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Frontal–subcortical neuronal circuits and clinical neuropsychiatry An update

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Abstract

Frontal–subcortical circuits form the principal network, which mediate motor activity and behavior in humans. Five parallel frontal–subcortical circuits link the specific areas of the frontal cortex to the striatum, basal ganglia and thalamus. These frontal–subcortical circuits originate from the supplementary motor area, frontal eye field, dorsolateral prefrontal region, lateral orbitofrontal region and anterior cingulate portion of the frontal cortex. The open afferent and efferent connections to the frontal–subcortical circuits mediate coordination between functionally similar areas of the brain. Specific chemoarchitecture and multiple neurotransmitter interactions modulate the functional activity of each circuit. Dorsolateral prefrontal circuit lesions cause executive dysfunction, orbitofrontal circuit lesions lead to personality changes characterized by disinhibition and anterior cingulate circuit lesions present with apathy. The neurobiological correlates of neuropsychiatric disorders including depression, obsessive–compulsive disorder, schizophrenia and substance abuse, imply involvement of frontal–subcortical circuits.

Keywords: Behavior; Cingulate; Dorsolateral prefrontal cortex; Frontal–subcortical circuits; Orbitofrontal cortex

Frontal–subcortical circuits and neuropsychiatric disorders

The frontal lobes have an important role in human behavior. Dysfunction of orbitofrontal, medial and dorsolateral prefrontal is associated with a variety of neuropsychiatric syndromes. However, similar neuropsychiatric symptoms may arise with lesions in subcortical brain structures. The pathophysiological basis for this shared phenomenology remained unexplained until anatomic investigations provided a framework for the cognitive architecture of the brain. A series of parallel frontal–subcortical circuits that link specific regions of the frontal cortex to the striatum, globus pallidus and thalamus have been defined [1]. These frontal–subcortical circuits aid in understanding the similarity of behavioral changes in frontal cortical and subcortical disorders.

There are five defined frontal–subcortical circuits. They are named according to their function or site of origin in the cortex. The motor circuit originating in the supplementary motor area and the oculomotor circuit originating in the frontal eye fields are involved in motor functions. The dorsolateral prefrontal, orbital frontal and anterior cingulate circuits are dedicated to executive functions, social behavior and motivational states in humans.

In this review, we summarize the anatomy of each circuit including direct and indirect pathways and the main connections to and from other brain regions. Then we describe the neurotransmitters involved and the neurochemical aspects of the circuits. Finally, we discuss the behavioral and cognitive changes specific to each circuit and the relevance of the frontal–subcortical circuits to various neuropsychiatric disorders. The three frontal–subcortical circuits primarily involved in behavioral and cognitive changes are emphasized.

Anatomy of frontal–subcortical circuits

The five frontal subcortical circuits share some common features [1]. The main anatomical structures are the same for all circuits. They originate in prefrontal cortex, project to the striatum (caudate, putamen, ventral striatum), connect to the

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globus pallidus and substantia nigra and from there connect to the thalamus. There is a final link back to the frontal cortex each circuit forms a closed loop. There are as well projections to and from other cortical and subcortical structures related to each circuit. They comprise "open loop" connections (Fig. 1).

The anatomical positions of the circuit structures remain segregated as they pass through the caudate and putamen, globus pallidus, substantia nigra and thalamus. The dorsolateral frontal cortex projects to the dorsolateral part of the caudate nucleus, the orbitofrontal part projects to the ventral striatal areas and the anterior cingulate cortex projects to the medial striatal/nucleus accumbens region [2]. The projections from each level are progressively connected to smaller areas as they proceed from cortex to subcortical structures, but each circuit is preserved as a largely discrete anatomical structure, consistent with their functional segregation [3].

There are two pathways within each circuit: a direct pathway connecting the striatum and the globus pallidus interna/substantia nigra complex, and an indirect pathway linking striatum to globus pallidus externa, then to subthalamic nucleus and back to globus pallidus interna/substantia nigra [4]. Both direct and indirect circuits modulate input to the thalamus. Direct and indirect pathways modulate circuit activities in response to different inputs. Dysfunction in the direct circuit causes abnormal thalamic inhibition, whereas indirect circuit dysfunction leads to disinhibition and thalamic overactivity. Each set of circuits is present in each hemisphere.

