Lateralization of Frontal Lobe Functions and Cognitive Novelty

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The two hemispheres are functionally different in ways not adequately captured by the classic distinction between linguistic and nonlinguistic processes. The right hemisphere is critical for processing novel cognitive situations. The left hemisphere is key to the processes mediated by well-routinized representations and strategies. The left frontal systems appear to be critical for the cognitive selection driven by the content of working memory and for context-dependent behavior, the right frontal systems for cognitive selection driven by the external environment and for context-independent behavior. The crucial role of the right hemisphere in processing cognitively novel situations underscores the importance of the right frontal systems in task orientation and in the assembly of novel cognitive strategies.

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Historically, hemispheric specialization has been cast in categorical and static terms: the left hemisphere the linguistic one, and the right hemisphere the visuospatial one. Although this premise has become extremely influential, significant developments have taken place in cognitive neuroscience that challenge this classic dichotomy. It is important to bring these developments to the attention of clinical neuroscientists.

In this article we will introduce a distinct approach to hemispheric specialization, called the *novelty-routinization* approach, and relate it to the functions of the frontal lobes.

The traditional assumption holds that the left cerebral cortex of the human brain controls the processing of linguistic information, whereas the right hemisphere controls the processing of information for which language encoding is less feasible. The available data suggest, however, that the actual distribution of hemispheric responsibilities is not so clear-cut: the right hemisphere is not irrelevant to language, nor is the left hemisphere irrelevant to processing nonlinguistic information.[1]

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THE RIGHT HEMISPHERE AND LINGUISTIC PROCESSES

Left hemispheric dominance is not equally strong for all aspects of language processing. The left hemispheric advantage is more evident for consonants than vowels, for long words than short words, for abstract words than concrete words, and for lower frequency words than higher frequency words.[2–7]

The effects of early hemidecortication also suggest that the left hemisphere is not equally necessary for the development of all verbal skills. Early left hemidecortication permits the subsequent development of phonemic discrimination between real words, but not between paralogs or phonologs (pseudowords).[8,9] Early left hemidecortication permits the development of propositional analysis, but it is limited to inference based on lexical information and general logical constraints, as opposed to the explicit appreciation of syntax.[10–12] Early left hemidecortication permits the development of a large auditory lexicon, but of only limited categorical links between lexical items.[10,12]

It has been concluded that the right hemisphere plays a significant role in the formation of the referential basis of the code, but the left hemisphere is particularly important for the rule-based internal derivations within the code.[13]

THE LEFT HEMISPHERE AND NONLINGUISTIC PROCESSES

A body of evidence indicates that the left hemisphere plays a role in the processing of nonlinguistic information, including visuospatial information. Lateralized damage to the left hemisphere may produce severe perceptual deficit in the relative absence of language deficit. Two families of agnosias exist: associative and apperceptive. They exhibit opposite, complementary patterns of localization relative to the two cerebral hemispheres.

Associative Agnosias

In associative agnosias, a patient cannot recognize an object as a member of a generic category, even though elementary perceptual analysis of its physical components and the ability to copy it may be relatively spared. Associative agnosias involve the degradation of, or impaired access to, the generic knowledge base—the long-term, categorical representations that normally allow us to perceive the world in terms of prespecified, invariant classes.[14] Teuber[15] referred to associative agnosias as "percepts stripped of their meaning."

Associative agnosias may be caused by bilateral or unilateral damage to the posterior association cortices. Unilateral lesions producing these syndromes invariably involve the left hemisphere and not the right hemisphere. Associative agnosias may exist in the absence of comparably severe language deficit.

Associative agnosias are modality-specific. The visual form of this syndrome is known as *visual object agnosia*.[16–24] The neuroanatomy of visual object agnosia involves damage to the occipital/occipitotemporal regions bilaterally or in the left hemisphere. The tactile form of this syndrome is known as *pure astereognosia*.[19,25–27] The neuroanatomy of pure astereognosia involves damage to the temporoparietal regions bilaterally or in the left hemisphere. The auditory form of this syndrome (an inability to understand the meaning of nonverbal sounds and noises and to associate them with the correct source) is known as the *semantic associative agnosia*.[28–31] The neuroanatomy of semantic associative agnosia involves damage to the region of the superior temporal gyrus bilaterally or in the left hemisphere.

