconscious components linked to conscious elements. Such a memory would theoretically be retrievable by representing either the conscious or unconscious components, since they would be bundled into a single memory representation. Reactivation may eventually allow some of the memory's unconscious components to become discoverable. In addition, each time a memory is reactivated, it is possible to link new components to it that were not part of the original encoding. It is even possible to create memories in the present that are attributed to the past, and this has been accomplished experimentally [18]. These mechanisms form the basis for the "recovery" of false memories.

The process of orthogonalization in the dentate gyrus, which allows the differentiation of memories which contain similar elements, gives rise to many interesting possibilities from the viewpoint of psychotherapy. Granule cells in the dentate gyrus are embedded in a matrix of inhibitory interneurons [11]. This arrangement ensures the sparseness of representations in this layer by permitting strongly activated neurons to inhibit less activated neighbors.

Theoretically, the number of available dentate gyrus cells should determine the precision with which memory patterns that contain similar elements can be encoded [19]. Experimental work has supported this hypothesis. Dupret et al. [20], for example, developed double transgenic mice whose neural precursor cells could be killed selectively through induction of the pro-apoptotic Bax protein. Mice with experimentally ablated adult-born dentate gyrus neurons had significant impairments in "…spatial relational memory, which supports a capacity for flexible, inferential memory expression. In contrast, less complex forms of spatial knowledge were unaltered." The authors concluded that their findings "…demonstrate that adult-born neurons are necessary for complex forms of hippocampus-mediated learning" [20]. The availability of adult-born neurons in the dentate gyrus, which appear to be critical for complex hippocampal-based learning, depends, in turn, on the level of dentate gyrus neurogenesis, which increases in enriched environments [21] and wanes in times of stress [22]. The enriched environment experiment mentioned earlier involved housing rats in "a large box (1.5×0.8×0.8 m) containing various toys, wooden blocks, climbing platforms, plastic tubes and small houses." The items in the box were rearranged daily to encourage exploration. A running wheel, which has been included in other similar experiments, was not used to eliminate the possible confounding influence of additional exercise.

The ability to support high memory discrimination in favorable times while promoting enhanced generalization in times of stress should have significant adaptive value, but also some drawbacks. The cessation of dentate gyrus neurogenesis and hippocampal shrinkage that result from chronic stress [23] should lead to faster responses to threatening stimuli by decreasing the complexity of encoded memories. On the other hand, as discriminative capabilities decrease, ever-increasing numbers of non-threatening stimuli could also activate specific threat reactions as a result of overgeneralization. Animals in the wild and soldiers in the field, for example, would react faster and differently to movements in the leaves than someone having a picnic in the park. When soldiers return from war, they have to make a potentially difficult readjustment to the higher complexity of life in peacetime, in which not every loud noise or sudden movement is likely to have rapid and deadly consequences.

Experiments with rats with dentate gyrus damage have confirmed that such lesions cause significant impairment in differentiating between closely spaced spatial cues [11]. In addition, genetically engineered mice with deficient dentate gyrus neurogenesis showed that it was easier to achieve contextual and cue-based fear conditioning in these animals [24]. These results provide experimental support for the hypothesis that dentate gyrus deficits inhibit the ability to represent complexity and, therefore, can lead to increased simplification and generalization. Such deficits would be expected to improve performance in simple discriminative tasks, while yielding poorer performance in more complicated problems. Limitations in dentate gyrus capacity have also been hypothesized to underlie the "black and white thinking," or overgeneralization, that characterizes borderline personality disorder [2], a condition that has been associated with hippocampal atrophy. A number of animal experiments [25] suggest that at least some of the behavioral effects of antidepressants may be mediated through enhanced neurogenesis in the dentate gyrus.

In view of the mechanisms described, memory formation represents far more than a simple method of information storage. It is, in fact, a method for wiring the higher cortices on the basis of important experiences. In this context, a commonly used animal model of schizophrenia involves damaging the hippocampus neonatally [26]. This procedure adversely affects subsequent organization of the prefrontal cortices and generates a state of hypofrontality that mimics many schizophrenic deficits. It has been hypothesized that the experiences that are used to direct cortical rewiring must have persisted within the hippocampal complex for several years [11], a requirement that would prevent relatively trivial organizing principles from being incorporated into the cortex. The hypothesis is based on reports of patients who have undergone bilateral temporal lobectomies for epilepsy. In these cases, no new hippocampal-based memories can be stored, and a relative retrograde gradient of memory impairment can be detected, in which only older memories are fully recalled, and more recent memories are lost to a degree that is inversely proportional to their age (reviewed in [10]).

From the perspective of psychotherapy, two critical points should be emphasized with respect to memory. First, memory systems provide continuous access to many levels of information acquired by the individual during his or her lifetime. However, memories can be modified continuously, and the details reported about a memory at an arbitrary time may differ considerably from the original experience. Second, and perhaps most importantly, the brain's memory system directs the creation of specialized processing circuits within the brain, as it binds the elements of memory into cohesive networks during the transition from consolidation to long-term storage. The identity of each individual and his or her individualized patterns of information processing are determined, to a large extent, by the memories that have been transferred to long-term storage.

