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Clinical neuroscience and imaging studies of core psychoanalytic constructs ☆

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Abstract

Core psychoanalytic constructs may be impossible to study directly using neuroscience and imaging methodologies. Nevertheless, experimental paradigms have been developed and are being applied that are at least relevant to understanding the neural bases of certain core theoretical constructs within psychoanalysis. These paradigms have demonstrated the likely contributions of: (1) the nucleus accumbens and related limbic circuitry in assigning valence within the pleasure/unpleasure continuum of affective experience; (2) the reticular formation, thalamus, amygdala, and cortex within arousal circuits in assigning personal salience to those affective experiences; (3) frontostriatal systems in subserving top-down processing in the CNS, which in turn contributes to numerous important psychological functions, including the control of drives and the construction of experience according to preestablished conceptual schemas—processes that likely underlie cognitive distortions, projection, and transference phenomena; and (4) multiple memory systems, particularly the procedural learning systems based within the dorsal striatum and declarative learning systems in the mesial temporal lobe, that likely contribute to memories within the domain of the descriptive unconscious, and the interactions across affective and cognitive memory systems, that might contribute to memory formations within the dynamic unconscious.

Keywords: Neuroimaging; Psychoanalysis; Impulse control; Self-regulation; Affect; Pleasure; Memory

1. Introduction

The advent of neuroimaging technologies has provided a window onto neural circuits that likely subserve functions closely related to numerous core psychoanalytic constructs. Although the constructs that are most central to and most defining of psychoanalytic theories and psychoanalytic process are still debated [1–3], most would agree that these include the concepts of drive, particularly drives toward pleasurable aims and away from unpleasureable ones, the regulation of drives or the activities that satisfy those aims, transference, and the existence of unconscious processes. Reviewed herein will be selected imaging studies that may relate directly or indirectly to neural systems thought to subserve these psychological functions.

2. Pleasure and unpleasure

Freud never fully elaborated a comprehensive theory of emotions. Instead, he defined a theory of biological drives, positing that all living organisms seek to maximize pleasurable experiences and to minimize unpleasurable ones. Anxiety was regarded as a byproduct of conflicts arising in the organism from pursuit of objects, the attainment of which would produce both pleasurable and unpleasurable consequences. Presumably Freud regarded the neural substrate of the pleasure/unpleasure continuum as comprising a single neurobiological system. In contrast to this simple and reductionistic theory of drives and emotions, however, the reigning theories and experimental paradigms in affective neuroscience have subsequently largely posited the existence of numerous emotional systems and corresponding neural substrates. These theories hold that

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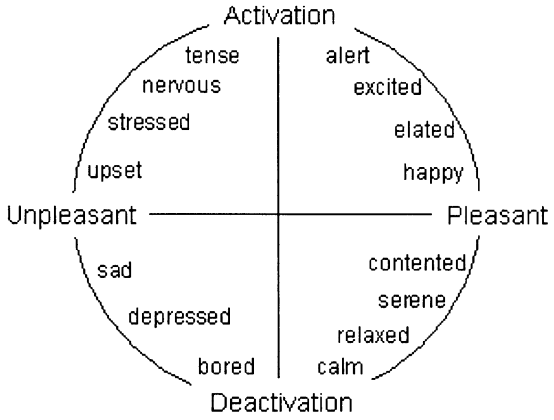

Fig. 1. Graphical representation of the affective circumplex. The horizontal axis represents the valence dimension and the vertical axis represents the arousal, or activation, dimension.

emotions can be divided into discrete and independent categories, with each emotional category being subserved by a discrete and specific neural pathway. These theories of discrete emotion have been critiqued elsewhere [4,5].

One particular experimental and theoretical model of affect in psychology and affective neuroscience, however, is remarkably consistent with the Freudian theory of affect. Similar to Freud's theory, this model also posits that valence (a pleasure-unpleasure continuum) contributes to all affective states. In contrast to Freudian theory, however, this model postulates the existence of a second neurophysiological system—an arousal or alertness system—that is independent of the first and that also contributes to all affective states. Varying linear combinations of these two physiological systems contributes to the experience of the full array of emotions that we experience [4]. Joy, for example, is the product of intense activity in the neural system that subserves valence or pleasure, together with moderate activity in the neural system that subserves arousal (Fig. 1). Sadness, in contrast, is the product of intense activity along the negative side of the valence system together with a slight reduction along the arousal system. Other emotions arise from these same two neurophysiological systems, but differ from joy in the degree of activity in each of the component systems. Cognitive interpretations of these core physiological experiences help to label and provide nuance that distinguishes affects positioned close to one another on the two-dimensional affective circumplex.

2.1. Studies of affective dimensions

Imaging studies thus far have not directly assessed activity in these two underlying dimensions of affect, although in principle, the valence and arousal dimensions can be manipulated systematically and parametrically; ratings of each of these affective dimensions can then be correlated with imaging-based indices of neuronal activity. Regions in which these correlations are significant would identify the two underlying neurophysiological systems that together and in combination support affective experience. Those experiments are underway now in our laboratory.

Until now, imaging studies have largely assumed that emotions are discrete and largely independent of one another. Most prior studies have employed subtraction methodologies that are problematic if the Circumplex Model of Affect is in fact correct. In these subtraction methods, neural activity associated with a cognitive process is identified by comparing one task with another that differs from the first in only one or a small number of cognitive processes of interest. This approach is problematic for studies of affect because of the difficulty in generating control stimuli that control adequately for the cognitive, affective, and behavioral processes that are not of interest, but that nevertheless are implicit or explicit components of the primary task [6]. In a traditional subtraction design, for example, neural activity during the viewing of prototypical and highly arousing stimuli that induce fear, such as snakes or a loaded gun, might be compared with neural activity during the viewing of putatively 'neutral' stimuli, such as household objects. Many would argue, however, that no stimulus is affectively 'neutral', and that snakes, guns, and household objects all activate both the valence and arousal systems. Viewing snakes or guns presumably induces automatically some degree of fear-like response—emotions with negative valences and high arousal (in the upper left quadrant of the circumplex); viewing household objects, in contrast, might induce boredom, mild aversion, or dysphoria—emotions with negative valences and low arousal (in the lower left quadrant of the circumplex). Following subtraction of the neural activity measured during the viewing of each of these two classes of stimuli, the negative valences will partially or completely cancel themselves, and the differences in activity across the stimuli will index primarily their differences in inducing arousal systems or, more problematic and confusing yet, some unpredictable difference in both valence and arousal. The subtraction of these stimuli will not, however, isolate neural activity associated only with 'fear' as a reified, discrete emotion. These difficulties with subtraction paradigms and with comparing physiological measures during the presentation of emotion-inducing stimuli are only compounded with the viewing of stimuli that emotionally are highly ambiguous, such as the facial expressions that are currently so ubiquitously studied. The facial expressions of surprise and fear can be indiscriminable and yet have greatly differing valences, whereas a smile can variously signal happiness, pride, or condescending sarcasm [7,8].

