NETWORK ARCHITECTURE OF BEHAVIORAL GUIDANCE

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Introduction

Brain function relies on information flow among regional nodes within large-scale distributed networks. Historically, studies of long-range network connectivity have relied upon invasive axonal tracer methods applied to monkeys and other mammals. These studies provided the basis for modern thinking about network organization, but it has remained uncertain how well this data transfers to humans. During the past decade, new neuroimaging techniques have begun to close this phylogenetic gap by investigating large-scale network connectivity in living humans. Diffusion tensor imaging (DTI) enables visualization of large fiber tracts running between regions, a measure of structural connectivity. Intrinsic connectivity network (ICN) fMRI, in contrast, can identify networks of brain regions that exhibit correlated blood oxygen level-dependent (BOLD) signal fluctuations in task-free settings, providing a measure of functional connectivity. To date, these novel methods have largely validated use of primate anatomical connectivity data to guide our understanding of human frontal systems, but further work is needed to identify facets of human brain organization that distinguish humans in comparison to other primates.

The frontal lobes, so central to how we think, feel, plan, decide, and act, continue to inspire a sense of awe with regard to the brain's capacities. The past four decades have witnessed major advances in our conceptualization of frontal lobe anatomy, networks, and functions. In this presentation, we will use modern network neuroscience approaches to highlight the anatomy, connectivity, functions, and clinical relevance of the major fronto-striatal networks.

History of thought

Until the early 1980's, cortico-striato-thalamic circuitry was widely conceptualized as a funnel, wherein diffuse cortical regions projected onto the same basal ganglia structures to integrate information from disparate sites. Serial processing was emphasized, and cortical regions were thought to conveniently project onto the most proximal striatal territories. All of striatum then projected to ventrolateral thalamus, which in turn sent efferents to motor cortex, triggering appropriate responses to integrated sensory information. Meticulous axonal tracer studies in monkeys soon revealed, however, that cortico-striatal projections are organized as longitudinal bands that run the length of the striatum and gather segregated information from cortical areas with close functional interrelationships.[1-2] Striatal subregions were found to project in an orderly topographical fashion to basal ganglia output structures in the pallidum and substantia nigra, which further relay information to distinct thalamic subnuclei, which in turn project back to the cortical sites of origin. This "cortico-striato-pallido-thalamic loop" was initially conceived as subserving motor system computations, but further study revealed that cognitive and social-emotional frontal systems adopt parallel connectivity patterns. Progressive refinement of the model provided by Alexander, Delong, and Strick[3] has culminated in the information presented in Figure 1.