Apperceptive Agnosias

In apperceptive agnosias, the physical rather than categorical object identification suffers. Although there is no elementary sensory deficit, the patient loses the ability to identify an object as being the same one under diverse conditions of observation, such as differing levels of brightness.[32,33] In associative agnosias, the ability to relate online percepts to preexisting generic representations is impaired. By contrast, the processes affected in apperceptive agnosia do not appear to involve long-term storage.

The neuroanatomy of apperceptive agnosias is different from, and in fact complementary to, that of associative agnosias. Apperceptive agnosias may be caused by bilateral or unilateral damage to the posterior association cortices. Unilateral lesions producing apperceptive agnosia invariably involve the right and not the left hemisphere.

COGNITIVE NOVELTY AND COGNITIVE ROUTINE

To account for these and similar findings, Goldberg and Costa[13] and Goldberg et al.[1] proposed the following principle of hemispheric specialization: the right hemisphere is critical for the exploratory processing of novel cognitive situations to which none of the codes or strategies preexisting in the subject's cognitive repertoire readily applies. The left hemisphere is critical for processing based on preexisting representations and routinized cognitive strategies. The traditional language/nonlanguage dichotomy then becomes a special case of this more

fundamental principle. The novelty-routinization principle of hemispheric specialization is different from the more traditional ones in several major respects.

First, the distinction between cognitive novelty and cognitive routinization is not limited to humans. It can be meaningfully applied to any species capable of learning. Because language is unique to humans, the assumption of the primacy of the linguistic-nonlinguistic dichotomy emphasizes the uniqueness of hemispheric specialization to humans and emphasizes an evolutionary discontinuity in cerebral functional organization. Lateralized asymmetries have been noted in other species,[34–37] but they do not permit meaningful homologies with humans within this framework. By divesting natural language of its cardinal role in hemispheric specialization, the novelty-routinization approach opens the avenue for tracing the evolutionary continuity in the development of cerebral lateralization and for the search of homologies across species through parallel experimentation. This position has the epistemological appeal of being more consistent with general biological assumptions.

In addition, the novelty-routinization approach emphasizes individual differences and argues against the fixed assignment of particular materials and tasks to one or the other hemisphere. What is cognitively novel to one individual is familiar and routinized to another.

Finally, the novelty-routinization hypothesis offers a dynamic rather than a static view of hemispheric specialization. It implies that the pattern of hemispheric specialization is different in a given individual at different developmental stages.[38] Specifically, it implies that the locus of cortical control shifts from the right to the left hemisphere in the course of cognitive skill development.

THE RIGHT-TO-LEFT SHIFT OF HEMISPHERIC CONTROL IN COGNITIVE LEARNING

The novelty-routinization hypothesis emphasizes the dynamic nature of hemispheric specialization. It predicts that the function of task acquisition is a unidirectional shift of hemispheric control from the right hemisphere to the left hemisphere.

The unidirectional nature of the shift of hemispheric involvement in the course of learning makes the novelty-routinization hypothesis testable and falsifiable. It is supported by a large body of experimental studies, which fall within several groups.

Cross-Sectional Evidence

In tachistoscopic and dichotic paradigms, task-naive healthy subjects show a right-hemisphere advantage and task-experienced subjects show a left-hemisphere advantage. This difference has been demonstrated for various nonverbal tasks in adults.[39–42] In normal children, the increase of the degree of left-hemisphere advantage with age and task proficiency has been demonstrated for a number of language tasks.[43–47] This relationship suggests a decreasing role of the right hemisphere in language as the function of the development of linguistic skills.

Quasi-Longitudinal Evidence

In healthy subjects introduced to a novel task tachistoscopically presented over blocks of trials, a right-hemisphere advantage exists during early blocks of trials and a left-hemisphere advantage during late blocks. This has been demonstrated both for nonverbal tasks[48–53] and for verbal tasks that entail uncommon use of language.[53–55] The right-to-left shift of hemispheric advantage as the function of learning appears to be universal and independent of stimulus modality. The novelty-routinization distinction overrides the linguistic-nonlinguistic distinction in determining the pattern of hemispheric involvement in a given cognitive task.