2.2. Valence and arousal systems

Despite these considerable and unpredictable difficulties inherent in subtraction paradigms during the presentation of emotion-inducing stimuli, extant imaging studies using such paradigms do provide suggestive but preliminary evidence

for the existence of distinct neural systems associated with valence and arousal. Imaging studies support findings from a large number of studies in animals that the mesolimbic dopamine system, which projects from the ventral tegmental area to the nucleus accumbens, amygdala, hippocampus, and prefrontal cortex, is centrally involved in the processing of rewarding and pleasurable experiences. Electrical stimulation of the orbitofrontal cortex and nucleus accumbens, for example, is so pleasurable that when allowed to self-stimulate these regions, animals will starve or dehydrate [9,10]. Imaging studies following intoxication with a variety of drugs have shown increases in blood flow that correlate strongly with subjective ratings of euphoria [11–15]. Conversely, hypoactivation or under-stimulation of the mesolimbic system is associated in studies of drug addiction with the experience of a wide range of negative emotions, or with unpleasure on the valence dimension of the Affective Circumplex [16]. This dysphoria and desire to relieve it is thought to drive drug-seeking behavior [17,18]. Activity in the nucleus accumbens has also been shown to change as subjects anticipate and respond to aversive stimuli [19,20], suggesting directly that differential activity within this region may signal differing responses within the mesolimbic system to both positive and negative emotional valences.

Whereas mesolimbic dopamine systems have been implicated in the processing of pleasure and unpleasure, the reticular formation has been implicated in mediating arousal levels through its connections with the limbic system and thalamus, and through those brain regions in turn to large expanses of neocortex [21,22]. The arousal system is thought to regulate the gating and tuning of sensory stimuli, which are relayed via dense projections from the primary and secondary sensory association areas to the thalamus and amygdala. Most investigators agree that the amygdala participates in the encoding and processing of emotional salience [23–25]. Recent imaging studies suggest increasingly that the amygdala responds both to appetitive and aversive (i.e. both to positively and negatively valenced) stimuli, and that greater activity in the amygdala is driven primarily by the presentation of more arousing stimuli [26–28]. Assessments of emotional arousal are then relayed to the reticular formation through the amygdaloreticular pathways [29,30] and possibly through the association cortices of the parietal lobe, as well [21]. Increased activity in the reticular formation sends excitatory projections to the thalamus [22] which in turn increases activity throughout the cerebral cortex, especially in the primary and secondary sensory cortices [22,31]. Descending projections from the reticular formation [22] also modulate muscle tone and sweat gland activity, each of which correlates strongly with subjective ratings of emotional arousal [32]. Consistent with this hypothesized role of arousal systems in the processing of emotional stimuli, amygdala lesions have been shown in humans to impair the ability to recognize affective stimuli; in non-human primates these lesions produce unusual behavioral responses in which both typically aversive and appetitive stimuli are treated as non-arousing and non-emotional [33–36]. Lesions to the reticular network can interfere with arousal even to the extent of producing obtundation and coma [31]. In contrast, imaging studies suggest that emotional hyperarousal in states such as panic and mania increase activity in both the amygdala and reticular activating system [37–39].

3. Self-regulatory control

The drives toward pleasurable activities must be weighed against possible unpleasurable consequences, whether those consequences are determined by internal (i.e. moral) or external (i.e. social) proscriptions and constraints. Self-regulatory control is required to take sufficient time to weigh prospects for temporally proximal gains with potential, temporally more remote, adverse consequences of action plans—i.e. self-regulation is needed to weigh cross-temporal contingencies of actions—as well as to monitor and update action plans on-line as they unfold. Within psychoanalytic theory, self-regulatory control helps to define the broad class of ego functions [40].

Depending on the theoretical school and discipline, self-regulatory processes are referred to by a variety of other names, including ‘attentional processes’ [41], ‘executive functions’ [42,43], ‘supervisory processes’ [44], ‘willed action’ [45], ‘impulse control’ [46], and ‘top-down processes’ [47–51]. Defined most generally, self-regulation refers to the ways in which individuals filter, coordinate, and temporally organize their innumerable perceptions, affective experiences, memories, thoughts, and reactions to stress during the planning, execution, and monitoring of goal-directed behaviors [52–57].

Maturation of these self-regulatory functions likely defines the ontogeny of human development. Moreover, disturbances in the maturation and function of these self-regulatory functions likely contribute to the development of a wide range of neuropsychiatric illnesses by releasing from top-down, regulatory control the various underlying vulnerabilities or diatheses to illnesses that every individual has to some degree. Those vulnerabilities could simply reflect normal, diurnal variations in mood or affect, an underlying need to move or to perform some kind of semi-compulsory behavior, or to act on various appetitive or aggressive impulses and drives. Interindividual variability in these underlying diatheses, together with disturbances in self-regulatory control, can tip an individual over from being predisposed to developing an illness into actually expressing overt symptoms. Age-specific vulnerabilities in the maturation of varying components of the neural circuitry that mediate these self-regulatory functions likely contributes to age-specific prevalence differences and characteristic ages of onset across various neuropsychiatric illnesses.

3.1. Bottom-up and top-down processing

Understanding at a broad, conceptual level how the brain is thought to effect self-regulatory functions requires understanding in general how the brain processes information, as a dynamic interplay of both bottom-up and top-down processing of sensory data (Fig. 2). In bottom-up processing, sensory information enters the cerebral cortex in primary sensory regions, which process and encode the most elementary features of sensory stimuli. Primary visual cortex, for example, encodes short line segments and their directional orientation, independent of position in the visual field; information about color and ocular laterality are kept segregated within particular cellular columns [58]. Primary sensory cortices then pass information to sensory association cortices, which bind together these elementary features of a single sensory modality into slightly more complex percepts. Elementary visual elements of primary visual cortex, for example, are bound together into more abstract visual percepts information, such that multiple line segments now encode form and movement, and information about ocular input now encodes depth perception. Information within the association cortices of multiple individual sensory modalities is then bound together into yet more complex, multimodal sensory percepts within heteromodal sensory cortices of the parietal and temporal lobes. Form, movement, and depth perception in the visual modality, for example, now become a rectangular, colored object in the distance moving through space and emitting a blaring sound. These multisensory percepts are further integrated within even more complex, heteromodal cortices, located primarily within the frontal lobe, that contribute to higher order cognitive processes. These higher order processes include, among others, working memory (the scratchpad of mental operations), longer-term memory, the binding of sensory percepts with affective valence and arousal, the planning and monitoring of motor responses, the execution of those motor actions, and the detection of errors in the actual responses compared with the planned responses [59,60]. The same rectangular, colored object moving through space in the distance and emitting a blaring sound that is transmitted from lower order heteromodal association cortices, for example, now is interpreted within frontal cortices to be an approaching car sounding its horn, prompting development of an action plan to avoid the car and to seek safety elsewhere.

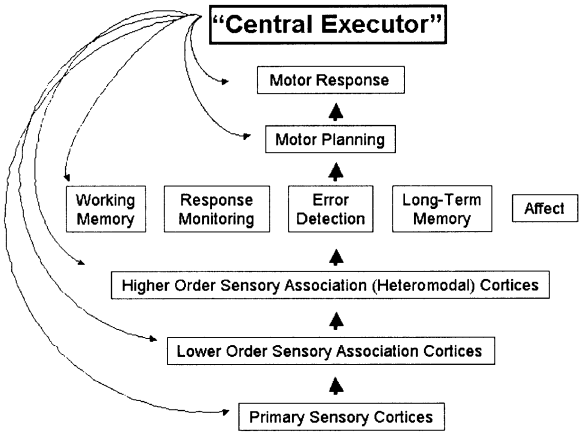

Fig. 2. Bottom-up and top-down information processing in the CNS. Information entering primary sensory cortices becomes increasingly more complex and abstract in representational quality as it is passed to cortices that are progressively more heteromodal. Projections from higher-order, 'central executor' regions within frontal cortices to lower order sensory regions help to filter incoming sensory stimuli and to coordinate their processing across space and time.

