Executive Control Function: A Review of Its Promise and Challenges for Clinical Research

A Report From the Committee on Research of the American Neuropsychiatric Association

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This report reviews the state of the literature and opportunities for research related to "executive control function" (ECF). ECF has recently been separated from the specific cognitive domains (memory, language, and praxis) traditionally used to assess patients. ECF impairment has been associated with lesions to the frontal cortex and its basal ganglia–thalamic connections. No single putative ECF measure can yet serve as a "gold standard." This and other obstacles to assessment of ECF are reviewed. ECF impairment and related frontal system lesions and metabolic disturbances have been detected in many psychiatric and medical disorders and are strongly associated with functional outcomes, disability, and specific problem behaviors. The prevalence and severity of ECF deficits in many disorders remain to be determined, and treatment has been attempted in only a few disorders. Much more research in these areas is necessary.

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The Research Committee of the American Neuropsychiatric Association has chosen the subject of executive control function (ECF) for this report because of its impression that ECF is vital to human autonomy and a major determinant of problem behavior and disability in neuropsychiatric disorders. The core of this review is based on a literature search conducted in the spring of 1998. It was the Committee's intention to examine factor analyses of putative executive measures, community-based epidemiological studies of the prevalence of ECF impairment, and placebo-controlled clinical trials with executive outcome measures. All English-language articles and reviews published after 1966 that contained the keywords "frontal" or "executive" and were listed in the MEDLINE, EMBASE, PsychLit, or PsycINFO databases were considered. These articles were then separately cross-indexed with the keywords "controlled" (including both "placebo controlled" and "controlled clinical trial" subheadings), "prevalence," and "factors." Broad terms were used because of our impression that few data would be available at this stage in the literature's development. Peer-reviewed articles were re-

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tained. As we expected, very few relevant articles were identified. However, the original search was then further supplemented by backtracking to original sources and scholarly reviews of related topics. In addition, the original computer search strategy was repeated in January 2001 to take advantage of the exponentially increasing volume of research in this area.

In this review, we hope to provide a comprehensive, albeit still superficial, overview of the progress in ECF assessment. This concept is rapidly evolving across a wide range of disciplines. We first discuss the history of ECF and review its anatomical substrates. Then we address the obstacles to defining an executive "gold standard." Next we examine recent functional neuroimaging studies. These have raised important questions about the localization of executive processes. We explore the relevance of ECF to various neuropsychiatric disorders. ECF may be particularly relevant to disability and problem behavior. Finally, we examine the possibilities for treatment of ECF impairment and suggest an agenda for future research.

HISTORICAL BACKGROUND

The "executive functions" broadly encompass a set of cognitive skills that are responsible for the planning, initiation, sequencing, and monitoring of complex goal-directed behavior. Although a coherent framework of executive control has yet to be developed, two central themes are emerging.

The first theme associates ECF with specific higher cognitive functions such as insight, will, abstraction, and judgment, which are mostly dependent on the frontal lobes.[1,2] This view implies that, like memory or language, the executive *cognitive* functions are acquired skills that can be directly measured. ECF impairment results in the loss of these capacities.

The second theme emphasizes the cybernetic (from the Greek *kybernetes*, meaning "pilot") aspects of executive function. Executive functions *control* the execution of complex activities. This view implies first that ECF interacts with nonexecutive processes, and second that ECF impairment is made visible only via the disorganized operations of nonexecutive domains. The cybernetic view of frontal function is not necessarily incompatible with the older emphasis on higher cognitive abilities, but it does bring a new emphasis on the dynamic interactions between frontal control systems and the processes they interact with.

The frontal lobes have been associated with the "higher" cognitive functions since at least the famous case of Phineas Gage.[3] However, the more limited sense of executive control has only recently emerged. This concept follows efforts to apply cybernetic principals to human behavior. For example, Miller et al. in 1960[4] applied the systems engineering concept of "TOTE" (Test Operate Test Exit) procedures to human cognition. Luria in 1969[5] initiated the modern era of clinical executive function assessment with his careful descriptive study of frontal head injuries among World War II veterans. In his book *The Working Brain* (1973),[6] he described the clinical manifestations of disruption to a functional system for the "programming, regulation, and verification" of behavior. As early as 1977, Butterfield and Belmont[7] described executive function as the faculty in use "[when] a subject spontaneously changes a control process . . . as a reasonable response to an objective change in an information processing task" (p. 244). Norman and Shallice developed the concept of a "supervisory attentional system" in 1980.[8] This idea has been further refined into the "central executive,"[9,10] although the nature and functions of the central executive are still a matter of debate.[11–13]

Clinicians soon associated frontal lobe injuries with the loss of behavioral regulation predicted by Shallice, Norman,[14,15] and Duncan.[16] Meanwhile, Marsden in 1982 pointed to the notable role of the basal ganglia in organizing and controlling motor actions.[17] Major advances followed the work of Alexander and colleagues.[18,19] Working with primates, they demonstrated that the frontal lobes were associated with distinct basal ganglia–thalamocortical circuits. Lesions to these circuits produce "frontal lobe" behavior and personality changes. Moreover, Goldman-Rakic and colleagues demonstrated that the effects of frontal cortical lesions can be reproduced all along the related circuit.[20–23] This research explained the appearance of "frontal" syndromes following subcortical lesions and greatly expanded the list of conditions that could potentially affect executive control.

In 1990, DeKosky and Scheff[24] identified mesiofrontal synaptic density as the strongest pathological determinant of dementia severity ratings that has yet been reported in Alzheimer's disease (AD). This finding opens up the possibility that frontal pathology, and by extension ECF impairment, may be the essential feature of dementia. Later studies have shown that only pathology in the frontal cortex (or select afferents) is both necessary and sufficient to explain the clinically recognized dementia in AD[25] and non-AD dementias.[26]

Concurrent with these developments, researchers using functional imaging began to identify frontal metabolic deficits and correlate them with clinical pathology in conditions as diverse as schizophrenia, major depression, and attention-deficit/hyperactivity disorder

(ADHD). These and other clinical correlations led, in 1994, to the inclusion of ECF in the American Psychiatric Association's definition of dementia.[27]

However, the clinical assessment of executive function has lagged behind these advances. This is partly because of the lack of suitable measures. The Stroop Color/Word Interference Test (Stroop), the Trail Making Test Part B (Trails B) of the Halstead-Reitan battery, the Conceptualization Task of the Dementia Rating Scale, and a variety of other tests of abstraction and mental control have been offered as putative ECF measures.[28] The Wisconsin Card Sorting Test (WCST) is perhaps the best described ECF test (see box, p. 391), but these and other formal executive measures are often impractical for widespread use outside of academic settings.

In 1990, Kaye et al. introduced the Behavioral Dyscontrol Scale (BDS), a brief compilation of clinical items adapted from the work of Luria.[29,30] In 1992, Royall et al. introduced the Executive Interview (EXIT25),[31] followed in 1998 by CLOX: An Executive Clock Drawing Task.[32] Most recently, the Frontal Assessment Battery (FAB)[33] has been introduced. This instrument is similar to the BDS and the EXIT25 in that it is a compilation of simple clinical ECF assessments. However, the FAB differs from earlier measures in that its item set was designed to elicit several distinct executive tasks, each of which can be significantly correlated with frontal metabolic changes.

Another approach to ECF assessment has been to identify the behavioral sequelae of executive dyscontrol and to measure these. Behavior rating scales, such as the Neuropsychiatric Inventory (NPI),[34] contain subtests for behaviors that have been specifically associated with frontal lesions. The Behavioural Assessment of the Dysexecutive Syndrome (BADS)[35] and the Frontal Lobe Personality Scale (FLOPS)[36] have been explicitly developed to measure "dysexecutive" behavior syndromes.

This new generation of ECF instruments can be administered by clinicians in almost any setting. Consequently, executive impairment has been demonstrated in almost every major neuropsychiatric disorder (reviewed below). In many of these conditions, measures of executive function are more strongly associated with functional status, level of care, and need for services than are either syndrome-specific positive symptoms (e.g., psychosis, mood disturbance, or memory loss) or nonexecutive cognitive domains.

ANATOMICAL SUBSTRATES OF ECF

The Prefrontal Cortex

The role of the prefrontal cortex in executive function is suggested by its unique structure and pattern of connectivity.[37] The prefrontal cortex (Brodmann areas [BA] 8–11, 24, 25, 32, 45–47) comprises more than 30% of the brain's weight and surface area. It is a phylogenetically recent structure, representing only 10% to 20% of the primate brain.[38]

The frontal cortex can be grossly divided into two cytoarchitectural regions. The posterior portion is "agranular" in nature. This term refers to the minimal representation of the internal granular layer IV in posterior frontal cortical sections. In contrast, the regions that are most closely associated with executive function (e.g., the anterior ["prefrontal"] portion of the frontal lobes, which comprises the dorsolateral and orbital/medial regions) consist of "granular cortex." This term refers to a cortical architecture in which layer IV is distinct and well developed. Layer IV is most developed in BA 46 and becomes progressively less distinct as one moves ventrally and posteriorly from there.

Cortical layer IV is rich in inhibitory GABAergic interneurons. These interneurons receive input from bioaminergic nuclei in the brainstem and "feed forward" to provide inhibition to local pyramidal cells in cortical layers III and V. GABAergic interneurons have been implicated in the executive impairments of schizophrenia[39] and may represent one of the principal targets of atypical neuroleptics.

Several unique aspects of the prefrontal cortex suggest that it mediates ECF. First, the prefrontal cortex is connected to more brain regions than any other cortical region. Only the primary sensorimotor cortices and subcortical sensorimotor relay nuclei do not have direct or simple indirect connections to the prefrontal cortex. Second, the frontal cortices are "metamodal": they receive direct cortical input only from other heteromodal association areas. Thus, they are positioned to act on information that has already been processed at lower levels. The integrative nature of prefrontal regions is reflected even at the cellular level. Many frontal neurons increase their firing rate in response to the *combined* activity of sensory and motor regions. Additionally, frontal firing patterns may be altered by manipulating the motivational importance of environmental stimuli. Third, the prefrontal cortex is the major neocortical target for information processed in the limbic circuits. It is the only cortical region positioned to integrate cognitive and sensorimotor information with emotional valences and internal motivations. Fourth, although wide areas of the cortex project into the basal ganglia–thalamocortical circuits, the prefrontal cortex is that system's major target. Thus, the frontal lobe is the only cortical region capable of integrating motivational, mnemonic, emotional, somatosensory, and external sensory information into unified, goal-directed action.

In addition, the prefrontal cortex has bilateral connections to the basal ganglia–thalamocortical circuits' targets in the thalamus. Similarly, the prefrontal cortex has bilateral connections to its afferents in the parietal, temporal, and occipital association cortices, the limbic circuits, and the major brainstem biogenic aminergic nuclei, as well as to the cholinergic neurons of the nucleus basalis of Meynert. These connections put the prefrontal cortex in a unique position to modify the information it acts on. Moreover, in the case of the major brainstem bioaminergic nuclei, which project diffusely to the cortex, the prefrontal cortex is positioned to indirectly influence the activity of the nonfrontal cortex as well.

