Cognition: Neuropharmacology

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The prefrontal cortex (PFC) is instrumental in coordinating, controlling, and executing cognitive and emotional processes using appropriate judgment, flexibility, and attention. The ability to organize appropriate responses to a changing environment requires maintenance and updating of relevant information as well as control over the processing of new incoming information. This careful choreography allows the regulation of impulses, language, attention, decision making, and error correction and is commonly referred to as the executive functions. These abilities require the representation of information not currently in the environment (sometimes referred to as working memory) and are mediated by the PFC. The PFC receives ascending inputs from diverse areas of the brain. The dorsal and lateral surfaces of the PFC interconnect with the sensory and motor association cortices and are key for the regulation of behavioral responses and attention; the ventral and medial regions of PFC interconnect with brain regions involved with emotion, such as the amygdala, hypothalamus, and nucleus accumbens. The ventral surface is often referred to as the orbital frontal cortex (OFC) because it sits above the orbits of the eyes. In rodents, the PFC is much smaller; there is a medial portion (the prelimbic and infralimbic mPFC) that is needed for cognitive control and an orbital area more ventral-laterally that has functions similar to the OFC in primates. The homology of the mPFC in rodents to the dorsolateral PFC in primates is controversial. It is likely that it is more homologous to the mPFC in primates and involves a combination of affective and cognitive functions.

Single-unit recording studies in monkeys have shown that PFC neurons are able to hold modality-specific information online over a delay and to use this represented information to guide behavior in the absence of environmental cues. PFC neurons can also fire in relationship to an abstract rule that is used to govern action. A unique feature of PFC neurons is their ability to maintain information in the presence of distracting stimuli. Delay-related firing also can serve as the basis for behavioral inhibition (e.g., having to look away from a remembered visual stimulus or reverse reward contingencies). Neuromodulators can have powerful effects on the patterns of PFC neuronal response and on PFC cognitive functioning.

The PFC is highly sensitive to its neurochemical state. Evidence to date suggests that the dorsolateral PFC is particularly sensitive to catecholamines (dopamine (DA) and norepinephrine (NE)), whereas the ventromedial PFC is more influenced by serotonin (5-HT). This view has emerged from both lesion studies in nonhuman primates that selectively deplete catecholamines (vs. 5-HT) and from pharmacological studies in humans that preferentially block catecholamine (vs. 5-HT) transporters. However, there are critical exceptions to this generalization; for example, NE α2A-adrenoceptor stimulation can improve ventromedial PFC functions, and 5-HT2A receptor blockade can impair dorsolateral PFC function. Acetylcholine (ACh) also has powerful influences on PFC functions, although there has been little research on cholinergic mechanisms in the monkey PFC. Most of the research examining direct cholinergic mechanisms in PFC have been performed in rats using attentional tasks, and thus it is difficult to compare results across paradigms.

It is noteworthy that the PFC also projects back down to the monoamine and ACh cells, and thus it is positioned to regulate its own modulatory input. Interestingly, the NE and DA cells respond to informative cues and receive projections from the dorsolateral PFC, whereas the ACh cells respond to rewards and response choices, and these cells receive inputs from the OFC. Recent studies indicate that NE cells also receive projections from the OFC and anterior cingulate and that these projections may regulate their tonic firing rate rather than the response to specific stimuli. Thus, there is a coordinated interplay between the subregions of the PFC and their modulatory inputs.

Dopamine

The pioneering work of Goldman-Rakic first revealed the powerful influences of DA on the working memory functions of the dorsolateral PFC. This initial study found that depleting catecholamines in PFC was as destructive as removing the cortex itself. Although this first study focused on DA, it is now known that the depletion of both DA and NE may be especially deleterious.

The DA inputs to the PFC arise from the dorsal cells of the substantia nigra and from the ventral tegmental area in the midbrain. DA neurons project throughout the primate cortex, with highest levels in primary and secondary motor cortices. Within the PFC, the medial PFC actually has a denser innervation than the

dorsolateral PFC, despite the established importance of DA to dorsolateral PFC function. Thus, the quantity of innervation cannot be equated with the importance of an input because it is possible that some delicate inputs may be relatively sparse because they are so powerful.