Activity in the centers that subserve these higher-order cognitive processes must be coordinated across spatially distinct brain regions and across time to produce smoothly orchestrated and integrated perceptual processing, planning, and motoric responses within highly complex environments and rapidly changing task demands. These task demands and plans for meeting them constitute a cognitive 'set' that enhances performance in meeting task demands by allowing a person to choose to attend preferentially to certain sets of sensory stimuli over others and to plan execution of certain sets of motor programs over other potentially competing programs. These preestablished cognitive sets therefore perform a vitally important filtering or 'tuning' function that likely confers a performance advantage for that individual and, ultimately, a survival advantage for the species. This survival advantage undoubtedly contributed to the rapid expansion of these neocortical 'executive control centers' throughout phylogeny.

These filtering and tuning functions are effected by monosynaptic and polysynaptic connections of centers for executive functioning within frontal cortices to all other lower-order information processing centers, including heteromodal, sensory association, and even primary sensory cortices [61–68] (Fig. 2). This means that cognitive sets—cognitive schemas that include biases, expectations, hopes, and desires that have been informed and sculpted by both constitutional predispositions and innumerable prior experiences—modulate incoming sensory experiences even in their most elemental form within primary sensory cortices, selecting for preferential processing a relatively small number of stimuli from among the billions of stimuli that bombard sensory organs and cortices at each instant of waking life.

3.2. Imaging studies of normal self-regulation

A number of experimental paradigms to study self-regulatory processes have been developed or adapted for the scanning environment. These paradigms generally have in common the requirement that they place on the subject of suppressing a more automatic behavior to perform instead a less automatic one. These tasks are therefore regarded as experimental models for studying the resolution of behavioral conflict and the regulation of impulse control.

Perhaps the most commonly studied paradigm of this kind is the Stroop Word-Color Interference Task. This task requires suppression of the over-learned, more automatic tendency to read words such as 'R-E-D' or 'B-L-U-E' to perform a less automatic task, the naming of visual colors. Colored words are presented visually to subjects who are instructed to name the visual color, not what the word reads. When the color that the word denotes matches the name of the visual color (e.g. when viewing the word 'R-E-D' written in red ink), subjects perform the task easily, as indexed by their rapid responses and infrequent errors. When the color that the word denotes does not match the name of the visual color, however (e.g. when the word 'R-E-D' is written in blue ink), subjects have much more difficulty with the task, as indexed by their slower responses and more frequent errors. In this latter condition of the task, they must inhibit the tendency to say 'Red' when the correct utterance is 'Blue'—i.e. they must engage self-regulatory control.

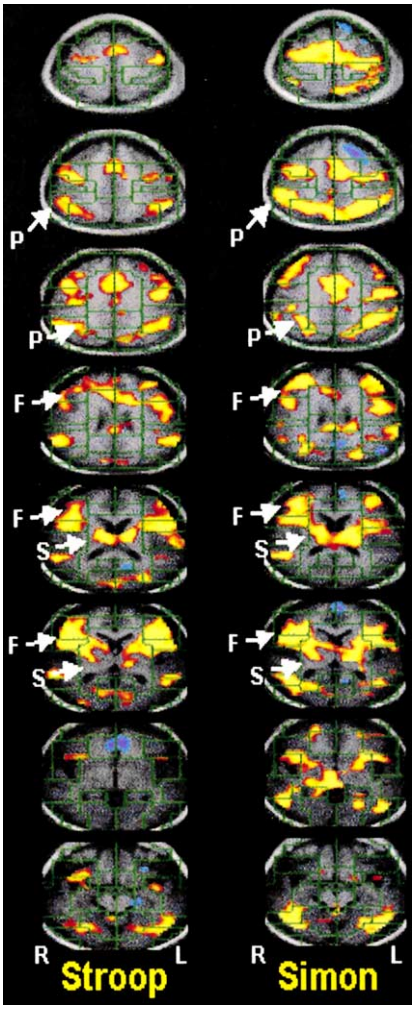

Fig. 3. Activation during self-regulation in the Stroop and Simon tasks. These are axial images (parallel to the floor in a standing person). Slices positioned lower in each column are positioned lower in the brain and move progressively higher in each successive slice with a higher position in the column. The similarity in pattern of activations across these two tasks, despite their drastically differing stimulus and response characteristics, is obvious. P, parietal cortex; F, frontal cortex; S, striatum; R, right; L, left.

When brain activity is measured and compared across these two conditions, broad expanses of the cortex and subcortex are shown to be more active during the second condition than the first (Fig. 3). These include prefrontal, anterior cingulate, anterior temporal, parietal, and visual association cortices, as well as basal ganglia regions [69–71], indicating that a large network of brain regions subserves self-regulatory processes in this task. Furthermore, neural activity during self-regulation within the anterior cingulate and associated mesial prefrontal cortices seem to correlate with activity in other brain regions significantly more often than would be expected on the basis of chance alone (Fig. 4), an impression that has been confirmed using formal statistical analyses of regional intercorrelations [69]. Although preliminary, these findings suggest that the anterior cingulate and mesial prefrontal cortices may compose the seat of higher-order activity in the frontal lobe that helps to organize the top-down regulation of activity across space and time in lower-order primary sensory and association cortices.

Other tasks involving self-regulatory control have been shown to produce nearly identical patterns of activation as the Stroop. The Simon Spatial Incompatibility Task, for example, instructs subjects to indicate, with one of two possible button responses, the direction in which an arrow is pointing (left or right). Individual arrows, however, appear on one or the other side of a screen. When the side on which

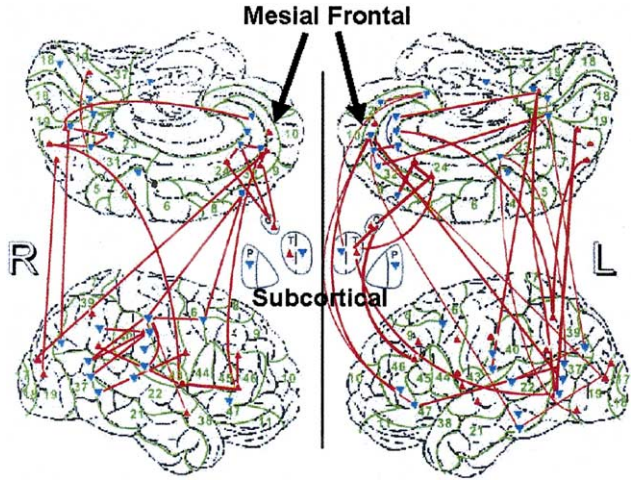

Fig. 4. Intercorrelations among regional activations during a self-regulatory Task. The lower row of images depicts the lateral aspects of each cerebral hemisphere. The upper row depicts the medial surface of the corresponding hemispheres, though inverted (the top of the image is the bottom of the brain, and vice versa), similar to window shutters for the low row. More of the correlations across long distances involve the anterior cingulate and mesial frontal cortices than would be expected on the basis of chance alone. Other correlations likely reflect local area connections within the brain. Red and blue triangles superimposed on the brain represent increases and decreases in activity during self-regulation, respectively. In green outline and green numbers are rough delineations of Brodmann's cytoarchitectonic units. R, right; L, left.

the arrow appears matches the direction in which the arrow points (e.g. a leftward pointing arrow appears on the left side of the screen), subjects perform the task rapidly and with few errors. When the side on which the arrow appears does not match the direction in which the arrow points, however (e.g. a leftward pointing arrow appears on the right side of the screen), subjects perform the task much more slowly and with more errors. Using rigorous statistical measures of concordance, this task was shown to produce a pattern of regional brain activation that was remarkably similar to that produced by the same subjects performing the Stroop task (Fig. 3) [71], despite the use of stimuli and response modalities that were entirely different from those of the Stroop. This similarity in pattern of brain activity suggests strongly that the Simon task is a nonverbal analogue of the Stroop, and that their common patterns of brain activation reflect an underlying similarity in task demands and information processing functions, which are to regulate the more automatic behavior in order to perform a less automatic one—i.e. to engage self-regulatory, top-down control processes.

