

Neuropsychopharmacology and Neurogenetic Aspects of Executive Functioning: Should Reward Gene Polymorphisms Constitute a Diagnostic Tool to Identify Individuals at Risk for Impaired Judgment?

Abdalla Bowirrat · Thomas J. H. Chen ·
Marlene Oscar-Berman · Margaret Madigan ·
Amanda LH Chen · John A. Bailey ·
Eric R. Braverman · Mallory Kerner · John Giordano ·
Siobhan Morse · B. William Downs · Roger L. Waite ·
Frank Fornari · Zaher Armaly · Kenneth Blum

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Abstract Executive functions are processes that act in harmony to control behaviors necessary for maintaining focus and achieving outcomes. Executive dysfunction in neuropsychiatric disorders is attributed to structural or functional pathology of brain networks involving prefrontal cortex (PFC) and its connections with other brain regions. The PFC receives innervations from different neurons associated with a number of neurotransmitters, especially dopamine

(DA). Here we review findings on the contribution of PFC DA to higher-order cognitive and emotional behaviors. We suggest that examination of multifactorial interactions of an individual's genetic history, along with environmental risk factors, can assist in the characterization of executive functioning for that individual. Based upon the results of genetic studies, we also propose genetic mapping as a probable diagnostic tool serving as a therapeutic adjunct for augmenting

A. Bowirrat · Z. Armaly
Clinical Neuroscience and Population Genetics,
The Nazareth English Hospital (EMME),
16100, Nazareth, Israel

A. Bowirrat
e-mail: bowirrat@netvision.net.il

T. J. H. Chen
Department of Occupational Safety and Health,
Chang Jung Christian University,
Tainan, Taiwan, Republic of China
e-mail: tjhchen@yahoo.com.tw

M. Oscar-Berman
Department of Psychiatry,
Boston University School of Medicine and Boston VA Healthcare
System,
Boston, MA 02130, USA
e-mail: oscar@bu.edu

M. Oscar-Berman
Department of Neurology, Boston University School of Medicine
and Boston VA Healthcare System,
Boston, MA 02130, USA

M. Oscar-Berman
Department of Anatomy & Neurobiology, Boston University
School of Medicine and Boston VA Healthcare System,
Boston, MA 02130, USA

M. Madigan · B. W. Downs · R. L. Waite · K. Blum
Department of Nutrigenomics and Personalized Medicine,
Lifegen, Inc,
San Diego, CA 92101, USA

M. Madigan
e-mail: MARGBETTS@HOTMAIL.COM

B. W. Downs
e-mail: bill@lifegen.org

R. L. Waite
e-mail: drw8@san.rr.com

A. L. Chen
Engineering and Management of Advanced Technology,
Chang Jung Christian University,
Tainan, Taiwan, Republic of China
e-mail: ac8858@gmail.com

executive functioning capabilities. We conclude that preservation of the neurological underpinnings of executive functions requires the integrity of complex neural systems including the influence of specific genes and associated polymorphisms to provide adequate neurotransmission.

Keywords Executive functions · Dopamine · Prefrontal cortex · Genetics · Reward deficiency syndrome (RDS)

Introduction

“Executive functions comprise those mental capacities necessary for formulating goals, planning how to achieve them, and carrying out the plans effectively. They are at the heart of all socially useful, personally enhancing, constructive, and creative activities. With the executive functions intact, a person can suffer many different kinds and combinations of sensory, motor, and cognitive deficits and still maintain

J. A. Bailey · K. Blum (✉)
Department of Psychiatry and McKnight Brain Institute,
University of Florida,
Gainesville, FL 32610, USA
e-mail: drd2gene@aol.com

J. A. Bailey
e-mail: baileyjo@UFL.EDU

E. R. Braverman
Department of Neurological Surgery,
Weill Cornell College of Medicine,
New York, NY 10065, USA

E. R. Braverman · M. Kerner · K. Blum
PATH Foundation NY,
New York, NY 10010, USA

M. Kerner
e-mail: mallory.kerner@gmail.com

K. Blum
e-mail: pathmedical@aol.com

J. Giordano · S. Morse · K. Blum
G & G Holistic Addiction Treatment Center,
North Miami Beach, FL, USA

J. Giordano
e-mail: michg@hotmail.com

S. Morse
e-mail: samorse10@aol.com

F. Fornari · K. Blum
Dominion Diagnostics, LLC,
North Kingstown, RI, USA

F. Fornari
e-mail: ffornari@me.com

the direction of his own life and be productive as well. Impairment or loss of these functions compromises a person’s capacity to maintain an independent, constructively self-serving, and socially productive life no matter how well he can see and hear, walk and talk, and perform tests” [1].

Defining Executive Functions

Executive functions are complex cognitive abilities requiring the synchronization of several sub-processes to achieve a particular goal [2]. They control and regulate other abilities and behaviors and involve cognitive control processes that regulate thought and action on representations stored in the prefrontal cortex (PFC) [3]. Executive functions are localized in neural networks and, when activated, enable access to the stored actions. Indeed, executive functions can be viewed as computational procedures or algorithms that are localized in neural networks [4]. Theorists differ with regard to whether executive functions are unified with respect to process, nor whether they include specific cognitive abilities [5–9]. Consensus is lacking with regard to which of many diverse cognitive functions are considered relevant to executive functioning. At the very least, the term encompasses a host of processes that act in harmony and are responsible for the higher-level action of monitoring and controlling behaviors necessary for maintaining focus and achieving outcomes in possibly adverse circumstances. The efficacy measure of any successful high mental skill is a function of our intellectual integrity and mental capabilities. The outcome of our behavior depends on the ability of our brain to exert control over its processing of reflexive reactions to the environment and directing those behaviors toward conscious as well as non-conscious goals [10].

