Frontal-subcortical circuitry and behavior

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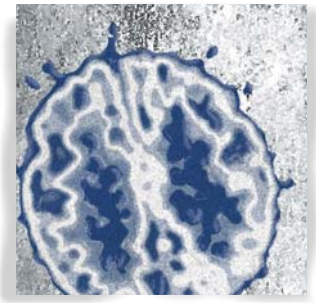

The neuropsychiatric manifestations of neurodegenerative diseases are closely linked to neurocircuitry defects. Frontal-subcortical circuits, in particular, are effector mechanisms that allow the organism to act on its environment. In this paper, we present the three main frontal-subcortical circuits: the dorsolateral prefrontal circuit allows the organization of information to facilitate a response; the anterior cingulate circuit is required for motivated behavior; and the orbitofrontal circuit allows the integration of limbic and emotional information into behavioral responses. Impaired executive functions, apathy, and impulsivity are hallmarks of frontal-subcortical circuit dysfunction. A variety of other neuropsychiatric disorders, such as Tourette's syndrome, Huntington's disease, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, schizophrenia, and mood disorders may result from disturbances that have a direct or indirect impact on the integrity or functioning of these loops.

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Neurophysiologists used to view the basal ganglia mainly as structures for regulating voluntary movement. The recent neuroanatomical, neuropsychological, and functional imaging literature, however, has made it increasingly clear that these subcortical structures are also intimately involved in regulating higher cerebral processes that control cognition, decision-making, the planning of complex behavioral strategies, and neuropsychiatric symptoms.[1,2] The frontal-subcortical circuitry provides a unifying framework for understanding the behavioral changes that accompany neurodegenerative disorders.[3] In the past three decades, a number of significant advances have been made in our understanding, not only of the neuroanatomy, but also of the neurophysiology and chemoarchitecture, of the frontal-subcortical circuits.[4] Parallelling this new understanding, an increasingly broad spectrum of neuropsychiatric phenomenology is recognized as being interpretable in the context of frontal-subcortical circuit dysfunction. A series of parallel segregated frontal-subcortical circuits are now known to link specific regions of the frontal cortex to the striatum, the globus pallidus (GP) and substantia nigra (SN), and the thalamus, constituting an important effector mechanism that allows the organism to interact adaptively with its environment.[5] Impaired executive functions, apathy, and impulsivity are hallmarks of frontal-subcortical circuit dysfunction. In a recent event-related functional MRI (fMRI) study, for instance, the authors concluded that the caudate nucleus and the putamen are particularly important, respectively, in the planning and the execution of a self-generated

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Selected abbreviations and acronyms

5-HT	*serotonin*
GP	*globus pallidus*
GPe	*globus pallidus externa*
GPi	*ventrolateral globus pallidus interna*
SN	*substantia nigra*
SNr	*substantia nigra, pars reticulata*
STN	*subthalamic nucleus*

novel action.[6] A variety of neuropsychiatric disorders may result from disturbances that have a direct or indirect impact on the integrity or functioning of frontal-subcortical circuits.

Background

Alexander et al[5,7-9] proposed that the basal ganglia and thalamus participate in five parallel segregated circuits with selected cortical areas in the frontal lobe. Two of these circuits are related to motor function, and influence skeletomotor and oculomotor areas of cortex. The remaining three loops are connected with nonmotor areas in the frontal lobe, including the dorsolateral prefrontal cortex, the lateral orbitofrontal cortex, and the anterior cingulate/medial orbitofrontal cortices. These frontal regions are known to be involved in aspects of planning, working memory, rule-based learning, attention, and emotional regulation such as the decision threshold in reaction time tasks or in the control of automatic visuospatial attention.[10-12] Basal ganglia functional connectivity, based on a recent meta-analysis of 126 positron emission tomography (PET) and fMRI imaging publications, showed that patterns of functional connectivity between the cortex and the striatal nuclei are broadly consistent with the predictions of this classical parallel loop model.[13]

The frontal lobe may be viewed as comprising two distinct anatomical and functional systems, reflecting its dual developmental origin.[14] The sequential processing of sensory, spatially related, and motivational information is mediated by a dorsal system, which involves dorsolateral and medial portions of the frontal lobes, interconnected with the posterior parietal lobe and cingulate gyrus. Emotional tone is mediated by a second, ventral system, which involves the orbital surface of the frontal lobes. The function of the frontal lobes as an integrator of information, related both to the external sensory and internal limbic worlds and its role in motivation and appropriate motor response, make this region and its subcortical connections critically important to an understanding of both normal and disordered psychomotor functions.