3.3. Self-regulatory systems in psychiatric illnesses

The self-regulatory circuits that have been identified in normal individuals have been implicated repeatedly in the pathophysiologies of a wide range of neuropsychiatric illnesses. Disturbances in these circuits are likely to be rarely, if ever, causal in and of themselves. Instead, disturbances in these circuits likely act in concert with underlying disturbances of a constitutional or acquired nature in other neural circuits that subserve important neuropsychiatric functions, such as those that subserve motor planning and execution, affect, and attention. The combination of disturbances in these latter circuits with dysfunction in self-regulatory systems may then take what is otherwise a vulnerability, predisposition, or diathesis for developing an illness and tip it over into the manifestation of symptoms and patterns of functional impairments that are designated an overt disease—as Tourette Syndrome (TS), for instance, Attention-Deficit/Hyperactivity Disorder (ADHD), or Bipolar Disorder.

Neuroimaging studies increasingly suggest that the neural basis for these disorders resides in anatomical and functional disturbances of Cortico-Striato-Thalamo-Cortical (CSTC) circuits. These circuits loop between cortical and subcortical brain regions. They are composed of multiple, partially overlapping but largely 'parallel' pathways that direct information from the cerebral cortex to the subcortex, and then back again to specific regions of the cortex. Although multiple anatomically and functionally related cortical regions provide input into a particular circuit, each circuit refocuses its projections back onto only a subset of the cortical regions contributing to the input of that circuit [72–74].

3.3.1. Tourette syndrome

TS is a disorder of motor and vocal tics. Tics are usually preceded by a vague discomfort or urge to move the body region affected by the tic [75]. This 'premonitory urge' relentlessly builds in intensity until the individual capitulates to the urge and performs the tic. This typically brings immediate but temporary relief from the urge, only to have the urge build quickly again and reinitiate the cycle of building tension, capitulation, and relief. Tics therefore involve sensorimotor impulses that individuals feel must be actively inhibited. Tics can be suppressed voluntarily, but not indefinitely [76,77]. TS is therefore regarded by many to be primarily a disorder of impaired control of impulses and disordered self-regulation, primarily in the motor domain.

In a functional imaging study designed to identify the self-regulatory systems that subserve the control of tic symptoms, adults with TS alternated between allowing themselves to tic freely and suppressing their tics completely [77]. Tic suppression produced increased activity in numerous cortical regions involved in self-regulatory control, especially prefrontal and temporal cortices, and in the right caudate nucleus (Fig. 5). Tic suppression decreased

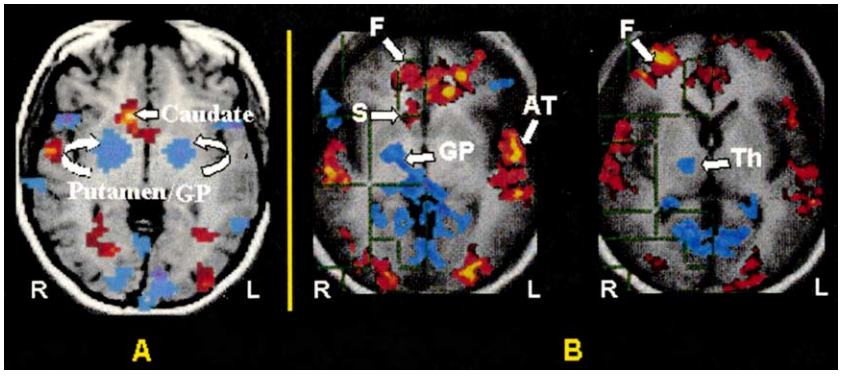

Fig. 5. Brain activation during the self-regulatory control of unwanted tic behaviors. These are all axial slices. (A) Activation in a single subject: This is a ventral slice positioned just above the orbits. The right caudate nucleus increases in activity and the lenticular nucleus (putamen and globus pallidus) decrease in activity during the willful suppression of tics compared with their spontaneous release. (B) Group activation. F, frontal cortex; AT, anterior temporal cortex; S, striatum; GP, globus pallidus; Th, thalamus; R, right; L, left; red or yellow, increase in neural activity; blue, decrease in neural activity during tic suppression.

activity in the ventral globus pallidus, putamen, and thalamus bilaterally. The severity of tic symptoms correlated with the change in activity of the basal ganglia and thalamus, indicating that as symptom severity increased, changes in subcortical activity during tic suppression decreased. Activity in prefrontal cortices, moreover, correlated positively with activity in the caudate nucleus, and caudate activity in turn correlated inversely with activity in the globus pallidus, putamen, and thalamus. These findings suggest that increases in activity in inferior prefrontal cortices during tic suppression increases activity in the caudate nucleus via excitatory frontostriatal projections. Increased activity in the caudate then decreases activity in the rest of the basal ganglia and thalamus via known GABAergic inhibitory projections between these nuclei. Inverse correlations of subcortical activation with symptom severity indicate that the changes in neural activity of subcortical regions—increases in the right caudate and decreases in the rest of the subcortex—participate in the suppression of tics, and when these frontostriatal braking mechanisms fail, tics are progressively more likely to escape the inhibitory influences of these circuits on motor behavior. The correlations of symptom severity with the magnitude of change in the pattern of these braking systems throughout all subcortical regions (Table 1) are likely initiated upstream at the point of entry to the subcortical portions of the CSTC circuits, in the projections either into or out of the caudate nucleus. Dysfunction of the circuits initiated within the caudate as the most likely site of origin of disturbances in the self-regulatory control of tic symptoms is consistent with the reduced size of the caudate nucleus that was detected in both children and adults in

Table 1
All subcortical regions changed in activity significantly during the voluntary suppression of tics

SUBCORTEX		TIC SEVERITY	
		r	*P*
Caudate	R	-.46	0.02
Putamen	L	-.40	0.07
	R	-.54	0.009
Globus Pallidus	L	-.47	0.03
	R	-.52	0.03
Thalamus	L	-.44	0.02
	R	-.41	0.02

The right caudate increased in activity and all other subcortical regions significantly decreased in activity during tic suppression. Furthermore, the magnitude of those respective changes in activity correlated inversely with the overall severity of tics for the month proceeding the scan in each of the subcortical regions, indicating that the more subjects were able to generate this overall pattern of change in activity, the fewer were their symptoms. Given the known pattern of information flow through the subcortex, the significant correlations with severity in these regions were hypothesized to originate upstream in this flow, in or around the caudate nucleus. *r*, Pearson's correlation coefficient; *P*, *P*-value; R, right; L, Left.

