CME

Neural Substrates of Psychotherapeutic Change

Part I: The Default Brain

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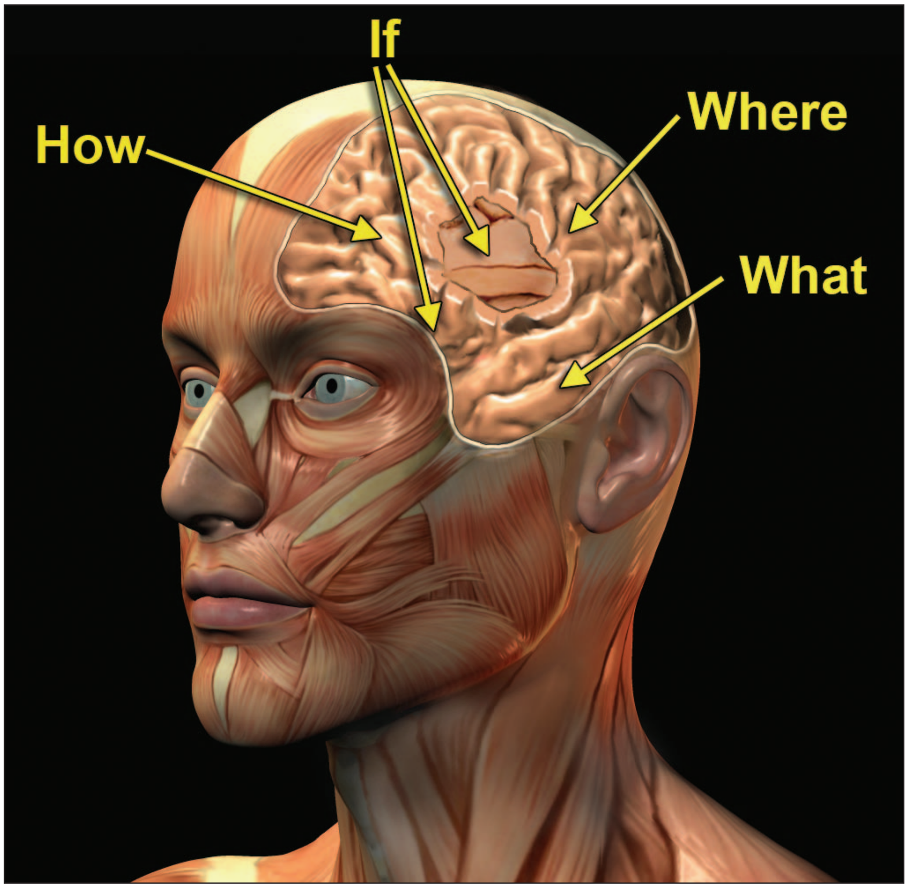

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Advances in neuroscience have begun to define the neural substrates through which psychotherapy produces adaptive change. This article describes the neural targets of psychotherapy in terms of the main functional circuits of the brain. It is the first of two parts, in light of the concept of "default mode" brain function introduced by Mesulam.[1] This first part describes default mode function as the end output of a collection of neural circuits that support individual and species survival at the most basic level. Major behavioral drivers within the default brain, including subconscious neural content, memory, and reward circuits, as well as the nature of neural representations, are discussed in detail.

The default brain, as we will call the set of circuits that drive default mode, motivates core behavioral functions effectively but lacks the power to organize the complex mental processes that support advanced social and occupational interactions. Its primary limitation is the relatively small number of variables that it considers before motivating behavior. A productive way to appreciate the practical applications of this concept is to consider child development, which begins with the default brain. As a child matures, increasing functionality of higher circuits and the acquisition of information allow gradual transcendence of the default brain and support the complex behaviors characteristic of adults. Psychiatric or neurological illness can damage the circuitry and informational overlays that support advanced behavior and often cause many aspects of the default brain to re-emerge.

FROM TOP-DOWN TO BOTTOM-UP

The human mind is a self-referential synthesis of the functional capacities that emerge as the brain addresses internal and external milieus. For technical reasons, the mind has been described traditionally in terms of what it does, rather than how it is implemented. Freud, for example, used metaphorical terms like ego, id, and superego to describe what he observed and developed techniques to access and influence these functional constructs. Others, like Skinner, focused on stimulus-response paradigms to define methodologies for the manipulation of behavior. Aaron Beck transcended his psychoanalytic background and developed cognitive therapy, a powerful technique for influencing behavior that focuses on the complex representations made possible by language.

As divergent as these psychotherapeutic frameworks appear, their formalized protocols share one common element — namely, they are all "top-down" approaches. Their evaluative and therapeutic interventions focus on higher order functions such as cognition, affect, and behavior, not on the neural circuitry that generates these phenomena. In practice, there is significant emotional, or bottom-up, communication in psychotherapy, although much of it is not formally structured, and none of it has been linked conceptually with neural circuits. Because of technological advances in neurobiology and functional brain imaging, the time is at hand to enhance the power of psychotherapeutic practice by starting to define a highly organized, bottom-up infrastructure that is rooted in an understanding of the brain.

CME EDUCATIONAL OBJECTIVES

1. Discuss the basic brain circuitry that controls memory, the pursuit of reward, and subconscious information processing.
2. Describe how physical objects are represented in the brain.
3. Explain the anatomy and function of "mirror neurons."

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BASIC PRINCIPLES OF BEHAVIORAL CONTROL

The perception of sensory stimuli and the generation of appropriate behavioral responses require coordination of a variety of representational, evaluative, motivational, and executive neural circuits. The contents and capabilities of these circuits define the battleground on which psychotherapeutic interventions unfold. In general (Figure 1, see page xxx), a stimulus is perceived by the senses, and neural processing leads to a behavioral response.

Between the sensory system that detects environmental and internal cues and the motor system that coordinates movement are arrays of neural circuits that generate predictions about the implications of sensory stimuli. As the predictions are evaluated, the most meaningful ones trigger the body states and cognitive constructs that drive behavior. Meaning in this context is defined by comparing current inputs to learned patterns that predict outcomes, and by correlating sensory data with prevailing internal states. For example, the smell of apple pie as one walks by a bakery suggests that palatable food is available. If the prevailing internal state includes hunger, then the possibility of eating a piece of pie might be pursued. However, concomitant feelings of depression or sickness, the knowledge that one is allergic to apples, or the cognitive information that one is on a diet might alter behavioral responses significantly.

Not all sensory stimuli receive such detailed evaluation. Certain classes of inputs are not correlated specifically with internal factors because they demand rapid responses. These stimuli, such as reflex withdrawal from heat or signals of extreme threat, bypass complex processing and trigger behaviors automatically, either before they reach the brain or shortly after they are represented neurally.

