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A "Conceptual Nervous System" for multiple sclerosis

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Abstract

Neuropsychological diagnosis requires a structure-function correlation model or a "Conceptual Nervous System." The unpredictably variable, widespread, and multifocal nature of pathological changes in multiple sclerosis (MS) challenges the neuropsychological localizationist assumption. To be adapted to MS pathological and clinical heterogeneity, a Conceptual Nervous System should explain impairments associated with multifocal, subcortical, and white matter lesions that cause information processing slowing and working memory/executive function impairment. Our main goal in this theoretical study was to develop a Conceptual Nervous System for MS by integrating current neuropsychological conceptions of structural-functional correlations in MS with a model of conscious mental activity developed by Ernst Pöppel , based on periodic reentrant activity between cortical and subcortical structures. Neuropsychological profiles in MS can be explained by both threshold and multiple disconnection mechanisms. The Conceptual Nervous System encompasses a functional and structural model of the human brain-mind. The functional model classifies mental function into material and formal. Material/semantic functions are modularly organized, and their impairment causes classical focal neuropsychological symptoms. Multiple sclerosis preferentially impairs formal/syntactic function related to widespread patterns of activation and temporal organization. The structural model specifies the system anatomically functions. The neuropsychological adequacy of the proposed Conceptual Nervous System to MS is analyzed by comparing its predictions to results of extant meta-analytic studies. **Keywords:** multiple sclerosis, white matter damage, working memory, executive function, information processing speed, structure-function correlation, Conceptual Nervous System

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Introduction

Neuropsychological diagnosis depends on a localizationist assumption. Patterns of deficits and preserved functions observed in patients are interpreted in terms of a structural or functional brain model. From a structural standpoint, neuropsychological symptoms are anatomically localized by anatomo-pathological examinations or neuroimaging (Kertesz, 1994). Functionally, symptoms are interpreted and "localized" as representational or processing deficits in an information processing model (Shallice, 1988). Functional neuroimaging studies assess *in vivo* associations between functional and structural aspects (Price et al., 2003). Neuropsychological diagnosis, therefore, is based on a model of anatomo-functional correlations that provide an interpretation of clinical observations and test results. Neuropsychology then needs what Hebb (1955) called a "Conceptual Nervous System."

Inter- and intraindividual heterogeneity of cognitive and psychiatric symptoms in multiple sclerosis (MS) challenges neuropsychological localizationist assumptions. Neuropsychological deficits in MS may occur early in the course of the disease (Amato et al., 2010), being sometimes very subtle, difficult to detect, and perceptible in 40-70% of patients in transversal studies (McIntosh-Michaelis et al., 1991; Rao, Leo, Bernardin, & Unverzagt, 1991). Interindividual variability of deficits restricts criterion validity of neuropsychological tests and their accuracy to discriminate individuals with MS from controls (Nocentini et al., 2006; Rao et al., 1991). Patients with predominantly spinal forms of the disease may present only mild cognitive impairment (Pelosi, Geesken, Holly, Hayward, & Blumhardt, 1997). More recent studies indicate, however, that many patients with primary progressive forms of MS may present cognitive impairment from the inception of the disease (Negreiros, Mattos, Landeira-Fernandez, Paes, & Alvarenga, 2008; Paes, Alvarenga, Vasconcelos, Negreiros, & Landeira-Fernandez, 2009). However, the studies showing cognitive impairment in primary progressive MS analyzed central tendency statistics and

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did not examine individual heterogeneity. The results show that at least 40-50% of primary progressive MS patients are not cognitively impaired in the early phases of the disease.

Heterogeneity is also associated with the fact that the same patient may present lesions with different pathological features (e.g., inflammation and degeneration) and variable evolutionary stages of the lesion, from the acute phase to scar formation (Stadelmann & Brück, 2008). The complexity of symptomatic expression may be further increased by synaptic plasticity and reserve capacity which add to the intraindividual clinical variability (Mainero et al., 2004). Neuroimaging research indicates that the cognitive deficits correlate better with the total lesion load than with the specific lesion locations (Nocentini et al., 2001).

The main goal of the present article is to formulate a model of anatomo-functional correlations that account for the symptomatic manifestations of MS, preserving the assumption of neuropsychological localizationism. We integrated two main contemporary conceptions—the threshold (Calabrese, 2006) and multiple disconnection (Gainotti, 2006) models of cognitive impairment in MS—with the ideas formulated by Pöppel (1993) on the role of periodic cortico-subcortical reentrant activity in conscious mental activity. To fulfill the needs of the neuropsychology of MS, we argue that a structural-functional correlation model must include an additional dimension of impairment, represented by the speed of information processing. To corroborate this model, evidence is examined from extant meta-analyses that compared neuropsychological impairment in MS, normal aging associated white matter lesions, and dementia of the Alzheimer's type to normal controls.

Neuropsychological heterogeneity in multiple sclerosis

Multiple sclerosis is a condition with complex etiopathogenetic mechanisms, symptoms, and clinical courses. Although its causes remain unknown, genetic and environmental mechanisms, probably a viral infection acquired before puberty, have been postulated to play a role as a multicausal pathway to disease expression (O'Connor, 2002). The pathological mechanism of the disease consists of episodes of demyelination in the central nervous system caused by a perivascular autoimmune inflammatory process, which may be elicited or exacerbated by prior demyelination episodes (Frisoni & Filippi, 2005).

Three main clinical forms of the disease are distinguished (Lublin & Reingold, 1996). Demyelinating episodes predominate in relapsing-remitting MS (RRMS), in which complete or partial recovery from symptoms may be achieved between relapses. After some years following disease onset, many patients with RRMS progress to secondary progressive MS (SPMS), characterized by axonal degeneration and the disease being progressive regardless of the occurrence of additional acute episodes. A small proportion of patients have primary progressive MS (PPMS), which is characterized by a progressive course from disease onset and a predominance of axonal degeneration.

The neuropsychological profile of MS is also very heterogeneous. The areas most often affected comprise attention and information processing speed (IPS), executive function, episodic memory, and motor function of the hands (Bobholz & Rao, 2003; Rao, 1986, 1995; Rao et al., 1991).