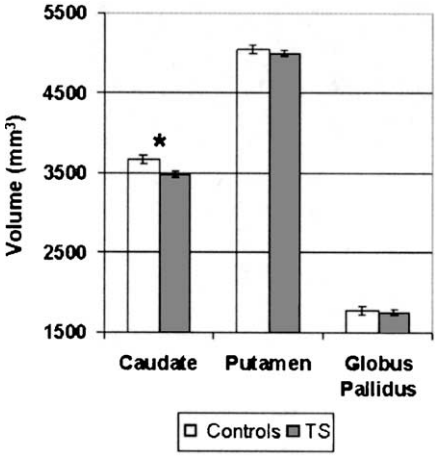

Fig. 6. Basal ganglia volumes in ts and normal control subjects. The asterisk denotes group differences in the caudate nucleus that are statistically significant.

a study of 154 individuals with TS and 130 healthy controls (Fig. 6) [78].

The massive activation of the cortex during the control of tic symptoms prompted measurement of cortical volumes in this same large sample subjects to determine whether anatomical disturbances in the cortical portions of regulatory systems are involved in the pathophysiology of TS [79]. Significantly larger volumes were detected in the prefrontal volumes in TS children and smaller prefrontal volumes in TS adults (Fig. 7). Volumes of prefrontal cortex moreover correlated significantly and inversely with the severity of tic symptoms—in other words, larger prefrontal volumes seemed to be helpful in reducing the severity of tics. The association of larger prefrontal volumes with fewer tics and activation of this region during the control of tic symptoms is consistent with a vast number of animal studies [80–86] and a growing number of human imaging studies [87–96]

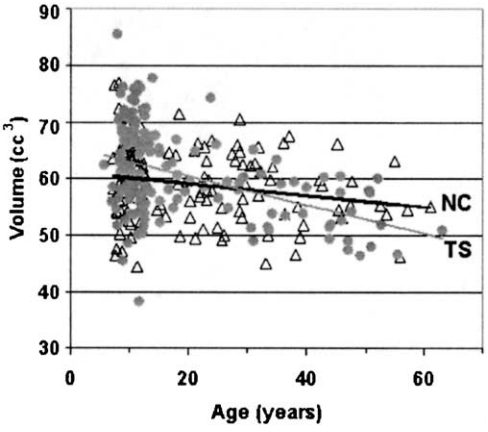

Fig. 7. Correlations of prefrontal volumes with age. In black, open triangles are volumes for normal control subjects. Volumes are minimally associated with age. In gray, solid circles are volumes for TS subjects. Volumes correlate inversely with age. Larger prefrontal volumes in persons with TS are attributable to larger volumes in children. Adults with TS have smaller prefrontal volumes than do control adults.

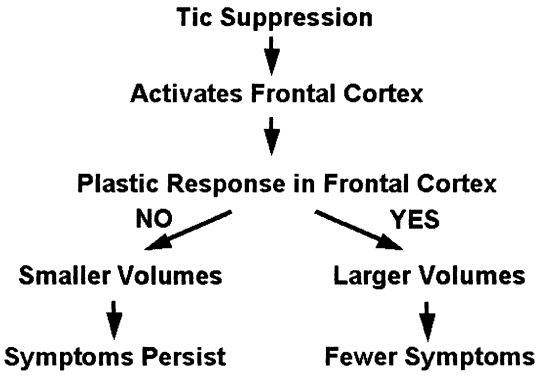

Fig. 8. Theory of frontal hypertrophy in persons with TS. Acitvity-dependent plasticity is thought to underlie the larger prefrontal volumes detected in children with TS. Failure of this plastic response may contribute to more severe symptoms and persistence of illness into adulthood, thereby accounting for smaller prfrontal volumes in adults with TS.

showing that the repeated activation of neurons changes the architecture of those neurons. Most often, this architectural change involves an increase in the number of synapses, but it can also involve a change in the pruning of axons or dendrites, or even a change in the overall number of neurons as a consequence of altered rates of neurogenesis and apoptosis, or naturally occurring cell death [97–100]. The persistent and continual need to suppress tics—throughout the school day, with friends in social settings, and at home—and the massive activation of prefrontal cortices that this entails, is thought to induce in children with TS an activity-dependent hypertrophy of neurons in the prefrontal cortex. Smaller volumes in these regions provide insufficient inhibitory reserve to help suppress tics, consistent with numerous preclinical and clinical studies suggesting that the prefrontal cortex plays an important role in inhibitory control [101–109]. A failure, for reasons unknown, in either the activation of prefrontal cortex or in the plastic hypertrophy in response to this repeated activation, is thought to contribute to disturbances in the ability to modulate the activity in the basal ganglia that we believe generates tic behaviors. Failure to induce this plastic response produces relatively smaller prefrontal cortices. Smaller prefrontal volumes in adults with TS in turn contributes to those individuals remaining highly symptomatic, which is uncharacteristic of the adult outcome of most children who have tics or TS (Fig. 8) [110–113].

3.3.2. ADHD

Comprising the symptomatic triad of inattentiveness, hyperactivity, and impulsivity, this is a prototypical syndrome of disordered self-regulatory control. Implicated most consistently in its pathophysiology are abnormalities in prefrontal cortex and basal ganglia. Reduced metabolic rates have been reported in the premotor and somatosensory cortices of ADHD adults [114]. Adolescents with ADHD have reduced metabolic rates in, among other regions, the left anterior frontal area, and metabolism in these areas correlate inversely with measures of symptom severity [115]. Volumes of the prefrontal cortex and globus pallidus may be smaller than in healthy controls [116–119].

A morphological study detected a 3% reduction in overall brain size in 152 ADHD children compared with 139 controls [120]. Group differences in brain subregions using relatively coarse measures exhibited little regional specificity, although the regions in which the largest percent reductions in volume were detected across diagnostic groups included the frontal and temporal white matter (6.3 and 9.2%, respectively). These findings may suggest that morphological abnormalities in children with ADHD affect widely distributed neural systems. Alternatively, the findings could also suggest that ADHD is morphologically heterogeneous, reflecting its undoubted etiologic heterogeneity, and that the morphological heterogeneities manifest as reduced overall brain size when using population-based statistics.

More refined morphometric procedures have yielded greater evidence of regional specificity in this condition. Detailed analyses of the cortical surface in a group of 27 school-aged children with ADHD and 46 matched control subjects found reduced regional brain size localized in inferior portions of the dorsal prefrontal and anterior temporal cortices bilaterally (Fig. 9) [121]. Prominent increases in gray matter were observed in large portions of the posterior temporal cortex bilaterally. These fronto-temporal abnormalities are consistent with the self-regulatory deficits long noted as the hyperactivity, distractibility, and impulsivity of children with ADHD. In particular, the volume decrements in inferior prefrontal regions are

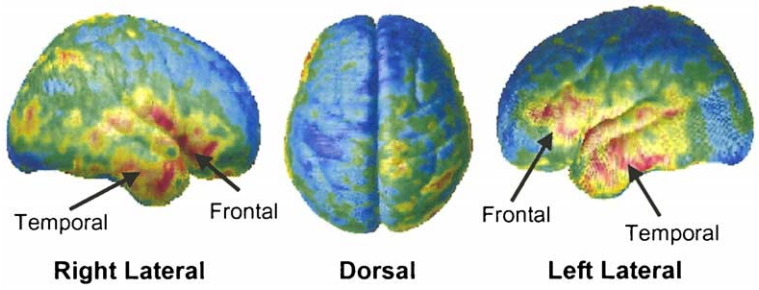

Fig. 9. Morphological abnormalities at the brain surface of children with ADHD. Red and yellow indicate regions that were significantly smaller in children with ADHD. These are in primarily inferior prefrontal and anterior temporal regions.