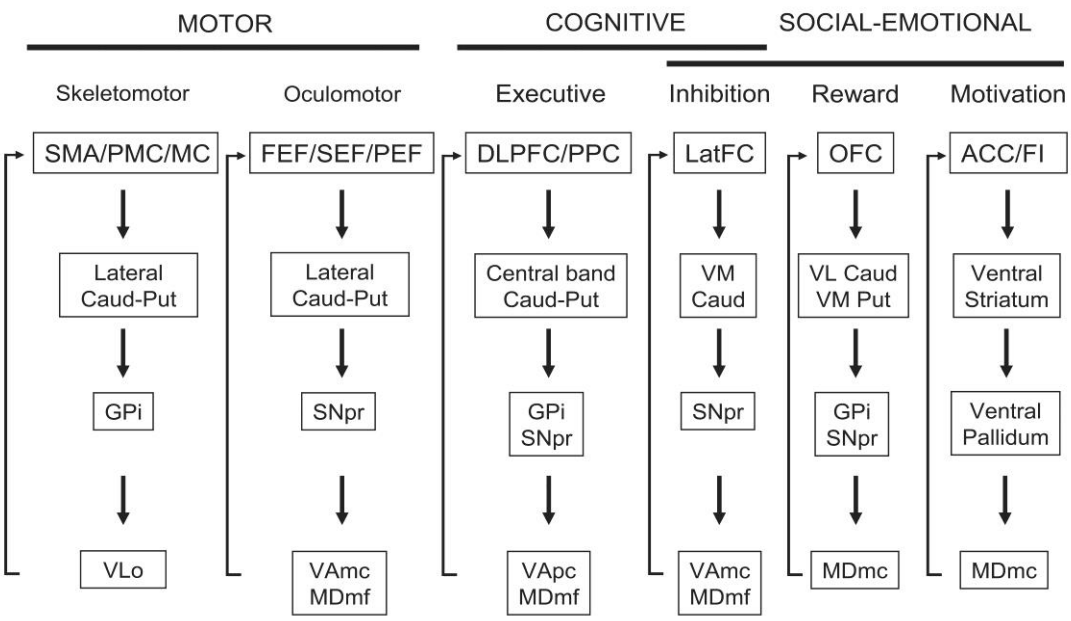

Figure 1. Updated account of frontal-subcortical networks, incorporating motor, cognitive, and social-emotional systems. In addition to the "closed loop" effector mechanisms illustrated for each network, a partial listing of cortical regions not receiving direct thalamic feedback is included alongside the major region receiving thalamic feedback. In addition, parallel frontal systems "laterally" interact, through cortico-cortical and cortico-limbic connections, to orchestrate flexible, adaptive interactions between emotions, motivations, actions, and the environment. Model adapted from Alexander, Delong and Strick[3] and updated with data reviewed by Ongur & Price[4] and Middleton & Strick[5]. ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; FI = frontoinsula; GPi = globus pallidus, interna; MDmc = medialis dorsalis, pars magnocellularis; OFC = orbitofrontal cortex; PEF = parietal eye field; PMC = primary motor cortex; PPC = posterior parietal cortex; SMA = supplementary motor area; SNpr = substantia nigra, pars reticulata; SEF = supplementary eye field; VAmc = ventralis anterior, pars magnocellularis; VApc = ventralis anterior, pars parvocellularis; VLo = ventral lateralis, pars oralis; VL = ventrolateral; VM = ventromedial.

Motor networks

Motor effector and integration systems remain the best characterized of the frontal-subcortical networks. Motor circuits follow a general mechanism for balanced excitation and inhibition in frontal systems. As detailed in Figure 2, cortical output proceeds in parallel via a direct pathway, which has a net effect of excitatory feedback on cortex from thalamus, and an indirect pathway, through which information is transmitted from cortex to striatum to globus pallidus (external segment) to subthalamic nucleus to globus pallidus (internal segment) and substantia nigra (pars reticulata), yielding a net inhibitory effect on thalamocortical transmission. This influential model has provided key insights in the medical and surgical treatment of movement disorders, and, applied to neuropsychiatric frontal-subcortical disorders, has begun to yield important advances. Because this seminar focuses on behavior and cognition, the motor networks will not be discussed further.

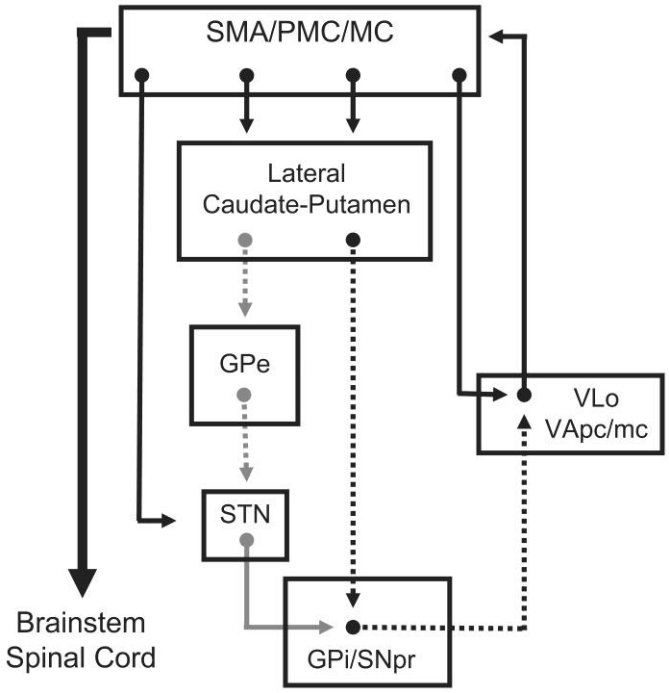

Figure 2. Direct and indirect cortical-subcortical pathways of the motor system. The direct pathway emanates from cortex to striatum to GPi, whereas the indirect pathway (gray lines) is channeled through the GPe and STN en route to the GPi. Dotted lines represent inhibitory connections. Adapted from Alexander & Crutcher[6]. STN = subthalamic nucleus; GPe = globus pallidus, externa. Abbreviations otherwise as in Figure 1.