There are two families of DA receptors: the D1 family (D1 and D5) and the D2 family (D2, D3, and D4). There are currently no drugs available that distinguish between D1 and D5 receptors; thus, reference to D1 usually means D1 or D5. The highest levels of DA receptors in the PFC are the D1 family, and these receptors have been the focus of most research on DA mechanisms in the PFC. D1/D5 receptors can be found in both superficial and deep layers of the PFC, with D1 receptors concentrated on spines and D5 receptors on shafts of pyramidal cells. In contrast, the D2 receptor family is more concentrated in layer V, the cells that project to the basal ganglia. Thus, the D2 family may be especially involved with modulating the response output. D4 receptors are especially numerous on γ-aminobutyric acid (GABA)ergic interneurons in the PFC.

Most research on DA influences on PFC cognitive function has focused on spatial working memory. In monkeys, spatial working memory generally has been assessed using an oculomotor or classical delayed response task. This paradigm requires the monkey to remember a spatial location over a brief delay (seconds). The location changes on each trial so that memory must be continuously updated. Electrophysiological studies of PFC neurons record single units from monkeys performing the oculomotor version of this task. Many neurons in PFC exhibit spatially tuned firing during the delay period; that is, the cells fire more for a preferred than for a nonpreferred direction. This is considered the electrophysiological signature of spatial working memory. In rats, spatial working memory is often assessed in a spatial delayed alternation task, within a T-maze, or using automated operant procedures. Delayed nonmatch-to-position is often substituted for delayed alternation, but it is substantially easier due to diminished proactive interference. In humans, spatial working memory is tested in a variety of paradigms, including a search task on the CANTAB battery and N-back tasks developed from the monkey delayed-response task. In addition, human studies often use the Wisconsin Card Sorting task, Stroop Interference task, and Stop-Signal tasks, which emphasize the inhibitory functions of the PFC.

The D1 family of receptors has powerful effects on spatial working memory function. Either too little or too much D1/D5 receptor stimulation impairs working memory; that is, there is an inverted-U dose–response curve that occurs within normal physiological parameters (see Figure 1). Insufficient levels of DA D1 stimulation probably contribute to cognitive deficits in Parkinson's disease and may also contribute to normal age-related cognitive decline. Excessive levels of D1 receptor stimulation occur during stress exposure and contribute to stress-induced PFC dysfunction. This inverted U in working memory abilities has been observed in monkeys, rats, mice, and human subjects. In humans, an inverted U has been observed in relation to the COMT genotype, whereby the substitution of methionine for valine weakens enzymatic degradation of DA and shifts the U curve rightward. An inverted U is also observed in single-unit recordings of monkeys performing a spatial working memory task. D1 receptor stimulation is especially important for suppressing cell responses to nonpreferred spatial directions. These suppressive effects are mediated by the activation of cyclic adenosine monophosphate (cAMP) intracellular signaling. The effects of D1 receptor stimulation probably depend on the endogenous state of the neuron (e.g., whether it is broadly or narrowly tuned) and on the cognitive demands on the subject. This may explain why D1 receptor blockade or DA depletion has little effect on some kinds of executive function such as self-ordered tasks.

The influence of the D2 family is more complex and less well studied. There has been almost no research on D3 receptors mechanisms in the PFC, and drugs which distinguish between D2 and D3 receptors are scarce. Early studies showed that D2/D3 receptor blockade did not impair working memory, but rat studies suggest that D2/D3 receptor stimulation (e.g., during stress exposure) may impair

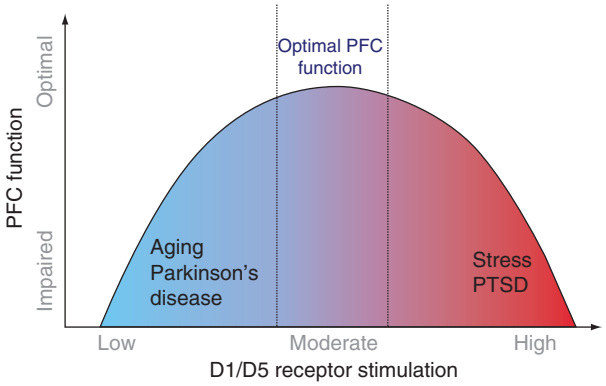

Figure 1 A schematic representation of the inverted-U relationship between D1/D5 receptor stimulation and PFC function; moderate levels of receptor stimulation produce enhanced delay-related firing in PFC neurons as well as optimal performance on working memory tasks, whereas insufficient or excessive D1/D5 receptor stimulation erodes spatial mnemonic tuning and impairs working memory. PFC, prefrontal cortex; PTSD, posttraumatic stress disorder.