The architectonic organization of the prefrontal cortex is reflected in the pattern of prefrontostriatal projections.[15,16] The dorsal architectonic trend, which originates in the rostral cingulate gyrus and culminates in the dorsal portion of the frontal eye field, maps onto the dorsal caudate nucleus. In contrast, the ventral architectonic trend, which originates in the ventral orbital region and culminates in the ventral portion of the frontal eye field, maps onto the ventromedial portion of the caudate and the adjacent portion of the nucleus accumbens. Cortical areas that are closely connected functionally appear to send converging projections into adjacent regions of the striatum.[17-20] Information derived from the cortex is recombined at the striatal level to form small, functionally specialized domains. Evidence from 2-deoxyclucose metabolic studies of neuronal activation within the striatum is consistent with the concept that discrete regions of the striatum support specific functional properties.[21]

Evidence for the role of a frontostriatal system in cognition and behavior was first suggested by a series of experimental observations.[22] Specifically, lesions of electrical stimulation of the dorsolateral prefrontal cortex or of the anterodorsal head of the caudate nucleus, to which this region projects, were found to produce deficits in the same behavioral domain—namely, delayed-response and delayed-alternation tasks.[23] Similarly, lesions or electrical stimulation, either of the orbitofrontal cortex or of the ventrolateral head of the caudate, resulted in comparable deficits in object alternation or response inhibition paradigms.[14] Accordingly, disruption to cognitive processes following striatal injury was interpreted as the "downstream" interruption of anatomically congruent outflow from the frontal cortex.[24,25]

Basic circuit structure

The five major frontal-subcortical circuits suggested by Alexander et al[5,7-9] are now generally accepted. These include a motor circuit that originates in the supplementary motor area, and an oculomotor circuit originating in the frontal eye field. The motor circuit originates from neurons in the supplementary motor area, premotor cortex, motor cortex, and somatosensory cortex, recently confirmed by fMRI findings.[26] These areas project principally to the putamen in a somatotopic distribution. The

putamen in turn projects to ventrolateral globus pallidus interna (GPi), globus pallidus externa (GPe), and caudolateral SN. The globus pallidus (GP) connects to the ventrolateral, ventral anterior, and centromedianum nuclei of the thalamus, whose major efferents are to the supplementary motor area, premotor cortex, and motor cortex, completing the circuit. Thalamic nuclei have reciprocal connections with the putamen and cerebral cortex, in addition to the connections contained within the circuit. Throughout the circuit, the discrete somatotopic organization of movement-related neurons is maintained. Information processing in the circuits is not strictly sequential; neurophysiological investigations of movement demonstrate preparatory premovement activity, serial processing of movements initiated in the cortex, and concurrent parallel processing in the structures of the circuit.[8,27,28] The oculomotor circuit originates in the frontal eye field (Brodmann's area 8) as well as prefrontal and posterior parietal cortex, and connects sequentially to the central body of the caudate nucleus, dorsomedial GP and ventrolateral SN, ventral anterior and mediodorsal thalamic nuclei, and frontal eye field.[8,9] The major frontal-subcortical circuits include three behaviorally relevant circuits with origins in the prefrontal cortex: a dorsolateral prefrontal circuit, which mediates "executive" functions (ie, the organization of information to facilitate a response); an anterior cingulate circuit, which is involved in motivational mechanisms[7-9] and an orbitofrontal circuit, which has lateral and medial divisions *(Figure 1)*. The medial portion of the