Executive Skills

A recent hypothetical mechanism for executive function postulates several sub-components. In a frequently cited classification, Smith and Jonides [3] distinguished between mechanisms relating to (a) attention and inhibition, (b) task management, (c) planning, (d) monitoring, and (e) coding. There is, however, no consensus on the number and the precise nature of functional subcomponents. Recent research has concentrated on those sub-processes that are relatively well-defined in both theoretical and empirical terms.

Executive skills include an array of conscious and complex mental abilities that help us to connect past experiences with present actions, plan future behavior when faced with novel tasks, judge, organize, change behavior and strategies, pay attention, and remember details for our decision making. Executive skills give us the ability to evaluate risks, recognize future consequences resulting from current actions, choose between good and bad actions, override and suppress unacceptable social

responses, determine similarities and differences among objects or events, initiate or postpone, negate actions, and prioritize and switch among tasks. These very complex sets of decisions are achievable only if the neurological structures and functions are intact. The need for an executive control mechanism has been postulated for non-routine situations requiring a supervisory system, for example, for selecting an appropriate action from variety of options, inhibition of inappropriate actions, and keeping in working memory the plan of action as well as the results of the plan. Flexible goal-directed behavior requires an executive control for optimizing behavior. Deciding which action to take is biased by the anticipation of the action's outcome. Mismatch between anticipated and actual outcome can be used to optimize behavior. If an anticipated reward is not delivered, the error can be used for changing the previously learned behavioral pattern. All of these features distinguish the healthy humans from other animals and primates because humans have a highly developed brain capable of abstract reasoning, language, introspection, and problem solving. Neuropsychological evidence suggests that executive processing is intimately connected with the intact function of the frontal cortices and their underlying connections. Hence, the brain has an executive system that is hierarchical and yet distributed rather than strictly localized [11].

The PFC and Executive Functioning

The English scientist Grey Walter in 1964 was one of first to confirm the involvement of the PFC in human executive functions by using electrophysiological evidence. He discovered the *contingent negative variation*, a slow negative potential recorded from the anterior part of the head during preparation of subjects to receive a stimulus or to make a movement. It is known that the PFC is a major brain structure with considerable functional heterogeneity in humans [12]. The PFC lies anterior to the motor and premotor areas and consists of multimodal association cortex (dorsolateral convexity and anteromedial surface) as well as limbic cortex (anterior cingulate and posterior orbitofrontal areas). The PFC is divided into three regions: lateral PFC, orbitofrontal (ventral) cortex, and medial frontal cortex (which include the anterior cingulate cortex). All PFC areas connect reciprocally with the dorsomedial thalamic nucleus.

A recent PUBMED search (January 22, 2012) resulted in 1,146 articles concerned with the relationship of the PFC and executive functions. It is well-known that the PFC is critical to many cognitive abilities that are considered particularly human and forms a large part of a neural system crucial for normal socioemotional and executive functioning in humans and other primates. PFC matures later in development than more caudal regions, and some of its neuronal subpopulations exhibit more complex dendritic arborizations. Comparative work as reviewed by Teffer and Semendeferi [13] suggests that that the human prefrontal cortex differs from that of closely related primate

species less in relative size than it does in organization. In fact a phylogenetically recent reorganization of frontal cortical circuitry may have been critical to the emergence of human-specific executive and social-emotional functions, and developmental pathology in these same systems underlies many psychiatric and neurological disorders, including autism and schizophrenia.

The neural architecture of human PFC is probably more sophisticated or organized differently compared to cortical areas in other species [14]. In spite of the fact that the major executive functions of the frontal lobes have been identified as higher-level reasoning, analytical thinking, multi-tasking, decision making, and problem solving, as well as creative thinking, important tasks of the PFC in executive function still need clarification. The exact role of other PFC structures involved in the neural circuits needs to be identified and their relationship to the subcortical structures elucidated. We argue that while the brain has networks that act in harmony and an executive system that is hierarchical and yet diffuse rather than strictly localized, the various sub-regions of the PFC perform a unified set of interrelated roles. These interrelations can to be studied through a neural network model incorporating the frontal lobes and other regions including: the basal ganglia, dorsomedial, lateral, and anterior nucleus of the thalamus, amygdala, hippocampus, cingulate cortex, cerebellum, temporal cortex, and parietal cortex. Computational neural network modeling may unravel clues that will fuel our understanding of how executive functioning works as a cohesive network of connectivity rather than an unrelated diffuse set of anatomical loci [15]. Another tool was used to learn how executive function actually works by evaluation of impairments in this precise and important complex system.

Impairments of Executive Functions

Executive dysfunction has been associated with a range of disorders generally attributed to structural or functional frontal lobe pathology. Neuroimaging, with PET and fMRI, have confirmed this relationship [16]; however, attempts to link specific aspects of executive functioning to discrete prefrontal foci have been inconclusive. Instead, the emerging view suggests that executive function is mediated by dynamic and flexible networks that can be characterized using functional integration and effective connectivity analyses. This vision is compatible with the clinical presentation of executive dysfunction associated with a range of pathologies. For example, both healthy adults and schizophrenic patients activate a qualitatively similar neural network during executive task performance, consistent with the engagement of a general purpose cognitive control network, with critical nodes in the dorsolateral PFC and anterior cingulate cortex (ACC). However, patients with schizophrenia show altered activity with deficits in the dorsolateral PFC, ACC, and mediadorsal nucleus of the thalamus. Increases in activity are evident in other PFC areas, which could be compensatory in nature [17].

An interruption of cognitive/executive function often results in a various pattern of deficits including distractibility, social unreliability, untrustworthiness, lack of initiative, impulsivity, and profound disinhibition. Cognitive symptoms may occur in many neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, psychiatric illness such as schizophrenia, depression, obsessive compulsive disorder and reward deficiency syndrome [18], as well as pervasive developmental disorders such as attention-deficit hyperactivity disorder. In fact, executive dysfunction syndromes are commonly encountered in psychosomatic medicine [19].