working memory performance. Electrophysiological studies show that D2 receptor stimulation increases response-related firing, but not delay-related firing, of PFC neurons in monkeys performing a working memory task. Because some response-related firing occurs after the motor response is initiated, it may act as corollary discharge, informing the brain that a motor command has been initiated. This may have particular relevance to schizophrenia, in which hallucinations may involve weakened corollary discharge.

Recordings from rat PFC slices and from awake monkeys indicate that D4 receptor stimulation inhibits GABAergic interneurons via G_i inhibition of cAMP signaling. Thus, D4 receptor stimulation may have an overall excitatory effect on PFC circuits. However, D4 also appears to inhibit some pyramidal cells, and so the picture may be more complex. Behavioral studies of D4 antagonists may find an inverted-U dose–response curve on working memory, but these agents have not been studied extensively. It should be noted that NE has a higher affinity for D4 receptors than for adrenoceptors and thus that the D4 receptor should properly be considered a catecholamine receptor rather than a DA receptor.

Norepinephrine

It is now appreciated that NE has just as powerful an effect on NE function as DA. In contrast to DA D1, NE appears to dissociate its beneficial and detrimental effects at different types of adrenoceptors. Thus, these may be more practical targets for pharmacological treatment of PFC dysfunction.

The NE innervation of the PFC arises from the locus coeruleus (LC) in the pons. As with DA, there is a delicate innervation of both the supragranular and granular layers, with particular density in layer I. The superficial layers are the focus of cortical–cortical connections and have dense α1- and α2-adrenoceptor binding. There are three α2 subtypes; of these, the α2A subtype is particularly prominent in the monkey PFC. Electron microscopy studies have documented α2A receptors postsynaptically in the spines and dendrites of PFC pyramidal cells, as well as in presynaptic locations on NE axons and terminals. β-Receptor binding is densest in the middle layers (i.e., layer IV), which receives projections from the thalamus.

As with DA, NE has dual effects on PFC function depending on the amount of NE release. Moderate levels of NE release during normal waking have vital, beneficial effects on PFC function via higher-affinity postsynaptic α2A-adrenoceptors, whereas high concentrations of NE released during stress impair PFC function via lower-affinity α1-adrenoceptors and possibly β1-adrenoceptors (see Figure 2). In most parts of brain, NE has potent effects via β-adrenoceptors. In contrast, the PFC seems more dramatically altered by α-adrenoceptors. Figures 3(a) and 3(b) illustrate the