The consolidation of memories is facilitated by emotional arousal. Memories that have a high emotional content are encoded and consolidated more efficiently than those that are emotionally neutral [27]. This requires the action of the basolateral amygdala, which can enhance memory processes by promoting the release of facilitatory neurochemicals such as norepinephrine and acetylcholine [27]. In pathological states such as depression, sustained activity of the amygdala can maintain a steady flow of negative emotions which can adversely influence memory systems [28].

The Default Mode of Brain Function

Mesulam [29] introduced the concept of the "default mode of brain function" to describe behavior that is driven by basic rather than higher cortical circuits. It is important to distinguish Mesulam's concept, which is based on evolutionary considerations, from the more recent conceptualization of the brain's "default *network*" [30], which refers to "…a specific, anatomically defined brain system preferentially active when individuals are not focused on the external environment" [30]. The default network is active "…when individuals are engaged in internally focused tasks including autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others" [30]. The putative components of the brain's default network include the ventral medial prefrontal cortex, the posterior cingulate/retrosplenial cortex, the inferior parietal lobule, the lateral temporal cortex, the dorsal medial prefrontal cortex, and the hippocampal formation [30]. As discussed elsewhere in this chapter, the hippocampal formation and lateral temporal cortex support explicit and spatial memory functions, while the dorsal medial prefrontal cortex supports executive functions, reasoning, problem solving, and contemplation of the future. In addition, the medial prefrontal region facilitates the use of memory information for the construction of mental simulations involving the self, and the posterior cingulate is an integrative area that has been found to be active when conceiving other peoples' thoughts (reviewed in [30]). The inferior parietal lobule represents the final node in the default network and is believed to play a role in spatial attention, multimodal sensory integration, and oculomotor control [31].

In the context of psychotherapy, some of the most important hypothesized functions of the default network include support of internal mentation, including the construction of dynamic simulations that are based on memories and involve the self, thinking about the future, and imagining possible alternatives to present circumstances. Alternatively, it has also been hypothesized that the default network may support surveillance of the external environment for unexpected events when focused attention is not directed externally [30]. The concept of the default network is an evolving conceptualization of the processes that occur within the brain when attention is not focused on external objects, and it has important implications with respect to psychotherapy, since its postulated functions can be involved in both the development of psychiatric illness and in the psychotherapeutic process itself.

Returning to Mesulam's conceptualization of the default *mode* of brain function, it is clear that his functional parameters describe the actions of the most primitive parts of the human brain, without the benefit of the inhibitory and reflective overlays provided by the prefrontal cortices. These primitive functions can meet basic survival needs through simple stimulus–response associations, but cannot support the complex social interactions and problem solving that are required for success in modern sociocultural settings.

From a simple biological perspective, adaptive behavior has four major components: homeostasis, acquisition and conservation of energy, avoidance of injury, and facilitation of reproduction. To accomplish these tasks, the brain integrates data from internal and external sensors, modulates bodily processes, and coordinates the pursuit of resources in concert with risk assessment and internal needs. As Mesulam emphasizes, the brain's default mode is focused on the here and now and has limited capacity to consider context, projected repercussions, or visions of the future. The default mode of brain function is driven almost exclusively by internal appetitive urges and by salient external stimuli. In other words, the major drivers of default brain function include the brain's reward circuits, as well as networks that control physiological functions such as eating, drinking, and sleeping, and the amygdalar–orbitofrontal circuits, which can detect both potential risk and reward. These circuits influence behavior by focusing attention on objects of interest and generating appropriate emotional states. Core motivational circuits require minimal information processing in the interval from stimulus to response and are efficient at the cost of limited functionality, heightened impulsivity, and low capacity for addressing novelty or complexity.

Analyses of normal brain development and the deficits of brain-injured patients have shown that the default brain function that Mesulam describes is at the core of every human being. A lifetime of training and experience, however, creates many "overlays" that modulate the actions of the default brain and define behavioral patterns with expanded adaptive value. In humans, the overlays that facilitate social and occupational functioning, creativity, problem solving, and future orientation depend on the function of the prefrontal cortex.

The development of advanced brains that can transcend appetitive urges and satisfy more complex demands was motivated by significant evolutionary pressures. The unrestrained pursuit of salient stimuli to serve internal urges is not adaptive in a world filled with danger. In addition, the ability to postpone gratification on the basis of context is essential to the development of social groups. For example, the lowest animals in a social hierarchy must wait to eat until more dominant members of the social group are sated. To make such advanced behaviors possible, special circuits evolved to modulate the internal urges and narrow external focus that are induced by the reward system. These circuits, whose major components are located in the prefrontal cortex, promote the pursuit of reward in a manner that is consistent with contextual considerations, learned rules, and a vision of the future [29]. Clinical work with brain-injured patients, animal experimentation, and functional brain imaging has defined both the general circuits that drive default brain function and those of the overlays that support higher levels of complexity and adaptability.

Adaptive Circuits of the Prefrontal Cortex: Ego, Superego, and Id

The term prefrontal cortex refers to the region of the brain directly in front of the premotor and motor strips. In humans, the prefrontal cortex permits the consideration of an expanded set of variables before the initiation of actions [29]. It coordinates adaptable, goal-directed behavior that considers internal and external circumstances, memory, applicable rules, and projected consequences.