The *motor circuit* originates from neurons in the supplementary motor area, premotor cortex, motor cortex and somatosensory cortex. These areas project to the putamen in a topographical pattern. The putamen in turn projects to specific portions of the globus pallidus externa, interna and substantia nigra pars reticularis. The globus pallidus connects

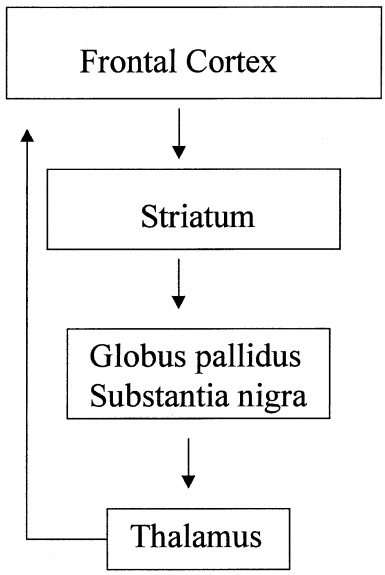

Fig. 1. General structure of frontal subcortical circuits.

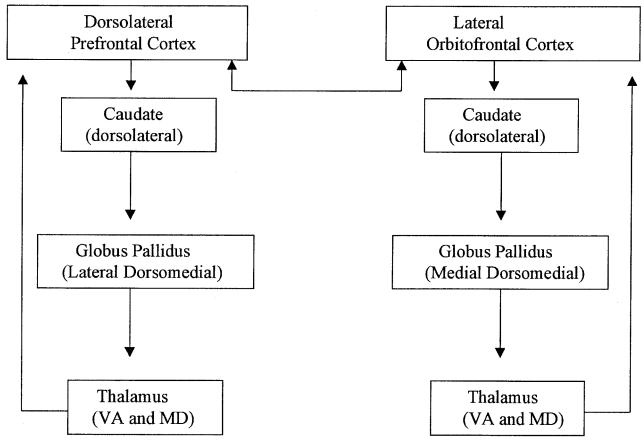

Fig. 2. The anatomy (direct pathways) of dorsolateral prefrontal and lateralorbitofrontal subcortical circuits. VA= ventral anterior; MD = mediodorsal.

to the ventrolateral, ventral anterior and centromedian nuclei of the thalamus which projects back to the motor cortex [2].

The *oculomotor circuit* originates in the frontal eye field (Broadmann's area 8) and posterior parietal cortex. The fibers then project to the body of the caudate nucleus, dorsomedial globus pallidus and ventrolateral substantia nigra. They reach the mediodorsal thalamic nuclei and close the loop by projecting back to the frontal eye field.

The *dorsolateral prefrontal circuit* originates in Broadmann's areas 9 and 10 on the lateral surface of the anterior frontal lobe and projects to the dorsolateral head of the caudate nucleus. Neurons from this site project to the lateral part of the mediodorsal globus pallidus interna and rostrolateral substantia nigra pars reticulata as the direct pathway. The fibers from the basal ganglia project to parvocellular portions of the ventral anterior and mediodorsal thalamus. The mediodorsal thalamus sends fibers back to the circuit origin in the dorsolateral frontal cortex (Fig. 2).

The *lateral orbitofrontal circuit* originates in Broadmann's areas 10 and 11 and sends fibers to the ventromedial caudate nucleus. Neurons form this region of the caudate project to the medial part of the mediodorsal globus pallidus interna and to the rostromedial substantia nigra pars reticulata. Fibers from substantia nigra and globus pallidus connect to the ventral anterior and mediodorsal thalamus. The circuit then is closed by fibers projecting back to the orbitofrontal cortex from thalamus. A *medial divison of the orbitofrontal circuit* has also been described. It originates in the gyrus rectus and the medial orbital gyrus of Broadmann's area 11 [5]. The projections go to medial aspects of the accumbens, to medial ventral pallidum and reach the mediodorsal thalamic nucleus.

