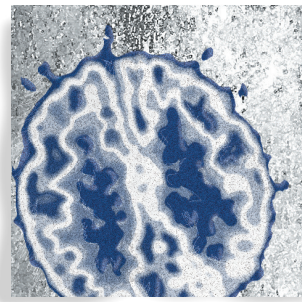# Basic research

Executive control: balancing stability and flexibility via the duality of evolutionary neuroanatomical trends

Robert M. Bilder, PhD

The concept of executive functions has a rich history and remains current despite increased use of other terms, including working memory *and* cognitive control. *Executive functions have sometimes been equated with functions subserved by the frontal cortex, but this adds little clarity, given that we so far lack a comprehensive theory of frontal function. Pending a more complete mechanistic understanding, clinically useful generalizations can help characterize both healthy cognition and multiple varieties of cognitive impairment. This article surveys several hierarchical and autoregulatory control theories, and suggests that the evolutionary cytoarchitectonic trends theory provides a valuable neuroanatomical framework to help organize research on frontal structure-function relations. The theory suggests that paleocortical/ventrolateral and archicortical/dorsomedial trends are associated with neural network flexibility and stability respectively, which comports well with multiple other conceptual distinctions that have been proposed to characterize ventral and dorsal frontal functions, including the "initiation/inhibition," "what/where," and "classification/expectation" hypotheses.*

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Overview

Executive functions have enjoyed diverse definitions, but most agree that these functions represent the pinnacle of phylogenetic and ontogenetic development within the brain. Many views of executive functions equate these with the functioning of frontal lobe systems, but changes in usage over the last few decades reflect differences in research focus on component processes, and the perspectives advanced in cognitive psychology and cognitive neuroscience relative to those that were the prior focus of clinical neuropsychology and neurology. This article provides limited historical perspective, summarizes several overarching theoretical views of executive functions, and suggests that it is valuable to focus on a fundamental functional distinction between operations supporting *stability* and *flexibility* of neural network activation states and associated cognitive representations. This functional distinction is linked to a fundamental duality in evolutionary cytoarchitectonic trends that map onto dorsomedial archicortical and ventrolateral paleocortical neural systems. This perspective may help align cognitive neuroscience research with

Author affiliations: Department of Psychiatry and Biobehavioral Sciences, UCLA David Geffen School of Medicine, and Department of Psychology, UCLA College of Letters & Science, Los Angeles, California, USA

Address for correspondence: Robert M. Bilder, PhD, Michael E. Tennenbaum Family Professor of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA and Professor of Psychology, UCLA College of Letters & Science, Room C8-849, 740 Westwood Plaza, Los Angeles, CA 90095, USA (e-mail: rbilder@mednet.ucla.edu)

functional distinctions that have clearer neuroanatomical bases, help us understand clinical impairments of executive control, and ultimately provide new clues to more effective treatments.

Historical context: a rose is a rose is a rose; or is it?

The concept of *executive functions* and the links of these functions to frontal lobe systems have rich legacies, with roots dating back to the mid-19th century and continued widespread use in the modern literature. Some early uses of the concept are found at least by 1861, when Gratiolet referred to the frontal lobes as the site of the "regulating mind" or the "supreme organ of the brain."[1] Luria also credits Broadbent[2,3] and Jackson[4,5] with early development of concepts regarding the importance of the frontal lobes in the hierarchical regulation of behavior.

The actual use of the term "executive function" to refer to frontal lobe function has been credited to Karl Pribram, who wrote in 1973: "… the frontal cortex appears critically involved in implementing executive programs when these are necessary to maintain brain organization in the face of insufficient redundancy in input processing and in the outcomes of behavior"[6] (p 312). Pribram's usage here was tied to then-current computer terminology referring to "flexible noticing order programs" that were applied in the sequencing and tracking of routines in a context-sensitive manner, and in this way he distinguished such control processes from strictly hierarchical programs which are context-free.