Early Lesion Effects

The effects of early hemidecortications on cognition are not symmetric. Early right hemispherectomy has subtle adverse effect on the subsequent acquisition of both nonlinguistic and linguistic cognitive skills. The earlier the age at which the right hemispherectomy was done, the greater the effect. Early left hemispherectomy has a significant adverse effect on the subsequent acquisition of linguistic skills but little adverse effect on the acquisition of nonverbal skills, and there is no interaction with age at hemispherectomy.[56,57] This suggests that the right hemisphere plays a major role at early stages of language acquisition and that this role decreases with age.

Biochemical Evidence

Norepinephrine (NE) and dopamine (DA) pathways are somewhat lateralized, NE to the right and DA to the left hemisphere in humans and rats.[58–63] At the same time, NE is critical in orienting to novel stimuli, and DA is critical in stereotypic behavior.[64–66] This implies a link between the right hemisphere, NE, and cognitive novelty, and between the left hemisphere, DA, and cognitive routinization.[67]

Computational Evidence

Grossberg[68] draws the distinction between computational "stability" and computational "plasticity" in ways similar to the distinction between the exploratory and routinized behaviors. Grossberg suggested that to en-

hance the computational efficiency of a neural net the stability and plasticity subsystems must be separate.

FRONTAL LOBES AND COGNITIVE NOVELTY

The prefrontal cortex is presumed to be singularly important in cognitive control over situations for which no set solutions are available in the organism's cognitive repertoire. The role of the prefrontal cortex is believed to be particularly great when the organism is challenged with a novel task that requires that the preexisting cognitive routines be accessed and configured in a new way.[21] On the other hand, the posterior association cortices are thought to provide the storage of cognitive routines and preexisting cognitive representations.[69]

Therefore, the prefrontal cortex has a particular affinity for cognitive novelty, the posterior association cortex for cognitive routinization. This points to an interesting implication of the novelty-routinization hypothesis: the left-right and anterior-posterior dimensions of cortical functional organization are not functionally orthogonal. In a sense, the left hemisphere is functionally dominated by the posterior association cortex, the right hemisphere by the prefrontal cortex. In terms of the novelty-routinization model advanced here, the nonorthogonal relationship between the anterior-posterior and left-right cortical dimensions suggests that the shift of the locus of cortical control as a function of learning involves both dimensions: from the right prefrontal systems to the left posterior systems.

It is curious that the anterior-posterior and left-right cortical dimensions are not entirely orthogonal in a structural sense either. The cerebral hemispheres are characterized by the Yakovlevian torque: the right frontal pole is thicker than, and protrudes over, the left frontal pole, and the left occipital pole is thicker than, and protrudes over, the right occipital pole.[70,71] The structural affinity between the frontal lobes and the right hemisphere captured in the Yakovlevian torque is consonant with the functional affinity between the frontal lobes, cognitive novelty, and the right hemisphere.

INTERNAL AND EXTERNAL DETERMINANTS OF COGNITIVE CONTROL: ARE THEY LATERALIZED IN THE FRONTAL LOBES?

Historically, research into hemispheric specialization has emphasized the posterior cortex. It was implicitly assumed that the hemispheric differences were less pronounced in the frontal lobes. A growing body of evidence, however, indicates that significant functional lateralization is found in the frontal lobes as well.

The earlier studies driven by the traditional language-versus-visuospatial distinction of hemispheric specialization had already provided evidence for a functional dissociation between the left and right prefrontal cortex. Such a dissociation was found on the "generation" tasks, in which subjects were asked to generate as many different responses as possible according to specific rules. Performance by subjects with lateralized left or right prefrontal lesions was impaired relative to normal control subjects in both the verbal and nonverbal generation tasks. When the two lesions groups were compared, the left prefrontal lesion group was more impaired on verbal generation tasks,[72-74] and the right prefrontal lesion group was more impaired on nonverbal generation tasks.[75,76]

Increasing evidence exists, however, that the functional differences between the left and right prefrontal systems are not limited to the verbal-nonverbal distinctions.