Functional and anatomical considerations have demonstrated three distinct circuits in the prefrontal cortex that modulate complex behavior. The oculomotor circuit, which controls automatic eye movements, is a fourth prefrontal network that will not be discussed here. All the prefrontal circuits have nodes in the thalamus, cortex, basal ganglia, and globus pallidus/substantia nigra pars reticulata [32, 33]. The circuits are somatotopically mapped, which defines numerous independent "channels" through each circuit component [32]. Under normal circumstances, thalamic circuitry is tonically inhibited by the globus pallidus. This inhibition can be removed for selected channels through the action of the basal ganglia, which can suppress default pallidal inhibition. Self-excitatory loops that sustain representations of interest in the brain can therefore be activated selectively. Because of their unique components, these circuits are given the general name of thalamocorticostriatal circuits.

The first thalamocorticostriatal circuit passes through the dorsomedial thalamus, the cingulate gyrus, the ventromedial caudate, and the nucleus accumbens. This circuit modulates the function of the rostromedial and ventral globus pallidus, which under normal circumstances continuously inhibit the dorsomedial thalamus [32]. When the circuit is activated, it relieves the inhibition of specific thalamic channels, enhancing selected cortical representations. This circuit is primarily involved in the motivation of goal-directed actions. The cingulate gyrus is a heterogeneous area with specific processing modules for emotion, cognition, sensation, and movement [34]. Important functions of the cingulate include the motivation of appropriate responses to internal and external stimuli, emotional-cognitive integration, "attention for action," motor preparation, and conflict monitoring [34].

The cingulate carries out these functions by triggering body states that focus attention on internal and external demands and motivate appropriate action. It generates emotional motivation through its projections to autonomic, visceromotor, and endocrine systems [35], and is an important component of reward circuitry through its connections with the nucleus accumbens. The cingulate receives cognitive data from the dorsolateral prefrontal cortex [36] and facilitates emotional-cognitive integration by generating emotional states appropriate to cognitive contents [35]. This is an important function that can provide the motivation for actions that are driven by abstract representations, such as postponing pleasurable activities to study for an exam. Conversely, the cingulate gyrus, which has rich connections to other limbic structures, conveys emotional information to the dorsolateral prefrontal cortex for cognitive processing. Damage to the cingulate gyrus can result in a state of apathy in which responses to internal and external stimuli are significantly diminished [32]. At the extreme, severe cingulate damage results in "akinetic mutism," a state with little spontaneous movement or speech [32].

The cingulate can organize "attention for action" by modulating arousal, motivation, autonomic tone, and attentional focus to drive behavioral responses that address the most salient internal or external stimuli [34]. Cingulate gyrus-nucleus accumbens circuitry figures prominently in addictive states. The cingulate gyrus is also thought to generate the autonomic tone necessary to support many types of movements, and it signals behavioral conflicts by increasing arousal and autonomic tone [35].

The second thalamocorticostriatal circuit passes through the ventral anterior and dorsomedial thalamus, lateral orbitofrontal cortex, ventromedial caudate, and dorsomedial globus pallidus and substantia nigra pars reticulata [32]. The latter two structures tonically inhibit the thalamus, and this circuit, when activated, can relieve the inhibition of selected thalamic channels. The lateral orbitofrontal circuit modulates the pursuit of reward by adding considerations of risk, context, and potential consequences to the behavioral equation. These are critical elements in the generation of adaptive behavior in occupational and social settings. The lateral orbitofrontal cortex can provide motivational forces that are based on higher-level principles and which can counterbalance the attraction of potential rewards whose pursuit would be inappropriate in the current setting.

The medial orbitofrontal cortex is reciprocally connected to the amygdala, and both act in concert to generate emotional states relevant to the pursuit of reward and avoidance of risk. Both orbitofrontal cortex and amygdala receive a rich set of inputs from all five sensory cortices, as well as from the insula. These define comprehensive views of both internal and external milieus. The inputs come primarily from downstream regions of the unimodal cortices, and therefore the information is probably at the whole object rather than the individual feature level [36]. In addition, sensory inputs are relatively blended, and provide multidimensional views of the environment. The amygdalar projections target specific sites in the orbitofrontal cortex that receive equivalent sensory inputs, and this arrangement may allow the orbitofrontal cortex to extract the emotional significance of sensory events [36]. Both amygdala and orbitofrontal cortex ignore neutral sensory inputs with no implications of risk or reward and stop responding to any inputs that lose their motivational value [36].

Barbas et al. [36] have elucidated the layout of orbitofrontal–amygdalar circuitry through experimental work with non-human primates. The amygdala can exert both inhibitory and stimulatory influences on hypothalamic autonomic nuclei. The central nucleus of the amygdala normally inhibits the hypothalamic nuclei, while the basolateral nucleus stimulates it. The orbitofrontal cortex can suppress autonomic centers through stimulation of the amygdala's central nucleus [36]. Activation of this nucleus causes autonomic inhibition. The opposite result, autonomic activation, can be achieved by the orbitofrontal cortex through stimulation of the intercalated masses of the amygdala. This diminishes the default inhibition of hypothalamic nuclei by the amygdala's central nucleus [36].