From a psychosocial perspective, in addition to stress and depressive symptoms, fatigue is a very prevalent manifestation, occurring in 70-90% of patients, and potentially exacerbating observed impairments (DeLuca, Genova, Hillary, & Wylie, 2008). Variables such as age, education, neurological function, age of onset, disease duration, and clinical forms of MS have been discussed as performance predictors and prognostic factors, but correlations are loose (O'Connor, 2002).

Symptomatic heterogeneity in MS is also manifest in the diverse association patterns of neuropsychological and neuropsychiatric symptoms. A few patients do not present any psychiatric or cognitive impairments (Amato et al., 2006b; Sayão, Devonshire, & Tremlett, 2007), whereas others have isolated psychiatric or cognitive symptoms. A fourth group of patients presents both psychiatric symptoms and cognitive impairments (Figved et al., 2008). In some patients, the presence of depressive symptoms contributes to a worsening of cognitive deficits (Landrø, Celius, & Stetvold, 2004; Arnett et al., 1999).

Neuroplasticity and functional regeneration mechanisms further exacerbate the clinical heterogeneity of MS. Using techniques of functional neuroimaging, Rocca et al. (2005) obtained evidence of cortical reorganization during the execution of manual gestures in MS patients. Patients with greater degrees of neurological impairment had broader patterns of cortical activation during gesture performance. More extensive cortical activation, compared with controls, was also observed in the performance of cognitive tasks (Mainero et al., 2004). Efforts to activate damaged areas result in the activation of additional cortical areas, potentially causing fatigue symptoms (DeLuca et al., 2008). An accumulation of cognitive impairments probably represents the exhaustion of neuroplasticity mechanisms.

Different patients, however, exhibit different functional recovery potentials. Clinical evidence indeed suggests that some patients may have a relatively benign course over many years, presenting a minimal cumulative lesion load and therefore a virtual absence of disease-associated impairment (Amato et al., 2006b; Sayão et al., 2007).

Clinical and physiopathogenetic heterogeneity associated with MS is reflected in neuropsychological assessments. In the longest lasting longitudinal study conducted on cognitive deficits in MS, although 74% of the patients did not show significant cognitive deficits initially, only 44% of them remained in this situation after 10 years of follow-up (Amato, Zipoli, & Portaccio, 2006a). Cognitive prognosis data, therefore, indicate that an accurate diagnosis, considering the typical neuropsychological structure-function correlations, is primarily important in predicting the clinical course of the disease.

The characterization of different neuropsychological phenotypes in MS raises questions about the structure-function correlations of the symptoms of the disease, which may not be easily explained by classical strictly localizationist models. Inflammatory and degenerative lesions damage, among other areas, white matter fibers responsible for connectivity and functional cortico-cortical and cortico-subcortical integration. Gainotti (2006) suggested that neuropsychological impairment profiles in MS could be explained in terms of a multiple disconnection model, according to which interruption at multiple sites of cortico-subcortico-cortical loops interferes with functioning in domains that require coordinated activity of wide areas of brain tissue, such as episodic memory and executive function, thus contributing to the slowing of information processing.

Calabrese (2006) proposed a threshold model to explain the expression of cognitive impairment in MS. According to this model, in the early phases of the disease, lesions most frequently have a low neuropsychological impact on patients because of both their small number and high rate of recovery. As the disease progresses, however, neuroplasticity mechanisms become exhausted. As a result, lesions and scars increase in number and begin coalescing. As a certain threshold is reached, the lesion load begins to have a more significant impact on neuropsychological assessment (Benedict, Caroni, & Bakshi, 2004).

The threshold and multiple disconnection mechanisms postulated to explain cognitive impairment in the several forms of MS are not mutually exclusive, and both may be integrated with data showing that IPS plays an important role in the neuropsychology of the disease. In the next session, we discuss how the slowing of cognitive processing may impair working memory (WM), a crucial domain of impairment in MS.

White matter impairment and information processing speed

Neuropsychological similarities in various types of cerebral hemispheric white matter impairments are now the object of growing interest. White matter dementia is the term used to identify this group of impairments (Campbell & Coffey, 2001). Several conditions, such as juvenile diabetes (Kail, Wolters, Yu, & Hagen, 2000), acquired immune deficiency syndrome encephalopathy (Reger, Welsh, Razani, Martin, & Boone, 2002), and MS (Demaree, DeLuca, Gaudino, & Diamond, 1999), are characterized by a profile of neuropsychological impairment, in which psychiatric symptoms, executive function, episodic memory retrieval, and WM deficits are present. The most salient feature in these conditions is a slowing of information processing, which can be either subtle (i.e., detected only by chronometric procedures) or more severely apparent (e.g., in the form of bradypsychism).

The Paced Auditory Serial Addition Test has been used by Demaree et al. (1999) to show that a deficit in IPS plays a crucial role in the cognitive symptoms of MS patients. These authors used auditory and visual versions of the test, administered with stimuli presentation at intervals of 2 or 3 s. They demonstrated that MS patients, who performed the traditional versions of the test very poorly, obtain results as accurate as controls when they can choose the speed of stimuli presentation that they find more convenient. Data from a meta-analysis confirmed the importance of timed tests in the diagnosis of cognitive deficits related to MS (Thornton & Raz, 1997). The Paced Auditory Serial Addition Test imposes strong demands on IPS, and it has been found to be one of the most accurate measures for detecting cognitive impairment in MS patients (Archibald & Fisk, 2001).

Hemispheric white matter-related cognitive deficits, especially a slowing of information processing, are also found in the context of both normal and abnormal aging, showing several similarities to MS (Campbell & Coffey, 2001; Gunning-Dixon & Raz, 2000). Research suggests a continuum between white matter modifications observed in normal aging and pathological white matter lesions observed in clinical conditions, such as MS, vascular dementia, mild cognitive impairment, and Alzheimer's disease (Frisoni & Filippi, 2005). Multifocal vascular lesions may also predispose individuals to psychiatric disorders, such as major depression (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002). White matter damage, the slowing of information processing, and depressive symptoms may interact in complex ways, resulting in different functional outcomes, both in normal and affected individuals.