Every waking moment, multiple streams of information flow into the brain. In general, the information elicits one of three responses: engagement, avoidance, or indifference (Figure 1, see page xxx). Most of the sensory data that we perceive, such as background noises and environmental objects, do not elicit expanded processing or dedicated behavior. Therefore, the response to these stimuli can be classified as indifference. The psychotherapeutic process deals most frequently with the other two responses, engagement and avoidance.

INTERNAL REPRESENTATIONS

A key evolutionary advance in information processing is the internalization of sensory stimuli (Figure 1). Simple brains have limited processing capacity between stimulus and response and are aided by peripheral filters that perform input selection before sensory signals reach the brain. The hearing capacity of frogs, for example, is limited to the two sound frequencies that define their species-specific mating call.[1] Because they lack the processing power to differentiate environmental sounds, frogs leave behind a world of information to ensure that they do not miss that one critical signal.

In contrast to simple brains with few behavioral options, human brains contain elaborate internal representations of the physical world, and it is these representations, rather than direct sensory stimuli, that guide behavior. The internalization of self and object representations make symbolic logic possible, as internal representations can exist independently of the physical objects that they symbolize and can be manipulated cognitively. In this context, object permanence is the ability to produce specific neural representations through top-down signals rather than by directly mapping perceived sensory inputs. It is important to note that these representations are not necessarily accurate in objective terms.

Human representational systems acquire their basic organization during the

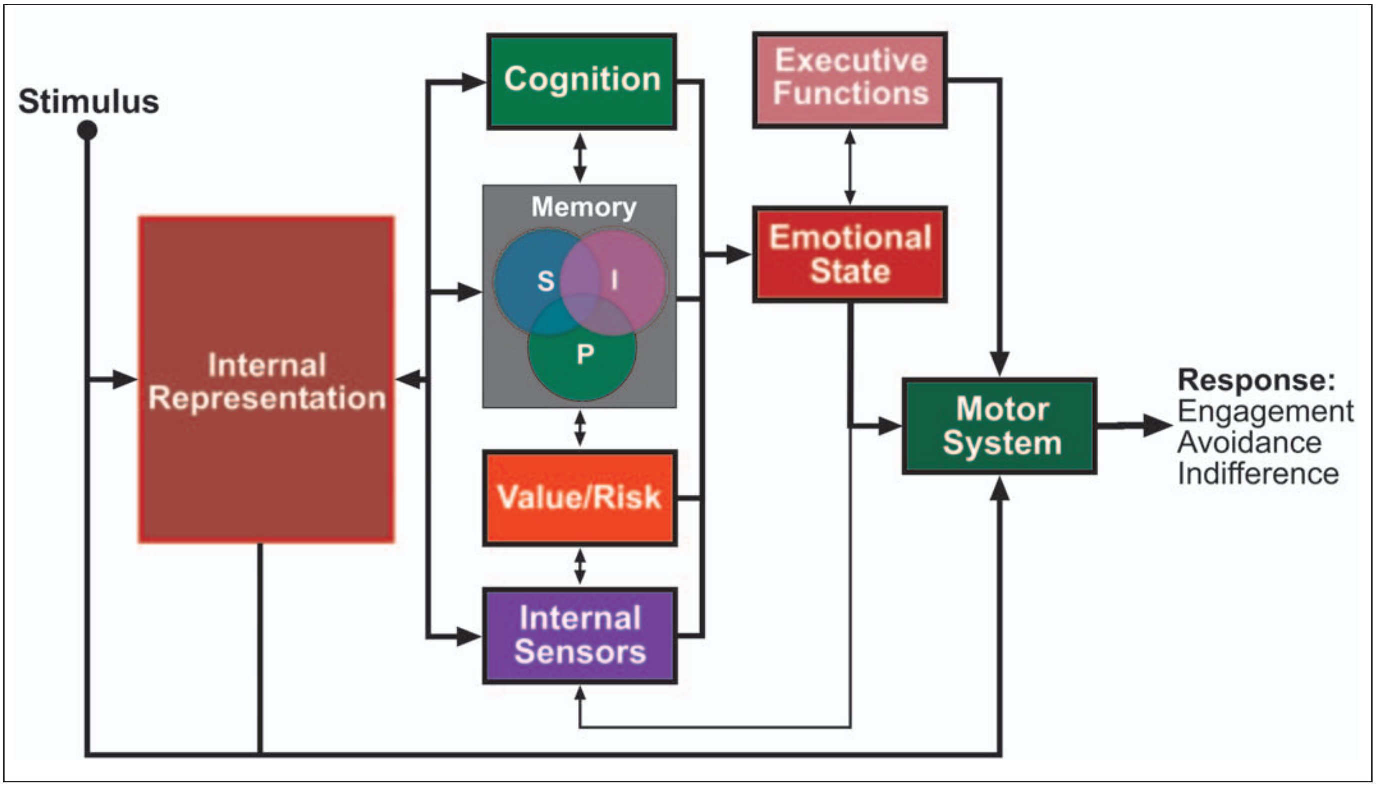

Figure 1. From stimulus to response. Sensory stimuli are internalized and form neural representations of the internal and external milieus. Certain stimuli trigger automatic responses that can be innate or learned. Representations are compared with stored memories (phyletic, sociocultural, and idiotypic; see text). If a match occurs, specific cognitive responses are elicited. Representations also trigger emotions with their corresponding body states (driven by autonomic, neurotransmitter and hormonal responses). Body states are represented in the brain and can amplify the impact of the original representation. Internal sensors sample the internal milieu and can signal such phenomena as thirst, hunger, sickness, tiredness, pain, etc. These signals modulate an individual's body state, and can also trigger memory representations. The combination of cognition and emotionality elicits engagement, avoidance, or indifference as a response to the original stimulus. Ideally, emotions and cognition are integrated, but often one overrides the other. (Figure ©2006 G. Viamontes. Used with permission.)

first few years of life and subsequently undergo continuous refinements. Each sensory region is an independent processing network with distinct functional specificity. Raw information is delivered to the five primary sensory cortices and subsequently is expanded to the corresponding unimodal cortices (Figure 2, see page xxx).

Feature detectors within each unimodal cortex respond to specific properties of the perceived object. In visual processing, for example, there are feature detectors for color, shape, and movement. If a feature detector is missing or damaged, whatever it represents will no longer exist in the brain and cannot be referenced or remembered. In humans, the fusiform gyrus[2] contains advanced feature detectors for the recognition of objects and faces. The famous "vase" illusion (Figure 3, see page xxx), in which a picture seems to alternate from a vase to a pair of faces, illustrates this principle. Imaging experiments[3] have demonstrated that, when the picture is perceived as a vase, the object detection area of the fusiform gyrus is activated, whereas the fusiform face area is activated when the object is perceived as a face.