Functionally, the orbitofrontal cortex induces anticipatory body states that promote reward seeking, as well as aversive body states that reduce the likelihood of risky actions [32]. The orbitofrontal cortex probably evolved to prevent injury in the pursuit of reward, to facilitate behavioral restraint by animals at lower levels of the social hierarchy, to promote the preferential pursuit of low-risk rather than high-risk rewards, and to inhibit pursuit of contextually inappropriate rewards, such as seeking food when sated. Humans with orbitofrontal cortex damage usually demonstrate personality changes that include high impulsivity, social inappropriateness, explosive behavior, disregard for rules and consequences, and the inability to use aversive emotions to inhibit risky behavior [32].

The third behavioral circuit of the prefrontal cortex is the dorsolateral prefrontal circuit, which modulates executive functions. This circuit passes through the ventral anterior and dorsomedial nuclei of the thalamus, the dorsolateral prefrontal cortex, the dorsolateral caudate, and the dorsomedial globus pallidus and substantia nigra pars reticulata. In similar fashion to the other two circuits, the dorsolateral prefrontal circuit can relieve tonic inhibition of selected thalamic channels.

The dorsolateral prefrontal circuit is essential for many of the intellectual functions that are most valued by humans. These include organization, problem solving, working memory and memory retrieval, self-direction, the ability to address novelty, and the use of language to guide behavior [32]. Without the dorsolateral prefrontal cortex, the ability to problem-solve that underlies the highest levels of human achievement completely vanishes. Behavioral organization becomes very coarse, and the ability to think abstractly disappears. The function of this cortex is highly correlated with standard measures of intelligence, and, in its absence, a default mode of brain function that relies on habits becomes apparent. Individuals with dorsolateral prefrontal damage become uneasy in novel settings and situations and prefer to live day to day in a repetitive series of well-rehearsed routines. Any deviation from the familiar can cause great distress, since the individual is not likely to succeed in situations that demand analysis, creativity, or self-direction [32].

The dorsolateral prefrontal cortex, like the orbitofrontal cortex, receives a variety of sensory inputs, although these are primarily from visual, auditory, and somatosensory cortices [36]. The frontal eye fields receive low-level visual information with a degree of detail that rivals what is found in the visual unimodal cortex [36]. Sensory information is less integrated in the dorsolateral cortex than in the orbitofrontal cortex, possibly facilitating more detailed analysis of specific stimuli [36].

In summary, individuals with damage to the dorsolateral prefrontal cortex have difficulty organizing behavior to meet internal or external demands and perseverate in their thoughts and speech. Decision-making is impaired, and there is a strong tendency to be drawn toward objects and situations with high salience, even if the interaction is contextually inappropriate. These individuals often engage in utilization behavior, which is the indiscriminate handling of any salient object encountered. They have significant difficulty with problem solving and are unable to address novelty [32].

Sigmund Freud defined ego, superego, and id to separate three functional components of the mind whose interactions, in his estimation, were central drivers of human behavior. Whether or not one agrees with Freud's theoretical constructs, the neurobiology that motivated his basic conceptualizations is apparent. The continuous tension between unconscious appetitive urges and more advanced control circuits that characterizes Freud's vision has a definable origin in neural circuitry.

The dorsolateral prefrontal circuit strongly resembles the Freudian ego. It facilitates executive functions such as integration of perceptual information, problem solving, and decision-making [32, 33]. Imaging studies have also shown that the dorsolateral prefrontal cortex, possibly in conjunction with the cingulate gyrus, plays a key role in the suppression of unwanted memories [37].

The manifestations of the id are in great part embodied in the cingulate gyrus-nucleus accumbens circuitry. This circuit, which receives modulation from the amygdala, amplifies signals that suggest the attainability of reward and generates body states that motivate pursuit of potential pleasures. In the presence of remembered cues, this circuit can generate overwhelming motivational pressure to engage in reward-producing behavior, as is the case in chemical dependence.

The functions of the superego are implemented by the lateral orbitofrontal circuitry, combined with the risk-avoidance function provided by medial orbitofrontal–amygdalar circuitry. The lateral orbitofrontal network evolved to temper the pursuit of pleasure with considerations of context and risk. To accomplish this task, orbitofrontal–amygdalar circuits project to autonomic centers and can generate body states conducive to disengagement and withdrawal. The actions of these circuits set limits on risk-taking and can give rise to visceral feelings that signal potential punishment or embarrassment.

As this brief review of the prefrontal circuits indicates, it is the specialized capabilities of these neural networks that make humans unique. It is possible to live without the prefrontal cortices, but it is impossible to succeed in any but the simplest endeavors without them. Psychiatric patients show various degrees of prefrontal dysfunction. In some, the dysfunctions are transient, while in others it is permanent. It is important for the psychotherapist to assess the functionality of prefrontal circuitry through observation and self-descriptions of patient behavior.

The prefrontal cortices facilitate all the higher social and intellectual functions. Without these cortices, human behavior coarsens, and focuses on obtaining reward in the here and now, without regard for past and future, and with little consideration for context or social propriety. As the study of patients with frontal lobe injuries indicates, the evolutionary addition of the prefrontal cortex and its advanced, adaptive circuits did not replace default mode functions, but merely overlaid them. At any moment, special circumstances or psychiatric illness can lay bare the brain's functional core, releasing behavioral responses that may be useful in emergent circumstances but will be maladaptive in normal sociocultural settings.