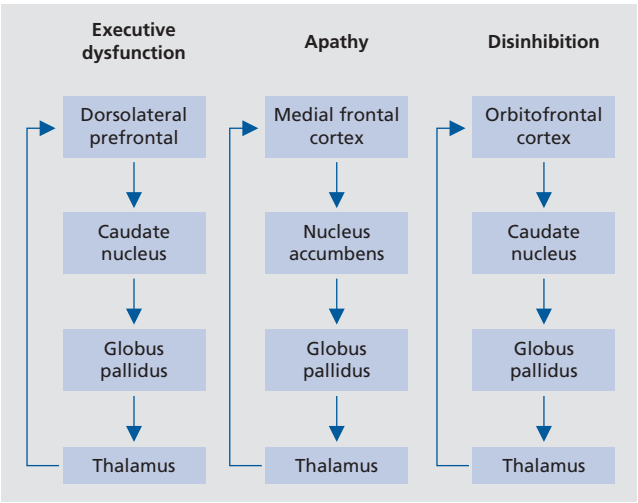

Figure 1. Pathophysiology of loop dysfunction in executive dysfunction, apathy, and disinhibition.

orbitofrontal circuit allows integration of visceral-amygdalar functions with the internal state of the organism, while the lateral portion is involved with integration of limbic and emotional information into contextually appropriate behavioral responses. Middleton and Strick[29] designate the lateral and medial portions of the orbitofrontal circuit as two separate circuit categories and an inferotemporal/posterior parietal circuit as an additional frontal-subcortical circuit in their revised scheme. Common to all circuits is an origin in the frontal lobes with projection sequentially to the striatum (caudate, putamen, or ventral striatum), to the GP and SN, and then to specific thalamic nuclei, with a final link back to the frontal lobe. Each circuit has two pathways: (i) a direct pathway, featuring a monosynaptic link between the GPi–SN pars reticulata (SNr) complex; and (ii) an indirect pathway that projects from striatum to GPe, linking to the GPi-SNr complex via the subthalamic nucleus (STN).[8] Both direct and indirect circuits project to the thalamus.

The five circuits thus share common structures and are parallel and contiguous, but remain remarkably segregated anatomically, even as succeeding projections are focused progressively onto smaller numbers of neurons. Thus, the dorsolateral prefrontal cortex projects to the dorsolateral region of the caudate nucleus; the lateral orbitofrontal cortex projects to the ventral caudate area; and the anterior cingulate cortex connects to the medial striatal-nucleus accumbens region. Similar anatomical arrangements are maintained in the GP and thalamus.

Although each frontal-subcortical circuit constitutes a closed loop of anatomically segregated dedicated neurons, "open"-loop elements are incorporated into the functional connectivity of these circuits. Circuit structures receive projections from noncircuit cortical areas, thalamic nuclei, and the amygdalar nuclei, and also project to regions outside the five circuits, including inferotemporal, posterior parietal, and prestriate cortex. Brain regions linked by these afferent of efferent projections are functionally related.[30-32] Circuits mediating limbic functions, for example, have connections to other limbic areas, whereas those involved with executive functions interact with brain structures involved with cognition.[33] In this way, circuits integrate information from anatomically disparate but functionally related brain regions. Examination of the open aspects of each circuit aids understanding of how information processed in different brain regions can be integrated and synthesized in the

processing cascade of the closed circuit, which constitutes the final effector mechanism.

Many brain regions thus ultimately project through the frontal-subcortical circuits; the direct cortical-basal ganglia connections go in the corticofugal direction only, and the cortical output from these circuits (ie, the thalamocortical projections) is routed primarily to the frontal cortex. This suggests that, regardless of the specific nature of the information that gains access to the frontal-subcortical circuits, the information processing that takes place in these circuits is "formatted" for potential executive action.[34]

Dorsolateral prefrontal circuit

The dorsolateral prefrontal circuit originates in Brodmann's areas 9 and 10 on the lateral surface of the anterior frontal lobe. Neurons in these regions project to the dorsolateral head of the caudate nucleus.[35] Fibers from this region of the caudate project to the lateral aspect of the mediodorsal GPi and rostrolateral SNr via the direct pathway.[36] The indirect pathway sends fibers to the dorsal GPe, which in turn projects to the lateral STN[37]; fibers from the lateral STN then terminate in the GPi-SNr complex. Output from the basal ganglia projects to parvocellular portions of the ventral anterior and mediodorsal thalamus, respectively.[38,39] The mediodorsal thalamus closes the circuit by projecting back to the circuit's origin in areas 9 and 10 of the dorsolateral frontal lobe.[40,41]