Many of the basic feature detectors in the brain are acquired during childhood, as the brain learns to categorize people, objects, and situations. Even at a few weeks of age, human infants smile and vocalize at people more frequently than at objects,[4] which indicates the presence of rudimentary feature detection. Additional feature detectors self-organize during infancy as a result of environmental interactions. This is thought to occur through the differential strengthening of synaptic connections in object representation areas and the linking of object representations with emotions and other internal states.[4]

By age 12 months, sets of feature detectors have developed in the infant's brain that support the recognition of people, objects, and events, and define their functions from the perspective of the child. Around age 18 months, with the rapid development of language, children increase their powers of discrimination significantly.[4] They perceive the physical similarities of objects through common activation of specific feature detectors, and learn "meaning" through the self-organization of synaptic linkages that relate objects and events to primary reinforcers or punishers, and to representations of internal states[4] (Figure 4, see page xxx).

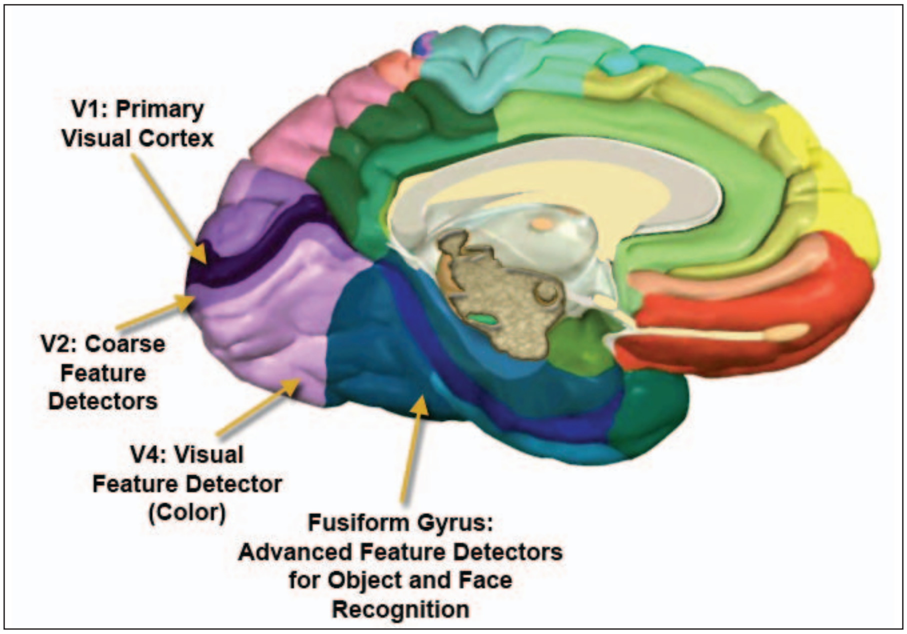

Figure 2. The visual cortices. Visual information is internalized and projected onto the primary visual cortex (V1). From here, data flow to the various feature detectors of the unimodal visual cortex (such as V2 and V4), and then to the heteromodal cortex of the fusiform gyrus, where identification of the visually perceived object takes place. Colored boundaries define specific Brodmann areas. Brain image copyright 3B Scientific GmbH 2001. (Excerpted from NEUROteacher™. Used with permission.)

The brain has several basic networks that evaluate and integrate sensory information (see image on page xxx). In general, the temporal lobe, which contains numerous feature detectors, specializes in object identification ("what"). The parietal lobe represents spatial information ("where"). Decisions about whether an object or situation demands engagement or avoidance ("if") are formulated in the limbic, dorsolateral prefrontal, and orbitofrontal circuits. In the case of novel situations, or those that require problem solving, dorsolateral prefrontal circuitry can provide the "how."

THE STRUCTURE OF THE SUBCONSCIOUS

An important feature of the brain's representational system is that the greater the synaptic distance from the first internal map of sensory data, the more "abstract" the representation.[5] For example, while representational patterns in the primary visual cortex correspond closely to the retinal image, expansion of information through several layers of feature detectors in the unimodal visual cortices generates representations that diverge significantly from the original retinal pattern.[5] The nature of represented features changes as a function of distance from the primary visual cortex, which is at the occipital pole. Caudal feature detectors represent concrete properties like shape, orientation, or color, while more rostral ones encode abstract categorizations such as fruit, animal, or tool.[5]

The process of abstraction has practical repercussions from a psychotherapeutic perspective. With each level of abstraction, some of the information that defines the uniqueness of a perceived object is "left behind." That is, while all the information available is represented at the lowest mapping level (the primary cortex), only the information that activates higher-level feature detectors in the unimodal cortices is carried forward.[6] For example, the primary visual cortex (V1) can record independent color changes that occur as fast as 60 times per second. The color feature detector (V4), however, can resolve color changes with a maximum frequency of just 15 times per second.[6] If a light flickers from yellow to blue 30 times per second, this information is represented in the primary visual cortex, but at all subsequent levels, the light will be represented as a stable green color.

In addition to this filtering effect, there are large sets of information in the brain that can be accessed by consciousness only indirectly. The evolution of the brain circuits that implement consciousness involved the addition of new functional capacities without replacing existing homeostatic systems. As a consequence, many streams of information reach consciousness only after they have already triggered emotions or sensations. Information about blood glucose and autonomic regulation, for example, become conscious only through the secondary perception of induced body states. The mapping of much of this internal information in a manner accessible to consciousness is thought to be carried out by the insula.[6]

We would like to hypothesize that limitations in the actual data that reach consciousness as information is organized into higher-level constructs, together with the special patterns of synaptic connections that define this organization, are the foundations of the subconscious. A vast array of information is internalized and represented in the primary and unimodal sensory cortices, as well as in the homeostatic centers of the brainstem, yet only a portion of the represented information ever makes it to consciousness. Despite the exclusionary nature of this process, the information at lower representational levels is neither lost nor devoid of effects.

For example, studies of patients with unilateral visual extinction as a result of right inferior parietal strokes have demonstrated that visual information that does not reach consciousness can nevertheless cause activation of neural structures that generate emotions.[7] In these patients, the simultaneous presentation of images to right and left visual fields causes extinction of the left visual image a large percentage of the time. Extinguished images do not reach consciousness, and the patient cannot describe them. However, extinguished images of fearful faces cause significant activation of the ipsilateral amygdala and lateral orbitofrontal cortex. Face-selective fusiform areas also are activated bilaterally by extinguished facial images, although the representations do not reach consciousness. A finding with possible relevance to psychotherapy is that extinguished images of both neutral and fearful faces elicit stronger amygdalar activation than conscious images, suggesting a modulatory effect of the higher cortices on the amygdala.[7]

Representational considerations are very important in psychotherapeutic communication. Visual perception of facial expressions and bodily movements by both patient and therapist can generate emotional activation whose source may not be consciously clear. In addition, the verbal exchanges of psychotherapy make use of words, which represent a high level of abstraction. To use a computer programming term, words are symbols that function as pointers to appropriate representational areas. The word "red," for example, derives its meaning from the fact that it points synaptically to the area in the unimodal visual cortex that represents this color. In other words, we can imagine the color red because thinking about the word causes top-down activation of the specific area in the visual cortex that encodes "redness."