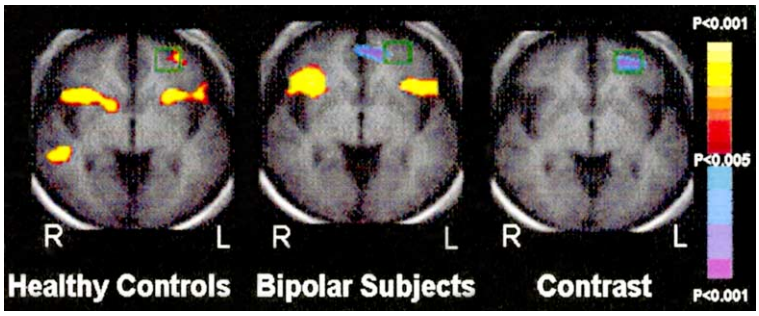

Fig. 10. Abnormalities in activation of ventral prefrontal cortices of adults with bipolar disorder. Disturbances in rostal portions of the ventral prefrontal cortex ('contrast') are shown here to be attributable to decreases in activation that was detected in healthy controls.

consistent with preclinical studies implicating this region in the regulation of impulses [101–109], whereas the anterior temporal region belongs to the heteromodal cortices that are thought to subserve an attentional focus.

3.3.3. Bipolar disorder

The core disturbance in persons with Bipolar Disorder (BD) may originate in dysfunction of self-regulatory systems. Individuals with BD, for example, could be considered unable to regulate emotions, behaviors, and thoughts, as evidenced by their emotional lability, thought disorder, and pursuit of hedonic activities in spite of adverse consequences, all of which constitute the core phenotype of this illness.

Findings from neuroimaging, postmortem, and neuropsychological studies suggest that state- and trait-related disturbances in the anatomy and function of frontostriatal circuits underlie the abnormalities in attention, cognition, and impulse regulation in BD. Mania has been associated with decreased activity in ventral and increased activity in dorsal prefrontal cortices [122,123]. Decreases in gray matter volume [124], glial cell density [125], and increased levels of intracellular second-messengers have been reported in the anterior cingulate and prefrontal cortices of persons with BD [126,127]. Neuropsychological disturbances on tests of attention, memory, and executive functions, have been reported in acute episodes of BD [128–135] and seem to endure between acute BD episodes, further implicating stable abnormalities in prefrontal functioning of persons with BD [130,134]. Lesions to the ventral and medial prefrontal cortex [136] can produce changes in regulation of emotions, attention, and behavior similar to the symptoms of BD [136–140].

The Stroop task has been used to study self-regulatory functions in 36 adults with BD (11 with elevated mood, 10 with depressed mood, and 15 euthymic) and 20 matched, healthy control subjects [141]. The elevated mood group exhibited deficient activation of inferior prefrontal cortices compared with the euthymic, depressed, and healthy control groups. The depressed group, in contrast, activated this region more than did either the euthymic, manic, or healthy control groups. These findings may represent state-specific abnormalities in regional brain function in the BD group. Furthermore, the BD subjects as a group, regardless of affective state, exhibited deficient activation in inferior prefrontal cortices of the left hemisphere compared with the healthy control subjects. The three BD mood groups did not differ from one another in this region, but they all differed significantly from activation in the control group (Fig. 10), suggesting that this finding represents a trait abnormality in adults with BD.

Scanning of adolescents with BD during performance of the Stroop showed that brain activation was greater in the left putamen of the bipolar group than in controls (Fig. 11A) [142]. In the BD group, the severity of depressive symptoms was associated with signal increases in the ventral striatum (Fig. 11B). Age correlated positively with bilateral rostroventral prefrontal and striatal activation in the healthy

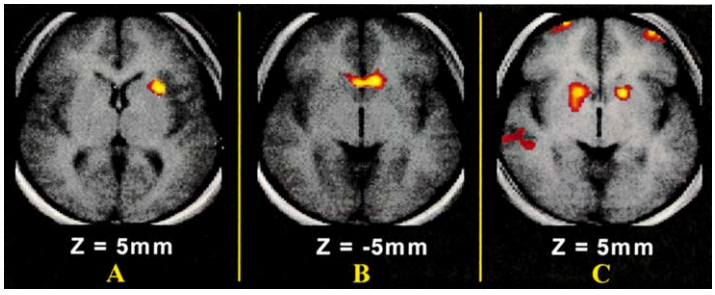

Fig. 11. Abnormal striatal activation in adolescents with bipolar disorder. (A) Increased activation in left putamen and inferior thalamus relative to control values. (B) Correlations of activation with depression scores in the bipolar subjects. (C) Activation correlated positively with age in healthy adolescents in striatum and rostroventral prefrontal cortex.

group but not in the bipolar group (Fig. 11C). The absence of prefrontal abnormalities observed previously in adults, and the absence of the age-related increases in prefrontal activity observed in normal controls, suggest that a developmental disturbance in prefrontal function may emerge during adolescence in individuals with BD.

Volumes of the amygdala and hippocampus were found to be smaller in adolescents and adults with BD and compared with those of healthy control subjects [143]. Volume reductions were more prominent in the amygdala (16%) than in the hippocampus (5%), and they affected adolescent and adult subjects equally, suggesting that the abnormalities likely manifest early in the course of illness. Together with the findings of prefrontal dysfunction in functional imaging studies, these volumetric studies suggest that abnormalities in the amygdala and hippocampus are released from the normal top-down, regulatory control that is based in the neural projections from the prefrontal cortex to the mesial temporal lobe. Release from regulatory control then may contribute to the exaggerated changes in mood and affect that define BD.

4. Transference

Despite impressive progress in understanding the neural bases of sensory and motor systems, learning and memory, and other higher cognitive functions, relatively little progress has been made in understanding brain organization that underlies the psychological functions that are encountered most frequently and consistently in therapeutic settings. These include cognitive distortions, projections, and transference phenomena. These psychological functions are difficult, if not impossible, to study using animal models. Insight into the neural bases of these processes in humans is therefore likely to be relegated solely to neuroimaging studies, the only means currently available for studying brain function noninvasively and in vivo. Neuroimaging studies of these complex processes, however, have been difficult to design, largely because if functional studies are to be interpretable, they require the comparison of images acquired during the task of interest (e.g. cognitive distortion, projection, or transference) with images acquired during a control task that differs from the first task by one or, at most, only a few cognitive processes [6]. Both the active and control tasks for the study of these processes have been difficult to design and implement. Clearly, the processes cannot be captured in neuroimaging experiments as they would arise in naturalistic, therapeutic settings, at least not with currently available technologies. The only alternative currently is therefore to develop paradigms that can serve as valid experimental models for these processes and that can be invoked on demand within a scanner.