While the changes required to transcend default mode are being implemented, the developing brains of children are vulnerable to abuse or neglect. First, the traumatic circumstances themselves can lead to structural changes as the child's brain seeks to adapt to trauma [38]. Such changes are likely to be maladaptive when the child is eventually re-integrated into a normal setting. In addition, the frontal cortical overlays that are essential for transcending the inflexibility and impulsivity of default brain mode [29] may never develop. An essential component of these overlays is the incorporation of a variety of abstract rules to govern behavior, and these have to be taught. Abused and neglected children are also likely to develop deficits in their social cognition circuitry, with serious functional consequences in complex social settings.

The Unconscious

Brain imaging technology has not only confirmed the existence of unconscious mental processes, but has made it possible to begin to map the anatomical substrates on which unconscious processes unfold. Viamontes and Beitman [39] have proposed a provisional, five-tiered classification for unconscious processes that will facilitate the development of explicit correlations between anatomy and function. Level 1 processes organize homeostatic functions, automatic actions, and stereotypic behaviors. Level 2 processes modulate the intensity of engagement with the environment and its objects. Level 3 processes govern interactions with primary rewards and punishers, which are encoded in the genes. Level 4 processes define unconscious reactions to secondary rewards and punishers, which have been learned. Level 5 processes are strictly interactive and control reactions to the appearance, movement, verbal outputs, and facial expressions of other persons.

Level 1 unconscious processes take place within the brainstem, basal forebrain, and hypothalamus [40]. Most of the body's homeostatic processes are unconscious. This is highly adaptive, since homeostasis is accomplished rapidly, accurately, and without taxing the resources devoted to conscious endeavors. In addition to a variety of psychiatrically trivial homeostatic processes, the brainstem, basal forebrain, and hypothalamus also support a number of body states involved in psychopathology. The outputs of these regions impact the physical state of the organism and include the actions of the well-known hypothalamic–pituitary–adrenal axis. These systems control such critical functions as heart rate, respiration, arousal, and autonomic tone. The functional pathways that coordinate the main outputs of level 1 unconscious processes are also used as outputs by a variety of other circuits, including the amygdala, the orbitofrontal cortex, the ventromedial prefrontal cortex, and the subgenual cingulate [36]. Inappropriate activation of level 1 pathways can cause pathological states of anxiety, anger, and fear.

Level 2 processes control the intensity of environmental interactions. They include the action of arousal and sleep centers in the brainstem, as well as the status of serotonin, norepinephrine, acetylcholine, and dopamine receptors throughout the brain, combined with the dynamic modulation of corresponding neurotransmitters. In addition, type 2 processes include such specialized reactions as the sickness response, which is mediated by cytokines, and a variety of systems for brain energy modulation. The latter are exemplified by the adenosine system, which produces lethargy when the brain has used a large amount of ATP. Caffeine rapidly blocks brain adenosine receptors after ingestion, a phenomenon that underlies the popularity of coffee.

Level 3 unconscious processes organize reactions to primary, or genetically encoded rewards and punishers [5]. The major nodes in the network that mediates these responses are the amygdala and the medial orbitofrontal cortex [5]. Both regions receive a rich selection of sensory inputs, share numerous reciprocal connections, and jointly modulate hypothalamic autonomic centers [36]. Both the amygdala and medial orbitofrontal cortex contain neurons that respond specifically to natural rewards and punishers [5]. In a sense, they act as a coupler that ties recognition of the primary reinforcer to the somatic state that has been genetically preprogrammed as a response. Primary reinforcers are limited to certain tastes and smells, pleasant touch, and possibly selected visual stimuli such as smiling human faces [5]. Human babies, for example, like sweet tastes from birth and do not have to learn this response [14]. Primary punishers that are genetically pre-wired include unpleasant tastes and odors, painful somatosensory stimuli, and possibly loud noises and angry or frightened human faces [5].

Encountering a positive primary reinforcer activates a genetically preprogrammed body state that increases the probability of engaging and eventually acquiring the reinforcer. This body state can include neurotransmitter and hormone release, the deployment of stereotypic movement sequences (e.g., suckling reflexes in a newborn), and autonomic arousal. In a similar manner, the amygdala and orbitofrontal cortex mediate rapid reactions to avoid primary punishers. For example, a common reaction to an unexpectedly bitter taste would be to spit the substance out, a stereotyped behavior that might prevent accidental poisoning. The basic states that are induced in encounters with primary rewards and punishers are the foundation of emotions [5].

The neural mechanisms for responding to learned reinforcers and punishers, or level 4 processes, are particularly important from a clinical perspective. Many categories of psychopathology involve the learning of inappropriate responses to previously neutral stimuli. In addition to mediating responses to primary reinforcers, the amygdala and orbitofrontal cortex can also mediate responses to simple objects that have become associated with intrinsic rewards or punishers. However, humans react not only to objects, but to verbal and cognitive content, as well as to imagined events. The hippocampus and associated structures are important in organizing responses to complex stimuli that require remembered information and transcend the simple perception of objects.