The *anterior cingulate circuit* originates in the anterior cingulate cortex (Broadmann's area 24). The neurons project to ventral striatum, which includes the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle. This area is known as the "limbic striatum." Projections from

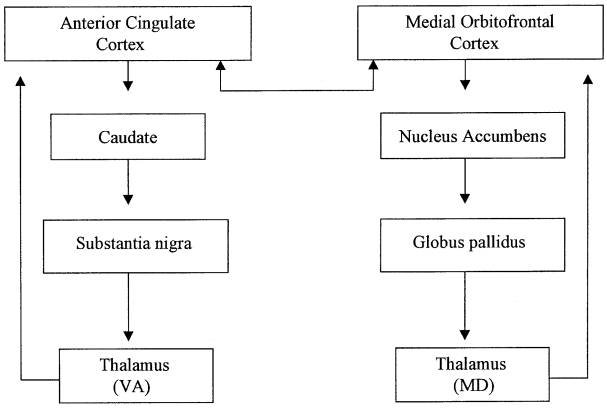

Fig. 3. The anatomy (direct pathways) of medial orbitofrontal and anterior cingulate circuits. VA = ventral anterior; MD = mediodorsal.

the ventral striatum pass to the rostromedial globus pallidus interna, ventral pallidum and rostrodorsal substantia nigra. The ventral pallidum connects to the ventral anterior nucleus of the thalamus. The anterior cingulate circuit is closed with projections from ventral anterior thalamus back to the anterior cingulate cortex. Limbic system connections involve both the anterior cingulate and medial frontal regions (Fig. 3).

Open connections of frontal–subcortical circuits

In addition to these closed frontal–subcortical loops, there are open connections of the circuits that integrate information from anatomically distant but functionally related brain areas. The open afferent and efferent connections mediate coordination between functionally similar areas of the brain and the frontal–subcortical circuits. The major open afferent and efferent connections of the three frontal–subcortical circuits are listed in Table 1.

Major cortical afferents to the dordolateral frontal–subcortical circuit are Broadman area 46 and parietal area 7a [6]. They are also strongly interconnected with each other. Area 7a has a role in visual processing including attention to specific stimuli, visually guided reaching and planning visuospatial strategies. There are also minor afferents to limbic structures. Main efferents of dorsolateral prefrontal circuit are to Broadmann areas 46 and 8, which comprise the frontal eye fields.

The orbitofrontal subcortical circuit receives open afferents from the superior temporal cortex, substantia nigra, dorsal raphe and midbrain tegmentum. There are heteromodal sensory and paralimbic divisions of the afferent connections. The heteromodal sensory division enters the orbitofrontal circuit at the level of caudate nucleus. Here, the information from different sensory modalities (auditory, visual or gustatory) is integrated with the lateral orbitofrontal circuit efferents. These projections are primarily from the superior temporal pole and the insula. The medial orbitofrontal circuit receives afferents mainly from the limbic and paralimbic areas at the level of ventral striatum. The only major prefrontal projection to the entorhinal cortex is from the paralimbic division of orbitofrontal circuit. Among all three circuits, the medial part of the orbitofrontal circuit also has the strongest association with amygdala. The amygdala sends efferents to the brainstem and hypothalamus, allowing the medial orbitofrontal circuit to participate in modulation of endocrine, autonomic and involuntary behavioral responses. The efferent connections of orbitofrontal circuit are to the lateral hypothalamus and the septal region.

The anterior cingulate circuit receives major afferents from the perirhinal area and hippocampus and sends efferents to substantia nigra, lateral hypothalamus and subthalamic nucleus. While the orbitofrontal cortex mediates information concerning the internal environment, the anterior cingulate circuit facilitates the intentional selection of environmental stimuli based on their internal relevance.

Neurochemistry of frontal–subcortical circuits

Neurochemical structure

The fibers in each circuit, originating from the frontal lobe are mediated by excitatory glutaminergic neurotransmission. They project to striatum, which is formed of caudate, putamen and ventral striatum. The connections from striatum to globus pallidus interna–substantia nigra complex as the direct pathway, and to globus pallidus externa as the indirect pathway, are both inhibitory and are mediated by γ-aminobutyric acid (GABA). In the indirect pathway, globus pallidus externa projects inhibitory GABA fibers to the subthalamic nucleus which then connects to globus pallidus interna–substantia nigra complex via excitatory glutaminergic fibers. The globus pallidus interna–substantia nigra complex then projects to thalamus through inhibitory GABA fibers. The final connections from thalamus to the frontal lobe are glutaminergic and excitatory [7].