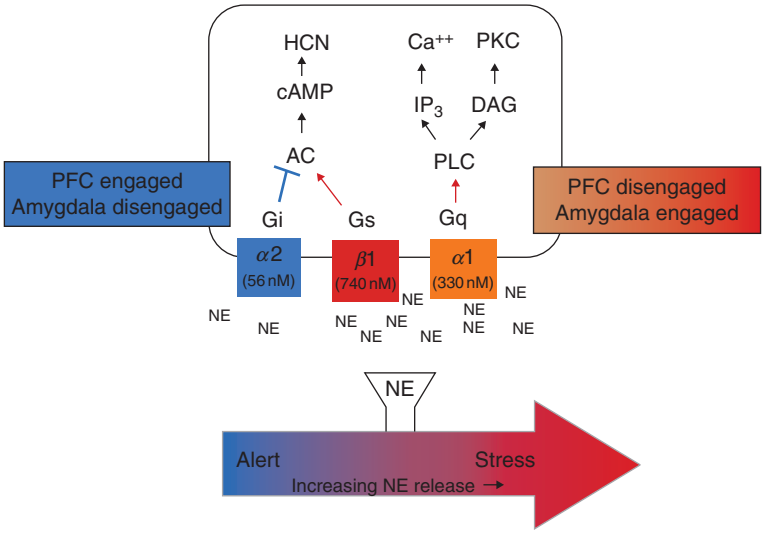

Figure 2 Levels of NE release determine the functional status of the PFC based on varying affinities for adrenergic receptors. Moderate concentrations of NE during the nonstressed, alert state lead to improved PFC function via binding to higher-affinity α2A-adrenoceptors (shown in blue). Higher concentrations of NE release in the PFC, which are observed in conditions of stress, lead to PFC impairment due to the binding to lower-affinity α1- and possibly β1-adrenoceptors. Recent studies have started to uncover downstream, intracellular signaling mechanisms that mediate these NE actions. In contrast, the amygdala is modulated in a manner opposite to the PFC, whereby α2-adrenoceptors impairs, and β- and α1-adrenoceptors strengthen, amygdala regulation of behavior. Thus, NE may act as a chemical switch to determine whether behavior is regulated by higher-order PFC operations or more primitive mechanisms mediated by the amygdala. AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate; NE, norepinephrine; PFC, prefrontal cortex; HCN, hyperpolarization-activated cyclic nucleotide-gated channels; PKC, protein kinase C; PLC, phospholipase C.