The term "working memory" (a coinage attributed to Miller, Galanter, and Pribram[7]) developed its own niche role as one of the components of "executive function." This may be attributed at least in part to the widespread uptake of the term in cognitive psychology following its use in influential works by Alan Baddeley and colleagues.[8] Many of these cognitive works assiduously avoided attributions to specific brain mechanisms, despite knowledge that the frontal lobes were critical for delayed response task performance.[9] Later experiments provided considerably greater detail about the specific nature of the deficit produced by frontal versus posterior cortical lesions on these behaviors, documenting firing patterns of prefrontal pyramidal cells during delay periods, and using selective lesions to reveal the roles of reciprocal connections between frontal and posterior

cortical regions, the relations of these transmissions to graded electrical potential changes over relevant cortical or scalp regions (reviewed by Pribram and McGuinness[10,11]), and then linking these sustained activation patterns to specific pharmacological manipulations, particularly of dopamine (DA) neurons.[12,13] Today this work has progressed to include biophysically detailed models of mechanisms responsible for stabilizing and introducing flexibility into sustained activation states of these neural networks.[14-16]

To highlight how construct labels may impact science, however, it is exemplary to consider what happened to the term "executive functions" in the project—Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). Considerable research already had documented impairment on multiple tasks of executive function, and many reports highlighted the impairments of executive control as among the most severe deficits in people with schizophrenia,[17-19] and showed that these were important in functional impairment,[20] leading to hypotheses that developmental dysfunctions affecting frontal lobe systems may be central to the pathophysiology of schizophrenia.[21-25] But in consensus meetings and reviews of factor analytic studies it was determined that the term "reasoning and problem solving" had the "advantage of distinguishing this domain from working memory."[26] Armed with these revised concept labels the team identified tests to measure this construct, but some tests upon which the original factor analytic studies were based were not evaluated further for various good reasons (eg, the Wisconsin Card Sorting Test had figured heavily in prior research, but is ill-suited for application in clinical trials). Then several tests were proposed that had not been used in the factor analyses, and which are quite reasonably considered tests of "reasoning and problem solving" but would less likely be selected as measures of "executive functioning" and almost certainly would not be selected as measures of "frontal lobe functions." For example, a maze-processing test was selected for the MATRICS final battery, even though no maze test was used in the original factor analytic studies, and while most scientists would agree that frontal function is important for maze performance, the contributions of nonfrontal systems are profound. Thus the construct label *executive functions* (associated with frontal system integrity), was split into *working memory* and *reasoning/problem solving*, the latter of which was untethered from its "frontal" system anchor. This highlights how

breaking a construct into subcomponents can have unintended consequences, and in general shows that cognitive construct labels may be misleading. Indeed, it only becomes clear what the labels really mean when these are specified with respect to the actual test variables used to measure the construct. These issues are discussed in greater detail elsewhere, along with other examples showing how construct labels may reflect fashion more than science, and calling for routine specification of constructs at the measurement level.[27-29] For example, in one literature-mining exercise the term "cognitive control" was defined completely at the measurement level by a set of four other labels including: working memory, response selection, response inhibition, and task switching/set shifting. Thus, the term "cognitive control" was used increasingly in the literature to describe results from the same tests that were previously branded with other labels.

By the time Pribram had offered the coinage of *executive functions* and participated in the coinage of *working memory*, substantial progress had been made in recognizing key aspects of frontal lobe organization based on both clinical and basic research by Jacobsen, Halstead, Teuber, Luria, Fuster, Mishkin, Sanides, Stuss, Benson, and others.[1,9,30-40] Among these contributions I single out for its elegance and simplicity the formulation of Luria[1,41] as elaborated by Goldberg.[42] This provides an overall functional framework within which the processes of executive function take place. Next I turn to characterization of the nature of control exerted by the frontal systems, relying here on formulations articulated by Pribram and McGuiness,[10,11,43] Fuster,[44] and Goldman-Rakic.[45] Finally, I attempt to show how the fundamental principles of frontal executive control mechanisms may operate to subserve stability and flexibility operations (which are a critical component particularly of Pribram's concept of frontal function) via an anatomic organization that has evolved specifically to provide autoregulatory control over stability and flexibility, based on the original work of Friedrich Sanides[37] as elaborated by Pandya and his colleagues.[46-49]