Executive dysfunction describes the inability to delay reward, modify behavior, and match context and a lack of capacity for self-control, an underestimation of harm, and a lack of regard for consequences, while executive function is associated with both the initiation and the modulation of behavior, lack of initiation, and lack of control of behavior that might be concurrent features of executive dysfunction [20]. It has been argued that reward processing and error signals after reward non-delivery are not generally considered executive functions, as such functions operate in a bottom-up, unsupervised fashion. However, Taylor et al. [21] found an interaction between reward and retrieval from working memory in the right dorsolateral prefrontal cortex. Main effects of load and reward occurred in adjacent regions of the ventrolateral PFC during retrieval. The data demonstrate that when subjects perform a simple working memory task, financial incentives motivate performance and interact with some of the same neural networks that process various stages of working memory. Areas of overlap and interaction may integrate information about value, or they may represent a general effect of motivation increasing neural effort.

Clearly, any loss of synchrony or timing in neurotransmission will disrupt mental processes dependent upon the integration of signal transmission for function. Primary factors disrupting brain integration are transitory mental, emotional, physical, or biochemical stress [22].

Stressors could be described as extremely powerful environmental and psychological incentives. According to Richard S Lazarus, stress is a feeling experienced when "the demands exceed the personal and social resources the individual is able to mobilize" [23]. Fatigue resulting from lack of sleep is one of the most common forms of physical stress affecting brain integration [24, 25]. In general and for most people, these factors causing loss of brain integration are transitory. Physiological stress, a major factor which could occur from psychological trauma, injury, or even from memory loss, is biochemical in nature and a direct result of our emotional states, particularly activation of our survival emotions, and is thus subconscious in origin [26].

Patients with traumatic brain injury, particularly when mild, may appear normal, claim to be normal, and show no impairment on standard cognitive-related testing. Nevertheless, they

may suffer a potentially devastating syndrome involving a constellation of disabilities, including executive functioning deficits. Interestingly, complete recovery of executive function in some patients can occur, perhaps due to functional reorganization within executive networks [27]. The destructive consequence of closed head injuries are potentially catastrophic neurobehavioral symptoms, following major or minor head trauma [28]. A number of studies suggest that the use of low pressure hyperbaric oxygen may have positive outcomes in patients presenting brain injury whereby executive functioning is improved and other associated symptoms like post-traumatic stress disorder [29–31].

Converging neuropsychological and neuroimaging evidence suggests that abnormalities in practical real-life decision making form a prominent part of the profile of the cognitive deficit associated with patients who have frontal damage restricted to the ventromedial PFC that includes the orbitofrontal region [12, 32–37]. Such cognitive deficits are considered in the context of risk taking or impulsivity because patients tend to pursue inappropriate actions, often without foresight, that are immediately rewarding but are likely to have undesirable consequences for the patient's well-being in the long-term. Damage or abnormalities in other structural regions such as the anterior cingulum circuit may cause malfunction to the motivation of behavior [38–40]. Damage to the dorsolateral prefrontal circuit causes instability in the organizational aspects of executive functioning and integrating information, focusing attention, and deciding on response. Also, injury to the lateral orbitofrontal circuit produces critical damage to the integration of limbic and emotional information into contextually appropriate behavioral responses [41–43] (see Fig. 1).

Recent research by Chen et al. [44] studying the relationship between executive dysfunction and frontal and non-frontal white matter using diffusion tensor imaging measurements on 13 subjects with amnesic mild cognitive impairment (aMCI), 11 subjects with early Alzheimer's disease (AD), and 16 control subjects provided important insights. The aMCI and early AD patients showed executive function impairments with differential performance in frontal-related behaviors. Both groups also showed increased mean diffusion in the genu of the corpus callosum and left frontal periventricular white matter (PVWM). The early AD group showed an additional decrease in fractional anisotropy of bilateral frontal PVWM and in the genu of the corpus callosum. The frontal PVWM was associated with performance on the Verbal Fluency Test, the Wisconsin Card Sorting Test, and Part B of the Trail Making Test (psychomotor performance/attention). Executive function was impaired in subjects with aMCI and early AD and was associated with frontal and parietal PVWM changes. These changes may be due to early AD degeneration of the lateral cholinergic projections or to early change of the superior longitudinal fasciculus.

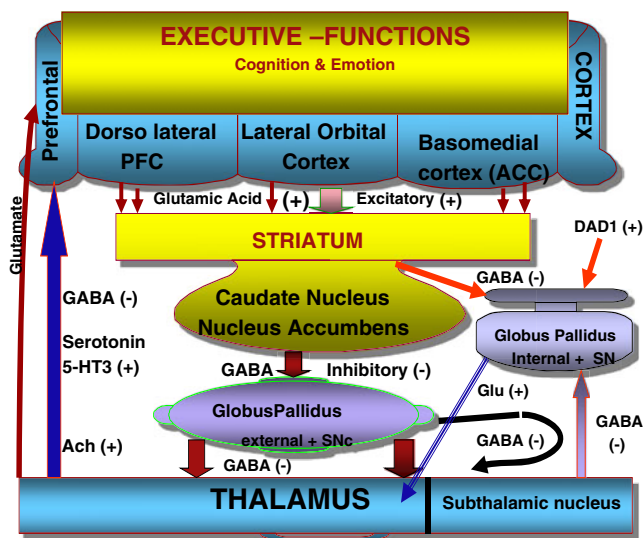


Fig. 1 The figure shows the division of the prefrontal cortex (PFC): the dorsolateral PFC, lateral orbital cortex, and basomedial cortex that originate in the anterior cingulate cortex (ACC) and their connection with the subcortical structures (striatum, globus pallidus, substantia nigra, and the thalamus). Neurotransmitters involved in modulations of frontosubcortical circuit are also shown. Damage or alteration of these structures or the neurochemistry will cause different emotional and executive dysfunction: - Damage to the dorsolateral PFC circuit will cause inflexibility of thought, problems solutions deficit, and deficit in regulating adaptive and goal-directed behavior. - Damage to the lateral orbital cortex and its connections will cause significant affective behaviors such as aggressiveness, hyperactivity, and labile emotions ranging from euphoria to dysphoria. - Damage to the basomedial cortex will induce cognitive impairment and mutism. Neurochemical pathology of the modulatory catecholaminergic (dopamine, serotonin, and noradrenalin) and cholinergic neurotransmitters is also known to play an important role in emotional and cognitive functions

Neurochemicals and Neuromodulators in the PFC

Concurrent with the elucidation of the connections between aspects of executive function and damaged neurophysiology, there is evidence that disorders and pathology of brain and behavior are partially a result of neurochemical imbalance of the modulatory catecholaminergic and the cholinergic neurotransmitters. This interest, in part, stems from the longstanding consensus that these neural systems play a critical role in many neuropsychiatric disorders, as well as in normal and pathologic aging [45–47]. In this review, we discuss separately the role of the important neurotransmitters involved directly in executive functions.