Imaging studies have shown that this phenomenon is a generalizable principle. We can imagine objects that are not physically present because we can partially activate, on command, the sensory regions that represent them.[8] The power of words, therefore, hinges on their ability to elicit top-down activation of appropriate representational areas (Figure 5). For words to serve as reliable tools for communication, they should point to similar representations in the individuals who are attempting to communicate. Many of the deficits in patients who seek psychotherapy are related to disparities between their representational systems and those of others in their milieu.

Object representations are not isolated but contain numerous linkages to each other as well as to emotional and functional neural regions.[9] The "mirror" neurons described by Rizzolatti and colleagues,[10] for example, demonstrate this principle. When a person observes the actions of another person, "mirror" neurons in the premotor cortex and the superior temporal sulcus are activated in the brain of the observer.[10] The term "mirror" refers to the observation that these neurons react in similar fashion when a person performs an action and when he or she observes another person performing it. From a representational perspective, it is essential for the observer to represent the other person's movements in his or her own brain to understand their "meaning." Only after internal modeling of the observed action will the appropriate representational spaces be activated in the observer's brain, and lead to understanding.

Unfortunately, misunderstanding is also possible if representational spaces in observing and observed people are not equivalent. From a functional perspective, the "mirror" neurons in the superior temporal cortex not only activate motor representations but also project to the amygdala and orbitofrontal cortex, an arrangement that is thought to provide an emotional understanding of observed actions.[10] The human capacity for abstract thinking has extended the scope of internal modeling beyond physical objects and movements to considerations of feelings, motives, and intent.

The ability to mentalize,[11] or to imagine what another person might be thinking, depends on the ability to model in the observer's cognitive and limbic circuits the expressed or inferred thoughts and emotions of the observed person. Imaging experiments, for example, have shown that observing the expressions of another human being who is experiencing pain activates the emotional pathways normally associated with pain perception.[12] Regions with increased blood flow during pain observation include the anterior cingulate cortex, the insula, the amygdala, and the orbitofrontal cortex.[12] Dysfunction in limbic circuits, manifested as deficits in the perception, modulation, or interpretation of emotions, also affect mentalizing, which relies on these circuits for implementation. It is important for the psychotherapist to understand the nature of this common complication of affect dysregulation, which can magnify the patient's interpersonal problems and make psychotherapeutic treatment

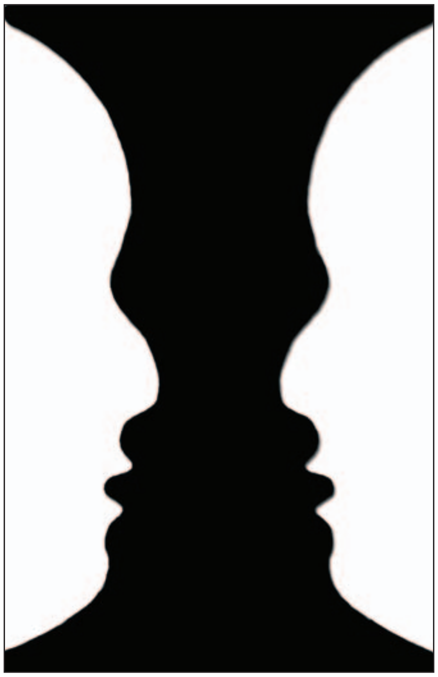

Figure 3. An example of the classical face–vase illusion. The image seems to shift from a vase to a pair of faces as object and face recognition areas in the viewer's fusiform gyrus are activated alternatively. This illusion exemplifies that "recognition" of the elements of external reality depends on their activation of pre-existing categorical classification regions that are created through a combination of genetic and developmental factors. (Illustrated by G. Viamontes.)