Table 1
Open afferent and efferent connections of three frontal-subcortical circuits

	Dorsolateral circuit	Orbitofrontal circuit	Anterior cingulate circuit
Major open afferents	Dorsofrontal area 46	Superior temporal area 22	Hippocampus
	Parietal area 7a	Orbitofrontal area 12	Entorhinal area 28
Major open efferents	Dorsofrontal area 46	Orbitofrontal area 12	Substantia nigra pars compacta
	Anterior frontal area 8	Mediofrontal area 25 and 32	Medial subthalamic nucleus
			Lateral hypothalamus

The dorsal striatum has two separate cytochemical structures [8]. These are striosomes and matrix. They differ in their ontology, chemistry and connections with other brain sites. Striosomal cells mature earlier, have lower concentrations of dopamine (DA), serotonin and acetylcholine and higher concentrations of limbic-associated membrane protein. Striosomes receive inputs from the orbitofrontal and temporal cortex as well as insula. They have high levels of D1 receptors with dopaminergic projections from the ventral substantia nigra pars compacta. On the contrary, the matrix component is rich in D2 receptors, cholinergic markers and enkephalin. The dopaminergic input arises from the dorsal substantia nigra pars compacta. The matrix receives inputs primarily from the sensorimotor cortex, parieto-temporo-occcipital association cortex and the cingulate gyrus. The matrix stains selectively for adenylate cyclase, whereas striosomes have high concentration of phosphoinositol. GABAergic output of matrix is mainly to globus pallidus interna, externa and substantia nigra as opposed to striosomes, which have GABAergic output to the medial portion of substantia nigra dedicated to the orbitofrontal circuit. Disease processes may affect the striosomes and the matrix neurons differentially. The chemical distinction between the two compartments of the striatum allows the same transmitters to have different effects on each system.

Modulatory neurotransmitters

In the frontal–subcortical circuits, the corticostriatal information processing is modulated by different neurotransmitter systems.

Dopaminergic neurons from the substantia nigra project to the striatum and effect all frontal–subcortical functions. The inhibitory and excitatory effects of DA are dependent on the type of receptors with which it interacts postsynaptically. Five different (D1–D5) DA receptors are defined. The substantia nigra has inhibitory connections with the indirect pathways of the frontal–subcortical circuits via D1 receptors and excitatory connections with the direct circuits via D2 receptors. There are nigral connections with the limbic circuits, which are rich in D3 and D4 receptor subtypes. This allows the interaction between the emotional input and motor activity, cognition and motivation. This anatomical structure forms the basis for multiple actions of dopaminergic agents including effects on motor activity, motivation, thought and behavior [2].

The cholinergic interneurons are located in the striatum and modulate the thalamic activation of the cortex. Pedunculopontine and lateral tegmentum are the principal areas, which send cholinergic input to the thalamus. The cortical areas receive their cholinergic input mainly from the nucleus basalis of Meynert [9,10].

There are interactions between the cholinergic and dopaminergic systems. Acetylcholine enhances striatal DA release via nicotinic and muscarinic receptors located on the presynaptic DA terminals. D2 DA receptors are located on cholinergic interneurons and inhibit acetylcholine release, whereas D1 receptor agonists enhance acetylcholine release [11].

Serotonin receptors are distributed at different levels of the frontal–subcortical circuits. The 5-HT1 receptor is the most abundant in the basal ganglia. 5-HT3 receptors are located mostly in the ventral striatum, hippocampus, septal area and amygdala contributing to the modulation of mesocortical and mesolimbic dopaminergic pathways. Interactions between dopaminergic and serotonergic systems may provide a basis for effects of serotonergic antagonists in diseases with excess DA, like schizophrenia.

Glutamate acts primarily through effects on NMDA receptors. Corticostriatal and thalamocortical projections are glutamatergic. Glutamate stimulates striatal DA release. NMDA receptor blockade decreases basal cholinergic release. The interactions between glutamate, DA and acetylcholine serve as a corticostriatal–thalamocortical negative feedback loop to limit cortical overstimulation.

GABA is the predominant neurotransmitter in the basal ganglia. The direct pathway consists of inhibitory GABA striatal fibers extending to the internal segment of globus pallidum and substantia nigra. Cortical stimulation of striatum inhibits globus pallidus and reduces the effect of inhibitory GABAergic projections to the thalamus. This reduces the thalamic inhibition and enhances the thalamocortical excitation.

Frontal–subcortical circuit syndromes

Frontal–subcortical circuit syndromes may be observed due to different etiologies. Some of the diseases that may lead to frontal–subcortical circuit dysfunction are summarized in Table 2.