Cognitive networks

Several distinct cortical-subcortical networks support related aspects of cognition. Best characterized among these is a network configured to integrate dorsolateral prefrontal cortex (dlFPC) and posterolateral parietal cortex. Anatomical experiments suggest that cortical nodes provide convergent inputs which interdigitate in terminal fields within a central longitudinal band of striatum. Further processing is channeled through the pallidum and ventral anterior thalamus before looping back to dlPFC (Figure 1). Extensive cortico-cortical connections via the superior longitudinal fasciculus also support this system by directly linking lateral frontal and parietal regions through "reverberating" attentional circuits. This configuration allows a useful division of labor. The blue collar parietal lobes represent perceptual-linguistic information in consciousness, while the supervisory frontal lobes, having greater access to information about goals and context, direct the parietal lobes to refresh and maintain perceptual traces in working memory so long as they remain goal-relevant. This system is especially devoted to events occurring in external space.[7] Thus, damage to either lateral frontal or parietal cortex can impair working memory, whereas lateral frontal damage is much more likely to impair "executive" mental manipulations such as sequencing, planning, set-shifting, and strategy formation (goal-oriented operations). Verbal, spatial, and non-verbal auditory representations—whether inwardly or externally cued—must last for at least a few moments, or as long as the need persists, in order to guide behavior, and sustained frontal-parietal co-activity is required to achieve this important mental feat.

As suggested in Figure 1, a second lateral frontal network participates in both cognitive and social-emotional functions. This PFC system emanates from the ventolateral inferior frontal cortex, spilling into lateral aspects of the orbital surface (BA 47/12), and plays a major role in cognitive and behavioral inhibition. To efficiently process sensory information, organisms must find a way to not only amplify and refresh relevant signal information but also to suppress distracting noise. The ventrolateral PFC network helps suppress or "tune out" extraneous stimuli and, perhaps more critically, to downgrade behavioral response considerations unlikely to achieve desired outcomes. For these reasons, the lateral OFC network should, and does, sit at a crossroads between cognitive and emotional processing systems.

Social-emotional networks

During the past 15 years, the limbic, paralimbic, and neocortical regions dedicated to social-emotional functioning have re-entered the limelight after decades of investigational neglect. These social-emotional networks were derived in our distant mammalian ancestors for basic homeostatic processing, but in our nearest extant primate relatives these systems help to meet the multifaceted, nuanced, and rapidly shifting emotional processing demands imposed by complex social environments. The frontal lobes play a primary role in social-emotional function, receiving a wealth of afferent information about the internal state and hedonic evaluation of stimuli in the environment. Participating frontal sites occupy the orbital and medial surfaces. Modern connectional network mapping, pioneered in monkeys by Joseph Price and colleagues, has identified two distinct yet interacting networks, emanating from transition zones between limbic and neocortical processing nodes.

An "orbital network" provides a stage for "afferent limbic" processing of all sensory information, including olfactory/gustatory, visceral/autonomic, and nociceptive stimuli. Upon this stage, changing stimulus reward values can be re-mapped in response to changing conditions. For example, the taste of chocolate is highly rewarding and produces robust activation within medial nodes of the orbital network when first consumed by a hungry subject. With successive chocolate bar consumptions, the taste or smell of chocolate becomes less pleasing, medial OFC activation wanes, and caudolateral OFC activation increases to inhibit feeding responses.[9] This reward-related processing is not specific to food rewards but applies to all forms of emotional stimulus-response association learning.