According to Calabrese (2006), white matter involvement causes multiple disconnections between cortical and subcortical areas. The symptomatic manifestation depends on both the location of the lesion and the progressive accumulation of damage, becoming obvious only when a certain lesion threshold is exceeded. In some patients, cognitive impairment can be detected already during the early stages of the disease (Achiron & Barak, 2003), whereas others remain relatively symptom-free even 20 years after disease

onset (Sayão et al., 2007). Multiple disconnections cause fatigue, reducing IPS, which affects executive control over various forms of memory, thinking, and decision-making (Arnett et al., 1997). Impairments of memory and executive function are caused by frontal subcortical lesions that disconnect the prefrontal cortex from other cortical and subcortical structures (Gainotti, 2006).

The relationship between IPS and cognitive performance can be demonstrated through a WM model developed by Salthouse and Babcock (1991), which is extremely relevant to the context of aging and MS. In this model, the executive component of WM is assessed through a task of keeping a progressively greater item number in mind while simultaneously resolving a progressively greater series of simple cognitive or perceptual tasks (Listening Span Task). Stimuli are presented orally, whereas the answers are written. Salthouse and Babcock demonstrated that task-related losses in WM associated with aging could be explained by the slowing of information processing. In a more detailed review, Salthouse (1996) showed that IPS accounted for more than 90% of the variance in normal cognitive aging. The model proposes that the executive component of WM corresponds to the ability to quickly and efficiently coordinate the storage and speed of verbal or simple arithmetic problem-solving.

In the process WM model proposed by Salthouse and Babcock (1991), coordination capacity corresponds to the central executive, whereas storage capacity corresponds to the slave systems of the Baddeley and Hitch WM model (Baddeley, 2003). The process model further assumes that both the coordination of operations and storage capacity depend critically on IPS, which is impaired in MS (Demaree et al., 1999). The reduction in IPS, therefore, affects the storage capacity and the ability to perform mental operations efficiently in WM. In the next section, we examine the way in which the understanding of impairments in processing speed in WM may be integrated with a functional model of conscious mental activity based on periodic neural activity.

The functional model

According to cognitive theory, the human brain may be conceptualized as a computational system (Pöppel, 1993, 2009**;** see Box 1). Perceptual processes are comparable to the information input, whereas external or internal action corresponds to the system output. Cognition corresponds to the steps between input and output processes (coding or subjective/emotional stimuli interpretation, storage/memory, communication, reasoning, and decision-making). This analogy allows neuropsychologists to identify, define, diagnose, and assess functional impact and eventually develop rehabilitation strategies for cognitive deficits observed in neurological patients.

Box 1. Taxonomy of mental functions cf. Pöppel (1993).

Material Functions "What?"	Stimuli Perception	Perception
	Stimuli Processing	Associations Learning Memory
	Stimuli Evaluation	Emotions Motivation
	Response to Stimuli	Action Reaction
Formal Functions "How?"	Activation	
	Temporal Coordination	Simultaneous Successive

Mental function can be classified into material and formal (Pöppel, 1993). Material functions identify the content of mental activity (e.g., emotions, feelings, and memories), matching the address in which information is stored in the digital computer. They may be modularly represented in the cerebral cortex and can be segregated into different patterns of impaired and preserved abilities after focal lesions. Each area of mental functioning is processed relatively independently for a given region of the cerebral cortex.

However, some form of logistics is a necessary tool for accessing mental content. Formal functions comprise organizational processes that make material functions possible. In a digital computer, they correspond to random access memory or WM. Working memory periodically regulates the activity of the system's structures. Whereas material functions are characterized by semantic content, formal functions can be compared with the formal syntax of the system.

A first formal function concerns the activation of the system, which is usually done by several neurochemical modulatory systems through diffuse projection fibers originating in the brainstem and basal forebrain (Mesulam, 2000). The second formal function is the temporal organization of operations in the system, which can be called chronometric or synchronized timing. From a series of psychophysical studies, Pöppel (1993, 2009) proposed that mental activity is organized periodically and that the pacemaker results from the oscillatory nature of neuronal activity, with information reverberating in cortico-subcortico-cortical loops. Mental events that occur in the synchronization of oscillatory neuronal phenomena, which has an upper limit of a few seconds, correspond to the so-called psychological moment of classical authors (James, 1890).

Pöppel (1993) proposed that the basic psychophysical laws formulated by Weber in the 1840s and Fechner (1860), which constitute the structural framework of conscious perception, are emergent properties of neural networks with a hierarchical,

parallel, re-entrant cortico-subcortical structure. The subjective psychological moment is constructed from associative processes that obey these laws. Mental activity is characterized by a cyclical temporal structure. Neural events are associatively incorporated until a limit of representational capacity in WM is reached. This integration depends on both the self-pacing oscillatory nature of neuronal activity and the reentrant interactions between the cortical and subcortical structures. Its period may correspond to the duration of reverberations in cortico-subcortical loops.

At a given moment, an upper capacity or time limit is exceeded, and an activity period closes. All contents or elementary mental/neural events are automatically integrated up to this capacity/temporal limit. Integrated contents are characterized by a holistic meaning, corresponding to a perceptual moment. Conscious mental experience consists of a series of such psychological or WM moments. The relationships between various psychological moments are conceptual and do not need to conform to psychophysical laws but to laws of logic or universal grammar (Haase, Diniz, & da Cruz, 1997).

The model assumes that multifocal, mainly subcortical, MS-associated lesions slow information processing, interfering with the distributed neural machinery that works in formal mental/neural functions. This model is built on a series of theoretical considerations and experimental results. Research by Salthouse and Babcock (1991) emphasized that WM performance depends on IPS. Kail and Park (1994) showed that a linear association exists between the speed of articulation and verbal short-term memory storage capacity and that both grow steadily from childhood to adolescence. Information processing speed has been consistently identified as a neurobiological foundation for general intelligence (Deary & Caryl, 1997). Neuroimaging research additionally shows that cognitive function in aging depends heavily on IPS, which is implemented by distributed connectivity between several cortical areas (Waiter et al., 2008).