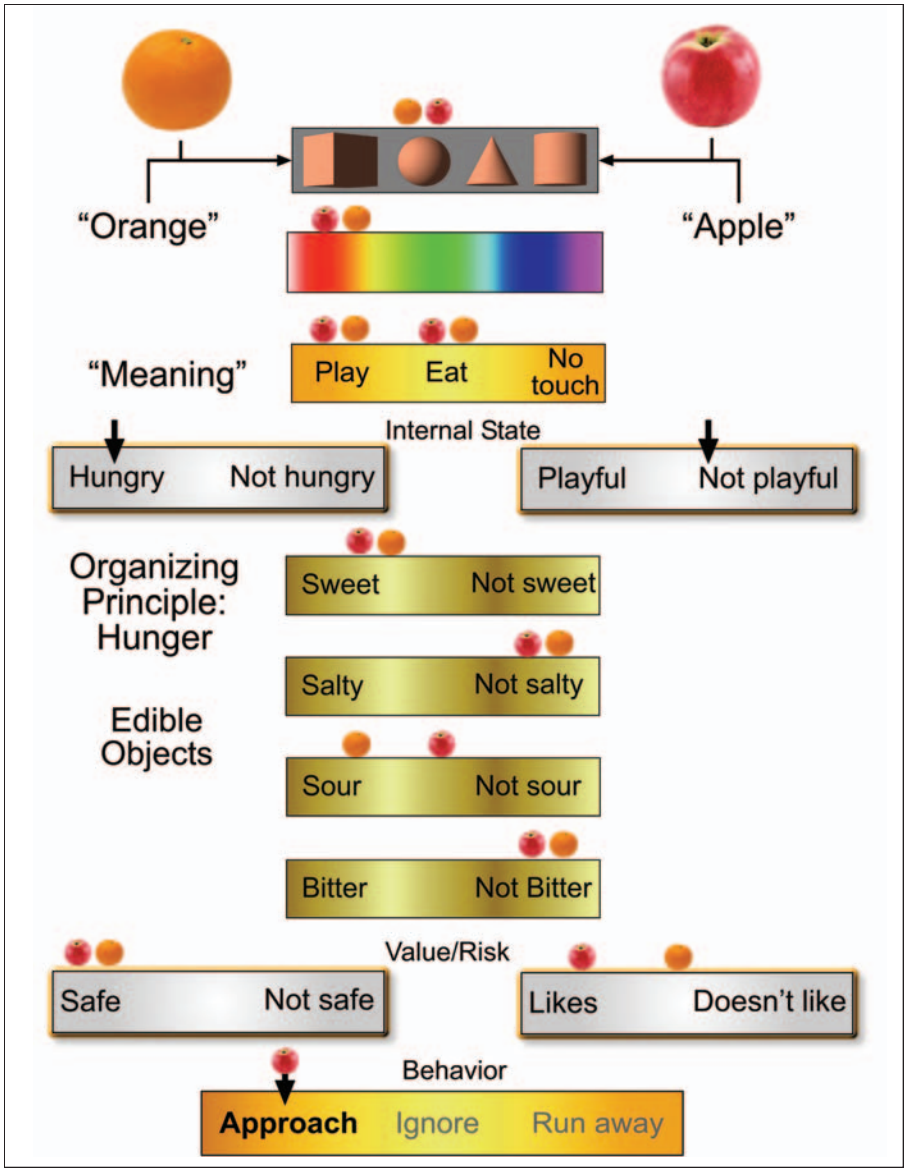

Figure 4. Visualization of putative feature detectors in the brain of a child who sees an orange and an apple and ponders what, if anything, to do with them. The objects activate concrete feature detectors such as those for shape and color close to the primary visual cortex and more abstract ones farther away. As the objects are neurally represented, their functions can be inferred by comparing their representational footprints to previously learned patterns. In this case, the child knows that the objects can be used for playing or eating. The child's internal state signals hunger; therefore, the objects are further processed with hunger as the organizing principle. Both objects are remembered as not salty or bitter. The apple is remembered as sweeter and the orange as more sour. The child remembers that both apples and oranges are safe to approach. Since the memory of the apple's taste and sensory features is more appealing, the child approaches the apple and begins to eat. As the child learns language, the words "apple" and "orange" elicit top-down recollections of these objects by "pointing" synaptically to all the remembered elements of their representations. These do not necessarily reflect reality accurately.

more difficult. In addition, the therapist must be aware that, as psychotherapy proceeds, the patient's emotions, cognitions, and inferred intentions are being modeled continuously in the therapist's own neural circuits.

Representational capacities, both for emotions and objects, are pre-programmed genetically. In contrast, the acquisition of the words that point synaptically to specific parts of the representational space requires simultaneous interaction with human teachers and the environment. Each of us spends a lifetime building the representations and vocabularies that will support occupational and personal functioning. People with genetic deficits, or those who have suffered neglect and abuse, may never develop some of the key representations that support adaptive social behavior. Psychotherapy may be able to help these people restructure representational spaces and develop the verbal pointers that serve to classify and access these spaces.

MEMORY

The human brain has multiple systems that store information about encounters with specific sets of internal and external stimuli. This information may include spatial, sensory, and emotional components, as well as abstract verbal descriptions. In addition, memories frequently store "how to" information, which facilitates responses to similar situations in the future.

Traditionally, long-term memory has been divided into explicit or declarative memory and implicit or nondeclarative memory. Explicit memories are recoverable by consciousness, whereas implicit memories consist only of automatic movements, body states, or emotions associated with particular representations. Implicit memories include habitual behaviors such as "knowing" how to drive a car or how to play tennis. Explicit memories can be subdivided further into semantic, or factual memories, and episodic, or event-based memories.[13]

In the context of psychotherapy, we can segment memories in a powerful manner by extending the concept of phyletic memory introduced by Fuster.[14] Phyletic memory refers to the genetically defined processing capabilities and limitations that result from evolution. Humans, for example, are better at visual than olfactory processing, while in dogs, the reverse is true. Humans also have the capability to learn languages, create art and music, and think abstractly. These inherent capacities are the legacy of our evolutionary past and represent a memory of the selective pressures and adaptations that have shaped our species.

The concept of phyletic memory can be extended by adding the categories of sociocultural and idiotypic memory. Sociocultural memory refers to the representations that are stored as a person interacts with others within a specific sociocultural setting. The languages, religion, customs, and "social graces" that we teach our children, as well as the food, dress, art, music, diversions, and lifestyles to which they are exposed, are the raw materials of sociocultural memory. Idiotypic memory, in contrast, does not reflect shared circumstances but encompasses that subset of life experiences unique to the individual. This category includes special training and personal occurrences that are not common to most other people in the individual's culture. Children with well-rounded upbringings will accumulate useful sociocultural and idiotypic memories. On the other hand, neglected and abused children may have a poor storehouse of sociocultural memory and a collection of idiotypic memories that trigger maladaptive behaviors when activated. Deficits in phyletic memory can cause serious behavioral dysfunction, because they involve malfunctions in the basic neural processes that support cognition, emotion, and behavioral control. Schizophrenia, autism, and obsessive-compulsive disorder are examples of psychiatric conditions caused by deficits in phyletic 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.[15] Simple association of previously neutral objects with natural reinforcers or punishers is accomplished by the circuitry of the amygdala and orbitofrontal cortex.[16] 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, nonverbal 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.[13]

The hippocampal complex receives many streams of information via the entorhinal cortex. These include projections from prefrontal regions, the cingulate gyrus, occipital lobe, superior and inferior temporal gyri, temporal pole, amygdala, sensory cortices, and insula.[16] From the entorhinal cortex, the information flows to the dentate gyrus via the perforant pathway (Figure 5, see page xxx). The dentate gyrus contains sparsely connected neurons and is thought to function in the orthogonalization of informational patterns.[17] Orthogonalization is a process through which the representations of the individual data sets that define discrete memories are made as different as possible to minimize interference with previously stored patterns and to permit later separability. The dentate gyrus is one of the places in the brain in which neurons are produced continuously, although this production can be interrupted by chronic stress or psychiatric illness.[17]

From the dentate gyrus, the information is conveyed to the CA3 region of the hippocampus. CA3 also receives direct inputs from the entorhinal cortex. Information undergoes a great deal of compression as it is conveyed to CA3, as it is encoded by fewer neurons than in previous layers.[18] Neurons in the CA3 region are connected extensively and are thought to implement actual memory encoding on a short to medium-term basis.[18] Selected memories, because of their affective impact or repeated reactivation, are consolidated for long-term storage.

We would like to propose the hypothesis that faulty orthogonalization, possibly due to unavailability of sufficient numbers of dentate gyrus neurons, combined with higher than optimal compression in the CA3 region, may be associated with a tendency to overgeneralize, or interpret situations as "black or white," without any shades of gray. An interesting finding that may have relevance to the compression hypothesis is that hippocampal volume has been found to be reduced in women with borderline personality disorder and a history of abuse.[19]

The CA3 region also has been proposed as the hippocampal component that "completes" previously encountered patterns when only parts of them are perceived.[20] This feature, which is based on the high interconnectivity of CA3 neurons, can have effects of interest to the psychotherapist, as automatic, maladaptive pattern completion could manifest itself as psychopathology. The pattern of connections in CA3 neurons is thought to play an important role in the binding of the multiple sensory, emotional, and cognitive elements that make up each individual memory.