Frontal Basal Ganglia–Thalamocortical Circuits

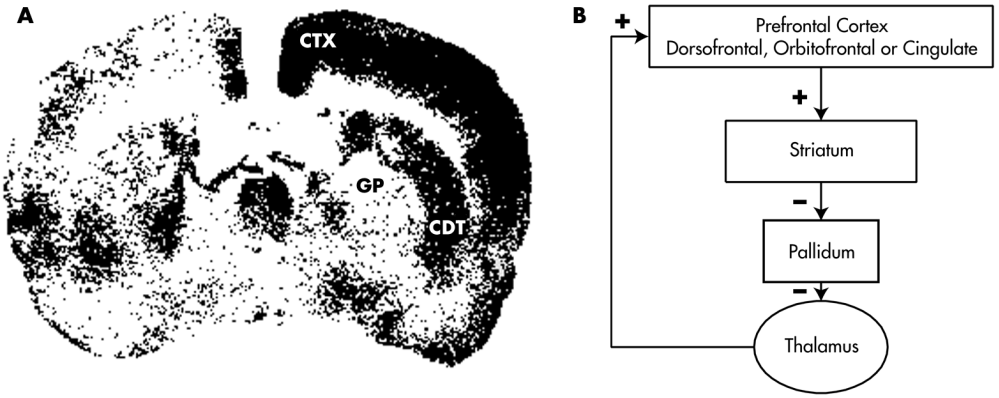
Certain subcortical lesions can affect ECF either directly or indirectly via frontal cortical metabolic changes (e.g., by diaschisis). The caudate, putamen, pallidum, nucleus accumbens, and thalamus are related to the frontal cortex through basal ganglia–thalamocortical behavioral control "circuits" (Figure 1A).[19,40,41] Although each of these circuits passes through different structures, all of the frontal circuits are similar in design.

The neurochemistry of these circuits' connections is known.[42] Excitatory glutamatergic fibers from the cortex project to the neostriatum (caudate, putamen); then inhibitory GABAergic fibers project to the globus pallidus/substantia nigra and from there to specific targets in the thalamus. These connections form dynamically balanced direct and indirect circuits connecting the prefrontal cortex to the thalamus. The thalamus closes the circuit by projecting back to prefrontal cortical regions via stimulatory glutamatergic fibers. Cholinergic projections to the frontal cortex facilitate thalamic activation of that structure. Dopamine (DA) projections from the ventral tegmentum also innervate the cortex. DA projections from the nigra innervate the striatum.

In each circuit, the corresponding frontal cortical region and striatum receives inputs from cortical regions that are more posterior.[43–46] These inputs provide insights into each circuit's functional role by revealing the processes with which it interacts. The dorsofrontal circuit receives information from the parietal and temporal cortex. These regions provide access to complex spatial and temporal information. The orbitofrontal circuit receives input from visual and auditory processing areas in the occipital and temporal lobes, as well as limbic centers in the amygdala and temporal poles. The anterior cingulate/mesiofrontal cortex receives input from the hippocampus, amygdala, and paralimbic cortex. Some authors have labeled the anterior cingulate circuit "paralimbic" for this reason.

Several aspects of this circuitry also deserve special mention. First, these circuits funnel information from widespread cortical areas into relatively small thalamocortical targets. These targets are all in the prefrontal cortex, consistent with the role of these circuits in behavioral/cognitive control. Second, the behaviors that mark each circuit can be reproduced by lesions at various points along their path. For example, the ability to perform certain visuospatial "working memory" tasks (which involve the short-term maintenance of information during its manipulation) is dependent on the integrity of the dorsolateral prefrontal cortex.[23] However, the same tasks are disrupted by lesions to the caudate[20] and to the mediodorsal thalamic nucleus[21,22] in the dorsofrontal circuit. This association suggests that frontal cortical damage is a sufficient but not a necessary cause of

FIGURE 1. Functional sequelae of caudate impairment (adapted from Kelly & McCulloch[87]). A: A functional lesion to the left caudate–putamen (CDT) results in disinhibition of the ipsilateral globus pallidus (GP), with resultant inhibition of the thalamus (Thal) and loss of cortical tone (CTX). B: These relationships are predicted by the basal ganglia–thalamocortical circuit anatomy of Alexander et al.[19] and can explain the loss of executive control following subcortical lesions in such circuits.



executive dyscontrol. Finally, the circuits appear to be discrete (i.e., nonoverlapping) and spatially constrained. At the level of the cortex, they are widely separated. Cortical lesions can divorce the behaviors associated with one circuit from another. Subcortically, however, the circuits are in much closer proximity. This anatomy suggests that subcortical pathology is likely to lesion multiple circuits simultaneously, mixing the syndromes together.

Three frontal circuits are particularly relevant to executive control: the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit, and the anterior cingulate circuit.[18,47]

Dorsolateral Prefrontal Circuit: The dorsolateral convexities of the frontal lobes consist of BA 8–12, 46, and 47. The blood supply for these regions is from the middle cerebral artery. In the dorsolateral circuit, corticofugal pathways project to the dorsolateral caudate nucleus, which also receives input from the posterior parietal cortex and the premotor area. The circuit then connects to the dorsolateral portion of the globus pallidus and the rostral substantia nigra reticulata and continues to the parvocellular region of the medial dorsal and ventral anterior thalamic nuclei. The circuit is closed via thalamic projections back to the frontal dorsolateral convexity. Lesions to this circuit have been implicated in a variety of higher cognitive functions, including goal selection, planning, sequencing, response set formation, set shifting, verbal and spatial working memory, self-monitoring, and self-awareness (metacognition).[38,48–52] The WCST consistently activates dorsolateral frontal regions.

Lateral Orbitofrontal Circuit: The "orbit" of the frontal lobes refers to a continuous region including ventral anterior and inferior lateral regions (BA 10–15 and 47). Medial regions are vascularly supplied by the anterior cerebral artery, and lateral regions lie in the territory of the middle cerebral artery. Cortical projections terminate on the ventromedial caudate nucleus, which also receives input from other cortical association areas, including the superior temporal gyrus (auditory) and inferior temporal gyrus (visual), as well as brainstem regions (e.g., the reticular formation). Projections continue to the dorsomedial aspect of the internal globus pallidus and to the rostromedial portion of the substantia nigra reticulata. Pathways continue to the magnocellular region of the medial dorsal and ventral anterior thalamic nuclei, and then return to the lateral orbitofrontal region.

The orbitofrontal circuit appears to be involved in the initiation of social and internally driven behaviors and the inhibition of inappropriate behavioral responses.[48,52] Orbitofrontal function may be particularly relevant to risk assessment. Choosing between small but likely rewards and large yet unlikely rewards activates inferior and orbitofrontal regions.[53] Impairment on the "go/no-go" task has been associated with orbitofrontal lesions in animals[54] and humans.[55] Orbitofrontal lesions also lead to clinical features such as environmental dependency and utilization behavior.[56–58]

Anterior Cingulate Circuit: Frontal regions involved in this circuit are medially located (BA medial 9–13, 24, and 32), and receive their blood supply from the anterior cerebral artery. The circuit connects to the ventral striatum (nucleus accumbens and olfactory tubercle), which receives additional input from "paralimbic association" cortex, including anterior temporal pole, amygdala, inferior hippocampus, and entorhinal cortex. The circuit continues to the ventral pallidum and rostrodorsal substantia nigra, and then to the medial dorsal thalamic nucleus. It terminates at the anterior cingulate, completing the circuit.

The anterior cingulate is important in monitoring behavior and error correction. The Stroop activates the anterior cingulate and its mesiofrontal extensions.[59] The EXIT25[31] has also been specifically associated with left mesiofrontal cerebral blood flow by single-photon emission computed tomography (SPECT).[60]

OBSTACLES TO DEFINING AN EXECUTIVE "GOLD STANDARD"

One of the obstacles to ECF research has been the lack of a clear "gold standard" measure against which putative ECF measures can be compared. This measure would presumably call upon specific frontal functions and be selectively vulnerable to frontal pathologies. However, this may not be an achievable goal for three reasons. First, since the frontal lobe represents so much of the brain's weight and surface area, it seems unlikely that any one measure could assess its functions comprehensively. We may be searching for a frontal-executive battery, not an executive measure. Second, the anatomy of frontal systems suggests that specific subcortical pathologies are also relevant to ECF. Thus, we may not even be looking for a frontal battery so much as a frontal *system* battery. Finally, the cybernetic character of ECF implies an intimate relationship between ECF and its associated targets. We will need to qualitatively distinguish between the loss of executive control over a non-executive domain and a primary disruption of the domain itself.

For example, although some tasks (e.g., the WCST, the

Stroop, the Category Test, the EXIT25, and Trails B) have been specifically associated with frontal structural or metabolic changes,[61–66] they can also be affected by more posterior lesions.[67–70] WCST performance is not specific for frontal lobe damage unless deficits in comprehension or visual search are controlled.[71] Furthermore, both the WCST and the Stroop measure multiple dimensions of executive control in factor-analytic studies. These dimensions may not be localizable to the frontal lobes even if frontal systems are a major determinant of their variance.

Peterson et al.[59] provide an example of this problem for the Stroop. This measure activated multiple nonfrontal cortical regions, which in turn resolved themselves into seven discriminable factors. These factors were interpreted as representing distributed neuronal networks supporting error monitoring, working memory, selective attention, and motor planning (among others). Although several Stroop factors shared the anterior cingulate, cingulate activation does not uniquely explain Stroop variance, and many nonfrontal lesions have the potential to affect Stroop performance. Nevertheless, activation studies have been criticized for their sensitivity to "subclinical" differences in performance.[72] Frontal lesions selectively affect the Stroop in actual patients.[73] Thus, poor Stroop performance may yet be indicative of frontal pathology, despite the complexity of activation studies.

It appears that neither the measures used to assess ECF nor the biological substrates they activate are easily localizable. Four important dichotomies need to be addressed before these apparent discrepancies can be resolved. Each will be discussed in turn.

1. *Frontal Lobe vs. Frontal System:* Frontal cortical lesions may be sufficient, but are not necessary causes of executive impairment.
2. *Structure vs. Function:* Frontal cortical function may be compromised by subcortical lesions (i.e., vascular disease) in the absence of demonstrable local cortical pathology.
3. *Control vs. Process:* Executive functions control performance in other neuropsychological domains. Some tasks that were previously ascribed to nonexecutive domains may be sensitive to frontal system pathology because they require executive control. Conversely, lesions outside the frontal systems may undermine ECF test performance, in the absence of executive dyscontrol, by disrupting the processes being controlled during the task.
4. *Executive Function vs. Executive Function(s):* Some measures may be sensitive to only a subset of executive functions.