Dorsolateral prefrontal syndrome

The dorsolateral prefrontal circuit is involved mainly in executive function. It includes abilities to solve complex problems like learning new information, planning ahead, activating remote memories, regulating actions according to the environmental stimuli, shifting behavioral sets appropriately, generating motor programs and temporal ordering of recent events [12]. Patients with dorsolateral prefrontal circuit dysfunction are usually concrete and perseverative and show impaired reasoning and mental flexibility. With an inability to maintain and redirect their attention, they are easily distracted during neuropsychological testing. Without constant direction from the examiner, they may exhibit disorganized behavior. They typically have decreased performance in the Wisconsin Card Sorting Test, which requires set shifting and maintenance, strategy generation and organization of behavior. Performances on verbal and design fluency (generating words and drawing novel

Table 2
Etiologies that cause frontal-subcortical circuit dysfunction at cortical and subcortical levels

Diseases	Cortical level	Subcortical level
Neurodegenerative		
Alzheimer's disease	+	–
Corticobasal degeneration	+	+
Frontotemporal dementia	+	–
Huntington's disease	–	+
Parkinson's disease	–	+
Progressive supranuclear palsy	–	+
Multiple system atrophy	+	+
Vascular		
Binswanger disease	–	+
Stroke	+	+
Vascular dementia	+	+
Psychiatric		
Schizophrenia	+	+
Obsessive compulsive disorder	–	+
Depression	+	+
Gilles de la Tourette's syndrome	–	+
Infectious/immunologic		
Creutzfeldt Jakob disease	+	+
HIV dementia	+	+
Multiple sclerosis	–	+
Sydenham's chorea	–	+
Others		
Epilepsy	+	–
Head trauma	+	+
Tumors	+	+
Carbon monoxide toxicity	–	+

designs) and alternating and reciprocal sequences (e.g., on Luria serial hand sequences) are also poor. The executive cognitive dysfunctions associated with lesions of the dorsolateral prefrontal circuit are listed in Table 3.

Executive dysfunction is one of the principal components of subcortical dementia. Patients with subcortical dementia are characterized by slowed information processing, mood and personality changes, retrieval type memory deficits and motor abnormalities like dysarthria and gait disturbance. Similarly, lesions in the dorsolateral prefrontal cortex and caudate nucleus lead to poor recall with preserved recognition abilities. Patients with Huntington's disease and Parkinson's disease, who have dysfunction of dorsolateral prefrontal circuit at the level of basal ganglia, show executive dysfunction correlating with their retrieval type memory loss. When subcortical lesions involve the thalamus, both recall and recognition are impaired producing an amnestic syndrome. The thalamus is the common structure involved in the temporal-limbic circuit as well as the frontal–subcortical circuits which mediate memory storage and memory search functions, respectively. Therefore, lesions in the thalamus combine the amnesia characteristic of limbic disorders with characteristics of subcortical dementia and frontal-subcortical circuit dysfunction.

Orbitofrontal syndrome

The orbitofrontal circuit connects the frontal monitoring systems to the limbic system. Dysfunction of the circuit is characterized by personality change including behavioral disinhibition and emotional lability. Patients are irritable and may experience explosive aggressive outbursts. They respond inappropriately to social clues and lack interpersonal sensitivity. Some patients may make improper sexual remarks or exhibit inappropriate jocularity. They usually lack empathy and judgement. Patients with more prominent degeneration of right orbitofrontal cortex than the left, have been reported to have more marked disinhibition and loss of social behavior [13]. Bilateral orbitofrontal cortex lesions are associated with utilization and imitation behavior implying increased dependence to environmental stimuli. Neurofibrillary tangles involving the orbitofrontal cortex bilaterally have been associated with agitation in patients with Alzheimer's disease [14]. Unlike patients with dorsolateral lesions, individuals with orbitofrontal dysfunction perform card-sorting tasks normally. Subcortical lesions in the orbitofrontal–subcortical circuit cause behavioral changes similar to those observed in patients with orbitofrontal dysfunction [15]. Personality changes observed in Huntington's disease patients, for example, are ascribable to medial caudate region involvement [16].