From CA3, information flows to another area within the hippocampus, CA1. This area is thought to facilitate the encoding of spatial information.[20] Hippocampal information completes a recurrent loop as it flows from CA1 back to the entorhinal cortices via the subiculum (Figure 6). Information flows are somatotopically mapped to allow the same entorhinal cells that originated a particular signal to receive the appropriate backprojections.[18] From the entorhinal cortex, information spreads to the perirhinal and parahippocampal cortices and eventually to many of the unimodal and polymodal cortices where the infor-

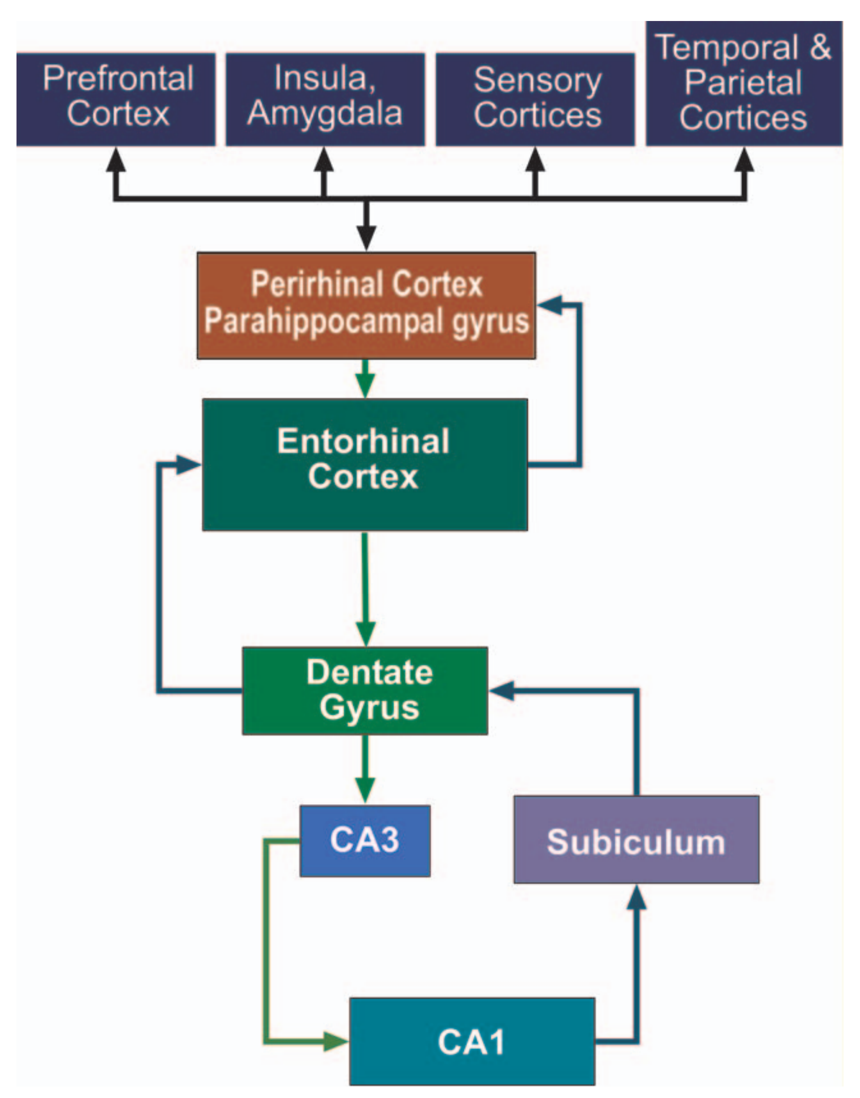

Figure 5. General information pathway through the hippocampus. The perirhinal cortex and parahippocampal gyrus receive a rich array of information about both internal and external milieus. This information is consolidated in the entorhinal cortex (which also receives independent inputs from other cortices - not shown in diagram) and transmitted to the dentate gyrus. The dentate gyrus is a site of active neurogenesis, and has been hypothesized to facilitate "orthogonalization" of information, which ensures that new patterns do not interfere with the old and remain separable. From the dentate gyrus, information is conveyed to CA3 via the perforant pathway. CA3 has fewer cells encoding information than the dentate gyrus; therefore, information is compressed as it is transmitted to CA3. CA3 neurons are highly interconnected, which is thought to facilitate the binding of multiple aspects of a single memory and to allow completion of incomplete patterns. Information is passed from CA3 to CA1, where it is believed that spatial data are added. The information loop is closed as backprojections activate the dentate gyrus, entorhinal cortex, and perirhinal cortices sequentially. Backprojections are believed to facilitate the extra-hippocampal encoding of memories, and linkages at the perirhinal cortex that represent learned information have been identified.

mation originated.[18]

Studies with nonhuman primates suggest the transition from short-term to long-term encoding of visual memory involves the creation of linkages in area 36 of the perirhinal cortex, under the guidance of stored hippocampal patterns.[9] Next, through the action of massive backprojections from the perirhinal cortex, linkages among individual memory elements are created in the anterior inferior temporal cortex, which is an important area for visual object representation.[9] 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.[9]

The consolidation of memories is facilitated by emotional arousal. Memories with high emotional content are encoded and consolidated more efficiently than those that are emotionally neutral.[21] This process is controlled by the basolateral amygdala, which can enhance memory encoding by promoting release of facilitatory neurochemicals such as norepinephrine and acetylcholine.[21] In pathological states such as depression, sustained activity of the amygdala can maintain the flow of negative emotions,[22] unbalancing memory systems by attaching emotional significance to normally trivial events, and therefore marking them as "memorable."

THE DEFAULT BRAIN

Mesulam[1] introduced the concept of a "default mode" for brain function. This term refers to the actions of the brain's core functions, including the ability to meet basic survival needs through simple stimulus–response associations. 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 brain, as we will call the collection of circuits that implement the brain's default mode, is driven almost exclusively by internal appetitive urges and highly salient external stimuli. This arrangement demands very little information processing in the interval from stimulus to response and is efficient, but at the cost of reduced functionality, high impulsivity, and little capacity for addressing novelty or complexity.

Analyses of normal brain development and the deficits of patients with brain injuries have shown that the "default" brain 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.