The Luria/Goldberg hierarchical and gradiental theories

Among the most successful and enduring general theories of frontal lobe functioning are the hierarchical models that were developed by Luria in the 1960s and elaborated and extended by others, including Joaquin Fuster and Luria's student Elkhonon Goldberg. A major premise of these models is that the frontal lobes are organized in a hierarchical fashion, which Luria referred to as primary, secondary, and tertiary divisions of the frontal cortex. These primary, secondary, and tertiary divisions approximate the cytoarchitectonic divisions referring to the primary motor cortex, the premotor cortex, and the prefrontal cortex, respectively. Syndrome analysis of patients with discrete lesions showed systematic increases in the complexity of behavioral disruptions paralleling the cytoarchitectonic progression. In brief, discrete lesions in the primary motor cortex cause loss of motor control (paralysis or paresis), at the level of individual motor units, with relatively little impact on other non-motor functions, and the dysfunction is well defined by a somatotopic representation mapped as a motor homunculus on precentral gyrus. In contrast, lesions to the premotor regions yield hierarchically "higher-order" functional deficits, impacting the combined activation of units in the primary motor regions, and preferentially affecting the spatially and temporally organized sequencing of motor movements; however, the capacity to execute elementary movements of individual motor units may be spared. While the impact of lesions in these premotor or secondary divisions continues to be predominantly motoric in character, and maintains elements of somatotopic representation, the "projective fields" are larger, involving multiple motor units. Finally, lesions to the prefrontal cortex are seen as hierarchically higher still, impacting the coordination of premotor activation and thereby regulating the organization of complex actions and plans for behavior. These prefrontal lesions may cause no obvious impact on motor control at all, and there is no clear relation to somatotopic maps.

This basic scheme has enormous explanatory power, and, with some refinements and elaborations, has been used to help understand wide-ranging lesion effects including not only elementary and complex motor syndromes, but also diverse deficits in expressive language, conceptual disorganization, and thought disorder, and more generally problems in the initiation and regulation of complex behavior. For example, the classic effects of ventrolateral prefrontal and premotor lesions on expressive speech (ie, "Broca's aphasia") may be more readily appreciated as breakdowns in the regulation of sequentially organized actions in regions that are somatotopically mapped to the motor control of the articulatory

apparatus (mouth, tongue, larynx, and pharynx), and this system better explains how some (more posterior frontal) lesions have greater effect on articulatory agility and buccolingual praxis, while other (more anterior) lesions leave the motor regulation of speech intact but nevertheless yield alogia or other higher-order speech impairments. Goldberg provides many examples, and also an elegant explanation of how agnosias emerge as a cardinal consequence of lesions in the secondary divisions of posterior cortical regions, and how analogous disruptions in the classification of behavioral programs may result from premotor cortex dysfunction.[42]

Some difficulties for these theories include: (i) the observation that the secondary divisions of the cortex (ie, premotor cortex) are actually phylogenetically *older* and *less differentiated* than either tertiary prefrontal cortex or primary motor cortex, which appear to have evolved more recently (see refs 50,51); (ii) a lack of specification about the nature of regulatory influence expressed by the frontal cortex in its connections to posterior cortical regions; and (iii) while the hierarchical theories account well for diverse motor and planning phenomena, they often pay less attention to the importance of frontal systems as regulators of the limbic, diencephalic, and brain stem systems, and thereby offer less insight into how frontal systems regulate visceral and autonomic function.

The Pribram-McGuiness hypothesis and other autoregulatory control theories

In his classic paper "The riddle of frontal lobe function in man," Hans-Lukas Teuber[31] highlighted dilemmas faced by the field in its attempts to identify a unitary theory of frontal lobe functions, and he focused on taking a "180-degree" shift in thinking by examining the impact of frontal systems on the rest of the brain including sensory cortices. Teuber's emphasis on "corollary discharge" anticipated interpretations that focused on the role of frontal projections in biasing the processing of other cortical systems to "prepare" for engagement in task-relevant activity, thereby providing representation of "expectation" and "context based on prior memory." [52] These ideas are similar to later theoretical contributions that attribute to frontal systems a unique role in guiding behavior via context.[53] But Teuber and others also recognized that part of the "riddle" of frontal function was likely posed by its structural heterogeneity.[54] Benson and others had established a dichotomy widely used in neu-

rology and neuropsychology, distinguishing dorsolateral from orbitofrontal syndromes, with the former marked by cognitive inertia, planning and organization problems, and the latter marked by pseudopsychopathy and disinhibitory psychopathology.[55] Luria distinguished three distinctive frontal syndromes, with a dorsomedial syndrome marked by "oneiroid" (dreamy) states, in addition to the dorsolateral and orbitofrontal/basal variants.[1] Pribram had earlier focused on the unique relations of frontal regions not only with the motor system but further with the visceral and autonomic nervous system (see discussion in ref 9), and subsequently refined these ideas in a grand theory of attention regulation.[10,11,43,52,56]