Both experimental and clinical data link the dorsolateral prefrontal cortex and frontal-subcortical connections with "executive function." Executive function incorporates anticipation, goal selection, planning, monitoring, and use of feedback in task performance.[42] Patients with restricted dorsolateral prefrontal cortex lesions have difficulty focusing and sustaining attention, generating hypotheses, and maintaining or shifting sets in response to changing task demands, as required by the Wisconsin Card Sorting Test (WCST).[14] Associated features include reduced verbal and design fluency, impairment of memory search strategies and of organizational and constructional strategies on learning and copying tasks, and motor programming disturbances. Similar syndromes have been reported in patients with lesions of subcortical structures of the dorsolateral prefrontal circuit.[43,44] Thus, impairments on tests of memory and executive function, including the WCST, have been noted in patients with dorsal caudate lesions,[45] bilateral GP hemorrhages,[46] and bilateral or left paramedian/mediodorsal thalamic infarction.[47,48] Executive function deficits and other features of "subcortical" dementia[49] in such conditions as Huntington's disease, Parkinson's disease, progressive supranuclear palsy, Wilson's disease, neuroacanthocytosis, and other subcortical disorders are believed to reflect involvement of the dorsolateral prefrontal circuit as it projects through the basal ganglia.[43,50] In patients with Huntington's disease and Parkinson's disease, performance on tests of executive functions are correlated with memory scores[51]; the normal registration, storage, and consolidation of memory stores is dependent on frontal lobe function. This is consistent with evidence linking working memory to prefrontal circuits.[52,53]

In Parkinson's disease, "frontal" functions are doubly jeopardized by the combination of caudate nuclear dopamine deficiency, which creates a partial "disconnection syndrome" of subcortical origin,[54-56] and the lesser reduction of dopamine in the dorsolateral prefrontal cortex.[57,58] In this disorder, specific cognitive deficits involving working memory, cognitive sequencing, and attention shifting may respond, at least partially, to dopaminergic therapies.[59,60] This is explainable by the fact that dopamine modulation in the basal ganglia locks the gate to working memory.[61] However, incomplete reversal of cognitive deficits with dopamine agonists is typically noted in Parkinson's disease,[59] reflecting the likely role of dysfunction of nondopaminergic neuronal systems in Parkinson's disease dementia.[62]

Psychiatric syndromes including schizophrenia, depression, and obsessive-compulsive disorder manifest executive dysfunction. The presence of executive abnormalities is these disorders imply that frontal-subcortical circuit function is compromised. Cognitive enhancement in these disorders will focus on facilitating frontal-subcortical function.

In attention-deficit/hyperactivity disorder and Tourette's syndrome, various agents having important effects on the noradrenergic system, the dopaminergic system, or both may ameliorate at least some features of executive dysfunction.[63,64] Such drugs include deprenyl, stimulant medications, low-dose tricyclic antidepressants, and the α_2-adrenergic agonists clonidine and guanfacine.[65,66] Both clonidine and guanfacine have been shown to enhance working memory performance in aged monkeys,[67,68] and cognitive tasks mediated by prefrontal cortex, such as Trails B, word fluency tasks, and the Stroop task, are

improved by clonidine in patients with schizophrenia and Korsakoff's syndrome.[69,70] In patients with dementia of the frontal lobe type, executive function may be selectively enhanced by the α_2-adrenergic antagonist idazoxan.[71] These observations are consistent with psychopharmacological and anatomical studies implicating the noradrenergic and dopaminergic systems as important modulators of frontal lobe function.[72]

The anterior cingulate circuit

Neurons of the anterior cingulate serve as the origin of the anterior cingulate-subcortical circuit. From Brodmann's area 24, they provide input to the ventral striatum[35] which includes the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle. This area is termed the limbic striatum.[73] Projections from the ventral striatum innervate the rostromedial GPi and ventral pallidum (the region of the GP inferior to the anterior commissure), as well as the rostrodorsal SN.[74] There may also be a less well-defined indirect loop projecting from the ventral striatum to the rostral pole of the GPe.[14] The external pallidum in turn connects to the medial STN, which returns projections to the ventral pallidum.[75] The ventral pallidum provides limited input to the magnocellular mediodorsal thalamus.[74] The anterior cingulate circuit is closed with projections from the dorsal portion of the magnocellular mediodorsal thalamus to the anterior cingulate.[40,76]