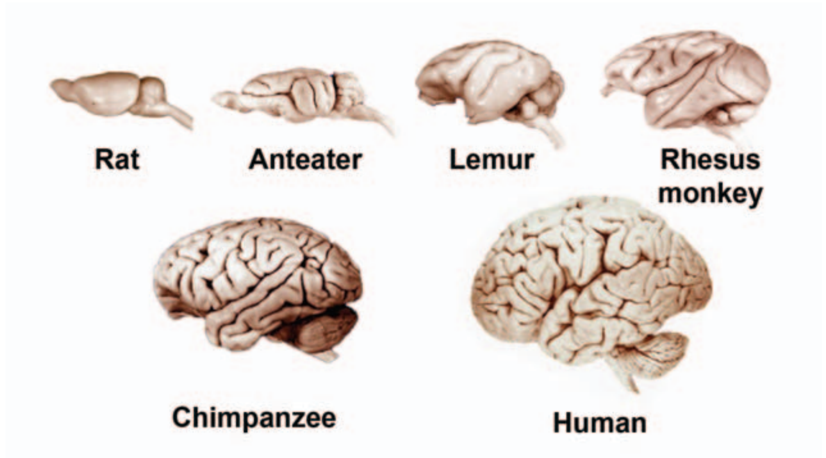

Figure 6. Brains of multiple species. The brain evolved around a central core whose circuitry can support basic functions such as homeostasis, acquisition and conservation of energy, avoidance of injury, and reproduction. As species became more complex, cortical overlays developed around the central core. These overlays support enhanced data processing and increase the number of variables that can be considered before initiating a course of action. Human brains are highly convoluted to increase their surface area and satisfy the processing demands of advanced neural functions such as speech and abstract thought. Images courtesy of the Comparative Mammalian Brain Collections, University of Wisconsin, Michigan State University, and the National Museum of Health and Medicine, who retain all rights. (Downloaded from http://brainmuseum.org. Specimen and image preparation were funded by the National Science Foundation and the National Institutes of Health.)

All successful psychotherapies engage the prefrontal cortex to create or repair the context-specific overlays that modulate the default brain and generate the complex behaviors needed for success in our sociocultural milieu. Clinical work with patients with brain injuries, animal experimentation, and functional brain imaging have defined both the general circuits of the default brain and those of the overlays that support higher levels of complexity and adaptability.

Adaptive behavior from a biological perspective 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, controls bodily processes, and coordinates the pursuit of resources in concert with risk assessment and internal needs. The default brain, as described above, contains the circuitry to accomplish these basic goals. Even the simplest brains, such as those of fishes, facilitate feeding, risk avoidance, and reproduction.

The evolution of enhanced behavioral capabilities required the development of species-specific overlays that enlarge the brain's information-processing capacity and its repertoire of behavioral responses. The major motivational systems of the default brain include the reward circuits described below and the amygdalar–orbitofrontal circuits, which can detect both potential reward and risk.[16] Activated memories and subconscious contents, as described above, also can generate significant motivational force by inducing internal states that influence the probability of specific behavioral responses.

All of the core motivational circuits make use of emotions (Part II, see page xxx) to drive behavior. Without further modulation, the default brain is an efficient system for acquiring environmental resources, satisfying internal drives, and avoiding obvious risk. The limited, self-centered strategies of the default brain, however, are not adaptive in advanced sociocultural settings. To achieve the benefits of these higher organizational schemes, the scope of the brain's representational, evaluative, and cognitive systems had to be enlarged.

The anatomical layout of advanced brains reflects their evolution. Essentially, the brain expanded outward from a central core (Figure 6, see page xxx), which contains basic circuitry for arousal, homeostasis, and simple stimulus-response behavior. The large cortical suprastructure that evolved around the brain's inner circuits expanded the scope of each basic system, creating new functionalities and expanding the set of variables that determine behavior.

THE BRAIN'S REWARD CIRCUITRY

The driving force behind the brain's pursuit of environmental resources and reproductive opportunities is the dedicated circuitry of the reward system. Evolutionary influences have defined many natural reinforcers as part of each individual's genetic inheritance. These can vary significantly among species. For example, the smell and taste of rotting flesh are naturally rewarding to vultures but repulsive to humans. In this context, human taste systems are pre-wired to prefer sweet flavors to bitter ones. This can be transcended by sociocultural and idiotypic overlays, as is the case with coffee, a bitter flavor that has become an "acquired taste" in many cultures through reinforcement by the desirable body state that it induces.

In primates, representations of natural reinforcers can be found in the amygdala and orbitofrontal cortex, which receive

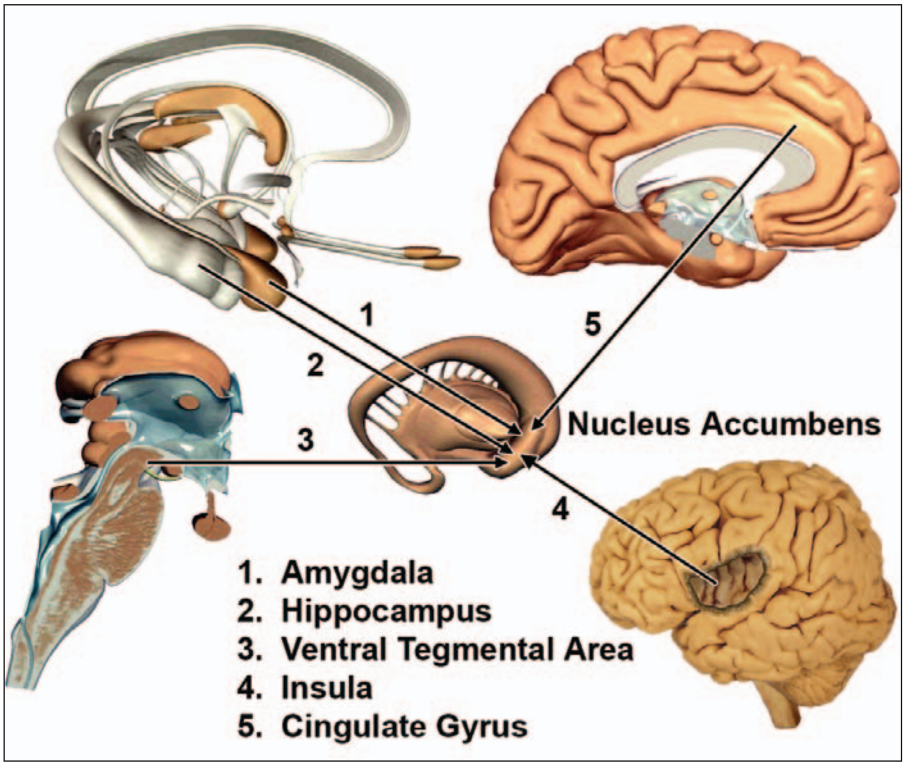

Figure 7. Selected inputs to the nucleus accumbens. The nucleus accumbens is a central node within the brain's reward system, and an area of confluence for various critical information streams. These include the amygdala, which provides inputs regarding potential reinforcers and punishers, as well as the facial expressions of others; the hippocampus, which plays a major role in activating nucleus accumbens neurons as patterns in memory are activated by current cues; the ventral tegmental area, whose dopamine output amplifies strong signals and diminishes the rest; the insula, which maps a variety of internal states, including visceral sensations and autonomic activation; and the cingulate gyrus, which provides access to cognitive contents and works with the nucleus accumbens to focus attentional and motivational resources on objects and events with high salience.