The Pribram-McGuinness hypothesis states that frontal systems contribute critically to integrated "arousal" and "activation" functions that have primary roles in regulating the flexibility and stability of brain activation states. This conceptualization extended from the early experiments of Morruzi and Magoun[57] and their followers, which revealed a fundamental duality in that electrographic desynchronization and "alerting" responses could be triggered not only via stimulation of the ascending reticular activating system (ARAS), but also by forebrain stimulation. Of particular importance, the ARAS stimulation resulted in *phasic* arousal, while the forebrain stimulation resulted in more enduring *tonic* activation. Pribram and McGuinness recognized the relation of the phasic arousal system to novelty detection and the orienting response, and of the tonic activation to maintenance of readiness to respond and the preparation of other cortical regions to engage in processing. An electrocortical representation of this tonic activation process was observed in the contingent negative variation (CNV) observed over the vertex in scalp EEG recordings selectively during the delay interval of delayed response tests; it was noted further that depth recordings revealed *transcortical negative variations* which occurred within those sensory regions that were *about to be engaged* in processing, and that both the CVN and TNVs could be obliterated by lesions in frontal or striatal components of the tonic activation system, thus confirming a frontal system contribution to preparation for processing elsewhere in the brain. Several decades later, elegant experiments by Patricia Goldman-Rakic and colleagues would corroborate and extend these studies, revealing the exquisite organization of reciprocal fronto-posterior projections and highlighting the sustained activity of prefrontal pyramidal

neurons in the maintenance of activation states in task-relevant posterior cortical regions. It was at this point that the processes of *working memory* received greater attention, referring particularly to those elements of tonic cortical activation previously labeled by Pribram and McGuinness as *activation*.

Other distinctions have been put forward to help understand the heterogeneity of frontal lobe function. Fuster has emphasized the role of more dorsal frontal systems in initiation of action and the more ventral systems in the inhibition of action.[44,58] Following elegant experiments that segregated the "what and where" functions of ventral and dorsal visual streams, respectively, one theory suggests this distinction is carried forward in frontal system function.[59] A similar theory suggests this distinction is better characterized as "what versus how."[60] Exploration and exploitation have been seen as a crucial dichotomy in both business systems and frontal function, though the anatomic attributions of these models do not always converge (ie, Cohen and colleagues have suggested that "exploration" is more mediated by frontopolar and dorsal systems that are engaged to overcome prepotent response tendencies).[61-63] Another recent review suggested that existing evidence is more consistent with the idea that dorsal frontal systems are associated with "expectation" while the ventral systems are more engaged in "classification." [64] Is there a way to reconcile these ostensibly different views of frontal system function?

The dual evolutionary cytoarchitectonic trends hypothesis

It has been said that in biology, function is always dictated by structure (see ref 65), so our understanding of functional distinctions in brain might best follow an analysis of its structure. Comparative anatomic studies going back to the 1930s highlighted a duality in the origins of the cerebral cortex, with one anatomic source originating from a laterally positioned cellular primordium comprising the primitive olfactory cortex (*paleocortical* trend) and another anatomic source derived from a medially positioned cellular primordium comprising the primitive hippocampal formation (*archicortical* trend).[66-68] In the phylogenetic progression from fish through reptiles to mammals and primates, this fundamental duality has been preserved as the cortex evolved progressively from three to six layers, with the most

recently evolved representation of the paleocortical trend apparent in the most ventral and lateral aspects of neocortex, and the most recently evolved representation of the archicortical trend in the most dorsal and medial aspects of neocortex.[69] This duality in origins of the entire cortical mantle is reflected in both distinctive patterns of local cytoarchitectonic development and long-range patterns of connectivity in both posterior and frontal regions. The posterior paleocortical progression includes parainsular cortex, from which further development of six layered isocortex emphasized granular cells and led to development of the primary sensory areas for the face, head, and neck, and to the central visual component of primary visual cortex, and to primary auditory cortex. The archicortical progression includes paralimbic cortex, from which isocortical developments included an emphasis on pyramidal cells and somatosensory representations of the limbs and trunk, and to cortical regions representing the peripheral visual fields. In frontal regions[70] there is a similar duality expressed in the elaboration of granular and pyramidal cells in the paleocortical and archicortical trends, respectively, and a parallel emphasis on the trends' respective representations of motor control of the face/head/neck versus limbs and trunk. Linking these observations to the theories described above, the hierarchical view is reinforced by the documented short-range projections from each region to nearby regions of both greater and lesser degrees of differentiation. Reinforcing the topographically organized patterns of frontoposterior projections described above, it is further important to note that these patterns of long-range projections honor the level of cytoarchitectonic differentiation across comparable anterior and posterior developments within each trend, and also connect similarly evolved regions between paleocortical and archicortical trends. These relationships have been summarized elsewhere,[71,72] and are further detailed and depicted elegantly in multiple works by Pandya and colleagues (for a recent update, see ref 46).