"Akinetic mutism" is closely related to lesions to the anterior cingulate.[77,78] It represents a wakeful state of profound apathy, with indifference to pain, thirst, or hunger; absence of motor or psychic initiative, manifested by lack of spontaneous movement; absent verbalization; and failure to respond to questions or commands. The most dramatic examples of akinetic mutism follow bilateral lesions of the anterior cingulate cortex[43,79,80] and may be predicted by lesions that extend from the cognitive effector region posteriorly into the skeletomotor effector division of the cingulate.[81] Unilateral lesions of the anterior cingulate cortex tend to produce transient akinetic mutism.[82,83] The term "abulia," derived from the Greek boul, or "will,"[77] refers to a similar but less severe psychomotor syndrome, encompassing lack of spontaneity, apathy, and paucity of speech and movement.

Akinetic mutism has been described with cerebrovascular disease, craniopharyngiomas, obstructive hydrocephalus, tumors in the region of the third ventricle, and other conditions involving the ventral striatum (nucleus accumbens and ventromedial caudate), ventral GP, and medial thalamus. In an analogous syndrome, patients with circumscribed supplementary motor area lesions demonstrated by computed tomography (CT) may demonstrate a disorder affecting the "drive" for both willed movement and speech.[77] Such patients evidence initial global akinesia and neglect, which subsequently tends to lateralize in unilateral cases. Part of the motor circuit, the supplementary motor area, also receives reciprocal projections from the anterior cingulate.

Several studies have examined the association between abulia or apathy and location of brain lesions.[73] Bilateral lesions of ventrolateral and dorsomedial thalamic nuclei frequently produce apathy.[84] Other studies have revealed a high frequency of apathy after lesions involving the GP and the adjacent internal capsule.[85,86] One of the main internal pallidal outputs, which traverses the posterior limb of the internal capsule en route to the pedunculopontine nucleus, is the ansa lenticularis[77] and this pathway may have a prominent role in goal-oriented behavior.[3,87] In a review of patients with focal lesions of the basal ganglia,[88] abulia occurred with 6 of 22 (27%) restricted GP lesions, all bilateral, and with 18 of 64 (28%) small and large caudate lesions sparing the lentiform nucleus, 15 of which were unilateral. In this study, abulia was not observed with isolated putamenal lesions, consistent with the integration of this structure with motor rather than limbic system circuitry.

Early observations in experimental animals showed that a syndrome similar to akinetic mutism could be produced by bilateral or unilateral injection of 6-hydroxydopamine into either the SN, ventral tegmental area, or nigrostriatal tract within the medial forebrain bundles of the lateral hypothalamus.[89,90] These behavioral deficits could be reversed by administration of apomorphine, a direct dopamine agonist,[91,92] and blocked by pretreatment with spiroperidol, a dopamine receptor antagonist.[93] Corroborating these observations was the initial report of a patient with akinetic mutism after surgical removal of a tumor from the anterior hypothalamus, who responded to treatment with the dopamine receptor agonists lergotrile and bromocriptine, but not to carbidopa/L-dopa or methylphenidate, presynaptic dopamine mimetics.[94] This suggested loss of dopaminergic input pointed to anterior cingulate or other corticolimbic structures rather than to the striatum as a cause of the patient's akinesia. Based on pathological studies of

23 patients, it was subsequently postulated that isolated damage to any of the projections of brain stem dopaminergic nuclear groups could result in akinetic mutism.[95] Chronic akinetic mutism secondary to mesencephalic infarction, destroying ventral tegmental area dopaminergic neurons at their site of origin, may also be reversed with dopamine agonists.[96,97] In children, akinetic mutism of differing etiologies may respond to bromocriptine with rapid and dramatic improvement, suggesting the same pathogenesis of the disorder in childhood as in adulthood.[98] Response to direct dopamine agonists may be poor, however, in cases where dopamine receptors have been destroyed—for example, in patients with lesions involving the anterior cingulate gyri.