Prefrontal cortex is critical for the selection of task-appropriate cognitive routines and representations.[21,77,78] This selection may be guided by internal contingencies represented in working memory[78] or by external contingencies reflecting environmental changes.[73,79] A preliminary but growing body of evidence suggests that the contributions of the prefrontal systems in executing the two types of cognitive control are lateralized in right-handed individuals. The left prefrontal system appears to be particularly important for guiding cognitive selection by working memory–mediated internal contingencies, the right for cognitive selection by external environmental contingencies. The evidence of the lateralization of frontal lobe control over these functions is based on the functional neuroimaging of activation patterns in healthy volunteers and in patients and from the observations of frontal lesion effects on behavior.

Functional Neuroimaging in Healthy Volunteers

A lateralized increase in the activation of the left superior prefrontal region occurs both on PET and measures of regional cerebral blood flow (rCBF) when subjects perform a task based on prior instructions.[80-86]

Electrophysiological studies offer similar results. Gevins and colleagues[87-89] found a consistently lateralized, left frontal "preparatory set" by use of EEG measurement and analyses. Subjects were given verbal instructions and practice on a visuomotor task. Between the presentation of a stimulus (a slanted line on a computer screen) and the response (pressing a switch with

the left or right index finger), a focal activation of the left dorsolateral prefrontal cortex region was consistently present, regardless of the response hand. More recently, using event-related potential methodology, Ruchkin et al.[90] reported a left frontal activation in a working memory task, both for verbal and visuospatial representations.

By contrast, tasks requiring orientation to unexpected external events and attention to external stimuli (without a preestablished "preparatory set") produce greater activation of the right than left prefrontal areas. These effects have been demonstrated with PET,[91] rCBF measures,[92,93] and ERP.[94]

Roland[93] found that during selective attention to a sensation (auditory, visual, or somatosensory), right prefrontal rCBF was significantly higher than left prefrontal rCBF. Pardo et al.[91] found a consistent right prefrontal activation on PET, regardless of the laterality of stimulus presentation, in subjects asked to sustain their attention to a particular sensory stimulus (visual or somatosensory). Nishizawa et al.[92] found a trend for increased right prefrontal rCBF activation when the subject was told to "just listen" to spoken words.

The above studies are particularly interesting in that the selective activation of the left or right prefrontal region depends solely on the nature of the task (following internalized instructions versus attending to external stimuli), and not on the side of stimulus delivery. The type of material (verbal or nonverbal) does not seem to matter, nor does the response hand.

Several tasks particularly sensitive to frontal lobe functions are commonly used to assess the integrity of the frontal lobes. Some of these tasks are dependent on the changing content of working memory, while others require selective attention to external stimuli. The Wisconsin Card Sorting Test (WCST) and The Tower of London (TL) are of the first type; the Continuous Performance Task (CPT) is of the second type. Distinct, complementary lateralized activation patterns have been elicited by these tasks in healthy volunteers on PET and SPECT: WCST and TL activated the left frontal systems, and CPT activated the right frontal systems.[95–97]

Furthermore, the degree of focality of activation was different in the two hemispheres. Roland and colleagues[81–86] found a more focal activation in the left hemisphere (probably the superior portion of Brodmann area 10 and/or inferior portion of area 9). Pardo et al.[91] and Mazziotta et al.[98] found a more diffuse activation in the right prefrontal region. Pardo et al. described it as "a variable coronal band of activity along the right dorsolateral convexity, corresponding to Brodmann areas 8, 9, 44, 46 (with concentration in area 9)" (p.63).

Consistent with these findings was the work of Mazziotta et al.,[98] who found that the right prefrontal region was more sensitive than the left one to the effects of sensory deprivation. As the degree of sensory deprivation increased (from the eyes open/ears open, to eyes closed/ears open, to eyes closed/ears closed condition), the decrease in activation was more pronounced in the right than the left frontal regions.

Neuropsychological and Functional Neuroimaging Findings in Brain Disease

Normally the two types of cognitive control, one guiding behavior by internal cues, the other by external cues, operate in concert and are in dynamic balance. Damage to the frontal lobes may disrupt this balance, and this disruption may result in two extreme types of behavior.