The periodicity of mental activity was documented by Pöppel and others in a series of psychophysical studies (Schleidt, Eibl-Eibesfeldt, & Pöppel, 1987; for recent review, see Pöppel, 2009)Temporal segmentation of human activity is observed in a series of daily living activities, such as gesture-making, perception, poetry, and music (Haase et al., 1997). A role for oscillatory neural activity in building psychologically relevant neuronal assemblies has been emphasized by Singer (1993; Fries, Nikolic, & Singer, 2007) in a series of neurophysiological studies conducted over the past 20 years. Neuronal oscillations in the so-called gamma band (30-40 Hz) may play a major causal role in synchronizing neural activity to build neuronal assemblies that underlie a series of phenomena, such as the continuity of visual perception. Singer (1993) proposed that widely spatially distributed neuronal activity may be glued by oscillatory synchronizing interactions, forming neural assemblies underlying several psychological states. Such elementary neuronal assemblies or events would then correspond to the elementary units of mental activity that are integrated in WM during an activity period.

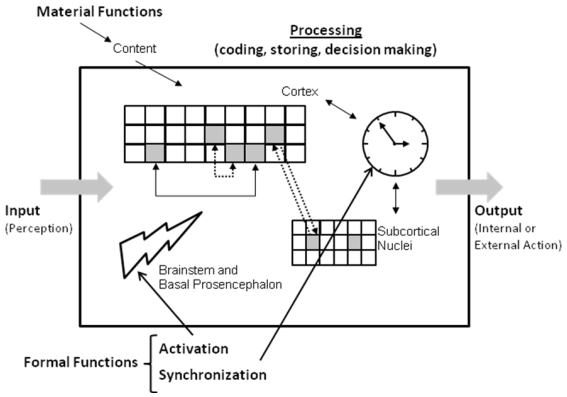

Figure 1. Cognitive model of the brain-mind. Cognition corresponds to coding, storing, and decision-making processes, which stand between the input (perception) and output (action) of the system. Formal cognitive functions have content and are modularly represented in the cerebral cortex and subcortical structures. Formal functions include activation (brainstem and basal prosencephalon) and activity synchronization (cortico-cortical and subcortico-cortical connections). (Adapted from Pöppel, 1993).

Figure 1 shows the cognitive model, which may be useful in the interpretation of neuropsychological deficits presented by several patients. Material functions are modularly represented in the cerebral cortex and subcortical structures. Activation functions are implemented by brainstem and basal forebrain structures. Timing functions depend on connections between adjacent and anatomically dispersed cortical areas and re-entrant cortico-subcortical loops. In the next section, we discuss the possible neuroanatomical bases of the cognitive functional model proposed by Pöppel (1993).

The structural model

To be useful in the last diagnostic step of a structural-functional correlation, the model must be better specified anatomically (Figure 2). Information flow between adjacent cortical areas allows analytic mechanisms to occur, such as those underlying language and symbolic arithmetic. Connections between widely dispersed cortical areas are important for more holistic forms of processing, such as spatial and executive function or WM. Holistic integration enables a consideration of a wider context of activity. Recruiting medial temporal lobe structures connected with prefrontal areas also results in the self-referential nature of mental activity and several possibilities of mental time traveling, such as remembering the past or anticipating the future.

There may be a degree of hemispheric asymmetry, with short-distance connections predominating in the left hemisphere and long-range loops predominating in the right hemisphere (Goldberg & Costa, 1981). According to Goldberg and Costa, the left hemisphere predominance of short range cortico-cortical connections could explain the involvement of this hemisphere with syntactic and phonological aspects of language, whereas more widespread connections in the right hemisphere would explain its role in pragmatics and text processing (see also Rourke, 1995). Impairment in text processing, for example, may be observed in traumatic brain injury, which may likely be caused by long fiber tract dissociations between different cortical areas related to discourse comprehension and production.

In the anterior-posterior axis, prefrontal areas have a greater degree of inter-regional connectivity than any other cortical loci, connecting directly with all other brain areas with the exception of primary cortical areas and the hypothalamus (Mesulam, 2000; Fuster, 2008). Prefrontal areas may then be considered an executive pole, whose impairment underlies psychiatric disorders (Mega & Cummings, 1994). Finally, information resonance between several cortical areas and subcortical structures, such as thalamic, dorsal, and ventral striatal nuclei and the amygdala, equipping the system with a kind of WM that operates as a pacemaker that defines a temporal frame or mental/neural activity (Pöppel, 1993).

The proposed model allows us to explain the neuropsychological expression of several clinical conditions traditionally studied by neuropsychology. Material or semantic mental functions rest on both the functional integrity of cerebral cortical areas and subcortical structures, such as the thalamus and striatum. Classical neuropsychological symptoms and syndromes (e.g., aphasia, agnosia, apraxia, and hemineglect) are frequently observed following focal cortical or juxtacortical lesions in a range of diseases, such as stroke (Engelter et al., 2006; Ringman, Saver, Woolson, Clarke, & Adams, 2004; Zwinkels, Geusgens, van de Sande, & van Heugten, 2004), trauma, and tumors (for review, see Larner, 2008). Classical neuropsychological deficits may also be seen in focal ischemia or hemorrhage in the thalamus or striatum (Koziol & Budding, 2009), although these deficits may result from secondary cortical hypoperfusion or dysachisis (Hillis et al., 2002). Both in traumatic brain injury and brain tumors, cortical-juxtacortical lesions are associated with classical neuropsychological syndromes, whereas subcortical white matter damage related to diffuse axonal injury and hydrocephalus impairs IPS (Bigler, 2001). Multi-infarct dementia, in contrast, may be a result of widespread multifocal damage to subcortical gray and white matter (Chabriat & Godefroy, 2007).