Frontal Lobe vs. Frontal System

It has proven difficult to localize specific executive operations to specific prefrontal regions. Rather, ECF may depend on the integrity of frontal systems. For example, L'Hermitte et al.[57] have described the phenomenon of "utilization behavior" (in which a patient automatically utilizes a familiar object in a habitual way, regardless of its appropriateness to the current context) following orbitofrontal lesions. The same behavior has been described following massive bilateral frontal lesions[74] and mesiofrontal lesions,[75] both of which might involve orbitofrontal regions. However, utilization behavior has also been reported following lesions to other frontal system structures, including the caudate[76] and thalamus.[77] The unity of frontal circuit activity can be deduced from factor analyses of regional brain metabolism: 70% of regional variance in total cerebral glucose utilization can be explained by a single factor that contains the frontal circuits (e.g., the frontal cortex, cingulate gyrus, caudate nucleus, putamen, and thalamus) and temporal cortex.[78]

There may be several reasons for the difficulty in making clinicopathological correlations between ECF and frontal lesions: 1) the taxonomy of executive impairments has not been adequately developed—many authors may not be comparing identical phenomena; 2) although discrete prefrontal pathways have been partially established, precise anatomical boundaries are not well defined, especially at the cortical level, and certain frontal functions are limited to subregions of traditional BA regions of interest;[79] 3) lesions to the frontal lobes are often not well defined or do not follow clear and reproducible boundaries across subjects (e.g., most frontal strokes cause additional damage to subcortical or posterior regions); 4) frontal lobe pathology, such as tumors, stroke, or trauma, frequently results in remote effects secondary to vascular changes, pressure effects, and disconnection of neural pathways. Data from psychosurgery (tumor evacuation or frontal leukotomy) can be especially difficult to interpret for several reasons: a) these studies often use abnormal patients to begin with, b) cognitive outcome assessment is often rudimentary, and c) follow-up is typically short term (i.e., months rather than years).

Nonetheless, it now appears that there are regional differences in behavioral sequelae of frontal cortical lesions.[5,38,80–82] Damage to the dorsolateral prefrontal cortex impairs planning, hypothesis generation, and behavioral control. Episodic memory encoding and retrieval is affected by ventrolateral lesions. Working memory is affected by more dorsal pathology. Orbitofrontal lesions lead to impaired insight, judgment, and impulse control. These traits were part of Phineas Gage's deterioration. Mesiofrontal/anterior cingulate le-

sions lead to indifference and attentional dyscontrol. Patients generate little speech or behavior spontaneously, yet may respond correctly if prompted.

Moreover, the dysexecutive neuropsychological profile of prefrontal *cortical* disorders such as frontotemporal dementia can also be observed in *subcortical* frontal system disorders such as Parkinson's disease (PD), Huntington's disease (HD), progressive supranuclear palsy,[83] or subcortical vasculopathy.[84] Even neuropsychiatric disorders such as major depression and schizophrenia are associated with a similar pattern on psychometric testing, suggesting that they too may involve frontal system pathology.[85,86]

In summary, executive functions have been difficult to localize within the frontal cortex. This situation might be improved with more careful attention to lesion location and a formal approach to frontobehavioral nomenclature. Nonetheless, the logic of frontal basal ganglia–thalamocortical networks suggests that frontal system lesions are both sufficient and necessary to executive impairments.

Structure vs. Function

Another dichotomy that deserves attention is that between frontal structure and function. Executive control can be compromised without a frontal cortical lesion. Frontal function can be indirectly affected by lesions to frontal lobe afferents or related frontal system circuit structures. Conversely, lesions to corticofugal tracts can disconnect the frontal operations from the processes they control.

Human and animal studies suggest that subcortical lesions to frontal system networks may remotely affect frontal cortical metabolism (e.g., by diaschisis), either increasing or decreasing frontal metabolism. Figure 1A presents the results of a study by Kelly and McCulloch[87] in which rats received a 500-ng injection of muscimol (a GABAergic agonist) to the left caudate nucleus. This lesion resulted in a functional caudate lesion on that side. The effects of this lesion were studied using [^{14}C]2-deoxyglucose autoradiography. Brain regions that were metabolically active at the time of injection took up this radioligand. Regions that were metabolically inactive, including the left caudate, did not take up the tracer. In each section, the right (unaffected) side served as the left's control.

Figure 1B demonstrates that the caudate lesion resulted in disinhibition of the ipsilateral globus pallidus, leading to increased inhibition of the ipsilateral medial thalamic nucleus, resulting in reduced activation of the ipsilateral cortex. In short, a discrete subcortical lesion in frontal networks may lead to remote changes in frontal cortical metabolic function. This finding can be understood in the context of frontal circuit anatomy (Figure 1A) and may help to explain the finding of frontal behavioral syndromes and ECF impairment in subcortical dementias,[88] as well as the specific association between subcortical vasculopathy and frontal hypometabolism in vascular dementia (VaD) and late-onset major depression.[89–91]

Patients with PD, major depression, and schizophrenia often appear "hypofrontal" by functional neuroimaging.[92–95] In PD and major depression, this may be related to cortical deafferentation of medial nigral or ventral tegmental DA inputs.[96] The hypofrontality of both disorders is associated with tests that are linked to DA physiology.[97,98] Alternatively, these deficits might be related to cortical deafferentation of the thalamic inputs.[19,90,99] Medial thalamic infarction results in frontal cortical hypometabolism by positron emission tomography (PET) and SPECT.[100,101] Thalamic outputs to the frontal cortex can be disrupted indirectly after globus pallidus lesions.[102]

However, executive impairments are not only associated with frontal hypometabolism. In obsessive-compulsive disorder (OCD), cortical hypermetabolism[103] is associated with poor performance on ECF measures.[104] Similarly, in HD the degree of prefrontal activation during the WCST is inversely proportional to the subject's performance, yet is statistically associated with the amount of caudate atrophy.[105]

These seemingly paradoxical findings may be understood from the point of view of frontal systems physiology. OCD has been associated with hypometabolism in the globus pallidus and thalamic disinhibition. Thalamic disinhibition might result in increased thalamocortical glutamatergic tone (Figure 1A). Thalamocortical glutamatergic inputs co-localize with inhibitory dopamine D_1 receptors on pyramidal cell dendrites in the prefrontal cortex.[40] The balance between these opposing influences affects prefrontal signal-to-noise processing.[106] Either increasing glutamatergic excitation or diminishing dopaminergic pyramidal cell inhibition should lead to increased pyramidal cell activity, at the expense of signal specificity. A precise range of DA receptor activity within the prefrontal cortex must be maintained for optimal function.[107–108] In the case of OCD, DA's inhibitory effects may be overwhelmed by increased glutamatergic tone.

In summary, executive control depends on the integrity of frontal systems. Executive impairment may follow disruption of frontal system information processing, regardless of the location of the lesion within the system or the direction of the perturbation. In some cases, remote lesions can affect processing within the frontal circuits.

Control vs. Process

Lezak[28] has offered a simple test for defining what constitutes an "executive" measure. Questions about executive functions explain "*how* or *whether* a person goes about doing something . . . questions about [traditional] cognitive functions are generally phrased in terms of *what* or *how much*." (p. 42). This simple dichotomy cleaves the vast array of frontal functions into control functions and their target processes. Either may be dependent on frontal activities; however, only the control functions are "executive" in a cybernetic sense. The subset of frontal functions that are "executive" depends on how the question is asked (Table 1).[28]

This distinction can be addressed experimentally. For example, there is an extensive literature associating schizophrenia with deficits on the WCST. However, patients with schizophrenia benefit from cueing during the WCST test procedure.[109] In other words, they can *generate* the abstract concepts demanded by the task, but they do not *apply* them unless prompted. Thus, although the abstract concept formation demanded by the WCST may in fact be localizable to the frontal lobes, it is not necessarily an executive control function in the limited sense required by Lezak because it merely addresses what patients *can* do and not whether they do it when needed. In contrast, the failure of patients with schizophrenia to inhibit automatic but inappropriate verbal responses on tests such as the Stroop[110] would be more consistent with Lezak's view of executive control.

Authors who emphasize a cybernetic view of ECF point to the potential to observe executive *dyscontrol* in performance on many seemingly "nonexecutive" tasks.[12,111] By analogy, at least some variance in all neuropsychometric tests may be specifically attributable to the executive control demanded by the testing paradigm (see "g" below). We will examine the executive control of clock drawing, memory, and language.

The clock-drawing task (CDT) has traditionally been viewed as a visuospatial task, sensitive to right hemisphere pathology.[112] However, frontal leukotomy selectively affects CDT performance relative to age, disease, and education-matched control subjects.[113] CDT failures among frontally impaired subjects challenge a chiefly visuospatial conceptualization of the CDT and suggest the need for a separate analysis of the executive control demanded by the testing paradigm.

Figure 2 presents a patient's performances on CLOX, an executive CDT.[32] CLOX1 is an unprompted task. CLOX2 is a copied version. The visuospatial components of these tasks are similar. However, CLOX1 entails executive control because it requires the subject to generate a figure in the absence of relevant visual cues. The validity of CLOX1 as an executive paradigm is suggested by the fact that, in elderly retirees, both CLOX1 and the EXIT25, but neither CLOX2 nor the Mini-Mental State Examination (MMSE) makes significant independent contributions to the number of categories achieved on the WCST.[114] Figure 2 presents the pattern of CLOX performance expected in a frontal system disorder. Executive measures (the unprompted CLOX1 and the EXIT25) are impaired. CLOX2 (copied) and the MMSE are not.

The same qualitative dissociation between control and process can be elicited in other domains, such as memory. Memory tasks can be affected by frontal, parietal, and mesiotemporal cortical lesions. However, the pattern of memory loss that follows frontal system lesions is discriminable from traditional limbic amnesia.[115–119] The ability of a "memory" task to activate dorsofrontal systems depends greatly on the structure provided to the subject during memory testing.[120,121] For example, the intentional, goal-directed retrieval of information results in frontal activation relative to incidental cued recall.[122] Patients with frontal lesions are unimpaired in their ability to recall cued information, but have difficulty with tasks that require them to organize, sequence, or monitor the information themselves. Thus, they have trouble with free recall, temporal order, and

TABLE 1. Examples of executive and nonexecutive frontal capacities (after Lezak[28])

This model emphasizes that executive control may be either only a subset of frontal functions or an emergent property of frontal systems. For example, the capacity to formulate an efficient problem-solving strategy, or to anticipate likely outcomes, although perhaps related to the frontal cortex, is not necessarily an "executive" skill. In contrast, the loss of executive control following frontal system lesions divorces capacity from its successful implementation.

Nonexecutive "frontal" capacities:
1. Can the patient form efficient problem-solving strategies?
2. Can the patient use past experience to anticipate future problems?

Similarly, we might ask:
Can the patient abstract?
Can the patient self-monitor his or her behavior?
Can the patient anticipate future consequences of his or her actions?
Can the patient give a reason for his or her actions?

"Executive" frontal system capacities:
1. Does the patient disregard nonadaptive strategies?
2. Does the patient modify ongoing behavior in response to dynamic task requirements?