Paralleling the observations in akinetic mutism, a clinically significant and sustained improvement in apathy may be seen with dopaminergic agents in a variety of neuropsychiatric disorders.[99] Effective agents in such conditions may include bromocriptine, amantadine, selegiline, modafinil, buproprion, amphetamine, and methylphenidate. Dopamine agonists, including bromocriptine and methylphenidate, have been used successfully to treat apathy in patients with anterior communicating artery aneurysm, Wilson's disease, and human immunodeficiency virus-related dementia.[14] In a case of successful methylphenidate treatment of apathy secondary to cocaine-related subcortical strokes,[100] behavioral improvement was accompanied by an increase in blood flow to the frontal cortex and selective improvement on a reaction time version of the Stroop task. The Stroop interference effect is associated with cerebral activation that is most prominent in frontal and cingulate cortex.[101]

Apathy is the most commonly observed behavioral disturbance in Alzheimer's disease, and is associated with anterior cingulate hypoperfusion.[102] The documented improvement in Alzheimer's-related apathy with cholinesterase inhibitor therapy[103] may reflect partial correction of cholinergic disconnection of anterior cingulate structures. The latter include the basal nucleus of the amygdala,[81] innervated by cholinergic projections from basal forebrain structures, and the midline thalamic nuclei, which receive input both from the basal forebrain and from cholinergic peduculopontine projections that form part of the ascending reticular activating system. Patients with apathy and akinetic mutism are typically alert, suggesting an intact reticular activating system. However, partial defects in this system may occasionally contribute to akinetic mutism, as exemplified by a patient whose akinetic mutism followed surgical removal of a fourth ventricular astrocytoma and responded well to methylphenidate.[104]

Apathy is prominent in many neurodegenerative disorders including frontotemporal dementia, Parkinson's disease, and progressive supranuclear palsy. Apathy must be distinguished from depression; apathy may occur with or without concomitant depressive symptoms.

The orbitofrontal circuit

The lateral division of the orbitofrontal circuit originates in the lateral orbital gyrus of Brodmann's area 11 and the medial inferior frontal gyrus of the areas 10 and 47 in humans.[81] These areas send projections to the ventromedial caudate, which projects in turn to the most medial portion of the mediodorsal GPi and to the rostromedial SNr.[105] The ventromedial caudate also sends an indirect loop through the dorsal GPe to the lateral STN, which then projects to the GPi and SNr.[75] Neurons are sent from the GP and SN to the medial section of the magnocellular division of the ventral anterior thalamus, as well as an inferomedial sector of the magnocellular division of the mediodorsal thalamus.[35,38] This division of the circuit then closes with projections from this thalamic region to the lateral orbitofrontal cortex.[38]

A medial division of the orbitofrontal circuit has also been identified, originating in the inferomedial prefrontal cortex, specifically the gyrus rectus and the medial orbital gyrus of Brodmann's area 11 in humans.[81] From this area, the medial division has sequential projections to medial aspects of the accumbens, to medial ventral portions of the pallidum, and thence, via the medial magnocellular division of the mediodorsal thalamic nucleus, back to the medial orbitofrontal cortex.[106] The medial orbitofrontal cortex has reciprocal connections with the medial portion of the basal and the magnocellular division of the accessory basal amygdale. Cortical areas that have reciprocal connections with the medial orbitofrontal cortex influence visceral function when stimulated, probably through their shared amygdalar connections.[81] Other regions reciprocally connected with the medial orbitofrontal cortex include the rostral insula, ventromedial temporal pole (area 38, and infracallosal cingulate areas 25, 24, and 32,[107,108] the latter regions being primarily part of the anterior cingulate circuit. The visceral effector areas of the infracallosal cingulate provides motivational tone to gustatory, olfactory, and alimentary information converging on the medial

orbitofrontal cortex from the anterior insular region. The medial division of the orbitofrontal circuit can thus be viewed as an integrator of visceral drives while modulating the organism's internal milieu.[81]