The Role of Dopamine in Executive Functions

The dopaminergic system of the brain is heterogeneous and multi-functional. Most dopamine (DA)-containing cells develop from a single embryological cell group that originates at the mesencephalic–diencephalic junction. The cell group

is divided into three systems with different projections. The best known is the nigrostriatal system, which originates in the zonal compact of the substantia nigra. Two others are associated with the ventral tegmental area. The boundaries between these “systems” are not well-defined [48]. At the pharmacological level, DA receptors are broadly classified into two families: the D1 like (comprising D1 and D5 subtypes) and D2 like (comprising D2, D3, and D4 subtypes) [49]. While DA receptors are found throughout the nervous system [50], they demonstrate high concentrations within the brain's limbic regions, basal ganglia, and frontal cortical areas, all of which are involved importantly in emotional and motivational regulation [51]. DA exerts its effects on PFC neural activity via multiple receptor subtypes. The DA receptors (D1, D2, D3, and D4) are localized within the PFC in different levels and distribution, although the subcellular localization of these receptors differs. Expression of D1-like receptors on principal pyramidal neurons in the PFC appears to be substantially greater than D2-like (D2 and D4) receptors [52], whereas both types of DA receptors were localized on GABAergic interneurons and may also reside on presynaptic excitatory glutamate terminals [53–56]. Expression of D3 receptors in the PFC is very low [57]. However, numerous studies showed that activation of D1, D2, or D4 receptors exert dissociable electrophysiological actions on the activity of different classes of PFC neurons [47]. Yet, despite these anatomical and neurophysiological findings, the majority of studies have focused on the role of PFC DA in functions such as working memory and on the role of D1-like receptors. Nevertheless, D1 and D2 receptors act cooperatively to mediate behavioral flexibility and a consensus of evidence highlights the position that DA acting via D1-like and D2 receptors is crucial. Because DA D1 receptors in the PFC are several times more abundant than D2 receptors [20], the relationship between D1 receptors and PFC functions has been widely investigated.

Wise [58] hypothesized that DA and PFC systems are critical for the control of thought and behavior. Additionally, the PFC is of central importance to higher cognition and plays a critical role in working memory and attentional control [59, 60], and the DA system is integrally involved with both motor control and reward/motivation [61–63]. The interaction of DA within the PFC also likely serves a specialized computational function. DA is thought to enable behavioral flexibility in these pathways by facilitating the learning and execution of adaptive behavioral responses [64]. The nonlinear interactions in the differing trajectories of these systems during development result in changing patterns of cognitive functions over time; they may also lead to paradoxical outcomes, for which enhancement of one function through dietary intervention (epigenetics) may be at the expense of another.

DA is one of a number of neuromodulators present in the PFC. The other neurotransmitters, noradrenaline and serotonin (5-hydroxytryptamine, 5-HT), and acetylcholine, are also known to play an important role in cognitive functions and are also widely distributed and participate in neurotransmission in the PFC [53, 54, 65–67]. The marked influence of these neurochemical systems on prefrontal working memory processes has been widely described.

Although the mechanisms by which DA modulates cognitive performance are still mysterious, experimental studies in both humans and animals have demonstrated a fascinating and multivariate role for DA transmission. Central DA systems have a role in processing and encoding of emotionally salient information, at the anatomical signal transduction levels of analysis [68]. In addition, a growing body of evidence also implicates central DA systems in cognitive processes dependent on integral frontostriatal connections [69]. Therefore, it appears that executive deficits in spatial working memory observed in frontal patients has a considerable degree of selectivity, but it is not simply produced by damage to the PFC. It seems likely that performance on this task is a product of interactions between cortical and subcortical structures and their neurochemical innervations, especially DA which serves to regulate performance depending on the precise task requirement and baseline levels of DA [70].

Muller et al. [71] reported that systemic administration of a mixed D1/D2 agonist facilitated working memory, whereas the selective D2 agonist had no effect, indicating that the dopaminergic modulation of working memory processes is mediated principally via D1 receptors. Also, D1 receptors are believed to have an inverted U-shaped dose/response curve for working memory whereby either too much or too little DA will result in sub-optimal performance that impairs prefrontal functions [72]. A seminal study by Brozoski et al. [73] showed a relatively selective role for prefrontal DA as distinct from other prefrontal monoamines (that is, noradrenaline and serotonin) in spatial working memory. Further work has elucidated this specific contribution of DA to working memory functions at the psychological [74–77], anatomical [78–80], cellular [81–83], and molecular (i.e., receptor) levels of analysis [81]. Thus, there is accumulation and considerable evidence for a special role for DA D1, but not D2 receptors in spatial working memory, based on evidence using iontophoresis or intracerebral drug infusion [84]. Overall there is consensus that spatial working memory function depends upon an optimal level of DA function within the PFC [77, 83, 85, 86]. Thus, whereas D4 receptor activity may act to antagonize the effects that D1 and D2 receptors exert over behavioral flexibility, the inverse correlations between D1 and D2 receptors or abnormal increases in D2 receptor activity also cause a more general impairment in behavioral flexibility. These findings suggest that

deficits in these forms of executive functioning observed in disorders linked to dysfunction of the DA system may be attributable in part to aberrant increases or decreases in mesoaccumbens DA activity.