Similarly, we might ask:
Does the patient remember what's important?
Does the patient get where he or she needs to go?
Does the patient make appropriate decisions?
Does the patient finish what he or she starts?
Does the patient comply with treatment?

source memory. Similarly, confabulation among amnestic subjects appears to reflect mesiofrontal/anterior cingulate impairment, resulting in a failure to ignore active but currently irrelevant memory traces.[123]

Not all memory tasks that activate frontal regions are necessarily "executive." In neuroimaging studies, tasks that call for relatively simple episodic or semantic encoding tend to activate the left ventrolateral prefrontal cortex.[124] Those that call for retrieval activate the right ventrolateral prefrontal cortex. However, if the subject is asked to manipulate the information while encoding or retrieving it, the focus of activation shifts toward more dorsolateral regions.[125]

Language skills are also affected by ECF impairment. Arbuckle and Gold[126] have associated disorganized and hyperverbose speech, but not language impairment per se, with impaired working memory and executive control. Similarly, only a small amount (25%) of variance in verbal fluency scores can be explained in multivariate regression models by tests of verbal memory, verbal attention, and vocabulary.[127]

The idea that ECF may explain some variance in most cognitive measures, regardless of the domains they purport to measure, is similar to Spearman's concept of "general intelligence" or "g."[128] "g" represents the shared variance across domains and has been repeatedly observed in batteries of multiple cognitive measures. For example, in normal aging there are significant declines in cognitive test performance across several domains. Salthouse et al.[129] found moderate age-related declines on a battery of tests that included the WCST, Trail Making, Wechsler Adult Intelligence Scale–Revised (WAIS-R) Block Design, and Digit Symbol Substitution (DSS).

However, correlation-based analyses revealed that the age-related effects on different measures were not independent. Instead, the effect of age was observed specifically in the fraction of variance (averaging 58%) *shared* across all measures (i.e., "g"); "g" has been localized to dorsolateral prefrontal cortex by PET[130] and associated with working memory (also associated with dorsolateral prefrontal cortex; see below)[131,132] and with formal executive measures.[133]

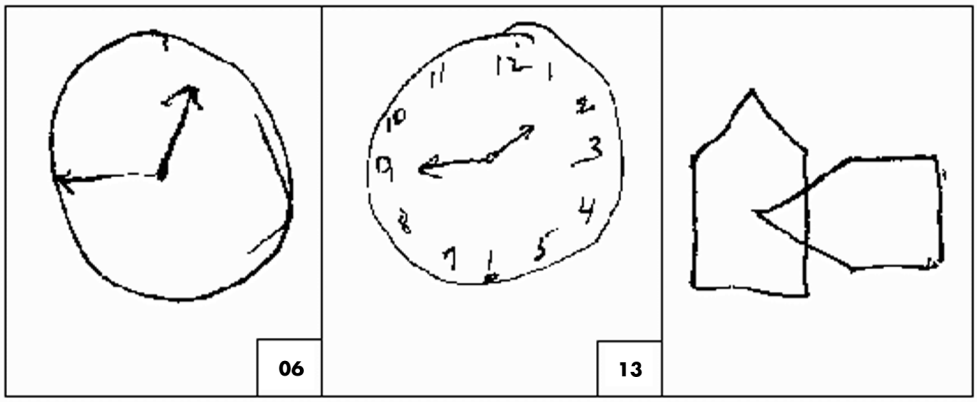
In summary, there is no established framework for interpretation of the executive functions. Some authors emphasize the frontal lobes and their importance in planning, hypothesis generation, and abstraction. Others, however, work within a more limited subset of frontal functions. These authors see ECF as a specific subset of frontal lobe activities, revealed by the examination of how the frontal systems interact with other systems to produce and control complex goal-directed activities.

Executive Function vs. Executive "Function"

Another dichotomy that has yet to be resolved is whether there is a single executive control, as opposed to multiple controls for discrete operations. The idea of a single executive is implied in the concept of the "cen-

FIGURE 2. CLOX performance in subcortical frontal system vasculopathy. Results shown are for a 77-year-old right-handed male with type 2 frontal system vascular dementia. CLOX1 is represented at left, CLOX2 at center; at right, the patient's MMSE pentagon item is provided for comparison. Total CLOX scores appear in the box below each drawing. CLOX is scored on a 15-point metric; lower scores indicate impairment.

The CLOX has been normed to young adult control subjects. A CLOX1 score of 10/15 or a CLOX2 score of 12/15 represents the 5th percentile for young adults. The pattern of CLOX scores obtained by this patient suggests the loss of executive control over intact constructional skills. An isolated impairment in ECF is supported by his other test scores: EXIT25, 19/50 (scores>15/50 impaired; 18/50 is the mean for elderly retirees living in assisted living settings),[251] and MMSE, 29/30 (scores <24/30 impaired). His ECF impairment affects memory functions as well. He freely recalls only 2 of 4 words after distraction on the Memory Impairment Scale,[296] but recalls 4 of 4 with cues (total MIS score 6/8).



tral executive" and the multimodal nature of the frontal lobe's anatomy and functional connections. Researchers have developed computer models of subject task performance on putative "frontal" measures that successfully model patient task performance on four frontal tasks (the WCST, the Stroop task, motor sequencing, and a context-dependent memory task).[134] Frontal-type errors on all tasks can be observed after degrading a single domain (working memory).

However, patients with frontal lesions often display disassociations in their performance on select frontal tasks. This effect might be due to regional differences in the types of processes to which frontal mechanisms are applied.[135] Although the frontal lobes appear to be less functionally committed than more posterior cortical regions,[136] their functions can be roughly divided along four spatial dimensions: left–verbal/right–nonverbal, anterior–cognitive/posterior–motor, ventral–perception/dorsal–action, and medial–internal focus/lateral–external focus. Thus, the verbal aspects of working memory tasks may activate the left dorsolateral prefrontal cortex and nonverbal aspects may activate the right.[137–139] Even within the domain of nonverbal working memory, recall of faces activates more ventral regions of the right dorsolateral frontal cortex than does recall of spatial location.[140] This functional specificity may go all the way down to the cellular level.[141]

Goldman-Rakic has suggested that different prefrontal areas may perform the same operation on different inputs.[23] This hypothesis is consistent with the functional segregation of the basal ganglia–thalamocortical circuits. Support for a modular organization of frontal function has been developed in humans.[142] Cognitive test performance is most closely related to dorsofrontal cerebral glucose metabolism, whereas social behavior and disturbances of comportment are related to mesio-/orbitofrontal metabolism. Similarly, dorsal regions of the anterior cingulate are activated by attention-demanding Stroop-like interference tasks, whereas ventral regions of the anterior cingulate respond when similar tasks are applied to emotionally laden content.[143]

Dimensions of Executive Control: There are many putative ECF measures[144] (Table 2). However, it is not at all clear that these all test the same dimensions of executive control. Our literature review identified several studies containing factor analyses of putative ECF measures (Table 3). Interpreting these studies can be difficult.[145] Few have been intentionally designed to address ECF. Prior to about 1998, most authors interpreted their results without regard to ECF or frontal function. Instead, factors with strong loadings by ECF measures were thought to represent "vigilance" or "attention." The differences between ECF and simple attention have been extensively studied.[146] It is relevant to the cybernetic formulation of ECF that "judgment," "concept formation," "problem solving," and "decision making" are seldom mentioned in factor analyses of ECF measures.

Putative ECF measures do not load onto a single, overarching executive construct. Most studies find multiple dimensions of executive control. The available studies tend to confirm a *rule discovery* factor labeled by

TABLE 2. Selected neuropsychological tests of "frontal" executive skills

Measures	Dimensions	Reference
Formal tests		
California Card Sorting Test	CG, P, I	Beatty & Monson 1990[297]
Category Test	CG, wM(v)	DeFilippis et al 1979[298]; Reitan & Wolfson 1995[299]
Concept Generation Test	CG, wM(v)	Levine et al 1995[300]
Porteus Mazes	P, wM(s)	Mettler 1952[301]; Porteus 1965[302]
Raven's Progressive Matrices	wM(s), CG	Raven et al 1977[303]
Stroop Color-Word Interference Test	I, wM(v)	Stroop 1935[304]
Tinker Toy Test	CG, wM(s)	Lezak 1995[28]
Tower of Hanoi	wM(s), P, I	Welsh et al 1990[305]
Tower of London	wM(s), P, I	Norman & Shallice 1980[8]; Shallice 1982[14]
Wisconsin Card Sorting Test	CG, P, I	Grant & Berg 1948[306]; Milner 1963[61]
Bedside screening instruments		
Behavioral Dyscontrol Scale	I	Grigsby et al 1992[30]
CLOX: An Executive Clock Drawing Task	wM(s), CG	Royall et al 1998[32]
Controlled Oral Word Association Test	CG, wM(v)	Benton & Hamsher 1989[307]
Design Fluency	CG, wM(s)	Jones-Gotman & Milner 1977[308]
Executive Interview (EXIT25)	I, CG wM(v & s)	Royall et al 1992[31]; Royall et al 1998[251]
Go/No-Go	I, wM(v)	Shue & Douglas 1992[309]
Trail Making Test, Part B	I, wM(s)	U. S. Army 1944[310]; Reitan 1958[311]; Reitan & Wolfson 1995[299]

Note: Dimensions of executive control functions (ECF) refer to those developed in factor-analytic studies, including Concept Generation (CG), Inhibition (I), spatial (s) and verbal (v) Working Memory (wM), and Planning (P).

tests such as the WCST categories; a *working memory* factor labeled by tests such as the California Verbal Learning Test, the Wechsler Intelligence Scale for Children–Revised (WISC-R), Digit Span (verbal), and the Tower of London (nonverbal); an *attentional control* factor labeled by tests such as the Continuous Performance Task or Digit Cancellation; and a *response inhibition* factor labeled by tests such as the WISC-R Digit Span Backwards, Trails B, or the Stroop. Rule discovery and working memory are most closely related to dorsolateral cortical function. Attentional control and response inhibition depend more on ventromedial regions.

These domains are fairly robust. Different authors have found the same instruments to load together in different samples. For example, Trails B and the Stroop co-label a single factor (*response inhibition*) in Grodzinsky and Diamond's study of boys with ADHD,[147] Robertson et al.'s study of normal adults,[148] Mahurin et al.'s study of schizophrenic patients,[149] and Arbuckle et al.'s study of elderly adults.[150] In addition, there is limited evidence that ECF factors are multimodal. For example, Taylor et al.[151] found that both verbal and design fluency tasks loaded on the same factor. This finding suggests that the executive control identified in this paradigm may be equally applicable to both verbal and constructional processes, presumably mediated by different cerebral hemispheres.

Unfortunately, most of the available ECF factor-analytic studies have methodological flaws. Large sample sizes are needed before stable factor structures can emerge. Executive and nonexecutive measures need to be included, and key reference measures should be used across samples to facilitate comparisons.