The processes of cognitive distortion, projection, and transference may have reasonable analogues that have been developed in the field of cognitive neuroscience. Common to all three of these psychological processes is the active organization of sensory percepts and experiences according to anteceding, preexisting mental schemas, which we have seen defines the top-down processing of incoming sensory information within the brain. This active organization and construction of sensory experience is facilitated by the inherently indeterminate nature of sensory experience [144–154], by which is meant that any given ensemble of sensory data can be assembled and constructed into multiple, mutually exclusive entities [155]. Four sensory elements (dots), for example, can be associated in various ways to produce a diamond, a square, or a circle (Fig. 12). A person viewing only the four data points might be predisposed to identify or 'see' in them either of those shapes, and that predisposition would presumably represent a preexisting schema that developed as a consequence of some biological or experiential determinant, or some combination of both. Interpreting indeterminate sensory experience according to predefined schemas is the basis for psychological projective tests of personality.

Several classic paradigms in cognitive neuroscience have been developed to study perceptual bias and top-down processing. One is the class of 'ambiguous figures', complex visual stimuli that, with practice, can each be perceived as representing two very different objects [156–158]. One popular example is the figure that can be perceived either as a vase or as a human profile. These stimuli have a distinct advantage for use in the subtraction paradigms of functional imaging studies, in that the same complex visual stimulus can be used in each of the active and control tasks, thereby controlling exquisitely for all of the basic sensory features of the visual stimulus, such as intensity, hue, saturation, and the complexity and spatial relationships among curves and edges. One disadvantage of these stimuli, however, and perhaps their only disadvantage, is that the two different percepts that these stimuli permit have widely varying semantic content, affective valence,

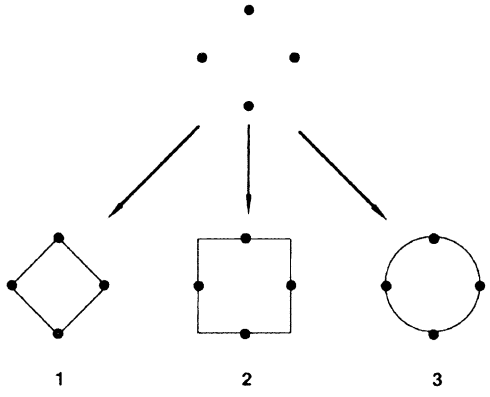

Fig. 12. Indeterminacy of sensory percepts. Sense data can be 'interpreted' according to predefined schemas in numerous ways. Which among several interpretations of the data is the one perceived is ultimately determined by conceptual schema that influence sensory perceptions via top-down projections from higher to lower order information processing centers within the CNS.

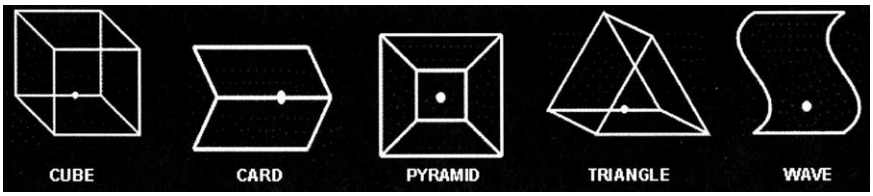

Fig. 13. Reversible geometric figures. Each figure can be perceived in one of two alternative spatial orientations—either with the dot as protruding out of or into the plane of the drawing. The volitional perception of either of these two orientations is thought to be attributable to top-down processing within the CNS.

and associative links (consider, for example, the semantic, affective, and associational links associated with the percepts of a vase and a human facial profile).

A class of stimuli has been developed that is similar to the class of ambiguous figures, but its differing percepts do not have obvious differences in the semantic, affective, and associative links. This is the class of reversible figures—typically, two-dimensional geometric forms that can be perceived in one of two differing three-dimensional spatial orientations. The example that every schoolchild knows is the Necker cube, in which the edges connecting the back and front faces of the cube can be seen as projecting either upward and to the left, or downward and to the right (Fig. 13). All that differs across the two percepts is their spatial orientation. Their semantic identities (e.g. 'cube') are identical, as presumably are their affective and associative links. These characteristics make reversible figures seemingly ideal for the study of the neural basis of top-down processing and perceptual bias in functional imaging studies, and therefore possibly ideal as well for use as an experimental model to study the neural basis of the top-down processing that is involved in producing and sustaining cognitive distortions, projection, and transference phenomena. Based on prior studies of top-down processing and self-regulatory processes, dorsolateral prefrontal, cingulate, and striatal regions were hypothesized to activate during the modulation and control of percepts when viewing reversible figures.

As predicted, the willful search and stabilization of a spatial perspective for the reversible figures relative to gaze fixation was associated with significant activation of frontostriatal circuits that included dorsolateral prefrontal and anterior cingulate cortices, and the dorsal striatum (left lenticular nucleus and bilateral dorsal caudate nuclei) (Fig. 14). Viewing of the forms in their back compared with their front orientation was associated with activation in the left dorsal parietal region. These findings provide compelling evidence that frontostriatal systems support the top-down regulation of sensory percepts and help to construct human experience according to predefined cognitive schemas [159].

5. Unconscious memory systems

Freud postulated that unconscious memories could be either topographically or descriptively unconscious. By 'topographically' or 'dynamically' unconscious he meant that conscious memories which were painful or morally unacceptable could be repressed and thereby moved from the metapsychological structure of the ego into the minimally accessible domain of the id [160]. By 'the descriptive unconscious', he meant that memories within the ego could temporarily pass below a threshold of conscious awareness while remaining relatively easily accessible to willed retrieval.

Neuroscience research has shown conclusively that memory is not a unitary phenomenon; rather, multiple systems subserve different memory functions. These include working memory functions based within the frontal lobe, conditioned motor learning based primarily within the cerebellum and brainstem, declarative memory functions within the mesial temporal lobe, affective memory based within the amygdala and limbic system, and procedural

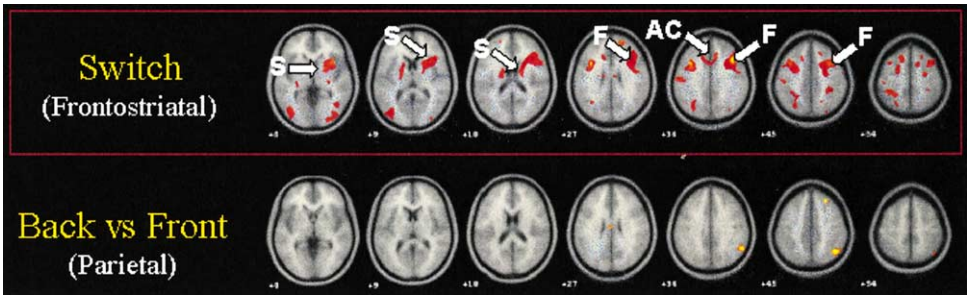

Fig. 14. Brain activity during the top-down regulation of sensory percepts. Increased acitivity in frontal and anterior cingulate cortices, as well as striatum, were detected as subjects willfully changed perception between alternative spatial orientations of the reversible figures (upper row). Increased activity in parietal cortex was detected when viewing figures in their backward facing projection compared with their frontward facing ones (lower row). AC, anterior cingulate cortex; F, frontal cortex; S, striatum.

memory based within the dorsal striatum (the caudate and putamen). Of these systems, not all subserve the conscious representation of memories. In particular, the learning of procedures, habits, or stimulus–response (S–R) associations within the striatum occurs largely outside of consciousness. This memory system allows one to walk and talk at the same time, or to navigate through complex traffic systems in a car while lost deep in thought about the day's events. This knowledge of procedures is typically gained gradually through repeated presentations of the stimulus and the learning of a correct response. This form of learning stands in contrast to the single trial learning of conscious facts, previous experiences, and semantics, which are collectively termed 'declarative' or 'episodic' memories and that are based primarily within the hippocampus [161].