a rich array of projections from all the sensory cortices.[16] Secondary reinforcers and punishers, or previously neutral stimuli that have become associated with positive or negative value, also are represented in these regions through synaptic modifications that occur with learning.[16] Whenever environmental cues are encountered that signal the possibility of acquiring something of value, the reward system is activated, and it generates internal states that focus attention and increase the probability of behavior that will obtain the valued object. The reward system continuously enlarges its list of potential targets by linking new environmental cues to natural reinforcers in a manner consistent with experience.[16]

The following description of the reward system is adapted in part from an earlier article.[23] The feeling of "reward" is a body state that the brain interprets as pleasant. When pleasurable stimuli are experienced, reward circuitry promotes the formation of memories that store details of the accompanying circumstances. This causes the individual to try to duplicate the events that led to the pleasurable experience. The neural circuitry of reward is implemented by a distributed network with epicenters in the nucleus accumbens, the ventral tegmental area, the hippocampus, the amygdala and orbitofrontal cortex, the prefrontal cortex (anterior cingulate gyrus and ventromedial cortex), the globus pallidus, the ventral pallidum, and the thalamus.[24]

Anatomically, the nucleus accumbens, which is at the center of reward circuitry, is part of the ventral striatum. It is an area of confluence where diverse streams of information are integrated, causing potentially rewarding objects and situations to receive attentional and behavioral focus. The nucleus accumbens has two main parts, a core that is continuous dorsally with the rest of the striatum and a shell that surrounds the core medially, laterally, and ventrally. Functionally, the shell mediates the "liking" of pleasurable stimuli, while core circuitry generates the sensation of actually "wanting" a specific pleasure that appears attainable.[25]

The nucleus accumbens shell contains opioid receptors whose activation is related to the intensity of sensory pleasure.[25] Agonism of these receptors enhances pleasure, whereas blockade diminishes it. Destruction of these receptors does not abolish pleasure, however. The only area that has been found to be essential for the experience of pleasure is the ventral pallidum, which receives extensive projections from the nucleus accumbens shell. Destruction of this area in rats, for example, completely abolishes pleasurable responses to taste stimuli, including primary reinforces such as sweetness.

The nucleus accumbens is part of a distributed network that functions in the linkage of motivation to action.[26] It receives a broad spectrum of inputs that carry information about available objects and their potential value (Figure 7, see page xxx). This includes projections from the amygdala, which signals potential reward and risk; from the hippocampus, which provides place and episodic information about previous encounters with currently perceived cues; and from the insula, which represents a variety of internal states.

Inputs from the hippocampal region, basal amygdala, and thalamus are organized somatotopically, which means that discrete, segregated pathways are maintained throughout the circuit.[26] The somatotopic organization creates channels that are related functionally to each of the many inputs that are evaluated continuously within the nucleus accumbens. Through this arrangement, the nucleus accumbens is able to generate amplified cortical and limbic representations of specific stimuli with high perceived value, while simultaneously attenuating the rest. This focuses attention and behavioral resources on objects and situations expected to yield high levels of reward, while ignoring less valuable possibilities.

In humans, about 70% of the cells in the nucleus accumbens core are medium-sized spiny neurons with high densities of synaptic spines. This is consistent with their role as information integrators.[26] The accumbens spiny neurons are GABAergic and inhibitory and project to the ventral globus pallidus. These projections give the accumbens the capacity to modulate thalamo-prefrontal circuits. Neurons from the accumbens shell also project to the central amygdala, lateral hypothalamus, cholinergic and dopaminergic nuclei, and a variety of other autonomic and somatomotor targets. These projections give the accumbens the ability to modulate arousal, autonomic tone, emotionality, and the amplification or suppression of cortical representations. Accumbens neurons are normally quiescent and will not fire unless activated by multiple stimuli. Neurons in the globus pallidus, on the other hand, fire continuously and exert inhibitory effects on the thalamus. When an accumbens neuron fires, it triggers a call to action by suppressing target neurons in the globus pallidus and indirectly disinhibiting specific channels within the thalamus. This conveys to the cortex an amplified representation of the object that triggered the accumbens.

Dopaminergic projections from the ventral tegmental area increase “contrast” in the nucleus accumbens through the modulation of voltage-gated ion channels and facilitate the amplification of a single, powerful input, while simultaneously suppressing weaker signals.[27] The “winner-take-all” function modulated by dopamine is a key to targeting important stimuli and is at the heart of both attentional and addictive problems.

As exemplified by Parkinson’s disease, inadequate dopamine levels are incompatible with physical movement. They are also incompatible with the critical mental functions of attention and motivation. Just as the body ceases to move in the absence of dopamine, the brain also loses its motivational energy. Without sufficient dopamine, brain function lapses into profound apathy, as neither internal nor external signals are amplified appropriately. In extreme cases, animals deprived of dopamine through genetic manipulation actually starve to death because they are not motivated to eat, even in the continuous presence of food.[28]

Without further modulation, nucleus accumbens circuitry focuses attention and behavioral resources on external objects that have become salient through past linkage with pleasurable internal states. This can be problematic, as the unrestrained fulfillment of internal urges and the pursuit of salient stimuli without regard for context can be physically dangerous and is maladaptive in social and occupational settings.

SUMMARY

Mesulam’s concept of the default mode of brain function[1] is a valuable organizing principle with relevance to the definition of a neurobiology of psychotherapy. The brain’s core survival mechanisms, which can surface under conditions of chronic stress, psychiatric illness, or neurological damage, are not sufficiently sophisticated to support adaptive behavior in our sociocultural context. It is important to consider, however, that every human brain contains this powerful, yet inflexible set of survival-oriented circuits at its center. Despite the adaptive overlays for behavioral control that are developed over a lifetime, manifestations of the default brain surface periodically.

Each of us constantly moves along a behavioral continuum that is driven at one pole by the default brain and at the other by the higher functions that are the subject of our second article (see page xxx). Intense emotional states, chronic stress, and the sense of risk demand efficiency and simplification in our interactions and can drive behavior in the direction of the default brain. Psychotherapy promotes behavioral adaptation by augmenting the modulation of the default brain by higher circuits, and increasing the quality and scope of the internal and external variables that determine our actions.

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