Two recent studies can serve as models for future work.[152,153] Kanne et al.[152] examined the factor structure of a comprehensive battery of neuropsychological measures, including several ECF measures, among 407 AD patients and 261 elderly control subjects. Control data exhibited a different factor structure than that found in data for AD patients. Control test scores loaded on a single factor (i.e., they showed high "g"). In contrast, the data from AD cases was best represented by a three-factor model. The authors labeled these factors Mental Control, Memory-Verbal, and Visuospatial. Digit Span, verbal fluency, and the Mental Control subtest of the Wechsler Memory Scale loaded on the Mental Control factor. This factor explained most of the variance in both early AD and moderately advanced AD subgroups. Autopsies were later performed on 41 AD subjects. Each factor was significantly correlated with the severity of AD pathology in a different cortical region. The "Mental Control" factor correlated significantly ($r = 0.39$, $P = 0.01$) with frontal cortical neurofibrillary tangle counts. Digit Symbol Substitution, a test that is often purported to measure ECF, did not load on the Mental Control factor, nor was it correlated with frontal pathology.

Miyake et al.[153] examined putative ECF measures, including the WCST, the Tower of Hanoi (TOH), random number generation (RNG), operation span, and dual tasking in a moderately large sample of college students ($N = 137$). A confirmatory factor analysis of these measures indicated three moderately correlated but discriminable factors, which they labeled Set Shifting, Inhibition, and Updating. Structural equation models showed that these three factors contribute differentially to each of the "complex" ECF measures. The Set Shifting factor contributed most to WCST performance, the Inhibition factor contributed most to TOH, and both Inhibition and Updating contributed to RNG. The Updating factor also contributed to operation span scores. This type of analysis reveals that 1) classical "ECF" measures are often multidimensional; 2) no single measure comprehensively assesses all ECF domains; and 3) specific combinations of ECF measures may compliment each other, while others may be redundant.

For a discussion of the Wisconsin Card Sorting Test as a possible gold-standard ECF measure, see box (p. 391).

FUNCTIONAL IMAGING AND EXECUTIVE CONTROL

Lesion studies associate *response inhibition* with the orbitofrontal region, *attentional control* with the mesiofrontal region, and *working memory* (verbal and nonverbal) and *rule discovery* with the dorsolateral region.[162] These observations are generally supported by neuroimaging. Bench et al.[65] studied the associations between a modified Stroop and regional cortical metabolism PET. During the Stroop's interference condition, the right orbitofrontal cortex and posterior parietal cortex were both activated (i.e., control and process). However, these regions may both be under the control of the anterior cingulate. The anterior cingulate is thought to be important in error detection and sequencing of ongoing action plans.[143] It has been shown to be activated by stimuli that are incongruent with expectation and that may need correction. Liotti et al.[163] have studied the temporal sequencing of cortical activity during the Stroop's interference condition, using event-related potentials (ERPs). Differences in ERP between Incongruent compared with Congruent trials first appear in the anterior cingulate (peaking at 410 ms), then in the temporoparietal cortex (500–800 ms post stimulus).

Working memory tasks activate dorsolateral prefron-

TABLE 3. Factor analyses including measures of executive control functions

Reference	*N*	Subjects	ECF Measures	Comments
Barroso 1983[312]	41	Volunteers	Stroop	Small *N*, but well ahead of its time. Stroop loads strongest on an "aspect of attention tapped whenever distractions must be overcome." Author identifies an "executive" factor best labeled by errors on a dichotic listening task that "controls other aspects of attention."
Goldberg et al 1988[313]	28	Schizophrenic patients	WCST, CT, Trails B, WF	No two load on the same factor. Note exceptionally small number of subjects.
Shute & Huertas 1990[161]	58	Young adult volunteers	CT, Trails A/B, WCST, DSS	Four factors explain 70% of variance. CT, WCST, perseverative errors, and Trails load on a single factor (19% of variance). DSS co-labels a second factor with Trails A.
Grodzinsky & Diamond 1992[147]	66 64	Boys with ADHD, ages 6–11 Controls	Stroop, Trails A/B, WF, WCST	ECF measures load on three factors. All WCST subtests co-label a single factor. Trails A/B and WF co-label a second. Stroop interference condition loads uniquely on a third.
Vanderploeg et al 1994[314]	115	Neurological patients	Trails B, DS, CVLT	Examines factor loadings of Trails B and DS on CVLT-derived factors. Five factors. ECF measures, CVLT "general learning" and CVLT "working memory" load on a single canonical correlate explaining 29% of variance in the data.
Greve et al 1995[315]	135	University students	CCST, Trails B, WCST	Four factors explain 94% of variance in a battery of ECF measures.
Seguin et al 1995[316]	177	Adolescent boys	DS, NCA, VF	Single "executive" factor labeled by NCA explains 15% of variance.
Deckel & Hesselbrock 1996[317]	83	Young adults +/– a family history of EtOH abuse	Trails B, CT, DS, WAIS-R Similarities	CT, Trails B, and Similarities load on a "frontal" factor that accounts for 56.3% of total variance ("g").
Giancola et al 1996[318]	291	Children ages 10–12 +/– a family history of EtOH abuse	PM	ECF tests loaded on a single factor, associated with aggressive behavior.
Goldman et al 1996[158]	343 356	Neurological patients Controls	WCST	Two factors derived from neurological cases: "perseveration" and "loss of set."
Levin et al 1996[169]	81 102	Children with closed head injuries Controls	WCST, TOL, CVLT, WF, design fluency	Five factors derived. WCST, verbal and design fluency co-label a single factor. TOL and CVLT load separately.
Mirsky 1996[160]	435	Children ages 7–9	WCST, DS, CPT	CPT, DS, and WCST load uniquely on separate factors. WCST categories and % correct load on a single factor.
Robertson et al 1996[148]	154	Adult volunteers	DS-backwards, Stroop, Trails B, WCST	ECF measures load on three factors. Stroop and Trails B co-label a separate factor than WCST categories. DS loads separately.
Taylor et al 1996[151]	53 170	Children surviving bacterial meningitis Controls	WF, DS	Five-factor solution explains 59% of total variance in a comprehensive battery. Three factors judged to be "executive," including "speed of processing," "inhibition," and "planning-sequencing." DS and WF load moderately on the "inhibition" factor.
Dowler et al 1997[319]	91 75	Spinal injury cases Controls	CVLT, DS, DSS, Stroop, WF, WCST	DS and WF label a single factor, separate from Stroop. WCST does not load significantly on any factor.
Greve et al 1997[320]	135	University students	WCST	Two factors explain 91% of WCST variance. The first, labeled "executive function," explains 70%. The second, labeled "attention," explains 21%.
Lundqvist et al 1997[321]	29 29	Patients with focal brain lesions Controls	DSS, Trails B, WCST	WCST labels an "executive capacity" factor, but DSS and Trails load separately. Patients performed significantly worse than controls only on the WCST's factor, but none of the tests predicted driving simulator performance.
Mariani & Barkley 1997[322]	30 34	Children with ADHD Controls	CPT, PM	Both label a single "working memory" factor.

Pennington 1997[323]	230 137 170	Reading-disabled children Co-twins Controls	CPT, WCST Also DS, RM, Stroop, Trails B in a subset ($n=145$)	In the larger sample, executive measures load on two factors, "inhibition" and "set shifting." Two additional factors extracted from the subset with more extensive testing: "working memory" and "Trails B." CPT labels "inhibition." DS labels "working memory"; WCST and RM label "set shifting." Trails B loads separately from the other measures.
Ardila et al 1998[324]	300	Normal volunteers ages 17–25	Complex battery that included "executive" measures and WAIS subtests	Five factors account for 63.6% of variance. "Executive" measures load on a single factor.
Burgess et al 1998[325]	92 210	Mixed neurology patients Controls	10 "ECF" indices derived from 6 neuropsychological measures	Factor analysis confirms three factors: "inhibition," "intentionality," and "executive memory."
Culbertson & Zillmer 1998[160]	129	Children with ADHD ages 7–15	TOL	Two executive factors: "concept flexibility" and "planning/inhibiton." Correlated, $r=0.42$
Della Salla et al 1998[326]	48	Patients with focal frontal lesions	DCT, EPM, HFT, WCFST, WF	In contrast to most other studies, a single factor explains 53% of the variance in the putative executive measures. Note small sample size.
Golden et al 1998[327]	112	Mixed brain injuries	WCST, CT	CT and WCST load on different factors; i.e., they are not interchangeable ECF measures. WAIS verbal tests load with WCST. Spatial tasks load with CT.
Kanne et al 1998[152]	407 261	AD Elderly controls	DS, DSS, WF, MC, Trails A	Controls have a different factor structure than AD. Control test scores load on a single factor ("g"). In AD, three factors are extracted: "mental control," "memory-verbal," and "visuospatial." DS, WF, and MC load on the "mental control" factor. 41 subjects later went to autopsy. The "mental control" factor correlated significantly ($r=0.39$; $P=0.01$) with frontal cortical NFT counts.
Koren et al 1998[328]	292 91 141	Patients with schizophrenia Nonaffected relatives Controls	WCST	Three factors extracted: "perseveration," "failure to maintain set," and "idiosyncratic sorting." Only "perseveration" factor distinguishes patients from control groups.
Mahurin et al 1998[149]	53	Hospitalized schizophrenic patients	WF, Trails B, DSS, DS, WCST, Stroop	Three factors: "verbal processing/memory," "cognitive flexibility/attention," and "psychomotor speed."
Pineda et al 1998[329]	124	Males ages 7–12	WF, WCST	Four factors, dominated by "abstraction and flexibility." This factor was impaired in ADHD.
Raz et al 1998[330]	95	Normal adults ages 18–77	WCST	WCST perseverative responses and perseverative errors load heavily on a single factor, "executive function," that explains 13.6% of variance in cognition. Prefrontal cortical atrophy by MRI correlates at –0.42 with this factor.
Robbins et al 1998[331]	341	Normal volunteers ages 21–79	TOL	Executive measures load distinctly from visual memory or learning.
Willis et al 1998[252]	65	AD patients ages 50–89 (mean = 73.87)	DS, DSS, Trails B, WF	Executive tests load on a single "executive" factor that explains 66% of their total variance. Each loads moderately, ranging from WF at 0.35 to DSS at 0.49. This "executive" factor contributes significantly to a model of functional disability, independently of a factor derived from "general cognitive measures," including MMSE and ADAS-cog.
Collette et al 1999[157]	20 20	AD Controls	HIT, SOPT	Two factors, labeling "inhibition" and "working memory." Inhibition, labeled by HIT, correlates significantly with left middle and superior frontal gyrus metabolism by PET. Working memory, labeled by SOPT, correlates with anterior cingulate metabolism.