The orbitofrontal cortex is the neocortical representation of the limbic system[14] and is involved in the determination of the appropriate time, place, and strategy for environmentally elicited behavioral responses. Lesions in this area appear to disconnect frontal monitoring systems from limbic input,[109] resulting in behavioral disinhibition and prominent emotional lability.[110] Patients lack judgment and social tact, and may exhibit inappropriate jocularity. Decreased impulse inhibition may be associated with improper sexual remarks or gestures and with other antisocial acts, although overt sexual aggression is rare.[14] Patients may appear irritable, and trivial stimuli may result in outbursts of anger that pass quickly without signs of remorse.[111] Inattention, distractibility, and increased motor activity may be seen, and hypomania or mania is not uncommon.[112] Marked personality changes have usually been documented in the setting of bilateral orbitofrontal lobe damage,[109] but circumscribed unilateral (left or right) orbitofrontal brain injury may cause a similar personality disorder, with disinhibition, poor judgement, and irresponsibility toward familial and social obligations.[113] In patients with frontal degenerations, those affecting the right hemisphere disproportionately are associated with greater disinhibition and loss of socially appropriate behavior.[114] Large bilateral orbitofrontal lobe lesions in humans may, in addition, result in enslavement to environmental cues, with automatic imitation of the gestures of others, or enforced utilization of environmental objects.[115,116] Patients with orbitofrontal dysfunction exhibit a dissociation between impairment of behavior necessary for activities of daily living and normal performance on psychological tests sensitive to dorsolateral prefrontal lobe dysfunction, such as the WCST.[109]

Patients with ventral caudate lesions may appear disinhibited, euphoric, impulsive, and inappropriate, recapitulating the corresponding orbitofrontal lobe syndrome.[45] It is likely that the early appearance of similar personality alterations in Huntington's disease reflects the involvement of medial caudate regions receiving projections from the orbitofrontal and anterior cingulate circuits that mediate limbic system function.[117] Similarly, mania may result not only from injury to medial orbitofrontal cortex and caudate nuclei (eg, Huntington's disease), but also from lesions to the right thalamus.[84,118-120] Mixed behavioral syndromes commonly accompany focal lesions of the GP and thalamus, reflecting the progressive spatial restriction of the parallel circuits at these levels.[43]

Disinhibition syndromes occur in frontotemporal dementia, following closed head injury, with frontal lobe tumors, and with focal vascular lesions.

Various pharmacological agents may be effective in modifying the disinhibited behavior of patients with orbitofrontal circuit dysfunction, although no agent is uniformly reliable.[121] Potentially useful drugs include the major and minor tranquilizers, propranolol, buspirone, carbamazepine, sodium valproate, lithium, and clonidine. In addition to their dopaminergic activity, neuroleptics may have a serotonergic mode of action in the treatment of impulsive aggression by binding to and downregulating the serotonin $(5\text{-HT})_2$ receptors,[122] a 5-HT receptor subtype that is represented in intermediate levels in the nucleus accumbens and striatum. Lithium's mood-stabilizing action may be mediated by effects both on the 5-HT system and on phosphoinositide,[123] which is selectively concentrated in striosomes (the striatum is organized as two separate systems, the striosomes and the matrix) of the medial and ventral striatum[124]—regions that receive dense orbitofrontal input. More specific serotonergic agonists, including clomipramine and fluoxetine, may also be effective for impulsive, aggressive, or sexually disinhibited behaviors.[125,126] This may reflect serotonergic modulation of orbitofrontal circuit dysfunction and is consistent with data linking behavioral disinhibition with central serotonergic deficiency.[122,126] Certain 5-HT_{1A} agonists ("serenics"), whose effects may be mediated by postsynaptic 5-HT_{1A} receptors, exert a dose-dependent decrease in aggression with a concomitant increase in social interest in animal paradigms.[14] Both propranolol and pindolol bind to somatodendritic 5-HT_{1A} receptors, present in limbic brain regions,[127] and appear to have 5-HT_1 agonist properties at dosages in the range of those used in the treatment of aggressive behavior in humans.[128] Similarly, the partial 5-HT_{1A} agonist buspirone may be effective in the treatment of aggression in a variety of neuropsychiatric conditions. An orbitofrontal syndrome with mania may be seen with bilateral orbitofrontal contusions, and may respond rapidly to clonidine,[118] and α_2-noradrenergic agonist that reduces central noradrenergic transmission by stimulating presynaptic autoreceptors.[129,130] The response to clonidine in such cases may be related to reduction in noradrenergic overactivity induced by lesions of prefrontal areas projecting to noradrenergic systems[131] which in turn innervate