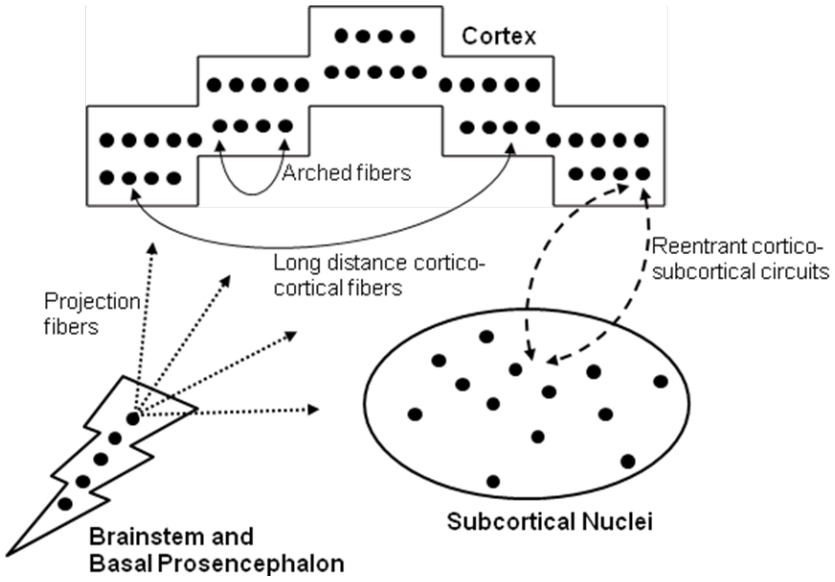

Figure 2. Simplified structure-function correlation model. The content of behavior and psychological experiences depends on the activation of cortical and subcortical modular representations, which are allowed by activation processes generated in nonspecific projection systems of the brainstem and basal prosencephalon and synchronizing functions of cortico-cortical and cortico-subcortical reentrant circuits. Cognitive analytical mechanisms are implemented by short-distance cortico-cortical connections. Holistic integration mechanisms are based on long-distance cortico-cortical connections. Anterior hemispheric areas present greater connectivity with other cerebral areas, constituting the executive pole of the system. Information reverberation in cortico-subcortical reentrant circuits creates a pacemaker that enables information storage and processing in random access memory. To synchronize the content of mental activity, the processor and working memory must function very rapidly to allow information to travel between several cortical and subcortical areas in every computational step. The content of subjective psychological experiences or psychological moments correspond to modules or material functions accessed in an activation period of the cortico-subcortical pacemaker.

Neary (1999) presented a simplified model to understand anatomo-clinical correlations in dementing illnesses. Degenerative conditions, such as Alzheimer's disease and fronto-temporal dementias, may be associated with simultaneous impairment of activation mechanisms dependent on forebrain structures and material functions represented in the cerebral cortex. Anterior cortical degenerative disorders, such as the frontal variant of fronto-temporal dementia, presents with personality and self-regulation disturbances, whereas cognitive disturbances (e.g., episodic memory failure, naming difficulties, and visuoconstructive disorders) occur more frequently in diseases with more posterior hemispheric expression, such as Alzheimer's disease, posterior cortical atrophy, and semantic dementia.

Some degenerative disorders, such as Alzheimer's disease and fronto-temporal dementia, may be associated with simultaneous impairment of the activation mechanisms that are dependent on the brainstem and basal prosencephalon and material functions represented in the cerebral cortex. This pattern of impairment results in amnesia associated with apathy, agnosia, and dementia. Anterior cortical degenerative lesions are more strongly related to self-regulation and personality alterations, whereas neuropathological processes of the posterior cortical pole create more cognitive symptoms (Neary, 1999).

Other degenerative conditions, such as Parkinson's disease, are associated with simultaneous impairment of activation functions (e.g., apathy, abulia) and chronometric functions (e.g., bradypsychism; Gauntlett-Gilbert & Brown, 1998). The neuropsychological pictures of subcortical impairment that may evolve to "subcortical dementia" are characterized mainly by bradypsychism and difficulties with WM and executive control over the memory operations. The symptomatic picture of a compensated internal hydrocephalus represents one of the typical forms of subcortical impairment, in which we observe gait and bladder disturbances and bradypsychism (Neary, 1999).

The model we propose here may be extremely helpful for understanding the structure-function correlation found in the MS context. As stated above, neuropsychological deficits in MS may be attributable to interference in nervous impulse conduction on axons affected by the initially inflammatory and later degenerative processes observed in the disease. Cognitive impairments in MS are most frequently caused by lesions in the cortico-cortical connections and cortico-subcortical re-entrant circuits (see lesions in Figure 3). These lesions create multiple disconnections between several cerebral areas or modules, disturbing the access and integration of the stored mental content and slowing WM operations (Calabrese, 2006; Gainotti, 2006). An example of functional disconnection is left arcuate fasciculus lesion, which has been involved in the origin of depressive symptoms (Pujol, Bello, Deus, Marti-Vilalta, & Capdavila, 1997). Focal neuropsychological syndromes, such as aphasia, may be caused by lesions that damage cortico-cortical connections or arcuate fibers (Miki et al., 1998; see lesion b in Figure 3).

Cerebral aging has similar features, although they are less marked than those seen in MS (Gunning-Dixon

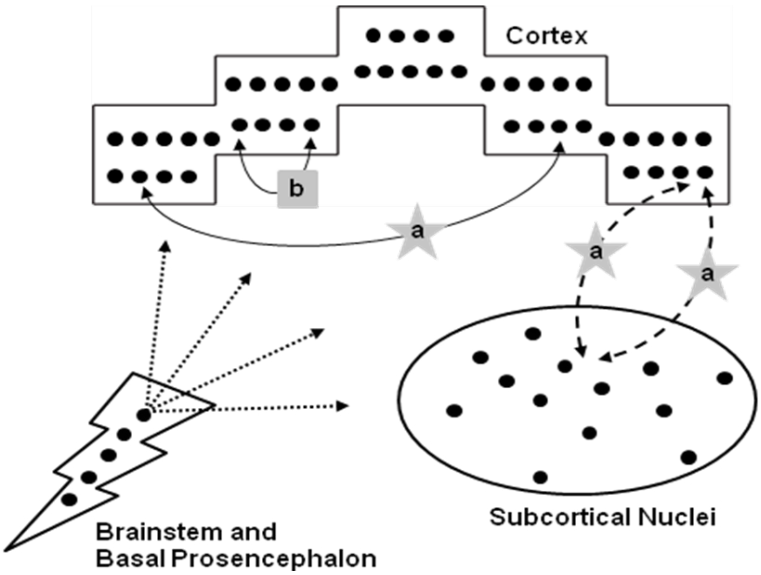

Figure 3. Structure-function correlation model for white matter multifocal/disseminated lesions. In MS, the inflammatory and degenerative process that affects long-distance cortico-cortical fibers and cortico-subcortical circuits ("a" lesions, represented by stars) causes multiple functional disconnections, resulting in memory and executive function deficits and a decrease in information processing speed. Deficits are clinically expressed only after a certain threshold is reached. Juxtacortical lesions may cause focal neuropsychological deficits, such as aphasia ("b" lesion, represented by the square).