A "medial" network, in contrast, motivates behavioral responses to the internal and external environment. This system includes the ACC complex (BAs 24/25/32), medial OFC (gyrus rectus, BAs 13/14), and the most lateral dome of the frontal insula (area Iai in monkeys; most likely homologous to area FI in humans), with reciprocal connections with the temporal pole/amygdala and extensive "efferent limbic" projections (largely arising from ACC) to hypothalamus, periaqueductal gray, and brainstem. The ACC has been linked to error monitoring, perhaps because it responds to feedback by generating visceral responses that produce awareness of error commission.[8] The anatomical connections of the "medial network" allow it to orchestrate motivating emotional responses to salient internal and external stimuli. These responses drive behavior. Although it remains uncertain which nodes within the medial network, if any, represent emotional salience, the frontoinsula provides a strong candidate in light of its robust structural connectivity to interoceptive, limbic, and "orbital network" regions and functional connectivity with the motivational apparatus of the ACC. The ACC, in turn, features major connections with dlPFC (enabling recruitment of executive control resources) and the motor system (enabling action). In summary, the medial network puts the will in willful behavior and links motivation to action.

The elusive frontal pole and rostromedial prefrontal cortex

Which brain regions oversee the social-emotional processing systems? Some authors have argued that the frontal pole (BA 10), which features reciprocal connections to both the medial and orbital networks but not to posterior parietal or inferotemporal cotices, is best situated to play a supervisory role in social-emotional processing by exerting control over interoceptive and abstract representations of the self and others.[10] Evidence for this hypothesis is growing, including the observation that the frontal pole, even compared to other frontal regions, may be disproportionately enlarged in humans and apes compared to other primates.[11] Further work is needed to adequately test these hypotheses and refine the anatomical framework.

Clinical manifestations of frontal systems injury

Although patients are often loosely described as "frontal," the symptoms arising from frontal injury vary according to the specific frontal system affected (Figure 3). Understanding frontal anatomy, network architecture, and function, as described above, greatly facilitates bedside interpretation of symptoms and findings, as described in this section. Patients with motor system damage will not be discussed here. As with all neurology, careful lesion localization narrows the etiological differential diagnosis, which ultimately leads to better informed decisions about further diagnostic evaluation and treatment.

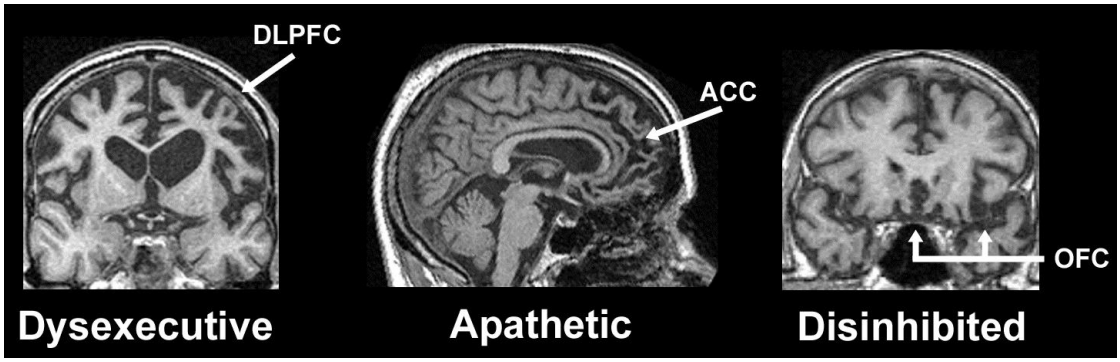

Figure 3. Frontal symptoms relate to the localization of frontal injury. Representative T1-weighted MR images and presenting symptoms are listed for three contrasting patients with degenerative dementia.