(continued)

TABLE 3. *(continued)*

Reference	*N*	Subjects	ECF Measures	Comments
Deckel 1999[332]	68	Outpatients with EtOH abuse	WAIS-R, WCST, Trails B	Two ECF factors identified, one labeled by WCST, the other by Trails B and WAIS-R Similarities/Picture Arrangement. High MAC scores predicted by WCST.
Epsy et al 1999[333]	117	Preschool children	AB, DA, SR, CR, SC	Age predicts all tasks. Four factors derived.
Provinciali et al 1999[334]	83	Patients with multiple sclerosis, mean age 43.3 years	DSS, WF, WCST	Measures of depression/fatigue do not load on "frontal" factor.
Swanson et al 1999[335]	90	Children with reading disabilities	Verbal and spatial WM tasks	Verbal and spatial WM tasks load on different factors and are discriminable from phonological tasks.
Arbuckle et al 2000[150]	455	Elderly volunteers ages 63–93	Trails B, Stroop	Trails B and Stroop label a common factor.
Ardila & Pineda 2000[336]	156	Adults ages 26–60	WCST	13 nonverbal tests retained from a battery of 32 load on five factors. "Executive function" explains 30% of variance, independently of the others. Two factors explain 72% of the variance in five WCST indices. Few other studies include multiple WCST indices (see Grodzinski & Diamond 1992).
Cirino et al 2000[337]	57	Children ages 8–16 with Tourette's syndrome	WCST, CCST	Each ECF measure loads on a different factor. ADHD symptoms do not load on either ECF factor.
Miyake et al 2000[153]	137	College students	Simple tasks of inhibition, set shifting, updating, WCST, TOH, RNG, OS, DT	Confirmatory factor analysis indicates three moderately correlated but discriminable factors. Structural equation modeling showed that these three factors contribute differentially to each complex "frontal" measure. WCST: Shifting; TOH: Inhibition; RNG: Inhibition and Updating; OS: Updating.
Oberauer et al 2000[338]	128	Volunteers ages 18–46	23 WM tasks	Specifically examines "control vs. process" in the context of WM tasks. Spatial WM tasks load separately from both verbal and memory WM. "Supervisory control" is dissociable from other aspects of WM.
Vignola et al 2000[339]	20 20 20	Treated elderly insomniacs Untreated insomniacs Controls	DS, DSS, Trails B, WCST	Four factors explain 66.8% of the variance in 13 cognitive measures. Trails B and WCST load on separate factors. WCST loads on an "executive" factor that explains 12.5% of total variance.
Bryson et al 2001[340]	33 57	Deficit schizophrenia Nondeficit	WCST, WAIS	Three factors identified: "executive functioning," "verbal memory," and "semantic memory." Deficit patients had worse executive function.
Leeds et al 2001[341]	83	Stroke patients	CAMCOG-R, RNG, WCFST	All tests load on a single factor.
Loewenstein et al 2001[342]	166	AD patients	DS, Trails B, VF	DS, Trails B, and VF load on a single "executive" factor, but IADLs load separately.
Willicutt et al 2001[343]	192 121	Children with ADHD or RD Controls	CPT, CNT, DS, SS, Trails B, WCST	Three factors, "working memory," "inhibition," and "set shifting," explain 67.7% of variance.

Note: AB = A-not-B; AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale–Cognitive; ADHD = attention-deficit/hyperactivity disorder; CAMCOG-R = Cambridge Cognitive Examination–Revised; CCST = California Card Sorting Task; CNT = Contingency Naming Task; CPT = Continuous Performance Task; CR = Color Reversal; CT = Category Test; CVLT = California Verbal Learning Test; DA = Delayed Alternation; DCT = Digit Cancellation Test; DS = Digit span; DSS = Digit Symbol Substitution; DT = dual tasking; ECF = executive control function; EPM = Elithorn's Perceptual Maze test; EtOH = alcohol; HFT = Hidden Figures Test; HIT = Hayling Inhibition Test; IADLs = instrumental activities of daily living; MAC = MacAndrew Alcoholism Scale; MC = Mental Control subtest of the Wechsler Memory Scale; MMSE = Mini-Mental State Examination; NCA = Nonspatial Conditional Association; NFT = neurofibrillary tangle; OS = operation span; PET = positron emission tomography; PM = Porteus Mazes; RD = reading disability; RM = Raven's Matrices; RNG = random number generation; SC = self-control; SOPT = self-ordered pointing task; SR = Spatial Reversal; SS = Sentence Span; TOH = Tower of Hanoi; TOL = Tower of London; Trails A/B = Trail Making Test Parts A/B; VF = verbal fluency; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WCFST = Weigl Color Form Sorting Test; WCST = Wisconsin Card Sorting Test; WF = word fluency tasks; WM = working memory.

tal regions. The left hemisphere may mediate verbal working memory. The right may mediate nonverbal working memory.[138] There is some overlap between these regions and other executive tasks. Verbal fluency tests tend to activate the left dorsofrontal cortex,[164,165] although in one study a test of category fluency activated the right dorsolateral prefrontal cortex relative to a baseline reading task.[166] Tasks requiring sustained attention have also been found to activate the right dorsolateral prefrontal cortex.[167]

However, the factor-analytic studies reviewed above suggest that most ECF measures are complicated tasks that may draw on several executive domains simultaneously. The Tower of London, for example, loads on two factors in Culbertson and Zillmer's study of boys with attention-deficit/hyperactivity disorder (ADHD)[168] and on three separate factors in Levin et al.'s study of head-injured children,[169] and it has been reported to activate the left dorsolateral prefrontal cortex[170] and mesiofrontal/anterior cingulate.[171] In a functional MRI (fMRI) study by Peterson et al.,[59] seven factors were derived from the brain regions activated by the Stroop. The an-

THE WISCONSIN CARD SORTING TEST AS A "GOLD STANDARD" ECF MEASURE

The Wisconsin Card Sorting Test (WCST) is arguably the best-characterized measure of executive control functions (ECF). It has been validated in lesion and neuroimaging studies. It has been employed in factor analyses of putative executive measures, and its internal factor structure has been studied. Norms are available for children and adults. It has been employed in a wide variety of clinical conditions.

However, the WCST is a complex task, ill suited for routine clinical applications. It requires equipment (the cards), considerable training and experience, and 45 minutes to administer. The subject is asked to match 128 response cards to one of four stimulus cards on the basis of a sorting rule that is determined by the examiner. Each response card contains a design represented by three features: color (yellow, green, red, blue), number (1–4), and figure (circles, stars, triangles, crosses). Sorts can be made by any of these features. The subject must deduce the current sorting rule on the basis of on feedback from the examiner. After the subject has matched 10 consecutive cards correctly, the examiner covertly changes the rule. This change requires the subject to deduce the new rule and successfully employ it. WCST summary scores reflect the total number of categories achieved, the total number of errors, the number and percentage of perseverative errors, and the percentage of conceptual level responses.

In neuroimaging studies, the WCST appears to activate the dorsolateral prefrontal cortex, particularly on the left.[64,95,154,155,163] However, activation of other brain regions has also been observed, including the right anterior prefrontal region[64] and, to a lesser extent, both mesiofrontal/anterior cingulate[65] and orbitofrontal regions.[167] Thus, the WCST appears to activate all three frontal circuits, bilaterally, with a preferential selection for the left dorsolateral prefrontal system.

The WCST's ability to activate widespread frontal regions may be due to the task's demands for multiple executive skills. In fact, lesion studies in monkeys given WCST analogs demonstrate regionally specific effects on certain WCST elements. Dorsolateral prefrontal lesions affect "extradimensional" (ED) set shifts, wherein the animal must shift its attention from one element of the stimulus to a different aspect of it. Orbitofrontal lesions spare ED set shifting, but selectively impair set "reversal," wherein a previously learned element must be ignored.[156]

In humans, concept generation, sustained attention, verbal and nonverbal working memory, and response inhibition could all be argued to contribute to overall WCST performance. To the extent that these features are discriminable aspects of the task, they ought to label separate factors. Factor-analytic studies of the WCST itself suggest three major factors in children,[157] normal adults,[158] and patients with psychiatric illnesses.[159]

However, results are mixed. WCST categories and WCST percentage correct co-label a single factor in Mirsky's factor analysis of putative ECF measures.[160] WCST conceptual responses label a factor that is shared by verbal and design fluency tasks in Levin et al.'s study of head-injured children.[161] WCST perseverative errors label a factor that is shared by the Category Test and Trail Making Part B in Shute & Huertas's study of normal young adults.[161] A distinction between WCST categories and WCST perseverative errors is supported by the observation that Trails B and WCST categories load on different factors in Robertson et al.'s study of normal adults.[148] However, five WCST subtests, including Categories and Perseverative Errors, load on a single factor in Grodzinsky & Diamond's study of boys with attention-deficit/hyperactivity disorder,[147] while Trails B and verbal fluency tasks load on another. Most of these studies have too few subjects to support an analysis of very many measures. In fact, most probably have too few subjects to produce a stable factor structure. This limitation may explain why most authors report data for only one or two WCST subscales, making their interpretation difficult. In the only factor analysis that reported all WCST subscales, they loaded on a single factor.

It should be noted that not all putative executive tasks are so difficult to localize. Working memory tasks such as delayed matching to sample, "go/no-go," or the "n-back" paradigm (in which the subject must keep track of a stimulus "n-back" in a continuous list of sequentially presented stimuli) consistently activate very specific regions of interest in the prefrontal cortex. The specificity of these tasks can be demonstrated down to the level of single-unit pyramidal neuron recordings. The difficulty in localizing putative ECF measures such as the WCST arises from their inherent complexities. However, although clinical tasks could be designed that might be more localizable, it is unclear that they would share more complex measures' associations with disability, problem behavior, or diagnosis/prognosis.

In summary, the WCST may be the best validated of any putative ECF measure. It is reasonably specifically affected by frontal lesions, and it reasonably selectively activates the left dorsofrontal cortex in activation studies. Multiple executive functions can be ascribed to the various WCST subtests, but this assertion is difficult to prove empirically. Neither neuroimaging nor factor analyses have localized specific and robust WCST-related factors to the frontal lobes.

terior cingulate (mesiofrontal system) loaded significantly on each of these seven factors (see Liotti et al.[163]).

The nonspecificity of putative ECF clinical measures is in sharp contrast to the relatively discrete frontal activations associated with certain tasks in neuroimaging studies. The "delayed response," "A-not-B," "go/no-go," "n-back," and "object retrieval" paradigms all reproducibly activate very specific frontal regions. However, it should be kept in mind that the skills represented by these tasks are achieved by human beings very early in development, long before clinically relevant executive skills have developed. The A-not-B, delayed response, and object retrieval paradigms are essentially in place in human infants by the age of 12 months.[172–174] Thus, these easily localized tasks, while clearly dependent on frontal functions, may be merely the heteromodal processes on which truly cybernetic "executive" functions operate.

APPLICABILITY TO NEUROPSYCHIATRIC DISORDERS

Assuming that the obstacles to ECF assessment can be overcome, what is the promise of this domain? First, it is important to realize that ECF impairment, frontal system lesions, and frontal metabolic deficits have been detected in a wide variety of both neuropsychiatric and medical disorders. This commonality offers the possibility of unified disability and behavioral outcomes assessments that could be validly applied across a wide variety of conditions.[175,176] Moreover, treatment and assessment strategies that are developed in one condition may be relevant to many others as well. Second, ECF may predict disability more accurately than tests based on other cognitive domains. And third, certain behavioral features may serve as indices of ECF impairment. These could have prognostic and treatment significance.