& Raz, 2000). Brain magnetic resonance imaging of old individuals frequently displays small hyperintense lesions scattered over the white matter of both cerebral hemispheres. The accumulation of these lesions is associated with cognitive deficits observed in normal aging, such as slowed IPS and lexical retrieval deficits. In pathological situations, small multifocal white matter lesions reach a certain threshold and are seen in the form of Binswanger's disease or atherosclerotic dementia (Neary, 1999).

In addition to describing structure-function correlations characteristic of MS, the proposed model also allows the comparison of MS with other nosologic entities, highlighting the specific patterns of each disease and lesion location. To initially assess the appropriateness of the model, we examine the results from extant meta-analyses that reviewed the neuropsychological manifestations of MS, white matter hyperintensities (WMH) related to normal aging, and Alzheimer's disease in the next section.

Comparison of the cognitive profile of multiple sclerosis, normal aging-related white matter hyperintensities, and dementia of the Alzheimer's type

After describing the structure-function correlation model (or the Conceptual Nervous System), we must evaluate whether it is appropriate for explaining the MS cognitive profile. To accomplish this task, comparing the cognitive impairment profiles of MS patients to those of patients with other conditions with a similar structural lesion pattern and different structural lesion patterns may be helpful. Normal aging-related WMH, which have a form of impairment similar to that observed in MS, and dementia of the Alzheimer's type, which has a different structural lesion pattern that affects mostly cortical gray matter, were selected for comparison.

White matter hyperintensities are frequently observed in the context of normal aging and resemble the white matter lesions observed in MS, sometimes even making differential diagnosis difficult. Accumulating evidence indicates that WMH may be responsible for cognitive alterations observed in normal aging, which are similar to those observed in MS. The cognitive profile observed in white matter disorders, such as normal aging-associated WMH and MS, can be defined as white matter dementia. This profile includes impaired sustained attention, memory retrieval, executive function, visuospatial skills, and psychiatric status, whereas language, procedural memory, and extrapyramidal functions are relatively preserved (Lafosse, Corboy, Leehey, Seeberger, & Filley, 2007; Filley, 2001, 2005). Disorders that predominantly affect cortical gray matter, such as dementia of the Alzheimer's type, in contrast, affect processing speed and cortical functions, whereas executive functions remain relatively preserved. Working memory and executive functions are impaired since the early phases of Alzheimer's disease, but the dominant and differentiating clinical picture is related to episodic memory (Royall et al., 2002). Relatively milder impairments of executive function, for example, are used to distinguish Alzheimer's disease from the frontal variant of fronto-temporal dementia (Harciarek & Jodzio, 2005).

An efficient method for analyzing the cognitive profile of these three conditions is to compare the results of meta-analyses that compare the performance of groups of patients and controls. Meta-analyses provide results in the form of effect sizes, which allow quantitative comparisons between the results of different studies. To find the necessary papers, a PubMed search was conducted using the terms "multiple sclerosis meta-analysis," "white matter hyperintensities meta-analysis," and "Alzheimer meta-analysis." Of the results, we selected meta-analysis papers that compared the performance of MS, normal-aging-WMH, and dementia of the Alzheimer's type to the performance of control groups and that organized the results by cognitive domain, which allowed for a more organized comparison. Following these criteria, we selected seven papers, which are discussed below.

Gunning-Dixon and Raz (2000) conducted a meta-analysis of the normal aging-WMH effects on cognitive domains in normal aging. They reported effect sizes as Pearson's product-moment correlations (r), which is different from the other meta-analysis included here, which reported effect sizes as Cohen's d coefficients. Convert r to d is necessary to make comparisons possible with the results of other meta-analyses, such as the one conducted by Thornton and Raz (1997) for MS. Product-moment correlations allow inferences in terms of the percentage of shared variance, but d coefficients are more intuitive in the context of group comparisons because they allow inferences for differences between means in terms of standard units.

The conversion from r coefficients to d coefficients is easily executed using a table provided by Cohen (1988, Table 2.2.1, p. 22). The results of this conversion are shown in Table 1, together with the original results supplied by Gunning-Dixon and Raz (2000, Table 2, p. 227).

Table 1 shows that normal aging individuals with WMH perform approximately 0.6-0.7 standard units below normal aging without WMH on executive function measures and approximately 0.4-0.5 standard units below in processing speed and global functioning tests. Figures for short- and long-term memories are of lower magnitude (i.e., approximately one-third of standard unit). In measures of fluid and crystallized intelligence, patients with normal aging-WMH are only

Table 1. Effect sizes for NA-WMH organized by cognitive domain

Cognitive Domain	Tasks	Pearson's r	Cohen's *d*
Global Functioning	MMSE	0.22	0.40 - 0.50
Processing Speed	SRT CRT TMT-A Stroop colors Stroop words Digit Symbol	0.22	0.40 - 0.50
Immediate-recent Memory	5-minute recall tasks WMS-PAL WMS-Logical Memory WMS-Visual Reproduction WAIS-Digit Span	0.12	0.20 - 0.30
Delayed Memory	30-minute Recall taks	0.20	0.40
Fuid Intelligence	Raven WAIS-Block Design	0.09	0.20
Crystalized Intelligence	Vocabulary WAIS-Information	0.09	0.20
Executive Functions	WCST Category Test TMT-B Stroop Interference	0.30	0.60 - 0.70
Motor Functions	Finger Tapping Perdue Pegboard	0.09	0.20

Gunning-Dixon & Raz (2000, p. 227)

0.2 standard units below normal aging without WMH.

After converting the normal aging-WMH data to *d* coefficients, we are able to compare them to the data from MS patients provided by Thornton and Raz (1997) and Zakzanis (2000). This comparison is shown in Table 2.