Bechara et al. [41] have hypothesized that the brain contains two main systems for responding to reinforcers in the environment: an impulsive system that generates somatic states in reaction to primary reinforcers and a reflective system that generates similar states from secondary reinforcers. An important difference between the two systems is that the first one generates somatic states directly via amygdalar activation of autonomic centers in the hypothalamus and brainstem, whereas the second uses pathways through the ventromedial prefrontal cortex (including the orbitofrontal cortex and subgenual cingulate) to activate the same autonomic centers. The latter pathway is able to engage high-level cognitive circuits before it generates an output.

The ventromedial prefrontal cortex is an integrative area that can access memories of previous instances of simultaneous firing in sensory and limbic structures. If a sensory pattern is repeated, its remembered limbic correlate is triggered automatically to recreate the specific somatic state that has been associated experientially with the perceived object [41]. Secondary reinforcers, therefore, are created during learning by attaching the somatic state pattern that normally accompanies a primary reinforcer to a previously neutral object.

In normal interactions with the environment, encounters with reinforcers induce parallel processing in rapidly responding, unconscious systems such as the amygdala, as well as in slower, more future-oriented areas such as the ventromedial prefrontal cortex. The system that is amplified most intensely in any given situation will control behavior. Adaptive functioning in social settings demands attenuation of the impulsive tendencies that arise when perceived reinforcers are coupled with motivational body states and the tempering of these primitive impulses with considerations of the future. Impulse control is a complex process that involves, in part, comparing the somatic state generated by exposure to a reinforcer with a second somatic state generated by neural simulation of the contemplated action with respect to the reinforcer. This internal simulation has been called an "as-if-body-loop" by Damasio [42] and Bechara et al. [41]. The tempering of initial impulses by the simulation of as-if-body-loops is essential for social organization, and it also inhibits the pursuit of potential rewards associated with high risk. Bechara further refines the definition of impulse control by distinguishing between motor impulse control, in which impulsive movements are inhibited, and perceptual impulse control, which facilitates contextually appropriate attentional shifts. Studies of motor impulse control have demonstrated that the critical region that inhibits impulsive motor reactions is the posterior region of the ventromedial prefrontal cortex, including the anterior cingulate. Perceptual impulse control, which allows attentional shifting on command, is provided by the lateral orbitofrontal and dorsolateral prefrontal cortical regions [41]. If unconsciously generated impulses are successfully inhibited, decision-making with consideration of many variables, including future consequences, takes place in the anterior regions of the ventromedial prefrontal cortex, specifically within the frontal pole and Brodmann Area 10 [41].

Type 5 unconscious processes, which mediate social functioning, have significant impact on behavior and are an important factor in psychopathology. In addition, an understanding of these processes is of critical importance for the psychotherapist. Living in social groups has been a highly adaptive strategy for the human species, and millions of years of natural selection have refined the tools necessary for success in the social setting.

Brothers [43] defined social cognition as "…the processing of any information which culminates in the accurate perception of the dispositions and intentions of other individuals." Social cognition has a number of components. First, human expressions are genetically encoded; therefore, it is reasonable to assume that the ability to interpret facial expressions is genetically encoded also and does not have to be learned. In addition to preprogrammed recognition networks, humans also have the ability to model the movements of others in their own brains to determine meaning. Finally, the ability to reason abstractly allows humans to make “theory of mind” interpretations, in which an observer attempts to guess the mental contents of another person.

Adolphs [44] reviewed the basic processing sequence involved in social cognition, and the following account is based on that review. The coarsest level of visual perceptual processing, which directs ocular saccades, takes place in the superior colliculus and associated regions. The structural processing of faces appears to be accomplished in the fusiform face area in the human extrastriate cortex. This region is selectively activated when humans view faces [45]. The fusiform face area is essential for determining identity from facial features and for subsequently linking known faces with pertinent memories.

One of the front line processors of observed facial emotions is the amygdala. The amygdala appears to contain pre-wired programs for the recognition of negative facial emotions, especially fear [46]. In addition to the amygdala, the orbitofrontal cortex, which is richly interconnected with the amygdala, plays a role in facial emotion recognition and has been shown to react to angry faces [47]. Faces which are judged to be attractive activate the ventral striatum and orbitofrontal cortex [44]. Evaluation of facial expression and inference of the observed person’s motivation is therefore carried out in the amygdala, orbitofrontal cortex, and ventral striatum. The latter regions are also able to generate autonomic responses in the observer as the emotions of others are evaluated. This can prepare the observer to react to the perceived emotions. Several cortical regions in the right hemisphere have also been implicated, through lesion studies, in the recognition of emotions [44]. They include the S-I somatosensory cortex (Brodmann areas 1–3), the insula, and the left frontal operculum (Broca’s area, or Brodmann areas 44 and 45).

Additional information about the recognition of gestures, as well as inferences about goal directedness and mental state attribution, is developed through processing in the superior temporal sulcus [48, 49]. The mirror neuron areas in the frontal operculum (Brodmann Area 44) and in the anterior part of the posterior parietal cortex provide the ability to infer the meaning of actions by modeling them in the observer’s brain. The cingulate gyrus, hippocampus, and basal forebrain modulate attention and engagement and facilitate the recruitment of memories. Finally, the ventromedial prefrontal cortex, including the orbitofrontal cortex and anterior cingulate, are essential for making social and moral judgments and for generating appropriate somatic states [44].