Less is known of the role of D2 receptors in cognition, but previous studies have shown that D2 receptors in the hippocampus might play some roles via hippocampal–PFC interactions [87]. Hippocampal D2 receptor binding shows positive linear correlations not only with memory function but also with frontal lobe functions, while hippocampal D1 receptor binding had no association with any memory and prefrontal functions. Hippocampal D2 receptors seem to contribute to local hippocampal functions (long-term memory) and to modulation of brain functions outside the hippocampus (frontal lobe functions), which are mainly subserved by PFC, via the hippocampal–PFC pathway. Takahashi et al. [88] suggested that orchestration of prefrontal D1 receptors and hippocampal D2 receptors might be necessary for human executive function including working memory. Indeed, Kemppainen et al. [89] reported that a reduction of D2 receptors in the hippocampus in Alzheimer's disease patients was correlated with memory impairments. In addition, hippocampal D2 receptors appear to be involved in synaptic plasticity. It has been reported that D2 antagonist inhibited long-term potentiation in the hippocampus [90, 91], the key mechanism underlying memory consolidation [92, 93]. While this may be true, we must be clear in that long-term hippocampal-mediated memory is not the same as with working memory, a main component in executive function.

In addition, it is becoming increasingly apparent that mesocortical DA transmission contributes to other forms of executive functions regulated by the frontal lobes that are distinct from working memory processes. Furthermore, the specific DA receptor pharmacology that underlies these effects appears to be substantially different from that which mediates working memory. It seems that the collective work of the PFC make it apparent that dopaminergic input to the frontal lobes forms an essential network of the neural circuits that mediate a variety of cognitive and executive functions, including working memory, behavioral flexibility, and decision making. Each of these executive functions engages distinct types of cognitive operations and functional neural circuits.

The anatomical distribution of dopaminergic projections strongly implicates DA in higher-level cognitive abilities, specifically in PFC functions [85, 94]. There is an anterior–posterior gradient in brain DA concentration, which is the highest in the PFC [67]. Thus, the distribution of the mesocortical dopaminergic fibers suggests a greater influence on anterior brain structures.

Several lines of pharmacological evidence confirm the role of DA in PFC function. First, in monkeys, depletion of

DA in PFC or pharmacological blockade of DA receptors impaired working memory tasks. This working memory impairment was as severe as the deficit in monkeys with PFC lesions and was not observed in monkeys when serotonin or norepinephrine was depleted [81].

Serotonin

The serotonin (5-HT) 2 family of receptors has three receptors (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), which are similar in terms of their molecular structure, pharmacology, and signal transduction effects [95–97]. However, 5-HT_{2B} and 5-HT_{2C} receptors are less important and not as widely expressed as the 5-HT_{2A} receptors. Serotonin (5-HT) 2A receptors are widely distributed in different regions in cortical and subcortical areas, with high levels in the frontal cortex, suggesting a particularly important role in PFC function [96, 97].

Postsynaptic activation may increase activity in pyramidal glutamatergic neurons and mediate various executive functions. More specifically, reciprocal cortical-raphé pathways may allow the ventral PFC to inhibit stress-induced neural activity in the brainstem when stressors are perceived as controllable. However, early adversity and negative attitudes may be associated with higher frontal 5-HT_{2A} receptor levels and greater risk for stress-induced psychopathology, and certain 5-HT_{2A} gene variants have been associated with increased risk for impulsive behavior.

5-HT_{2A} receptors are ideally located to play a role in reciprocal cortical-raphé pathways [98] which, in turn, help regulate the stress response based on assessments about stressor controllability [99]. Particular gene variants, early adversity, and negative attitudes may be associated with higher frontal 5-HT_{2A} receptor levels and greater risk for stress-induced psychopathology.

Manipulations of Cholinergic, Serotonergic, and Noradrenergic Systems

Other neurotransmitters also play a role in the PFC and executive functioning [66]. One of the important direct strategies that may explain the role of cholinergic, serotonergic, and noradrenergic (NA) systems on fronto-executive processing is by observations following manipulations of these systems. Indeed, manipulating the cholinergic system demonstrates its strength in predicting patterns of attentional dysfunction, and direct manipulations of 5-HT levels have only been explored using dietary tryptophan depletion which has little effect on tasks that require the integrity of the dorsolateral PFC [100] but does impair visual discrimination reversal [100–102]. There is increasing evidence suggesting that abnormalities in serotonergic innervations of the frontal cortex may contribute to decision-making deficit [100, 103].

This further supports the general hypothesis that decreased 5-HT function increases impulsivity [104].

These effects of neurochemical manipulations in the PFC provide some insight into the nature of the functional interactions between these neurochemical systems. It now seems likely that the central 5-HT system and its interactions with acetylcholine probably mediate reward-related information processing, and this has implications for a number of neuropsychiatric disorders [105–107].

There is burgeoning evidence that the NA system, specifically the coeruleus–cortical NA projections to diverse forebrain sites, including the neocortical mantle and the hippocampus, is implicated in attentional set shifting. There is already substantial evidence that manipulations of the NA system effect working memory functions in nonhuman primates in a way perhaps similar to the effects of DA neuro-modulation [108, 109]. NA has been shown to be a key neurotransmitter for working memory in human in study carried out by Chamberlain et al. [110]. Similarly to DA, an optimal level of NA appears critical for working memory. Parallel investigations have also suggested a role for central, particularly prefrontal, NA in attentional functioning based on electrophysiological studies in monkeys [111] and studies in rats of the effects of profound cortical depletion of NA [112–114].

Additional Neural Circuitry Involved in Executive and Cognitive Functions

Aspects of cognition are integral components of executive functions. They require neural processes necessary to support the flexible use of information in the execution of adaptive and goal-directed behavior. Of the many different processes involved, learning and memory are two essential components. However, in addition to learning and memory, the ability to enable adaptive behavioral responses also depends on the capacity to focus and sustain attention on the relevant stimuli and to hold this information in working memory while choosing and executing the appropriate motor response. It also involves more complex information processing functions, such as the ability to abstract information and to establish a system of rules for responding appropriately in different contexts and to suppress other competing behavioral responses.