The first type is *perseveration*,[99] an inability to extinguish the representations evoked in the context of a prior cognitive task. Perseveration can be thought of as a diminished ability to switch behaviors in response to changing demands.

The second type is *environmental dependency*,[99–101] in which the subject's behavior becomes dependent on incidental, external factors. Environmental dependency can be thought of as a diminished capacity for internally generated planning to guide behavior.

There appears to be a relationship between the side of lateralized frontal lesions and the type of extreme behavior caused by them. This relationship was apparent in two studies of the effects of lateralized frontal lesions on the Wisconsin Card Sorting Test performance by subjects with lateralized frontal lesions. Drewe[102] found that although both the left and right prefrontal lesion groups performed worse than healthy volunteers on the number of categories sorted, the right prefrontal lesion group made more perseverative errors and the left prefrontal lesion group made more nonperseverative errors. Robinson et al.[103] found that even when the left and right frontal lesion groups had equivalent scores on the Halstead-Reitan Average Impairment Rating, the right frontal lesion group made more perseverative responses on WCST. By contrast, the patients with left prefrontal lesions were unable to maintain the correct pattern of response and kept switching between the different possible categories. These findings are tempered, however, by the failure to find lateralized effects of frontal lobe lesions on WCST performance by Anderson et al.[104]

Milner and Petrides[105–107] also reported findings not easily understood in terms of the verbal-nonverbal distinction. On the basis of their work with recency memory tests and subject-ordering tasks in patients with lateralized frontal lesions, they concluded that the left prefrontal cortex was important for "programming" internally ordered events and the right prefrontal cortex

was important for programming externally ordered events, regardless of whether the stimulus was verbal or nonverbal.

McCarthy and Warrington[108] reached a similar conclusion. They proposed that "failure on those tasks which require internal generation of strategies and/or control of motor-executive functions shows a greater tendency to be associated with damage to the left frontal lobe rather than the right." (p.356). McCarthy and Warrington also concluded that very few tasks are both sensitive and specific to unilateral right frontal lobe lesions.

Goldberg et al.[109] found that on an inherently ambiguous cognitive task, two different, and opposite, response selection patterns were observed following left and right prefrontal lesions in right-handed males. Left prefrontal lesions produced an extremely context-independent response selection bias, and right prefrontal lesions produced an extremely context-dependent response selection bias. Healthy subjects performed in the middle of the response range.

Furthermore, a strong relationship could be demonstrated between the functional lateralization of the frontal lobes and handedness in males.[109] This may be the first demonstration of a strong relationship between handedness and hemispheric specialization. That this relationship involves the frontal lobes is particularly remarkable, given that the functional lateralization of the frontal lobes has been downplayed in the past.

Extreme perseveration and environmental dependency are found in certain frontal-neostriatal disorders even in the absence of macroscopic structural lesions. Obsessive-compulsive disorder (OCD) and Gilles de la Tourette's Syndrome (GTS) are among such disorders. In OCD, left frontocaudate and/or left orbitofrontal hyperactivation has been found by the use of PET, rCBF measures, and event-related potentials.[110-113] In GTS, by contrast, right frontal hyperactivation has been reported when SPECT and rCBF are used as measures.[114] Although OCD is usually characterized by perseveration-like stereotypic behaviors, GTS is characterized by heterogeneous clinical presentations, some of which are dominated by excessive and forced exploratory behaviors.[115]

CONCLUSIONS

It is becoming increasingly obvious that the frontal lobes are characterized by robust hemispheric specialization. This specialization is not adequately described by the classic distinction between linguistic and nonlinguistic processes. The right hemisphere appears to be critical for dealing with novel cognitive situations, the left hemisphere for the processes mediated by well-routinized representations and strategies. The left frontal systems appear to be crucial for cognitive selection driven by the content of working memory and for context-dependent behavior; the right frontal systems appear to be crucial for cognitive selection driven by the external environment and for context-independent behavior. The role of the right hemisphere in processing cognitive novelty highlights the importance of the right frontal systems in task orientation and the assembly of novel cognitive strategies.

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