The Psychotherapeutic Process

The Therapeutic Alliance

The working alliance between therapist and patient is a critical determinant of psychotherapeutic success [50]. During therapy, personal interactions between participants activate cognitive and emotional circuits, and therapist and patient will experience many spontaneous reactions to one another as therapy unfolds. One of the most important elements of the therapeutic alliance is empathy. Several studies have demonstrated a positive correlation between patient-perceived therapist empathy and therapeutic outcome (reviewed in [51]).

A study of the physiologic correlates of perceived therapist empathy has been published [51]. The experimental design involved simultaneous measurement of skin conductance, which is a measure of sympathetic arousal, in 20 therapist–patient pairs during psychodynamic psychotherapy sessions.

To clarify the significance of the skin conductance measurements, patients completed the Barret-Lennard Relationship Inventory Empathic Understanding Sub-Scale, a 16-item instrument that evaluates patient perceptions of therapist empathy [52]. The results were consistent with the hypothesis that shared episodes of autonomic activation, as identified by simultaneous increases in skin conductance of both patient and therapist, correlated significantly with perceived therapist empathy.

An important feature of empathy is that it is a mutual acknowledgement of a shared moment of emotional understanding. Someone is empathic if he “knows” how I feel. Carr et al. [53] described the putative neural circuits by which humans are able to understand emotional expressions in others and develop empathy, which is in essence a sharing of emotion. Functional brain imaging was obtained while subjects either observed or imitated emotional expressions in pictures of human faces. Similar neural circuits were activated during both observation and imitation of emotion, with stronger activation during imitation. Specifically, increased activation was observed in premotor and frontotemporal areas, in the amygdala, in the anterior insula, in the face region of the pre-supplementary motor area, in the rostral cingulate face area, in the frontal operculum, and in the superior temporal sulcus. Additionally, during the imitation of observed emotions, the mouth region of the primary motor cortex was activated.

Activation of the amygdala during emotion observation and imitation is consistent with its postulated role in the assessment of emotional expression in the faces of others. The superior temporal sulcus has been shown in a number of studies to be active during action representation (reviewed in [49]). The premotor cortex, rostral cingulate, and pre-supplementary motor area, together with the frontal operculum and frontotemporal area, appear to be parts of complex circuitry that facilitate the understanding of observed actions and emotions by representing them in the observer’s own brain. The observer is able to understand what is observed by “trying it out” in his or her own brain. The frontal insula, which is activated during both the observation and the imitation of emotions, is believed to provide a link between action representation systems and the emotional content of the limbic system [53]. In addition, the insula represents the observer’s own changing body state as observed emotions and actions are internally represented. The regions that are activated during emotional observation and imitation show considerable overlap with the mirror neuron system originally described by Rizzolatti et al. [54], which facilitates an understanding of bodily actions. As the therapist works toward engagement, a key task is to be able to “model” the patient’s situation internally, within the therapist’s own neural circuits.

Another important neurobiological phenomenon with relevance to formation of the therapeutic alliance has been described. Release of oxytocin during interpersonal exchanges appears to play an important role in the establishment of stable relationships, since it promotes a feeling of trust and enhances the ability to accurately interpret the emotional signals of others [55]. Exogenous oxytocin, which can be delivered as a nasal spray, has been tried as an adjunct to exposure therapy in the treatment of social anxiety disorder [56]. In a limited, double-blind experiment, administration of oxytocin improved mental representations of self following exposure therapy, but did not affect overall therapy outcomes [56].

Successful therapeutic engagement, which includes the development of trust in the therapist as well as a lessening of the patient’s inhibitions with respect to self-disclosure, is an important prelude to the subsequent aspects of psychotherapy. In some situations, an alliance is formed almost instantly. In other cases, it requires arduous therapeutic work. In the most difficult cases, or in cases in which therapist and patient are incompatible, a therapeutic alliance may never form at all. Ideally, engagement culminates in the development of a therapeutic alliance, and, with this important foundation in place, the psychotherapeutic process can unfold in a favorable environment.

Neural Substrates of Adaptive Change

Until recently, psychotherapy has not been correlated with specific neural changes, because the technology that could define such a linkage was not available. Instead, psychotherapeutic processes have been validated according to impact on subjectively experienced internal states as well as behavior, which are indirect manifestations of neural changes. The modern conceptualization of psychotherapeutic action, however, asserts that in order to affect internal states and behavior, psychotherapeutic interventions first have to change neural contents, connections, or the amplification of specific brain circuits through top-down manipulations. These alterations in the brain's structure and function are in turn the physical substrate that underlies behavioral improvements.

The primary tools with which a therapist precipitates adaptive change in the brain are words. At first, this might be difficult to conceptualize. However, words are wielded routinely by psychotherapeutic experts as refined tools that can probe and adjust brain organization, albeit indirectly. In a sense, words are special pointers that can refer not only to all the objects and events encoded within the brain, but also to their subjective value, and to all the connections within which they have become entangled during an individual's lifetime.