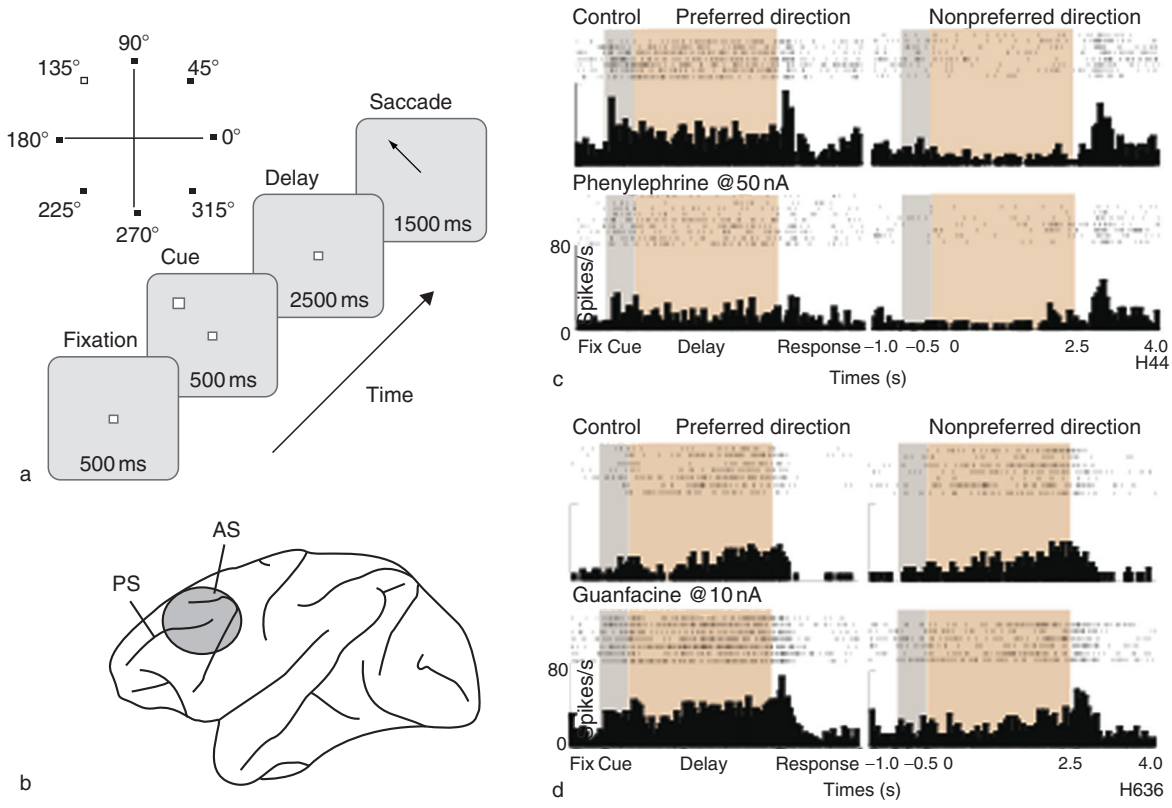

Figure 3 The delay-related activities of neurons of the monkey PFC provide a cellular representation of working memory: (a) the oculomotor delayed-response task often used for *in vivo* electrophysiological recordings; (b) an electrode is lowered into the monkey's dorsolateral PFC to record responses while the monkey is performing the task; (c) the response of delay-related neurons altered by the iontophoretic application of phenylephrine, an α1 agonist, acting on adrenoceptors; (d) the response of delay-related neurons altered by the iontophoretic application of guanfacine, an α2A agonist, acting on adrenoceptors. As shown in (a), following a cue at a specific orientation, there is a delay period during which the monkey must keep the previously presented cue in mind in order to guide the appropriate saccade (response). As shown in (c) and (d), cells show preferences for particular orientations (preferred vs. nonpreferred), and specific neurons fire selectively during either the cue, delay, or response periods. The iontophoretic application phenylephrine suppresses delay-related firing (c), whereas the application of guanfacine enhances delay-related firing (D). PS, principle sulcus; As, arcuate PFC, prefrontal cortex. This figure was generously supplied by Dr. Min Wang, Yale University.

influence of α1- versus α2-adrenoceptor stimulation on the delay-related firing of PFC neurons in monkeys performing an oculomotor delayed response task. Stimulation of α1-adrenoceptors with phenylephrine reduces delay-related cell firing for the preferred direction (Figure 3(c)), whereas stimulation of α2A-adrenoceptors with guanfacine enhances delay-related firing for the preferred direction (Figure 3(d)). However, β mechanisms are just beginning to be understood and may involve opposing actions at β1 versus β2 receptors that are obscured with nonselective compounds. The administration of α2A agonists improves spatial working memory in mice, rats, monkeys, and humans, especially in subjects with PFC dysfunction. In addition to working memory, the α2A agonist, guanfacine, has been shown to improve a number of other PFC functions, such as lessening distractibility, improving reversal performance and other measures of behavioral and cognitive inhibition (e.g., in humans, improving performance on the Stroop interference task), and strengthening conditional motor learning. It has little effect on posterior cortical functions and, indeed, can impair amygdala function. Conversely, the blockade of endogenous α2 receptors in the PFC with yohimbine impairs working memory, weakens no-go responding, and induces locomotor hyperactivity. Thus, this system is particularly relevant to attention-deficit hyperactivity disorder (ADHD). Recordings from PFC neurons in monkeys performing spatial working memory tasks show similar effects; α2A-adrenoceptor stimulation increases delay-related firing for the preferred direction (see Figure 3(d)), whereas yohimbine suppresses delay-related firing. These enhancing effects on working memory result from the stimulation of postsynaptic α2A receptors in the PFC, inhibiting cAMP production, closing HCN channels on dendritic spines, and strengthening the functional connectivity of PFC circuits. Based on

research in animals, guanfacine is now in use for the treatment of ADHD, Tourettes syndrome, posttraumatic stress disorder (PTSD), and mild traumatic brain injury. Recent studies indicate that mutations on the Disordered In Schizophrenia 1 (DISC1) gene may lead to excessive cAMP signaling in patients with schizophrenia-like illnesses and that agents such as guanfacine may be useful in treating PFC deficits in these disorders as well.

In contrast to α2A-adrenoceptors, stimulation of α1-adrenoceptors impairs working memory. α1-Adrenoceptor antagonists have no effect on working memory when infused into the PFC during nonstress conditions, but they protect PFC cognitive function under conditions of uncontrollable stress. Conversely, infusions of α1-adrenoceptor agonists such as phenylephrine mimic the stress response and impair working memory. These detrimental actions are mediated by phosphotidyl inositol–protein kinase C intracellular signaling. Detrimental α1-adrenoceptor actions have been observed at the cellular levels as well, at which iontophoresis of phenylephrine onto PFC neurons decreased the delay-related cell firing necessary for working memory function (see **Figure 3(c)**). As with cognitive performance, this collapse in delay-related firing was reversed by a protein kinase C inhibitor. These mechanisms are especially relevant to PTSD, bipolar disorder, and schizophrenia, all of which are caused by, or worsened by, stress exposure. The α1-adrenoceptor antagonist prazosin is now used to treat patients with PTSD, and all atypical antipsychotic medications have α1 and 5-HT2 receptor-blocking properties. 5-HT2 receptors, like α1 receptors, are coupled to phosphotidyl inositol–protein kinase C intracellular signaling. Genetic and biochemical studies suggest that phosphotidyl inositol–protein kinase C intracellular signaling is overactive in bipolar disorder and schizophrenia (e.g., due to loss of function mutations in the genes encoding for DAG kinase or RGS4). Most antimanic agents reduce the activity of this signaling pathway. Thus, these agents may restore PFC regulation of behavior, thought, and affect by normalizing phosphotidyl inositol–protein kinase C intracellular signaling.