Cognition is not a solitary function but rather contingent on the efficacy of multiple and divisible central nervous system networks. The neural circuits that have been implicated most prominently in mediating executive functions, the information processing, and decision-making processes of the human brain comprise reciprocal cortical–subcortical connections. These circuits originate in the PFC and project to various subcortical structures such as the ventral and

dorsal striatum (nucleus accumbens and basal ganglia [115], respectively). They then go back by way of the thalamus to the region of the frontal cortex from which they originated [116]. The subcortical centers can have an important impact on behavior, but their effect will depend on command processes at higher centers, governed by both feedback (phasic arousal/reinforcement) and synaptic action at higher levels [117]. Synaptic action depends on cortical receptor levels, which degrades when it is either over-aroused or under-aroused [118]. Therefore, a reciprocal relationship exists between the higher cortical centers and the lower subcortical centers. In fact, cortical activities regulate subcortical activities through executive modulation of prepotent assessments and emotional responses. Subcortical systems alternatively regulate the cortex by tuning its activities to the demands or opportunities provided by the environment. Cortical controls buy us time, as needed for planning and intelligent action. Subcortical controls provide energy, focus, and direction, as needed for relevant emotion-guided behavior [119, 120].

It is becoming increasingly apparent that cortical–subcortical pathways operate with dexterity and in harmony. They do not operate autonomously and randomly, and they are subject to the influence of input from many other areas of the brain. For example, in addition to the PFC, vital sources of input to the nucleus accumbens are the hippocampus and amygdala [121]. The functional relationship between these structures is fundamental to both behavioral and physiologic regulation, and this understanding has served to challenge the traditional distinction made between the cognitive and affective contributions to decision making [122]. The hippocampus is necessary for the formation of long-term memories and contributes to higher-level decision-making processes by representing the relations between discrete stimuli, thereby providing information relating to the overall context [123]. The amygdala is involved in processing the emotion (i.e., affective) valence of sensory stimuli and relaying this information to the PFC as well as the instigation of the synchronized pattern of physiologic and behavioral changes that constitute the stress response to real or perceived dangers [124]. This includes the release of glucocorticoid hormones, where appropriate concentrations of glucocorticoids are necessary for mnemonic functions to be accomplished effectively [125]. The hippocampus in turn, together with the PFC, is involved in the feedback regulation of these glucocorticoid concentrations [126]. These processes are part of the executive functions that are engaged during the activity of decision making—which is just the ability to choose between the available options. It is also through our executive functions that we can appreciate cause and effect and thus anticipate the possible outcomes of our actions. The PFC generates possible behavioral alternatives in response to the specific nature and emotional valence of sensory stimuli. This information is then relayed to the

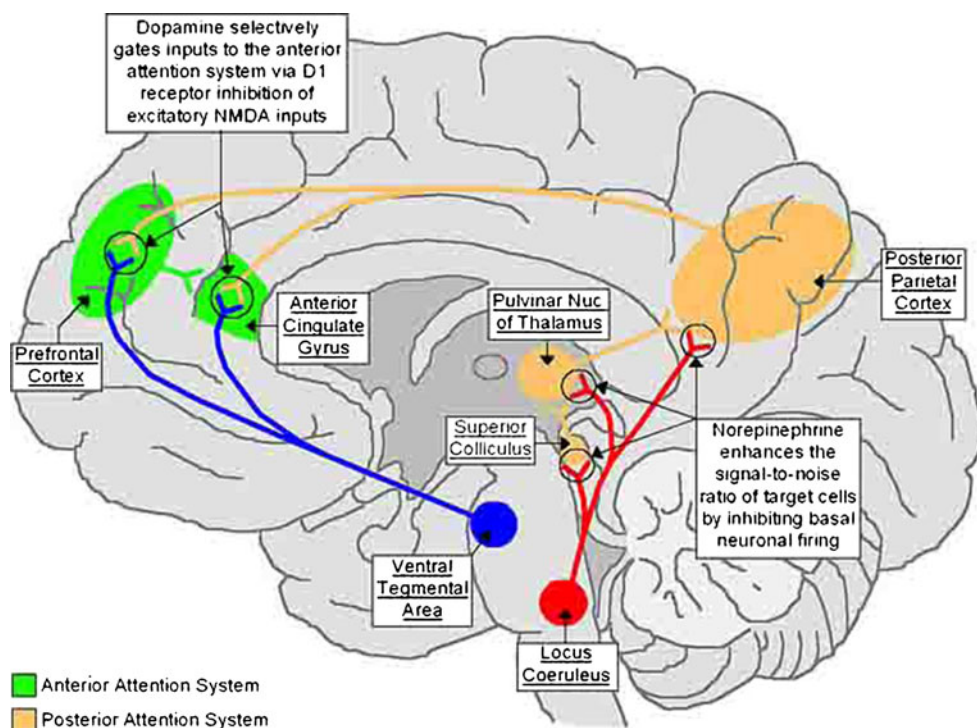
nucleus accumbens, where input from the hippocampus is thought to “gate” neural activity in such a way that the motor response chosen is that most appropriate to the overall context [127]. In this way, the circuitry involving the hippocampus, PFC, and nucleus accumbens plays a key role in enabling behavioral flexibility [128]. This is in contrast to the trajectory that includes the basal ganglia (dorsal striatum), which has been associated with the learning and implementation of the sequences of motor output that constitute habitual learned behavioral response patterns [128, 129]. It is thought that the system involved to support behavior and which of these systems is engaged depends on the nature of the circumstances; that is, it depends on the integration of these systems with other systems that can access the organism’s goal in the context of the task at hand as well as the organism’s past victories and failures in reaching such goals [130]. Under routine and familiar conditions, customary responses may be the most effective, but any unexpected change will necessitate a switch either from one set of learned responses to another or to an entirely new set of behaviors based on a novel combination of internal representations gained from previous experience.