Anterior cingulate syndrome

The anterior cingulate mediates motivated behavior and dysfunction associated with lesions in this area reflect decreased motivation. Akinetic mutism occurs with bilateral lesions of the anterior cingulate. Akinetic mutism describes a wakeful state with prominent apathy, indifference to pain, thirst or hunger; lack of motor and psychic initiative, spontaneous movements, verbalization and response to commands. Patients may be incontinent. Abulia is a less severe form of this psychomotor retardation. The major neuropsychological deficit of patients with damaged anterior cingulate circuit structures is response inhibition

Table 3
Executive cognitive dysfunction associated with dorsolateral prefrontal cortex abnormalities

Poor organizational strategies	Poor word list generation
	Reduced design fluency
	Poor copy
Poor memory search strategies	Poor recall of recently learned and remote information
Environmental dependency	Imitation behavior
	Utilization behavior
	Attract to high stimulus objects
Impaired set shifting	Impaired card sorting
	Perseveration on multiple loops and reciprocal programs
	Poor go/no-go performance
Verbal/manual dissociation	Impaired Luria serial hand sequences

on "go/no-go" tests. They also experience a decreased ability to understand new thoughts and to participate in creative thought processes [10,17].

Focal lesions in the basal ganglia may cause akinetic mutism and abulia. Isolated globus pallidus lesions, for example, lead to akinetic mutism. Akinetic mutism has been reported in patients with infarcts, tumors of third ventricle, obstructive hydrocephalus, hemorrhage, encephalitis, degeneration and trauma [18]. It also has been described in association with conditions affecting the nucleus accumbens and ventromedial caudate. Transient akinetic mutism may occur with one-sided lesions.

Apathy is observed with bilateral lesions in the ventrolateral and dorsomedial thalamic nuclei. Globus pallidus and adjacent internal capsule lesions also may produce apathy. Apathy occurs in a wide variety of disorders and is increasingly appreciated as a disorder common to many neurological diseases. Patients with Parkinson's disease and Huntington's disease involving the subcortical components of the anterior cingulate circuit often manifest apathy. Apathy is the most commonly observed behavioral change in Alzheimer's disease. Functional imaging studies in Alzheimer's disease patients show decreased activity in the anterior cingulate cortex correlating with apathy [19].

Neuropsychiatric disorders and frontal–subcortical circuits

A variety of neuropsychiatric disorders have associations with frontal–subcortical circuit dysfunction [20].

Obsessive–compulsive disorder (OCD) is characterized by intrusive and unwanted ideas, thoughts, urges and images known as obsessions together with repetitive ritualistic cognitive and physical activities comprising compulsions. The clinicopathological, functional and structural imaging studies support the involvement of frontal–subcortical circuit structures in the pathogenesis of OCD. Pericallosal tumors compressing the posterior cingulate gyrus, trauma to the anterior cingulate or orbitofrontal cortex, epileptic discharges originating from the anterior cingulate gyrus, subcortical ischemic lesions in the caudate nucleus or putamen may lead to OCD.

F18 fluoro-2-deoxyglucose positron emission tomography studies demonstrate abnormally increased activity in orbitofrontal cortex and caudate regions in patients with OCD [21,22]. These areas show increased functional activity when OCD symptoms are provoked. The anterior cingulate gyrus, which has limbic connections and close associations with orbitofrontal cortex, also exhibits increased activity in studies of OCD [23]. Magnetic resonance spectroscopy studies show decreased striatal and cingulate *N*-acetylaspartate, implying neuronal loss in these areas. Such lesions result in decreased pallidal inhibition with subsequent thalamocortical excitation. When patients are treated with serotonin reuptake inhibitors, the functional activity in the orbitofrontal cortex and caudate nucleus declines towards normal. Patients with OCD show decreased right caudate and left orbitofrontal region functional activity also following behavioral therapy techniques including methods of exposure and response prevention [24].

Positron emission tomography studies also suggest altered cortical–subcortical interactions in Gilles de la Tourette (GTS) syndrome. Patients with GTS show increased metabolism in the frontal motor regions and decreased glucose utilization in paralimbic prefrontal cortex and the ventral striatum [25]. DA dysfunction in the caudate nucleus is thought to mediate ideational and motor symptoms of GTS.

Depression has been observed in patients with lesions in the frontal cortex and the caudate nucleus. Functional imaging studies in patients with Alzheimer's disease and depression show decreased metabolism in the orbitofrontal and dorsolateral prefrontal cortices. Similarly, depression in Parkinson's disease, Huntington's disease and epilepsy are correlated with reduced metabolic activity in the orbitofrontal cortex and the caudate nucleus [26,27]. Depression may follow strokes in the dorsolateral prefrontal area and the basal ganglia.