Serotonin

The raphe nuclei send widespread and dense 5-HT projections throughout the cortex, including the PFC. Electron microscopy studies indicate that these 5-HT projections make connections with both pyramidal cells and interneurons in the PFC. PFC neurons project back to the raphe nuclei, where they may have an inhibitory influence. There are a multitude of 5-HT receptor subtypes (at least 13); however, the localization and function of these receptors within the PFC are poorly understood. The 5-HT1 family appears to be more densely localized in superficial layers, whereas 5-HT2 receptors are more concentrated in middle layers.

It is well established that 5-HT plays a critical role in affective regulation by the OFC, whereas its effects on dorsolateral PFC function appear to be more complex. The most unambiguous evidence for the role of 5-HT in executive processes comes from studies of reversal learning in marmoset monkeys. In reversal learning, subjects are presented with two stimuli and initially learn to associate reward with one stimulus. After this pairing has been established, a subsequent reversal between stimulus and reward takes place, such that the animals must now make the previously unrewarded response in order to receive a reward. Studies in humans as well as lesion studies in nonhuman primates indicate that the performance of this task depends on the OFC as well as the ventromedial PFC. Selective reductions in 5-HT via injections of 5,7-dihydro-testosterone (DHT) directly into the OFC of marmoset monkeys impairs performance on serial discrimination reversal tasks. In contrast, performance is preserved on an attentional set-shifting task that requires subjects to reverse rules and learn new rules regarding a perceptual dimension of a stimulus (i.e., shape or color) or a specific feature of a percept (see **Figure 4**). Monkey studies have shown that set-shifting performance depends on the dorsolateral PFC. Similar results have been observed in humans, in whom rapid tryptophan depletion impairs reversal learning while preserving attentional set-shifting performance. Interestingly, studies in monkeys as well as rats have shown that OFC depletion of DA had no effect on performance of a serial reversal learning task.

In addition to regulating attentional set shifting, the lateral PFC inhibits inappropriate motor responses, which can be evaluated by performance on a stop-signal task. A study in humans found that increases in NE, via NE reuptake inhibition, led to faster reactions on a stop-signal task. Performance on a probabilistic learning task, an analog to reversal learning, was not affected by NE reuptake inhibition. Conversely, increased basal 5-HT levels produced impairments on a probabilistic learning task but did not influence stop-signal performance. These findings support the findings from depletion studies in humans and monkeys. Together, these data have led to the hypothesis that 5-HT and catecholamines have dissociable and specific roles in the modulation of PFC operations.

One significant barrier to interpreting studies using global depletions or enhancements of 5-HT action is