The modulation of states that allow the organism to be receptive to stimulation (e.g., alertness or arousal) is likely mediated by several ascending pathways, which are generally identified by their neurotransmitters: the dopaminergic pathways that originate in the midbrain; the cholinergic, serotonergic, and adrenergic pathways that originate in the brainstem; and the cholinergic pathways that originate in the basal forebrain [110, 131, 132]. Although the specific functions in which these subsystems are involved are not yet fully understood, these pathways have widespread cortical targets, and substantial evidence suggests that their input can also be modulated by feedback from cortical sites (see Fig. 2).

Can We Modulate Executive Functions Through Epigenetics?

Neuronal plasticity (e.g., neurogenesis, synaptogenesis, cortical re-organization) refers to neuron-level changes that can be stimulated by experience. Cognitive plasticity (e.g., increased dependence on executive function) refers to adaptive changes in patterns of cognition related to brain activity. Mechanisms of neural plasticity underpin cognitive plasticity, and in turn, neural plasticity is stimulated by cognitive plasticity. Greenwood and Parasuraman [133] have suggested that neural plasticity is stimulated by learning and novelty, and the plasticity is enhanced by dietary manipulations (low-fat, dietary restriction) and aerobic exercise. Moreover, studies supporting the use of environmental manipulations, compensatory strategy training, and techniques to improve underlying

Fig. 2 This schematic illustrates the neuroanatomy of the mesolimbic system highlighting specific neurotransmitters such as dopamine and norepinephrine and receptor interactions



skills, including attention and prospective memory, have been reviewed by Mateer [134].

The availability of certain neurotransmitters can be influenced by dietary supply of their amino acid precursor. For example, tryptophan is the dietary precursor of serotonin and tyrosine is that of DA and norepinephrine [135]. Many of these neurotransmitters serve a dual role, functioning also as growth factors that influence the intricate choreography of growth of neural systems in the developing brain [136, 137]. Thus, one of the mechanisms whereby changes in the availability of nutrient supply may result in disturbances of specific brain and behavioral functions during development is through their selective effect on some of these systems and not others. This emerging understanding has important implications for the design and interpretation of studies on the cognitive effects of specific nutrients during development [138].

Reward-Related Genes and Executive Functions

Bertolino et al. [139] demonstrated that a functional SNP (rs1076560) within the dopamine D2 receptor gene (DRD2) predicts striatal binding of the two radiotracers to DA transporters and D2 receptors as well as the correlation between striatal D2 signaling with PFC activity during performance of a working memory task. These data are consistent with the possibility that the balance of excitatory/inhibitory modulation of striatal neurons may also affect striatal outputs in relationship with prefrontal activity during working memory

performance within the cortico-striatal-thalamic-cortical pathway. Furthermore, Markett et al. [140] found a significant interaction between nicotinic acetylcholine receptor (rs#1044396) and a haplotype block covering all three dopaminergic polymorphisms (rs#1800497, rs#6277, rs#2283265) on working memory capacity. This effect only became apparent on higher levels of working memory load. This is the first evidence from a molecular genetics perspective that these two neurotransmitter systems interact on cognitive functioning. Frank and Hutchison [141] found that effects of the commonly studied Taq1A polymorphism on reinforcement-based decisions were due to indirect association with C957T of the dopamine receptor gene.

It is noteworthy that overexpression of D2 under pathological conditions such as schizophrenia and Parkinson's disease could give rise to motivational and timing deficits [142]. The increase in DA D2 receptors has been shown by others to prevent storage of lasting memory traces in PFC networks and impair executive functions [143].

Interestingly, Stelzel et al. [144] showed that catechol-*O*-methyltransferase (COMT) Val (158)Met polymorphism effects on working memory performance are modulated by the DRD2/ANKK1-TAQ-Ia polymorphism. Val- participants—characterized by increased prefrontal DA concentrations—outperformed Val+ participants in the manipulation of working memory contents, but only when D2 receptor density could be considered to be high. Stelzel et al. [144] suggested that this beneficial effect of a balance between prefrontal DA availability and D2 receptor density reveals the importance of considering epistasis effects and different

working memory subprocesses in genetic association studies. However, these genetic effects may not be present or are too subtle to detect in healthy subjects [145]. Moreover, it has also recently been found that participants with Val/Val of the COMT gene involved in a 17-week running exercise program improved cognitive performance to a greater extent compared to individuals carrying a Met allele. From the present results, it is concluded that an increase in physical fitness provides a means to improve cognitive functioning via dopaminergic modulation [146]. In a related study of HIV and methamphetamine dependence, dopaminergic overactivity in PFC conferred by the Met/Met genotype appeared to result in a liability for executive dysfunction and potentially associated risky sexual behavior due to poor judgment [147].

To reiterate, the dopaminergic system of the brain is heterogeneous and multi-functional. It is a system with many important neurochemical functions and has been credited with resultant behavioral effects such as “pleasure,” “stress reduction,” and “wanting” [148–151]. In addition to its contributory role in addressing higher-order cognition and executive functions, it is very important in relapse of substance seeking behavior [152]. It is well-known that acute alcohol intoxication significantly impairs executive functioning and judgment. Most recently, Lyvers and Tobias-Webb [153] found a dose-dependent selective disruption of PFC functioning by alcohol. They suggested that alcohol-associated perseveration on the Wisconsin Card Sorting Test may reflect the inhibitory effect of alcohol preventing DA release in the PFC.

Finally, being somewhat complex, abnormal increases in D(2) receptor activity cause a more general impairment in behavioral flexibility especially in patients with attention deficit hyperactivity disorder [154]. These findings suggest that deficits in these forms of executive functioning observed in disorders linked to dysfunction of the DA system may be attributable in part to aberrant increases or decreases in mesoaccumbens DA activity [155–160]. The control of DA release in PFC and other brain regions is regulated by many neurotransmitters and second messenger genes and constitute a genetic map that could provide important information relating to a predisposition to poor judgment.