prefrontal cortex and modulate its function.[72,132] Clonidine may ameliorate symptoms characteristic of orbitofrontal circuit dysfunction, including inattention, distractibility, impulsivity, and emotional lability, in patients with attention-deficit/hyperactivity disorder and Tourette's syndrome.[66,133] Several classes of drugs thus have the potential to favorably influence symptoms of orbitofrontal circuit dysfunction, reflecting serotonergic, dopaminergic, and noradrenergic modulation of functions of the orbitofrontal cortex and connected brain regions.[121]

Conclusions

Neuropsychiatric manifestations of neurodegenerative diseases are closely linked to neurocircuitry defects. Involvement of these circuits in a variety of neuropsychiatric diseases such as Tourette's syndrome,[134,135] Huntington's disease,[136] obsessive-compulsive disorder,[137] attention-deficit/hyperactivity disorder,[138] schizophrenia,[139] and mood disorders[140] has been proposed recently. Frontal-subcortical circuits are effector mechanisms that allow the organism to act on the environment. The dorsolateral prefrontal circuit allows the organization of information to facilitate a response; the anterior cingulate circuit is required for motivated behavior; and the orbitofrontal circuit allows the integration of limbic and emotional information into behavioral responses. Impaired executive functions, apathy, and impulsivity are hallmarks of frontal-subcortical circuit dysfunction. A variety of other neuropsychiatric disorders may result from disturbances that have a direct or indirect impact on the integrity or functioning of frontal-subcortical circuits. ❑

Circuitos fronto-subcorticales y conducta

Las manifestaciones neuropsiquiátricas de las enfermedades neurodegenerativas están íntimamente relacionadas con los defectos en los neurocircuitos. Los circuitos fronto-subcorticales son especialmente mecanismos efectores que permiten que el organismo actúe en su ambiente. En este artículo se presentan los tres principales circuitos fronto-subcorticales: el circuito prefrontal dorsolateral que permite organizar la información para facilitar una respuesta; el circuito cingulado anterior que necesario para la conducta con motivación y el circuito órbito-frontal que permite la integración de la información límbica y emocional en respuestas conductuales. Las funciones ejecutivas deterioradas, la apatía y la impulsividad son distintivas de la disfunción del circuito fronto-subcortical. Una variedad de otros trastornos neuropsiquiátricos, como el Síndrome de la Tourette, la Enfermedad de Huntingon, el trastorno obsesivo-compulsivo, el trastorno por déficit de atención con hiperactividad, la esquizofrenia y los trastornos del ánimo pueden deberse a alteraciones que tengan un impacto directo o indirecto en la integridad o el funcionamiento de estos circuitos.

Circuits fronto-sous-corticaux et comportement

Les manifestations neuropsychiatriques des maladies neurodégénératives sont étroitement liées aux anomalies des circuits neuronaux. Les circuits sous-corticaux-frontaux en particulier, sont des mécanismes effecteurs qui permettent à l'organisme d'agir sur son environnement. Les trois principaux circuits fronto-sous-corticaux sont présentés dans cet article : le circuit dorsolatéral préfrontal permet à l'information de s'organiser pour obtenir une réponse ; le circuit cingulaire antérieur est sollicité pour le comportement motivé et le circuit orbito-frontal intègre l'information limbique et émotionnelle dans les réponses comportementales. L'altération des fonctions exécutives, l'apathie et l'impulsivité sont les marques de la dysfonction des circuits sous-corticaux-frontaux. Des perturbations directes ou indirectes de l'intégrité du fonctionnement de ces circuits peuvent entraîner d'autres troubles neuropsychiatriques comme le syndrome de Gilles de la Tourette, la maladie de Huntington, les troubles obsessionnels compulsifs, les troubles de l'attention/hyperactivité, la schizophrénie et les troubles de l'humeur.

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