Several functional distinctions map either explicitly or implicitly onto this neuroanatomical duality *(Table I)*. For example, the paleocortical and archicortical trends have been seen as the potential substrate of object versus spatial processing, respectively,[46] following the "what versus where" distinction noted above. Randall O'Reilly[73] argues that this distinction may better be broadened to consider "what versus how" processing, similar to the hypothesis of Goodale and Milner.[60]

Basic research

Petrides sees the dorsolateral (archicortical) system as more critically engaged in "monitoring of information in working memory" while the ventrolateral (paleocortical) system is more involved in "…active judgments on information held in posterior cortical association regions that are necessary for active retrieval and encoding of information…" (p 793).[74] Gary Goldberg suggested that the paleocortical system mediates "responsive" control over action, while the archicortical system mediates "projectional" control over action,[75] and this idea is highly compatible with the distinction that Frith and Done[76] made between "stimulus intentions" and "willed intentions" in describing two distinct routes to action (which incidentally can help explain both unusual phenomena such as the "alien hand sign" seen rarely with lesions to the archicortical divisions of the premotor system, and certain hallucinatory behavior in syndromes like schizophrenia). Further compatible with these views is the recent hypothesis of Borst and colleagues, suggesting that the dorsal/ventral distinction in frontal function is best captured by dimensions of "expectation" versus "classification." [64]

Key elements from each of these suggestions should probably be accounted for in a mature model of frontal lobe function. In prior work it was suggested that integrating the evolutionary cytoarchitectonic trends model with the Pribram and McGuinness theory of attentional control might have merit.[70,71,77-83] Specifically, it has been argued that the dorsal and medial archicortical systems may emphasize the stabilization of behavioral programs,

thus subserving what Pribram and McGuinness referred to as "tonic activation"—and this would be consistent particularly with roles in mediating "projectional control," "willed intentions," "monitoring of information in working memory," and "expectation" as invoked above. In contrast, it was suggested that the ventral and lateral paleocortical system is biased towards flexibility and is engaged in mediation and moderation of "phasic arousal"—and this would be compatible with the ideas espoused above regarding "responsive control," "stimulus intentions," and elements of "retrieval and encoding" particularly those that demand or are triggered by perceptual "classification" processes. This functional distinction is also likely linked to both neurochemical distinctions and differences in cellular signaling pathways that are under strong genetic regulation. For example, this distinction between maintaining the stability (through tonic dopaminergic activation) or introducing more flexibility (through phasic dopaminergic arousal) in corticostriatal networks was seen as a key mechanism through which genetic variation in the catechol-O-methyltransferase (COMT) gene may impact diverse cognitive functions.[83] The putative identification of these features and characteristics with paleocortical and archicortical trends is summarized in *Table I*.

Future directions

Modern neuroimaging studies, particularly those using functional magnetic resonance imaging (fMRI), have

Feature/characteristic	Paleocortical	Archicortical
Derivative from primordial cellular moiety	Olfactory (piriform)	Hippocampal
Intermediate (allocortical and periallocortical) representation	Parainsular	Paralimbic
Neocortical representation in frontal lobes	Ventrolateral and orbitofrontal cortex	Medial and dorsal frontal cortex
Somatic emphasis	Face, head, neck	Trunk, limbs
Control mode	Responsive, reactive	Projectional, proactive
Route to action	Stimulus intentions	Willed intentions
Relations to visual streams and posterior cortical processing	Where/how system	What system
Relation to memory and working memory processes	Promote active retrieval and encoding	Promote maintenance and monitoring of working memory
Orientation with respect to input-output processing	Input oriented	Output oriented
Information processing bias	Novelty biased	Redundancy biased
Cognitive proficiency	Classification	Expectation
Physiological/functional emphasis	Flexibility	Stability
Mode of dopaminergic transmission	Phasic	Tonic