ECF Deficits Are Common

Our literature review identified only a single community-based study of the prevalence of ECF impairment. Presumably, such studies have been limited by the dearth of reliable, valid ECF measures that could be suitable for use in epidemiological or clinical trials. Grigsby et al.[177] used a brief ECF measure, the Behavioral Dyscontrol Scale (BDS), that is essentially a compilation of items based on the work of Luria. They examined the prevalence of BDS failure in a community sample ($N = 1{,}145$; mean age[$\pm$SD] = 72.9 ± 7.2 years) of community-dwelling elderly persons residing in southwestern Colorado. The mean level of education in this sample was 10.5 ± 3.7 years. Many subjects were Hispanic.

The authors found a high prevalence of ECF impairments: 25.5% of their subjects showed impairment on the BDS. Half of these had normal Mini-Mental State Examination scores.[178] The MMSE has been criticized for poor sensitivity to early cognitive decline in older persons and for poor specificity for dementia in minority and undereducated samples.[179] However, the BDS was a stronger predictor of impaired functional status than the MMSE, suggesting that this sample's ECF impairment was already functionally significant.

This study is notable for several reasons. First, it points out how little is actually known about the community prevalence of ECF impairment. Second, it illustrates how traditional measures tend to underestimate the severity of cognitive impairment in ECF-impaired subjects. These issues are relevant to both case definition and disability assessment.[180] The American Psychiatric Association in 1994 added ECF impairment to its list of the domains that should be considered when making a diagnosis of dementia.[27] Nonetheless, there are no large dementia studies that use ECF-sensitive measures in their case definitions. The frequency of ECF impairment reported by Grigsby et al.[177] is almost twice the rate of dementia reported by most studies. Royall et al.[181] have reported similar results among well elderly retirees with advanced education and excellent health ($N = 561$; mean age = 78.1 years). Although 86% pass the MMSE at 24/30 (mean 27.7), 32% fail the EXIT25 and 42% fail CLOX1 at the 5th percentile for young adults. The EXIT25 and CLOX 1, but neither the MMSE nor CLOX2, distinguish level of care in fully adjusted models. The advent of bedside ECF measures such as the BDS, CLOX, EXIT25, and FAB now makes it feasible to explore the epidemiology of this domain.

The need for this work is suggested by the previous documentation of ECF deficits in a wide range of neuropsychiatric disorders. Some "functional" disorders, such as schizophrenia, major depression, alcoholism, and certain personality disorders, have been found to be associated with regionally specific frontal atrophy and cytoarchitectural disorganization.[182–184] ECF is affected by both cortical and subcortical structural disorders.

Schizophrenia: A well-developed literature links the functional, behavioral, and cognitive deficits of schizophrenia with frontal system impairment.[185,186] Schizophrenia is associated with diminished frontal gray and total white matter volumes[187] without clear cell loss.[188] These changes disproportionately affect frontal, particularly inferior ventrolateral and orbitofrontal, regions of interest.[187] The severity of orbitofrontal atrophy is correlated with negative symptoms.[189] There are dorsolat-

eral prefrontal metabolic and regional cerebral blood flow reductions at rest[95,190] and during activation by executive tasks.[97,191] Executive deficits are present from the beginning of the disorder, even among drug-naïve, first-episode cases.[192] It may be interesting to note that only measures related to rule discovery and working memory are initially affected (see Dimensions of Executive Control, pp. 386–387 above). Attentional control and response inhibition impairments appear later.[193]

Major Depression: There is also evidence of frontal system pathology in major depression.[194] Major depression is associated with reduced frontal metabolism in both unipolar and bipolar presentations.[94] There is also evidence of selective cortical atrophy[195] and widespread alterations in frontal cortical architecture in depressed patients.[183,196,197] Frontal stroke is strongly associated with poststroke depressive syndromes.[198] Frank major depression may also follow basal ganglia lesions.[91,102,199] The executive impairments of depression improve with resolution of its symptoms.[200]

Structural Brain Disease: Frontal system pathology is common in AD,[201] VaD, and traumatic brain injury.[202] In addition, ECF impairments have been reported in a wide variety of neurodegenerative disorders, including amyotrophic lateral sclerosis, frontotemporal dementia, HD, Lewy body dementia, PD, and progressive supranuclear palsy.[203–207]

In AD, frontal lobe pathology generally correlates better with dementia severity than hippocampal or temporal cortical AD pathology.[25,208] In fact, frontal cortical synaptic density is the strongest reported pathological correlate of dementia severity ($r = 0.79$ vs. the MMSE).[24,209] This pathology is associated with reduced cerebral blood flow by SPECT and is associated with an early decline in ECF measures.[210] ECF impairment is correlated with functional status in AD[211] and is present relative to age-matched control subjects in preclinical cases of age-associated memory impairment.[212]

VaD disproportionately affects frontal systems.[213,214] Subcortical lesions indirectly affect frontal cortical metabolism, particularly if they include lacunar infarctions of the basal ganglia and thalamus, or anterior periventricular hyperintensities.[90] White matter lesions are specifically associated with poor performance on tests of frontal function.[215,216] Aneurysm of the anterior communicating artery is another common cause of ECF impairment.[217]

Diabetes Mellitus: Patients with diabetes mellitus show impairment on ECF measures. These tests include the DSS,[218,219] verbal fluency[220] (not found by Perlmuter et al.[218]), abstract reasoning,[220,221] Grooved Pegboard,[222] Trail Making,[222,223] Stroop-Word Naming,[222] Picture Arrangement,[222] CLOX1, and the EXIT25.[223] Keymeulen et al.[224] have documented regionally specific frontotemporal hypoperfusion by SPECT in chronic type 1 (insulin-dependent) diabetic patients, but not recent-onset cases or age-matched normal control subjects. The potential causes of ECF impairment among diabetic patients might include subcortical vascular disease, polypharmacy, iatrogenic hypoglycemia, and/or concurrent major depression.

Normal Aging: Old age may be associated with frontal system deficits even in the absence of AD or ischemic vascular disease.[225–228] Reduced executive control can be detected in healthy adults as young as age 45 to 65 years relative to education- and gender-matched 20- to 35-year-olds.[229] In longitudinal studies, ECF deteriorates at an exponential rate.[230] Interestingly, the pattern of age-related cognitive decline in "nonexecutive" domains is most consistent with the loss of executive control over intact processes (see Control vs. Process, pp. 384–385 above).[115,116,231,235]

Disproportionately frontal age-associated metabolic deficits have been observed by functional neuroimaging in healthy volunteers ranging in age from 18 to 78 years.[236] In animals, age-related frontal task performance has been associated with diminished dopaminergic (D_2) and alpha-2-adrenergic (α_2) activity in the prefrontal cortex.[107,237,238] In humans, the age-associated decline in regional D_2 receptor density is linearly related to frontal cortical and anterior cingulate metabolism by PET and associated with diminished WCST and Stroop performance.[239,240]

There is also structural age-associated frontal system pathology. Coffey et al., examining the MRIs of healthy elders free from vascular disease or hypertension, reported an age-related cortical atrophy that disproportionately affected frontal relative to temporal, parietal, and hippocampal regions.[241] Recent studies suggest that age-related atrophy disproportionately affects mesiofrontal and dorsofrontal more than orbitofrontal regions. There are also age-related increases in caudate and putamen hyperintensities. These lesions occur in many apparently healthy elderly persons and can produce executive impairment that is comparable in severity to frontal lobe degeneration.[242]

ECF Impairment and Disability

Because functional outcomes, medication compliance, cooking, housekeeping, and working are all examples of goal-directed activities, they are inherently vulnerable to executive dyscontrol.[243] Thus, frontal system pa-

thology/metabolic impairment and psychometric ECF measures are emerging as robust predictors of disease severity and functional disability across diagnoses.

For example, the effects of ECF impairment have been described in rehabilitation settings.[244] Allen[245,246] has developed the Allen Cognitive Levels (ACL) Assessment. The ACL is essentially a functional status measure that provides information on a variety of executive tasks. Scores on this version correlate moderately to strongly with performance on activities of daily living in subjects with dementia (Feeding, $r = 0.83$; Toileting, $r = 0.75$; Grooming, $r = 0.74$; Dressing, $r = 0.74$; Housekeeping, $r = 0.68$; Ambulation, $r = 0.67$; Bathing, $r = 0.65$; Cooking, $r = 0.65$; Shopping, $r = 0.64$; Laundry, $r = 0.60$; Telephone, $r = 0.58$; Finances, $r = 0.52$; Transportation, $r = 0.32$; Medication, $r = 0.32$; all significant at $P < 0.05$). Velligan et al.[247] have associated the majority of variance in ACL scores with neuropsychological measures of working memory and response inhibition (e.g., ECF factors derived from factor analyses). In schizophrenia, frontal neuroimaging and ECF performance are better predictors of long-term functional outcomes than is successful treatment of psychosis.[248] Roughly 25% of community-dwelling schizophrenic adults can be expected to have ECF impairment.[249] This is comparable to the prevalence of ECF impairment in well elderly persons.[177] Elderly retirees are as executively impaired as schizophrenic patients when the two groups are matched to the services they receive from their respective institutions.[250]

The association of ECF with level of care has been specifically examined in the context of retirement communities.[31,181] Retirement communities are essentially closed systems in which a resident's living setting may change in proportion to the services and supervision he or she requires. Royall et al.[251] examined the relative ability of the EXIT25, the MMSE, demographic variables, physical health status (age, Cumulative Illness Rating Scale score, and number of medications prescribed), and behavior problems (Nursing Home Behavior Problem Scale score) to predict level of care in one such facility. In a stepwise linear regression model, five variables made significant independent contributions. Together, these variables accounted for 57% of the total variance in level of care ($R^2 = 0.57$; $F = 29.2$, df = 7,154, $P < 0.0001$). The EXIT25 loaded first ($R^2 = 0.43$; $F = 119.52$, df = 7,154, $P < 0.0001$).

In a second retirement community, Royall et al.[181] found that ECF measures distinguish levels of care even among noninstitutionalized retirees with normal MMSE scores. Moreover, the use of prosthetic devices declined with ECF impairment, even as level of care increased. This finding suggests that ECF impairment may undermine a disabled person's capacity to adopt assistive devices and that this impairment develops before cognitive impairment is detected in nonexecutive domains. In elderly community residents, executive measures explain independent variance in functional status, beyond that explained by specific cognitive domains[29,252] and may be the strongest determinant of functional status.[253] The effect of longitudinal change in ECF on functional status is comparable to that of age and more important than that of comorbid medical conditions.[230] These results suggest that ECF is a major determinant of level of care in elderly populations.