Theoretically, in order to treat a patient, a therapist must first create a "virtual" model of the patient's cognitive and affective organization within his or her own brain. This involves not only cognitive and symbolic analysis of facts learned from the patient, but also "trying out" some of the patient's emotional expressions and actions in order to understand them. This occurs automatically as the therapist observes the patient's actions and emotional expressions and they are replayed within his or her own neural circuits. As the virtual representation of the patient's mind is refined, strategies for changing its organization through the use of language can be formulated according to the practical rules of the therapist's theoretical school. At present, most therapists' understanding of their patients' psychic structures cannot be articulated in neurobiological terms due to a lack of the necessary studies. However, the data that will make this possible are already accumulating.

Neurobiology supports the concept that the problems facing patients are specifically rooted in subjective reality, and not necessarily in objectively verifiable circumstances. The substrate that the brain uses for evaluation is not the external world, or even its direct physical properties. Instead, the brain internalizes peripheral sensory data, and edits them according to internal rules, using subjective content to fill "gaps" and resolve discrepancies. The "meaning" of this composite map is defined by existing feature detectors and their connections, by cognitive and emotional processing, and by prevailing internal states. Representation is the first level of information processing at which malfunctions can cause psychopathology. Brains that have developed under conditions of neglect or abuse may not possess adequate numbers or types of feature detectors, since exposure to sociocultural information may have been inadequate, and chronic stress is associated with brain simplification, including loss of cells and neuronal dearborization [23]. Such modifications can save energy and decrease response time at the cost of diminished powers of discrimination. In this context, the psychotherapist should be aware that basic experiential concepts such as empathy, happiness, and love might not be adequately represented in a patient's brain. Without such representation, the words that name these concepts have no meaning, and the body states that normally accompany these experiences will not be elicited.

Memory symptoms are common among individuals in psychotherapy. Fuster's [1] concept of phyletic memory can be extended by adding to it sociocultural and idiotypic memories [2], which are acquired through the individual's cultural activities and personal experience. Individuals with faulty phyletic memory have serious problems that may be difficult to treat, since they have deficiencies in basic representational or processing capabilities. Individuals with dysfunctional sociocultural memories may never have assimilated the basic knowledge and behavioral rules that are necessary for success in occupational and social settings. Dysfunctional idiotypic memories, especially when based on traumatic experiences, can cause significant behavioral problems because their conscious or unconscious recollection can result in explosive emotional amplification. In addition, such memories can contain associational patterns that precipitate interpersonal difficulties. Finally, it is also possible that excessive compression of memories, or the filtering out of many of the details that normally differentiate experiences, can lead to "black or white" thinking, which engenders numerous perceptual and social problems [2].

The prefrontal circuits described earlier, which support adaptive behavior by making it possible to consider many variables before responding to a stimulus, are important targets for the psychotherapist. First, dorsolateral prefrontal circuitry must be enlisted in order to use words as tools for shaping behavior. This circuit is also responsible for executive functions, including organization, problem solving, abstract thinking, creativity, strategic planning, and future orientation. Many common psychotherapeutic problems are rooted in suboptimal function within this circuit.

The generation of motivational and emotional states appropriate to context is an important function of the cingulate gyrus [35]. The amygdala and orbitofrontal cortex, by virtue of their connections to hypothalamic autonomic centers and other subcortical targets, are also able to generate emotional body states. One of the most common conditions for which individuals seek psychotherapy is emotional dysregulation. Imaging studies have shown that orbitofrontal and amygdalar circuits can be modulated through conscious cognitive processes, such as would occur during psychotherapeutic interactions [9].

The lateral orbitofrontal circuit is responsible for tempering the unbridled pursuit of reward or salience. Deficits in this circuit can present as impulsivity, social inappropriateness, lack of empathy, lack of respect for social conventions, and little response to the threat of personal risk, embarrassment, or punishment.

The psychotherapist who seeks to bring about adaptive change needs to be fully aware of the power of verbal tools, which can mobilize neural contents and activate critical circuits in the patient's brain. To facilitate change, the words of psychotherapy must first point accurately, in terms that the patient can understand, to the representational, memory, or processing deficits that are maladaptive. It may take time to arrive at this point, with therapist and patient working together to define the elements that need changing. As the psychotherapeutic process unfolds, the psychotherapist can modify the patient's maladaptive representations, increasing their verbal accessibility and complexity, while lessening emotionality and generalization. Eventually, the patient can learn to recruit the versatile prefrontal circuits for the purpose of optimizing behavior. It is this circuitry that can help fulfill occupational and interpersonal expectations and that can gradually lessen the impact of maladaptive emotional responses. With the optimization of information processing that accompanies positive psychotherapeutic change, the patient will be better prepared to cope with external challenges, and to maintain stable internal states that are both adaptive and personally satisfying.

Psychotherapy is, by nature, a top-down process. In other words, it relies on higher levels of communication, including verbal and emotional expressions, to access and modify neural circuitry. Over time, the targeted communications of psychotherapy can modify dysfunctional neural representations and their emotional connections. By applying psychotherapeutic principles in a systematic manner, a skilled therapist can reshape the patient's internal representations and their subjective meaning, decreasing impulsivity and emotional amplification, increasing the number of variables considered in behavioral decisions, and eventually leading to more adaptive behavior.

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