Table I. Summary of neuroanatomical progressions within paleocortical and archicortical trends and their putative functional characteristics.

already produced an enormous amount of evidence that remains to be well integrated with our understanding of connectional anatomy and with functional anatomic hypotheses that are constrained by structural anatomic architecture. It is hoped that data emerging from the human connectome project will help advance application of these anatomic constraints to functional models.[84] Surging interest in the "default mode network"[85] may also help by increasing understanding of functional network activation free of the constraints of specific cognitive hypotheses that may lead to reification of certain functional networks because these are dictated by the experiments. In the same way that genome-wide association studies may provide an "agnostic" and unbiased approach to the study of genetic association, future studies of brain activation may benefit from adopting a "cognome-wide" strategy that samples brain function broadly, and with fewer preconceptions.[86] Meanwhile, the field is witnessing a burgeoning of intriguing new "mod-

ular" hypotheses about frontal regions and their putative roles in mediating discrete cognitive operations.[87] Some aspects of these new theories already appear consistent with the evolutionary cytoarchitectonic trends hypotheses (for example the role of frontal pole region 10 as reflecting a merger zone with influences on both dorsal and ventral trends), but a high future priority will be fuller integration of current concepts of reward-system function with cognitive process hypotheses. Research that will enhance understanding of functional links between frontal systems and deeper limbic, subcortical and axial systems may be among the most promising directions, and may help to fulfill the legacies seeded more than 50 years ago by the pioneers of frontal lobe territories. ❏

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Basic research

Control ejecutivo: equilibrando la estabilidad y flexibilidad a través de la dualidad de las tendencias neuroanatómicas evolutivas

El concepto de funciones ejecutivas tiene una rica historia y se mantiene vigente a pesar del incremento del empleo de otros términos, incluyendo los de memoria de trabajo y control cognitivo. Las funciones ejecutivas algunas veces se han identificado con funciones dependientes de la corteza frontal, pero esto no aclara mucho, dado que a la fecha se carece de una teoría comprensible de la función frontal. Mientras se espera una comprensión mecanicista más completa, las generalizaciones de utilidad clínica pueden ayudar a caracterizar tanto la cognición normal como múltiples variedades del deterioro cognitivo. Este artículo revisa algunas teorías que incluyen el control jerárquico y la autorregulación, y sugiere que las tendencias de las teorías evolutivas de la citoarquitectura aportan un valioso soporte neuroanatómico para ayudar a organizar la investigación de las relaciones entre función y estructura frontal. La teoría sugiere que las vías paleocortical/ventrolateral y arquicortical/dorsomedial están asociadas con la flexibilidad y la estabilidad de la red neural respectivamente, lo que concuerda bastante con otras múltiples distinciones conceptuales que se han propuesto para caracterizar las funciones frontales ventral y dorsal, incluyendo las hipótesis de "inicio/inhibición", "qué/dónde" y "clasificación/expectación".

Contrôle exécutif : équilibre entre stabilité et flexibilité via la dualité des tendances neuroanatomiques évolutionistes

Le concept de fonctions exécutives a une histoire riche et reste actuel malgré l'utilisation accrue d'autres termes, comme la mémoire de travail et le contrôle cognitif. Les fonctions exécutives ont parfois été assimilées aux fonctions favorisées par le cortex frontal, ce qui éclaire peu le sujet, car nous manquons jusqu'à maintenant d'une théorie complète de la fonction frontale. Dans l'attente d'une compréhension mécaniste plus complète, des généralisations cliniquement utiles peuvent aider à caractériser à la fois une cognition saine et des variétés multiples de déficits cognitifs. Cet article passe en revue plusieurs théories de contrôle hiérarchique et d'autorégulation, et suggère que la théorie des tendances cytoarchitectoniques évolutionistes apporte un cadre neuroanatomique très utile pour aider l'organisation de la recherche des relations structure-fonction frontales. La théorie suggère que des tendances paléocorticales/ventrolatérales et archicorticales/dorsomédiales sont associées respectivement à la stabilité et à la flexibilité du réseau neuronal, ce qui concorde avec de nombreuses autres distinctions conceptuelles proposées pour caractériser les fonctions frontales dorsales et ventrales, comme les hypothèses d'« initiation/inhibition », de « quoi/où », et de « classification/anticipation ».

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