Finally, we note that ECF may explain significant variance in more specialized functional capacities, such as financial and medical decision-making.[254,255] Dymek et al.[256] found that the EXIT25 explained 45% of the variance in a "rational reasons" standard of decision-making and 56% of the variance in "understanding treatment," independently of a comprehensive battery of cognitive measures, including verbal fluency. This is remarkable because the EXIT25 has little face validity as a measure of verbal reasoning or abstraction. Instead, like the Stroop, it appears to invoke response inhibition or attentional control factors. These may be more relevant to complex decision-making than is widely appreciated (see Control vs. Process, pp. 384–385 above, and Table 1).

ECF Impairment and Problem Behavior

Certain problem behaviors can be specifically associated with frontal system dysfunction in general, and with ECF impairment in particular.[257] Informant-based ratings of these behaviors may be useful as indicators for damage to these networks.[82] The FLOPS attempts to isolate frontal-type behaviors into three domains: apathy, disinhibition, and "executive dysfunction" (i.e., impaired abstraction), each theoretically linked to a different frontal circuit (mesiofrontal, orbitofrontal, and dorsolateral, respectively).[36]

The latter construct may be misleading. First, it implies that apathy and disinhibition are not "dysexecutive" behaviors, when in fact they fit the cybernetic definition of ECF. Second, it implies that impairments in judgment and abstraction are indicative of executive impairment, when in fact they may not be (see Dimensions of Executive Control, pp. 386–387 above). Items addressing working memory might have been a better behavioral indicator of dorsolateral executive dysfunction.

Frith has described the behavioral deficits of schizophrenia in terms of three similar factors based on factor-analytic models derived from clinical ratings,[258,259] namely negative symptoms (apathy), positive symptoms (hallucinations and delusions), and disorganization. Negative symptoms arise from the inability to

generate plans, goals, or intentions. Patients cannot spontaneously initiate complex behaviors. Martinot et al.[260] have specifically correlated negative symptom indices to central D_2 receptors in schizophrenia. In contrast, disorganization arises from the failure to control automatic attentional resources. Patients do not inhibit their attention from wandering to irrelevant cues in the environment. Negative symptoms and disorganization, but not positive symptoms, are associated with poor cognitive test performance in schizophrenia,[149,261,262] particularly on tests of ECF, including the WCST, the Stroop test, and Trail Making.[263,264] It is important to note that these symptom clusters are not unique to schizophrenia. Apathy and negative symptoms can be recognized across the full spectrum of conditions that affect ECF.[265–267]

Attempts have been made to fit Liddle's system of three frontal syndromes into the neuroanatomical model of cortical-striatal-thalamic circuits described by Cummings.[82] Mahurin et al.[149] have associated negative symptoms and disorganization with poor performance on specific, but not overlapping, ECF measures. Negative symptoms were associated with tests of verbal fluency, cognitive flexibility, and working memory (all associated with dorsolateral prefrontal cortex, especially left). Disorganization was associated with attentional ECF measures such as Trails B and the Stroop (associated with dorsolateral and orbitofrontal cortices, respectively, especially right). Similarly, Liddle and Morris[264] associated Psychomotor Poverty with verbal fluency, the Stroop, and Trails A. Disorganization was associated with Trails B and WCST perseverative errors. These same instruments label the first extracted factor Cognitive Flexibility in Shute and Huertas's study of normal young adults.[174] Berman et al.[268] have associated reality distortion and positive symptoms with deficits on measures of working memory.

TREATMENT OF ECF IMPAIRMENT

ECF offers a new perspective from which to study the pharmacotherapy of major neuropsychiatric disorders. Moreover, there may be regionally specific differences in ECF treatment response. Dopamine D_1 receptor agonists improve performance on working memory–related tasks that are thought to be dependent on dorsolateral prefrontal activity. The response is nonlinear (an inverted $\cup$ shape). Too much or too little DA activity can adversely affect function.[269] The response to DA can be predicted by performance on working memory–sensitive tasks such as Digit Span. Normal aging is associated with both diminished dopaminergic function and impaired Digit Span performance, suggesting one possible and potentially reversible explanation for age-associated cognitive decline. Norepinephrine α_2 agonists also improve working memory–related tasks,[107] whereas α_1 agonists impair working memory.[270] In contrast, serotonin deficiency impairs function on tasks that have been related to orbitofrontal activity.[271]

Nevertheless, our literature review did not identify any clinical trials of ECF impairment. However, our collateral review identified many studies that could be interpreted from this perspective. Much depends on one's definition of an "executive measure." DSS or WAIS-R subtests such as Category Formation are sometimes suggested to invoke ECF. However, they seldom co-label factors with other ECF measures. On the other hand, the recognition that frontal lesions lead to reproducible patterns of behavioral disorganization suggests that even behavioral outcomes may be sensitive to ECF-related change. We have chosen to limit our discussion to the few studies with less ambiguous executive outcomes. Initial results look promising. ECF psychometric and frontal system neuroimaging deficits have been found to respond to treatment in ADHD, major depression, and schizophrenia. Each has well-documented frontal/ECF deficits and a well-developed ECF literature.

In ADHD, studies have repeatedly demonstrated the effect of stimulants such as methylphenidate (Ritalin, Focalin), *d*-amphetamine (Dexedrine) or pemoline (Cylert) on impulsive behavior and response inhibition tests.[154,272] Stimulants also appear to improve verbal and spatial working memory.[273,274] These drugs have mixed agonist effects at postsynaptic dopaminergic D_1 and noradrenergic α_2 receptors.

An emerging literature suggests that selective serotonin reuptake inhibitors (SSRIs) may have efficacy against the cognitive impairments of depression[275,276] However, all SSRIs may not be equally effective. The apathetic behavior profile of depression, along with the relationship of apathy to hypodopaminergic states, provides a rationale for the specific use of sertraline against depression-associated ECF impairment[277] (see ECF Impairment and Problem Behavior, pp. 394–395). Ventral tegmental DA inputs are directed largely toward the mesiofrontal cortex and nucleus accumbens (in the mesiofrontal circuit). Wolfe et al.[98] have associated a dysexecutive pattern of neuropsychological test scores with low cerebrospinal fluid (CSF) homovanillic acid levels in patients with Parkinson's disease, major depression, and an apathetic subset of AD cases. Similarly, negative symptoms in schizophrenia have been associated with low levels of CSF DA metabolites.[278] Sertraline, unlike the other available SSRIs, is a potent DA reuptake inhibitor.[279] It is roughly half as potent as amphetamine,[280] although this effect is not likely to be seen at usual therapeutic doses.

Keefe et al.[281] have published a meta-analysis of the effects of atypical antipsychotics on cognitive function among patients with schizophrenia. Fifteen studies were reviewed (including three double-blind controlled trials). After correction for multiple comparisons, significant improvement was found in the DSS, verbal fluency, and "executive function." Three double-blind trials have compared the effects of atypical antipsychotics to haloperidol on cognition, using ECF measures. Schizophrenic subjects treated with risperidone have been found to perform better than those treated with haloperidol on Trails B (but not Trails A)[282] and tests of verbal working memory.[283] Schizophrenic subjects treated with clozapine have been found to perform better than those treated with haloperidol on tests of verbal fluency.[284] And schizophrenic subjects treated with quetiapine have been found to perform better than those treated with haloperidol on tests of verbal and design fluency.[285] The ability of atypical agents to improve ECF specifically would be important. Frontal metabolic function and performance on ECF measures are better indications of long-term functional outcomes than is the successful reduction of psychotic symptoms.[248]

It is important to note that antipsychotic medications may have differential effects on ECF-related symptom clusters. Positive symptoms remit with traditional antipsychotic treatment, but cognitive impairment does not.[286,287] Both positive symptoms and cognition improve with the atypical antipsychotic clozapine. These differential effects may reflect frontal cortical DA receptor distributions.[288] Prefrontal cortical GABAergic interneurons (in layer IV) express dopamine D_2[289] and D_4[290] receptors that may mediate the antipsychotic effects of neuroleptics. In contrast, pyramidal cells in layers III and V express high densities of D_1 receptors. D_1 receptors mediate WCST performance in humans.[108] These receptors are downregulated in schizophrenia[291] and by conventional antipsychotic agents.[269] D_1 receptor blockade can lead to worsened performance on putative executive measures.[292–294]

RESEARCH AGENDA

Much more research is needed with regard to ECF. First, there needs to be a definitive taxonomy, both of the different dimensions of executive control and of the clinical phenomena associated with them. Both questions can be approached through latent class analyses, which are useful in the absence of a gold standard.[295] This taxonomy should be independent of the features of any single disorder. "Negative symptoms," for example, are no more specific to schizophrenia than "apathy" is to depression.

Second, neuroimaging and advanced statistical techniques are pushing us toward the limits of a localization model of executive control. Neither the executive functions themselves nor the instruments that purport to measure them map reliably into specific regions of interest. However, once factor analyses, cluster analyses, grade of membership, or discriminant modeling studies have defined the major frontal syndromes and their associated psychometric characteristics, it will be possible to map them to specific (yet distributed) neural networks. Notable advances in this regard have already taken place (e.g., Liddle and Morris's[264] approach to the neurobehavioral symptoms of schizophrenia, Mahurin and colleagues'[149] efforts to co-localize psychometric factors with distributed networks of cortical regions derived from functional neuroimaging, Kanne and coworkers'[152] pathological correlations with "frontal" factor scores, and Peterson's recent fMRI study of the Stroop[59]).

Third, ECF needs to be incorporated into routine clinical assessment. The prevalence and severity of ECF impairment in most disorders is still unknown, but ECF impairment is likely to be common and also to predict behavioral/functional disability independently of impairment in traditional cognitive domains. Clinicians may not be appropriately trained to recognize ECF impairment at the bedside and distinguish it from affective or behavioral impairments. Similarly, cognitive assessments and screening batteries are increasingly being recognized as deficient in their ability to sensitively detect ECF impairment. This can lead to the underdetection or underestimation of cognitive impairment, particularly in those disorders that disproportionately affect frontal system function.

Fourth, the risk factors for ECF impairment need to be understood. Little is known about ECF-specific risk factors. Both genetic and environmental factors need to be considered.

Fifth, there is a pressing need for pharmacological treatment trials directed at specific ECF domains. It may be that we have already been seeing treatment-related improvement in ECF, but, without ECF-specific outcome measures, this effect is likely to be misattributed to change in "depressive symptoms," "noncognitive behaviors," "functional status," nonspecific attentional factors, or other cognitive domains.

CONCLUSION

"Executive control functions" can be separated from the specific cognitive domains (memory, language, and praxis) that are traditionally used to assess patients. ECF

impairment has been associated with lesions to the frontal cortex and its basal ganglia–thalamic connections. Although there is no "gold standard" ECF assessment, many measures are available for each executive domain. Newer instruments can facilitate widespread clinical assessment of executive control. Attention to this domain promises major rewards. ECF impairment, frontal system lesions, and frontal metabolic deficits have been detected in a wide variety of both psychiatric and medical disorders and are strongly associated with functional outcomes, disability, and specific problem behaviors. Although treatment of ECF impairment has been attempted in only a few disorders, initial results look promising. Much more research is needed.

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