Development of a Genetic Map to Identify Individuals at Risk for Impaired Judgment

Executive dysfunctions are linked to flawed DA metabolism and especially to low D2 receptor density, as well as other neurotransmitter deficits due to specific gene polymorphisms. Moreover, executive dysfunctions result from abnormalities in the mesolimbic system of the brain, which directly links abnormal craving behavior with a defect in the DRD2 gene, as well as other dopaminergic genes (D1, D3,

D4, and D5, DATA1, MAO, COMT), including many genes associated with the brain reward function [161] as listed in Table 1.

The genesis of all behavior, be it “normal” (socially acceptable) or “abnormal” (socially unacceptable), derives from an individual’s genetic makeup at birth. This genetic predisposition, due to multiple gene combinations and polymorphisms, is expressed differently based on numerous environmental factors including family, friends, educational and socioeconomic status, environmental contaminant exposure, and the availability of psychoactive drugs and unhealthy foods. The core of predisposition to these behaviors is a set of genes interacting with the environment, which promote a feeling of well-being via neurotransmitter interaction at the “reward center” of the brain (located in the mesolimbic system) leading to normal DA release [162].

Subjects afflicted with executive decision making dysfunction carry polymorphic genes in dopaminergic pathways that result in hypodopaminergic function caused by a reduced number of dopamine D2 receptors, reduced synthesis of DA (by DA beta-hydroxylase), reduced net release of pre-synaptic DA (from e.g., the DA D1 receptor), increased synaptic clearance due to a high number of DA transporter sites (DA transporter), and low D2 receptor densities (DA D2 receptor), making such people more vulnerable to addictive behaviors and relapse because of poor judgment [163].

The inability to make good decisions involves shared genes and their mRNA expressions and behavioral tendencies, including dependence on alcohol, psychostimulants, marijuana, nicotine (smoking), and opiates, altered opiate receptor function, carbohydrate issues (e.g., sugar-binging), obesity, pathological gambling, premeditated aggression, stress, pathological aggression, and certain personality disorders, including novelty seeking and sex addiction. The common theme across all of these substances and behaviors is that they induce pre-synaptic DA release [164]. Spectrum disorders such as ADHD, Tourettes syndrome, and autism also are included due to DA dysregulation. Other rare mutations [165] have been associated with Tourettes and autism. One example includes the association with neuroligin 4, a member of a cell adhesion protein family that appears to play a role in the maturation and function of neuronal synapses [166] that could have an impact on executive functions. The roles of many of these reward genes and associated polymorphisms have been reviewed in a recent paper by Blum et al. [167].

Limitations and Future Directions

We have suggested that examination of multifactorial interactions of an individual’s genetic history, along with

Table 1 Reward pathways and candidate genes involved in executive function physiology

Signal transduction	Serotonin	GABA	Dopamine	Cannabinoid	Glycine	Cholinergic	Opioid	NDMA	Adrenergic	Stress	Drug metabolizing	Others
ADCY7	HTR1A	GABRA2	COMT	CNR1	GLRA1	CHRM1	OPRM1	GRIK1	ADRA1A	CRH	ALDH1	BDNF
AVPR1A	HTR1B	GABRA3	DDC	FAAH	GLRA2	CHRM2	OPRK1	GRIN1	ADRA2B	CRHEP	ALDH2	CART
AVPR1B	HTR2A	GABRA4	DRD1		GLRB	CHRM3	PDYN	GRIN2A	ADRB2	CRHR1	CAT	CCK
CDK5R1	HTR2C	GABRA6	DRD2		GPHN	CHRM5	PMOC	GRIN2B	SLC6A2	CRHR2	CYPZE1	CCKAR
CREB1	HTR3A	GABRB1	DRD3			CHRNA4	PRD1	GRIN2C	DRA2A	GAL	ADH1A	CLOCK
CSNKLE	HTR3B	GABRB2	DRD4			CHRNB2	OPRL1	GRM1	DRA2C	NPY	ADH1B	HCRT
FEV	MAOA	GABRB3	DRD5				PENK		ARRB2	NPY1R	ADH1C	LEP
FDS	MAOB	GABRD	SLC18A2				PNOC		DBH	NPY2R	ADH4	NR3C1
FOSL1	SLC64A	GABRE	SLC6A3							NPY5R	ADH5	SLC29A1
FOSL2	TPH1	GABRG2	TH								ADH6	TAC
GSK3B	TPH2	GABRG3									ADH6	
JUN		GABRQ									ADH7	
MAPK1		SLC6A7										
MAPK3		SL6A11										
MAPK14		SLC32A1										
MPD2		GADI										
MGFB		GAD2										
NTRK2		DB1										
NTSR1												
NTSR2												
PPP1R1B												
PRKCE												

Source: modified from Blum et al. [168]

environmental risk factors, can assist in the characterization of executive functioning for that individual. We also have proposed that genetic studies may provide genetic mapping as a probable diagnostic tool serving as a therapeutic adjunct for augmenting executive functioning capabilities. However, considerable additional research is required prior to any definitive interpretation. Thus, we encourage other investigators to extend this work by analyzing families with histories of executive dysfunction for determining genotypes. This especially should include examination of a variety of reward genes. Certainly studies involving larger populations even in a few families over many generations (if possible) would strengthen this potentially important concept.

Conclusions

The differential modulation of fronto-executive function by discrete neurochemical systems highlights a degree of specificity for these “nonspecific” neuromodulatory pathways, which hitherto have been underestimated. These systems interact not only within the PFC at the level of single pyramidal neurons but also at the level of functional modules in order to optimize overall executive control. Preservation of the neurological underpinnings of executive functions requires integrity of entire neural systems as well as specific genes and associated polymorphisms. Genetic mapping may serve as a probable diagnostic tool and a therapeutic target for eventual augmentation of executive functioning capabilities.

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