Dorsolateral frontoparietal-subcortical systems injury results in a dysexecutive syndrome. Patients may remain socially engaged and emotionally sensitive but can no longer plan, organize, and prioritize their lives. Bedside frontal-executive tests (Table 1) become crucial to identify such patients, because gross episodic memory, language, and spatial test scores often fall within normal ranges. Short-term working memory (digit span) and mental manipulation (reverse digit span) are impaired, and tests of set-shifting (Trails B, Wisconsin Card Sorting Test) or generation (letter or design fluency) may show prominent deficits. From an etiological perspective, cognitive frontal networks are brittle and fail in response to many forms of systemic and neurological illness. In particular, acute attentional-executive dysfunction should raise concern for toxic-metabolic-infectious delirium, subacute for endocrine-nutritional-infectious causes, and chronic-progressive for degenerative disease, although one cannot predict the underlying neurodegenerative histopathology from executive deficits alone. Patients with Alzheimer's disease (AD), frontotemopral lobar degeneration (FTLD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), Parkinson's disease (PD) or multiple systems atrophy (MSA) may all present with prominent executive deficits, reinforcing the pervasive vulnerability of this system. Finally, demyelination and neoplasia should be ruled out in subacute or chronic settings, and vascular injury to subfrontal white matter, overlying cortex, or deep gray nuclei can present with executive frontal deficits on almost any time scale but perhaps most commonly as a progressive or step-wise decline that prompts consideration of vascular cognitive impairment or dementia.

Table 1. Useful bedside tests of dorsolateral frontal system function

Function	Test	Time required
Working memory	Digit span	3 minutes
Mental manipulation	Reverse digit span	2 minutes
Visuomotor attention and search	Trails A	3 minutes
Set-shifting	Trails B – Trails A	3 minutes
Generation - Verbal	Letter fluency (D-words/minute)	2 minutes
Generation - Visual	Design fluency (Novel designs/minute)	2 minutes
Concept formation	Proverbs and similarities	3 minutes

For the social-emotional frontal systems, day-to-day life remains the best available diagnostic test. Patients are often brought in by family members due to job loss, behavioral change, criminal conduct, or failure to complete household responsibilities. Executive functioning tests may be normal (when adequate time is provided), and elemental neurological signs. Abnormal Luria hand motor sequences, primitive reflexes, and failure on response suppression (oculomotor go-no-go) tasks, for example, are insensitive and not specific to localization or etiology despite widespread awareness of these signs among even medical students. Caregiver-based instruments, such as the Neuropsychiatric Inventory,[12] and careful behavioral observation in the exam room remain the best measures that can be readily implemented in the general neurology clinic.

Patients with focal medial frontal netowork damage (especially when it involves the ACC) typically present with features of the amotivational spectrum, from mild apathy to profound abulia to akinetic mutism, depending on the

severity of the insult. Spontaneous verbal or motor output is limited and responses to direct stimulation may show dramatic increases in initiation latency. Acute and subacute presentations should raise concern for the usual suspects (particularly vascular disease), but most outpatient apathy syndromes are progressive and relate to neurodegenerative disease. When apathy is the first and most prominent symptom of a progressive dementia, it is usually as part of behavioral variant frontotemporal dementia and predicts FTLD pathology. Other dementias, including AD, PSP, DLB, and VaD can also present with early and prominent apathy, usually in association with other, more characteristic features.

In contrast, patients with orbital network injury present with floridly disinhibited social, sexual, and eating behavior, relating to a loss of ventrolateral frontal inhibitory control and failure to use the orbitofrontal cortex to model changes in reward schedule. Gluttonous overeating, often associated with carbohydrate craving, may reflect inability to update food reward value in response to intake or to integrate satiety signals from the viscera into the decision to eat. At the bedside, patients may be overly chummy, jocular, or argumentative. They violate social norms (asking the examiner's age or marital status, picking nose or clearing ear wax without embarrassment), overstep interpersonal space boundaries (touching examiner, talking at close distances), and engage in childish joke-telling, punning, and imitative showmanship. Etiologically, acute presentations are uncommon but should raise concern for limbic seizures. A subacute disinhibition syndrome, usually accompanied by profound amnesia and psychosis, can be seen with paraneoplastic or autoimmune limbic encephalitis. Insidious progression is the most common tempo, uncommonly in association with orbital groove meningiomas despite the spectacular (and treatable) nature of such cases. Most often, these progressive syndromes relate to bvFTD or a right temporal lobe predominant presentation of semantic variant primary progressive aphasia; in either case, the underlying pathology is FTLD.

Summary

The frontal lobes make us human, and loss of frontal function is devastating to patients and families. Armed with an understanding of dissociable frontal-subcortical systems, the neurologist can recognize, diagnose, and treat neurological diseases that impact frontal function. Future research will shed important new light on the basic neuroscience of frontal systems in health and disease.

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