The comparison of the neuropsychological profiles in normal aging-WMH and MS allows the identification of qualitative similarities and quantitative differences. Qualitatively, both conditions compromise episodic memory (d = 0.4 for normal aging-WMH and 0.74 - 1.44 for MS), processing speed (d = 0.4 - 0.5 for normal aging-WMH and 0.3 - 1.36 for MS), and executive function/WM (0.6 - 0.7 for normal aging-WMH and 0.46 - 0.99 for MS). Quantitatively, however, impairment levels in MS are higher than in normal aging-WMH. We may infer then that in both normal aging-WMH and MS, a "subcortical" pattern of impairment related to dysfunction in frontal-subcortico-frontal loops is observed, but the severity is higher in MS.

Having established the similarities between two conditions characterized by predominantly subcortical, diffuse, or multifocal white matter damage, comparing this "subcortical" profile with a more "cortical" one, such as dementia of the Alzheimer's type, may be interesting. Bâckman, Jones, Berger, Laukka, and Small (2005, Table 2, p. 524) provide data for preclinical dementia of the Alzheimer's type, whereas Zakzanis (1998) investigated patients in the intermediate stages of dementia of the Alzheimer's type. Helmes and Ostbye (2002, Table 2, p. 184) reported data from a large demographic representative sample and organized their results according to tests. Christensen, Griffiths, Mackinnon, and Jacomb (1997, pp. 638, 639) systematically reviewed papers that compared groups of patients with dementia of the Alzheimer's type or depression to control samples. Data compiled from these four sources are shown in Table 3.

Cognitive domains most strongly affected in patients with dementia of the Alzheimer's type are oral language (d = 0.39 - 2.13), visuospatial processing (d = 0.64 - 2.34), episodic memory (d = 0.83 - 3.3), and processing speed (d = 0.62 - 1.58), whereas WM (d = .38) and short-term memory (d = .0 - 0.46) are only very slightly altered (Table 3). An interpretative synthesis for the comparisons between normal aging-WMH, MS, and dementia of the Alzheimer's type is shown in Table 4.

Table 2. Effect Sizes for NA-WMH and MS organized by Cognitive Domain

Cognitive Domain	NA-WMH[1] Tasks	*d*	MS[2] Tasks	*d*	MS[3] Tasks	*d*
Global Functioning	MMSE	0.40 - 0.50	-	-	MMSE Blessed Dem. Rating	0.49 1.54
Fluid Intelligence	Raven WAIS-Block Design	0.20	-	-	Raven	0.53
Crystalized Intelligence	Vocabulary WAIS-Information	0.20	-	-	-	-
Language (oral)	-	-	-	-	Boston Naming Test WAIS Vocabulary WAIS Comprehension Token Test	0.54 0.4 0.30 0.29
Reading	-	-	-	-	Nat. Adult Reading Test	0.04
Visuospatial	-	-	-	-	WAIS Block Design JLO Rey Figure Copy WAIS PIQ WAIS VIQ WAIS FIQ	0.50 0.33 0.11 0.59 0.50 0.40
Processing Speed	SRT CRT TMT-A Stroop Colors Stroop Words Digit Symbol	0.40 - 0.50	-	-	Digit Symbol SDMT TMT-A	1.03 1.36 0.30
Short-term Memory	-	-	Digit Span Visual Span	0.35	Digit Span Backward Digit Span Forward Corsi	0.42 0.37 0.22
Working Memory	-	-	Brown-Petersen PASAT	0.72	PASAT	0.48
Executive Functions	WCST Category Test TMT-B Stroop Interference	0.60 - 0.70	-	-	Semantic Fluency COWAT Stroop Interference WCST Pers. Resp. WCST Categories WCST Pers. Errors Category Test	0.99 0.78 0.62 0.57 0.52 0.51 0.46
Immediate-Recent Memory	5-minute Recall Tasks WMS-PAL WMS-Logical Memory WMS-Visual Reprod. WAIS-Digit Span	0.20 - 0.30	Prose Memory Figural Memory PAL List Learning	0.7	CVLT Short Delay Log. Memory Immed.	1.00 0.71
Delayed Memory	30-minute Recall	0.40	-	-	SRT Delayed Recall Log. Memory Delayed RAVLT Trial 5 CVLT LA Trial 5 RVLT Delayed Rey Figure Delayed	1.44 0.99 0.84 0.84 0.74 0.74
Motor Functions	Finger Tapping Perdue Pegboard	0.20	-	-	-	-

[1]Gunning-Dixon & Raz (2000, p.227), [2] Thornton & Raz (1997, p. 360), [3] Zakzanis (2000, p. 122)

Table 3. Effect Sizes for DAT organized by Tasks and Cognitive Domains

Cognitive Domain	Preclinical DAT[1]		Initial DAT[2]		Intermediate DAT[2]		Intermediate DAT[3]		Intermediate DAT[4]	
	Tasks	*d*	Tasks	*d*	Tasks	*d*	Tasks	*d*	Tasks	*d*
Global Functioning	MMSE Camdex	1.19	3MS	4.33	3MS	6.54	-	-	MMSE SPMSQ Blessed Dementia Scale	2.47 1.65 0.83
Language (oral)	COWAT Boston Naming Test WAIS Vocabulary	0.79	Similarities Comprehension Naming Token Test Verbal Fluency Animal Fluency	1.22 1.18 1.34 1.34 0.99 1.44	Similarities Comprehen-sion Naming Token Test Verbal Fluency Animal Fluency	1.38 1.37 2.13 1.31 1.24 1.39	-	-	Western Aphasia Battery Boston Naming Test WAIS Vocabulary Synonyms Learning Test Verbal Fluency	0.57 1.12 0.87 1.51 0.39
Reading	-	-	-	-	-	-	-		Nat. Adult Reading Test	0.17
Visuospatial	WAIS Block Design Rey Figure Copy Clock Drawing	0.64	WAIS Block Design Drawing	1.29 1.71	WAIS Block Design Drawing	1.68 2.34	-	-	WAIS Block Design	1.08
Agnosia	-		Object Recogn. Color Recogn.	0.83 0.24	Object Recogn. Color Recogn.	1.53 0.63	-	-	-	-
Processing Speed/ Attention	TMT-A WMS Mental Control WAIS Digit Symbol Letter Cancellation	0.62 1.11	WAIS Digit Symbol	1.3	WAIS Digit Symbol	1.58	-	-	WAIS Digit Symbol TMT-A	0.95 0.74
Short-term Memory	Digit Span Forward	0.00	-	-	-	-	-	-	Digit Span Forward	0.46
Working Memory	-	-	-	-	-	-	-	-	Digit Span Backward	0.38
Executive Functions	TMT-B Stroop Interference Alphabet Span	1.07	-	-	-	-	-	-	-	-
Episodic Memory	CVLT BVRT Logical Memory	1.03	-	-	-	-	CVLT WMS	3.3 2.8	BVRT WMS	0.83 2.17