Recently, a model for depression has been proposed involving dysfunctional coordination of limbic–cortical pathways. In this model, a dorsal compartment composed of superior limbic structures is thought to regulate attentional and cognitive symptoms of depression including apathy, psychomotor retardation, impaired attention and executive dysfunction. A ventral compartment formed of limbic, paralimbic and subcortical structures is proposed to mediate the vegetative and somatic aspects of depression, such as sleep, appetite and endocrine disturbances. Rostral cingulate area has a regulatory role for the interactions between the two compartments. Dysfunction of this coordinating area may result in disintegrated mood, cognitive, somatic and autonomic responses.

Schizophrenia is characterized by dissociation or disorganization of thought processes and deficits in planning and attentional functions. Positive symptoms such as delusions and hallucinations and negative symptoms including flattened affect and anhedonia are important aspects of the symptomatology. Schizophrenia has been associated with frontal lobe dysfunction as well as abnormal regulation of subcortical DA systems [28]. Functional imaging studies in patients with schizophrenia, show decreased cerebral blood flow in the dorsolateral prefrontal cortex during a variety of cognitive tasks [29]. Frontal lobe glucose utilization also is decreased in schizophrenic patients with prominent negative symptoms [30]. Dorsolateral and medial frontal hypofusion have been demonstrated in patients Alzheimer's disease patients and delusions. As neuroanatomical changes, postmortem and structural imaging studies reveal a reduction in the cortical volume in patients with schizophrenia [31,32].

Neurochemical markers in the dorsolateral prefrontal cortex and hippocampal region are decreased in schizo-

phrenic patients, suggesting dysfunction of frontal limbic circuits [33]. Since cortex regulates subcortical subcortical dopaminergic function, it has been suggested that hypofrontality in schizophrenia may lead to hyperactivity of subcortical dopaminergic systems. To support this hypothesis, investigators showed that lesions in the prefrontal cortex enhance the responsiveness of subcortical dopaminergic system to pharmacological challenge and stress [34,35]. Similarly, augmentation of dopaminergic transmission in the frontal cortex, suppressed subcortical DA turnover and release.

Nucleus accumbens, which receives excitatory input from multiple frontal cortex and limbic structures, also is thought to be dysfunctional in patients with schizophrenia. Nucleus accumbens is involved in both the glutamatergic and dopaminergic neurotransmission [36]. The shell region of nucleus accumbens is an important locus for therapeutic effects of antipsychotic drugs. The neuronal function in this area is altered by repetitive use of antipsychotic agents. Deficits of sensory filtering in patients with schizophrenia suggest involvement of ventral pallidum and thalamus in the pathogenesis of the disease.

The thalamus, orbitofrontal cortex and limbic parts of basal ganglia are the anatomical structures involved in *substance abuse* and *addiction*. The mesocorticolimbic dopaminergic system has been the main focus of research in the neurobiology of addiction. Important structures in the drug reward circuit are the ventral tegmental area, frontal cortex, nucleus accumbens and amygdala, which are also impotant elements of the frontal–subcortical circuits. The anterior cingulate and amygdala link substance addiction to motivational and reward systems in the brain. Neurochemical changes in these areas by chronic drug exposure lead to neuroadaptations underlying the substance addiction [37].

Summary

There are five frontal–subcortical circuits providing the neuroanatomical basis for movement and behavior. Each of the circuits shares the same member structures including the frontal cortex, striatum, globus pallidus/substantia nigra and thalamus. Neurotransmitters like DA, acetylcholine, glutamate and serotonin mediate and modulate the neurotransmission through the circuits. Frontal–subcortical circuits are named according to their cortical site of origin. The dorsolateral circuit conveys executive function. Executive dysfunction is one of the main characteristics of subcortical dementia. The orbitofrontal circuit mediates empathic and socially appropriate behavior. Personality change with disinhibition is evident in orbitofrontal circuit dysfunction. Anterior cingulate circuit is involved in generating motivated behavior and apathy is observed in lesions of this circuit. OCD, depression, psychosis and substance abuse are some of the neuropsychiatric disorders associated with frontal–subcortical circuit dysfunction. The frontal–subcortical circuits comprise an integrative framework for understanding motor, cognitive and emotional functions in a variety of neurological and psychiatric disorders.

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