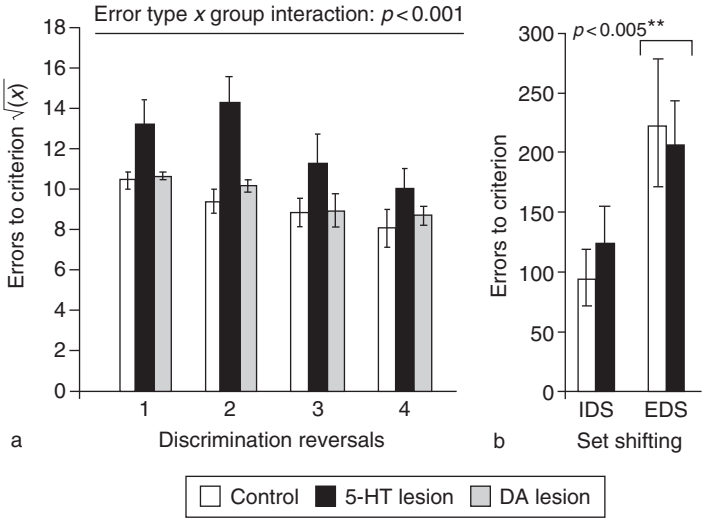

Figure 4 Effects of prefrontal serotonin depletions on learning and attention: (a) depletions of prefrontal serotonin (but not prefrontal dopamine) disrupt discrimination reversal learning; (b) prefrontal serotonin depletions have no effect on shifting an attentional set. In (b) note the greater number of errors made in performing a discrimination requiring a shift of attentional set (EDS) compared to one involving the maintenance of a previously acquired attentional set (IDS), in both groups. 5-HT, serotonin; DA, dopamine; EDS, extra-dimensional shift; IDS, intradimensional shift. Courtesy of Dr. Angela Roberts, Cambridge University, UK.

unraveling the heterogeneous actions of different receptor subtypes. Future studies need to examine the role of specific 5-HT receptor subtypes and determine whether dorsolateral PFC operations are altered when the 5-HT system is probed more selectively. For example, electrophysiological studies indicate that 5-HT2 receptors may influence spatial working memory operations, and these findings need to be pursued at the behavioral level.

In summary, 5-HT plays a distinct, if complicated role in the affective flexibility and the execution of primed behaviors and many of the activities of the mPFC and the OFC. Through its connections with limbic areas, the medial OFC is critical in connecting associative information regarding outcomes with the representational memory processes of the PFC. Ultimately, this positions the OFC to regulate the generation and use of outcome expectancies, which underlie the ability to make adaptive decisions. Thus, it is not surprising that studies of major depressive disorder in humans implicate dysfunction of the OFC as well as the dorsal raphe nucleus. Future studies using receptor-selective agents and behavioral paradigms probing a wide array of PFC-mediated cognitive functions will bring an improved understanding of the complex role of 5-HT in higher-order cognitive and affective processes.

Acetylcholine

Cholinergic neurons project from the basal forebrain to virtually all layers and all regions of the cortex, with approximately 75% of cholinergic cortical innervation originating from the nucleus basalis. Cholinergic axons make synapses in all layers of the monkey PFC, targeting pyramidal, and nonpyramidal cells. Most synapses on pyramidal cells target dendritic shafts, although there are some on spines and very few on the cell bodies. There are two general families of cholinergic receptors: muscarinic and nicotinic receptors. There are five muscarinic subtypes. Of these, the M2 receptor serves as both a presynaptic autoreceptor and a postsynaptic receptor on PFC pyramidal and nonpyramidal cells. In PFC pyramidal cells, M2 receptors are observed on dendritic spines receiving excitatory (asymmetric) inputs. The M1 receptor is also found postsynaptically on dendritic shafts and spines. Nicotinic receptors are often found presynaptically on the terminals of monoamine or ACh axons, where they can regulate transmitter release. They are most dense in layer I of the monkey PFC, which contains the highest levels of catecholamine fibers.

Although there have been detailed anatomical studies of the ACh inputs to the PFC, there has been little or no research on the function of these inputs in monkeys. Many studies have found alterations in working memory with systemic administration of muscarinic and nicotinic compounds, but these agents have powerful actions throughout the brain (e.g., in the thalamus), and thus alterations in cognitive performance cannot be necessarily attributed to PFC actions. In contrast, there has been a great deal of progress outlining ACh actions in the rodent mPFC, in which

infusions of muscarinic blockers such as scopolamine directly into the mPFC induce working memory deficits. Much of this research has focused on the important role of ACh in attention, specifically vigilance. These effects are evident both in the early stages of sensory processing and in subsequent top-down processing, which is regulated by the PFC.