[1]Backman et al. (2005, p. 524),[2] Helmes & Ostbye (2002, p. 184),[3] Zakzanis (1998, pp. 265, 266,)[4]Christensen et al. (1997, pp. 638, 639)

Table 4. Interpretative comparison of the cognitive profiles of MS, NA-WMH and DAT

Cognitive Domain	MS (*d*)	NA-WMH (*d*)	Preclinical DAT (*d*)	DAT (*d*)
Global Functioning	0.50	0.50	1.19	6.54
Verbal IQ	0.50	0.20	-	1.38
Performance IQ	0.60	0.20	-	1.68
Oral Language	0.50	-	0.80	2.13
Reading	0.04	-	-	0.17
Visuospatial Functions	0.60	-	0.64	2.34
Visual Recognition	-	-	-	1.53
Attention / Processing Speed	1.40	0.50	1.0	1.58
Short-term memory	0.40	0.30	0.0	0.46
Working memory	1.00	-	-	0.38
Episodic memory	1.40	0.40	1.0	3.30
Executive Functions	0.80	0.70	1.0	1.40

Discussion and conclusions

Neuropsychological diagnosis is an inferential process sustained by a triad of neuropsychiatric clinical epidemiology, psychometrics, and anatomo-clinical correlations. The basic reference used for interpretation of structure-function correlations is a Conceptual Nervous System (Hebb, 1955), which has a virtual nature. Most frequently in clinical practice, correlations are built in the neuropsychologist's brain-mind by the use of both anatomo-clinical correlations from the literature and the professional's previous clinical experience. Simultaneously, carefully planned individual case studies enable him to discover and consolidate new structure-function correlations. Cognitive models of information processing allow a more precise and quantitative operation of the signs and symptoms generated by cerebral lesions. Cognitive models are therefore systems with links between patients and their families' subjective complaints, objectively detectable behavioral abnormalities, and the anatomo-functional basis that has been disturbed by the pathological process.

Functionally, the cognitive model proposes an analogy of the human brain-mind with a digital computer. Perceptive mechanisms represent the input operations, and internal or external actions represent the output operations. Cognition is everything between input and output.

Structurally, mental functions may be classified into material and formal. Material mental functions are modularly represented in the cerebral cortex and basal ganglia. Typical impairment of material mental functions is manifested in the classical neuropsychological syndromes that result from focal cortical or subcortical lesions. Formal mental functions, in contrast, are those related to activation and chronometric functions. Activation functions are implemented by structures of the brainstem and basal prosencephalon, and their disturbance results in either apathy or hyperexcitability. Chronometric functions are responsible for temporal organization of behavior and are implemented by re-entrant circuits between segregated cortical areas and reverberant cortico-subcortical circuits.

The cognitive-neuropsychological model of a structure-function correlation allows only virtual and coarse localization of lesions in terms of a system of spatial coordinates with three axes. In the latero-lateral axis, analytical functions of the left hemisphere are explained by its predominantly local connections, whereas holistic functions of the right hemisphere derive from its more global pattern of connectivity. In the antero-posterior axis, differences between the perceptive/representational pole in the posterior areas and the executive/action pole in the anterior areas are explained by the larger connectivity of prefrontal areas, which are connected in parallel with a number of more basic neuronal circuits that are hierarchically organized in successive levels of sensory-motor integration. A successive increase in the number of synaptic chains between the inputs and outputs at several hierarchical levels elicits the forms of information processing that correspond to cognition (Mesulam, 2000). Finally, in the vertical axis, two distinctions are established, one between the pathologies that predominantly affect the cortical or subcortical structures and another between damage of the prefrontal limbic system of dorsal

or ventral origin. The subcortical lesions decrease processing speed, interfering with several cognitive functions, especially WM.

The emphasis given by this model to impairment of formal functions on the vertical axis contributes to the elucidation of the relatively nonspecific deficits of degenerative or multifocal subcortical pathologies, such as Parkinson's disease and MS.

Admittedly, this model may be a didactic oversimplification of the situation and has some limitations inherent to neuropsychology itself. In clinical practice, this model enables one to make merely virtual structure-function correlations. Its accuracy is also low (e.g., only approximately 70% for aphasia; Willmes & Poeck, 1993). Nevertheless, it is still better than any other currently available methods. In everyday practice, interpreting the results of neuropsychological tests based on a relatively coarse structure-function correlation model is still more prudent than simply applying tests and generating scores.

A second limitation of this model is the fact that it is based on a strictly modular approach (i.e., the classical theory according to which information processing occurs in a localized and serial fashion). Current neural network models and studies of functional neuroimaging indicate that information processing occurs in a parallel and massively distributed fashion in the brain. Advances in the parallel and distributed information processing models, however, have only had a very small impact on the practice of neuropsychological diagnosis. Some works have also shown that the several perspectives provided by computational modeling, neuroimaging, and clinical neuropsychology are compatible and complementary (Price et al., 2003).

One important limitation of the present study is that the usefulness of the Conceptual Nervous System is not analyzed in the context of the diverse clinical forms of the disease. Currently unknown is whether the several clinical forms of MS represent different nosological entities or whether they eventually constitute only manifold phenotypic expressions in different patients or phases of its natural history. Neuromyelitis optica, for example, which was once considered a variant of MS, is currently established as a distinct nosological entity with well characterized genetic and physiopathological mechanisms (Jacob et al., 2007). Future work must analyze neuropsychological specificities related to each clinical form of MS and their relevance to the proposed Conceptual Nervous System.

As a final cautionary remark, any model is necessarily a simplification of reality. In the long run, a model's utility may only be corroborated by its utility in clinical practice. A model is like a map. Its usefulness depends on the ease with which it helps one arrive at a certain place. In the case of the neuropsychology of MS, the goal is to reduce the complexities related to disease heterogeneity to better understand the mechanisms underlying cognitive impairments.

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