Procedural learning based within the dorsal striatum of subcortical nuclei would seem to relate most closely to the Freudian construct of the topographical unconscious, although even declarative memories can at face value pass below the threshold of consciousness while remaining relatively easily accessible to willed retrieval. None of the multiple, neuroscience-defined learning systems correspond clearly with the Freudian dynamic unconscious. Nevertheless, we will see that activity in affective neural systems as well as psychological stress can both preferentially predispose to use of procedural or habit learning systems for learning, which generally occur outside of consciousness. Thus, the dynamic unconscious and repression, if they are related to any of the currently known memory systems, probably map to interactions across the systems for affective and procedural learning, although any claims to the existence and nature of this correspondence are highly preliminary and speculative.

The declarative and procedural memory systems have been studied most extensively in animals moving through various maze-like environments under controlled sensory, motoric, and motivational conditions. One set of paradigms (the 'radial arm maze') involves a maze with eight identically appearing arms extending radially outward from a central platform, with extra-maze objects visible from within each portion of the maze. In the more standard 'win-shift' version of this paradigm, rats obtain food rewards by visiting each arm of the maze once, with re-entries into maze arms previously visited scored as errors. In a more recently developed 'win-stay' version of this task, rats obtain food rewards by visiting twice each of 4 randomly selected and illuminated maze arms, with visits to unlit maze arms scored as errors. Performance on the win-shift task requires rats to remember those arms that have been previously visited; the task is therefore generally regarded as a prototypical test of spatial memory or cognitive mapping. The win-stay task, in contrast, requires learning to approach a sensory stimulus (the lit arms). It therefore is regarded as a test of S–R, or procedural, learning. Rats with electrolytic or neurochemical lesions of their dorsal striatum or hippocampus exhibit a double dissociation during learning of these tasks: lesions of the striatum impair acquisition of the win-stay task but not the win-shift task, whereas lesions of the hippocampal system impair acquisition of the win-shift but not the win-stay task [162,163].

Another paradigm using a water maze task has been used similarly to study declarative and procedural learning systems. In a circular pool of water, two rubber balls or flags protruding above the water surface serve as cues. One ball (the correct one) is located on top of a platform that can be used to escape the water, while the other ball (the incorrect one) is located on top of a thin rod that only provides support for the ball but does not allow escape. The two balls also differ in physical appearance (e.g. differing horizontal or vertical stripes). In a declarative learning version of the task, the correct platform is located in the same spatial location but the visual appearance of the ball varies on every trial. Thus, rats learn to approach the correct ball on the basis of their memory for spatial location and not visual pattern. In the procedural learning version of the task, the correct platform is located in different spatial positions, but its visual appearance is unchanged across trials. Therefore, rats learn to approach the platform of the basis of stimulus properties alone, which again is an S–R, habitual, or procedural learning solution to the task. Striatal lesions impair the procedural learning but not declarative learning forms of the task [164,165]. Electrophysiological recordings within the basal ganglia and hippocampus during declarative and procedural learning tasks have confirmed the central and specific involvement of these regions in learning and memory [166–168].

5.1. Interaction between memory systems

Procedural and declarative learning systems interact, compete, and can even interfere with one another's functioning [169]. Injection of anxiogenic drugs into the amygdala, for example, induces the predominant use of caudate-dependent procedural learning, presumably because the use of habit is an adaptive response to stress [170]. Pretraining lesions not only leave the unlesioned system intact, but they also enhance its functioning relative to performance in unlesioned control animals [162,163,171–173]. Furthermore, human imaging studies of procedural learning paradigms have reported an inverse correlation of basal ganglia and hippocampus activation across individual trials [174,175].

5.2. Interaction with prefrontal systems

The basal ganglia have been hypothesized to use the cortical–subcortical loops in essence to 'train' the cortex to produce learned motor responses in the presence of a particular pattern of sensory information [176]. If this hypothesis is borne out more fully, it would suggest that prefrontal cortices later in life might take on the functions of

subserving procedural memories that were previously based within the striatum earlier in development. It is possible, for instance, that the functions of striatal portions of frontostriatal systems required for self-regulatory functions are, with increasing age, progressively transferred from the striatum to the prefrontal cortices. Furthermore, prefrontal cortices and the working memory functions they subserve are known to interact in complex ways with memory systems in the mesial temporal lobe and striatum [177–179]. Although the precise functions of these interactions are unknown, the prefrontal cortices are thought to contribute to top-down control of the encoding and retrieval of higher-level representations from heteromodal association cortices by modifying and elaborating them within striatal and hippocampal memory systems on the basis of current goals, task demands, and affective salience [179].

5.3. Human studies of memory systems

The dramatic advances in understanding of memory systems, fostered by the development of suitable behavioral paradigms in animals, have motivated the development of behavioral paradigms within virtual reality environments that are nearly identical to those used in animal models. Development of these virtual reality paradigms has allowed study of multiple memory systems in humans within the laboratory and within MRI scanners. If the neural bases of these systems prove to be the same as their bases in animals, then new knowledge gained in either the animal or human work will complement one another and more rapidly advance progress in understanding the neural systems subserving memory functions in both domains.

Considerable progress has been made in developing these virtual reality environments and in demonstrating similarities in the neural bases for memory systems in the brains of humans and animals. One group has developed a virtual water maze task and demonstrated a robust behavioral advantage in men compared with women [180], similar to findings from another group using a different maze task [181] and consistent with animal and other human cognitive studies [182–185]. Another group developed a virtual reality paradigm similar to the water maze task and reported impaired spatial learning in individuals with traumatic brain injury [186]. One human fMRI study examined regional brain activity in humans during a version of the win-shift radial arm maze paradigm [187]. They reported that the right hippocampus activated during use of spatial learning strategies, while the caudate nucleus activated during use of nonspatial learning strategies. Frontal and parietal cortices activated during use of both learning strategies. Activation of either the right hippocampus [188,189] or the closely related parahippocampus [185,190] has been reported in several other studies employing forms of spatial navigation that were not adapted from animal paradigms.

6. Conclusion

Although core psychoanalytic constructs may be impossible to study directly using neuroscience and imaging methodologies (i.e. brain activity cannot be studied in patients during psychoanalytic sessions), experimental paradigms have been developed and are being applied that are at least relevant to the study of these constructs. Like all scientific paradigms, these neuroscience paradigms simplify the field of variables that are to be examined. Important early insights into the neural bases of core theoretical constructs within psychoanalysis suggest that the nucleus accumbens and related limbic circuitry contribute to the assigning of valence in the pleasure/unpleasure continuum of affective experience. The reticular formation, thalamus, amygdala, and cortex within arousal circuits assign alerting salience to those affective experiences. Frontostriatal systems subserve top-down processing in the CNS, thereby contributing to numerous important psychological functions, including the control of impulses and drives that are established within affective systems, and the construction of experience according to preestablished conceptual schemas—processes that likely underlie cognitive distortions, projection, and transference phenomena. Procedural learning systems likely contribute to memories within the domain of the descriptive unconscious, and interactions across affective and cognitive memory systems conceivably may contribute to memory formations within the dynamic unconscious. Progress in further defining the neural bases of these core constructs will require the close collaboration of neuroscientists and psychoanalysts in the development of experimental paradigms that simplify the analytic field for systematic study while maintaining reliability and ecological validity. This type of collaboration, however, merely defines the hard work of empirical research.

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