It is widely accepted that ACh-mediated enhanced processing of sensory information underlies the cognitive process of attention. Attention encompasses a variety of operations that together contribute to the detection and discrimination of stimuli; and the integrity of attention processes contributes to the efficacy of higher-order cognitive functions such as learning and memory. Numerous behavioral studies have implicated basal forebrain cortical cholinergic inputs in sustained attention functioning. Tasks measuring sustained attention, or vigilance, require an animal to distinguish signal trials, which typically use a panel of lights illuminated for a short duration of time, from nonsignal trials, in which no light is illuminated. Accuracy is measured by training the animals to make a designated response for both signal and nonsignal trials. A range of stimulus intensities, presentation intervals, and the introduction of distracters are often used to manipulate the difficulty of this task.

Performance on sustained attention as well as distracter tasks stimulates ACh release. Behavioral and electrophysiological studies have implicated the association areas of the cortex, most notably the mPFC, in the ACh facilitation of sustained attention. First, the PFC appears particularly sensitive to ACh. In rats, local administration of ACh stimulated mPFC neuronal activity. In addition, several studies have indicated that the mPFC requires ACh to effectively suppress the processing of irrelevant or distracting information. One study observed increases in ACh release in the frontal cortex of rats as they recovered from a distracter introduced in a sustained attention task. A separate study found rats with ACh depletion to be unimpaired on tasks of attention under normal conditions; however. the introduction of distracters into the task resulted in a significant decrease in performance as compared to their sham counterparts. These findings further support the importance of ACh to the maintenance of information and attention under challenging or unpredictable conditions, such as the presentation of distracters or the erosion of signal.

The modification of information processing and more complex operations by knowledge-driven or goal-oriented information is referred to as top-down regulation. Basal forebrain cortical cholinergic input is mediated by efferent projections from the PFC; thus, the PFC is well positioned to orchestrate cholinergic innervation throughout the brain. PFC-driven top-down control of signal processing is thought to be one mechanism through which the PFC filters distracting stimuli and directs thought and behavior appropriately. In primates, ACh cells probably receive information from the OFC regarding reward or other affective information that may motivate attentional state. It was recently shown in rodents that PFC cholinergic stimulation resulted in increased ACh release in the posterior parietal cortex, a region that has been implicated with attention. Thus, following stimulation, the PFC is positioned to deploy ACh release in other cortical regions.

Overactivity of ACh has been linked to attention performance deficits, specifically to an increased response to nonsignal stimuli. This impaired signal-to-noise processing results in overprocessing, leading to generically amplified and unfiltered information and ultimately to false-positive responses. However, underactive cholinergic input to the cortex may likewise contribute to cognitive and attention deficits. In Alzheimer's disease, cholinergic inputs from the basal forebrain deteriorate, and this loss of input is may contribute to impaired signal detection as well as subsequent impairments in the PFC-mediated or top-down regulation of attention. Although this ACh dysregulation appears to contribute to the symptoms of disorganized thought and behavior, at this time, no conclusive studies have distinguished the ramifications of ACh underactivity from gross impairments in executive centers that would otherwise direct this input. In sum, studies of dysregulated ACh processing in disease states reiterate that moderate levels of ACh are necessary for the appropriate signal-driven activation of cortical processing centers and for the subsequent regulation of attention via PFC-dictated ACh release.

Summary

The PFC subserves executive functions by organizing information required for future thought and action. A vast body of literature across species indicates that the cognitive tasks of the PFC are sensitive to a variety of neurochemicals and that different neurotransmitter systems have distinct roles in cognitive functions of the PFC. However, there are several formative obstacles to fully delineating the neurochemical modulation of executive functions, most notably, the myriad actions of specific receptors and the broad range of tasks regulated by the various subregions of the PFC. Understanding the intricacies of these powerful neurochemical influences on PFC function is key to our understanding of the etiology and treatment of many neuropsychiatric illnesses, including schizophrenia, ADHD, and PTSD, as well as the decline in PFC cognitive functions with advancing age.

See also: Acetylcholine Neurotransmission in CNS; Dopamine; Executive Function and Higher-Order Cognition: Definition and Neural Substrates; Norepinephrine: CNS Pathways and Neurophysiology; Prefrontal Cortex: Structure and Anatomy; Prefrontal Cortex; Serotonin (5-Hydroxtryptamine; 5-HT): Neurotransmission and Neuromodulation; Strategic Control of Memory; Working Memory: Capacity Limitations.

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