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SYMPOSIUM INTRODUCTION

Subcortical functions in cognition: Toward a consensus

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SYNOPSIS

Behavioral neurologists and neuropsychologists have debated the role of the thalamus and basal ganglia in cognition and behavior for more than a century (e.g., Bucy, 1942; Marie, 1906; Penfield & Roberts, 1959; Wernicke, 1874). However, over these 100-plus years, there is little consensus regarding whether or how these structures contribute to cognition. Fortunately, recent research findings are rapidly changing this state of affairs. It is now obvious we will not understand how the brain controls complex activities until we understand the contribution of these deep brain structures. In healthy and brain-damaged individuals, application of methodologies such as semantic priming, event related potentials, and functional neuroimaging to the question of subcortical functions is beginning to resolve this conundrum. This symposium demonstrates the utility of combining these different approaches. It features empirical work from six laboratories that have engaged in systematic inquiries regarding the role of the thalamus and basal ganglia in cognition. This body of work represents both new directions and convergence of recent findings in the quest to integrate our understanding of this complex issue.

The pattern of errors in thalamic aphasia suggests the role of the thalamus in language is semantic in character (e.g., Cappa & Vignolo, 1979; Crosson, 1984; Raymer et al., 1997). Work by Hart and his colleagues is defining the nature of this semantic function. In a recent fMRI study of semantic functions, Kraut et al. (2002) demonstrated that thalamic nuclei participate in binding linguistic features (e.g., desert, humps) to represent a known object (e.g., camel). In the study for this symposium, the authors extend these findings by examining the time course of hemodynamic responses in a variety of cortical regions and in the dorsomedial thalamus and the pulvinar. Results suggest the dorsomedial nucleus has a role in early search processes, but the pulvinar participates in binding features into object representations. In addition to these data, the authors cite electrophysiological evidence from their lab in support of the feature binding hypothesis (Slotnick et al., 2002).

The contributions of Copland, Kotz et al., and Crosson et al. all address the role of the basal ganglia in language. Copland used a semantic priming paradigm with the lesion method and the disease model to explore the role of subcortical structures in resolving lexical-semantic ambiguities. The failure of nonthalamic subcortical lesion patients and of Parkinson's disease (PD) patients to demonstrate normal suppression of a word's nondominant meaning at long interstimulus intervals indicates that the basal ganglia play a role in controlled as opposed to automatic cognitive processes. When compared to the earlier work of Copland and colleagues (2000a, 2000b), these findings indicate the nature of this controlled processing is complex. Further, although vascular lesions of the basal ganglia and PD produced similar findings with this particular paradigm, it should not be expected that this automatically will be the case for every cognitive paradigm. Dopaminergic deafferentation of the striatum will change the output level of striatal neurons, with the direction of change depending upon the target of striatal efferents (Gerfen, 1992), but destruction of striatal neurons in vascular lesions abolishes striatal output. The circumstances under which performance converges and diverges between PD and lesion patients could be instructive regarding striatal function.

Kotz et al. have used the lesion method in combination with event-related potential techniques to assess the impact of basal ganglia lesions on processing syntax. Patients whose lesions included the basal ganglia failed to show a normal P600 response to syntactically anomalous sentences, while patients with lesions confined to the cortex continue to show this response. Based upon the understanding of this phenomenon from previous studies (Frisch et al., 2002; Kaan et al., 2000), the authors concluded that the basal ganglia are involved in controlled (as opposed to automatic) pro-

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cessing of syntax. This finding extends recent evidence from the same group of investigators (Friederici et al., in press; Frisch et al., in press). Further, patients with basal ganglia lesions showed an extended period of negativity starting around 300 ms after the syntactic anomaly. This extended period of negativity has been interpreted as a slowing of semantic processes. The reader should note two points of convergence with the findings of Copland: (1) involvement of the basal ganglia in controlled linguistic processing and (2) impaired semantic processing in patients with basal ganglia lesions. Indeed, it would be interesting to test the hypothesis that the deficit in resolving semantic ambiguities implied by Copland's data accounts for the extended negativity in syntactic processing in the Kotz et al. paradigm.

Crosson et al. have used functional MRI in neurologically normal subjects to explore the functional anatomy of word and nonsense syllable generation. Whether words were generated using a semantically based cue (category) or a lexically based cue (rhyming word), three left-hemisphere structures were consistently activated: pre-SMA, the dorsolateral caudate nucleus, and the ventral anterior thalamus. These structures were not activated in nonsense syllable generation. Based in part on Copland's work (see current issue and Copland et al., 2000a), the authors speculated that a pre-SMA–basal ganglia–thalamic loop is involved in biasing word production toward one of multiple possibilities, with the basal ganglia serving to maintain the bias across time. The right basal ganglia (caudate nucleus, putamen) also were active in word but not nonsense syllable generation. With a lack of right frontal activity in the same tasks, the authors suggested that the right basal ganglia were involved in suppressing right frontal activity. If this hypothesis can be confirmed in future studies, we could be closer to understanding the anatomic foundations of language lateralization. When viewed within the context of the Copland and Kotz studies, we can conclude that the left basal ganglia are involved in lexical, semantic, and syntactic processes. It would be of interest to ascertain whether the same pre-SMA–basal ganglia–thalamic loop is active in the paradigms used by Copland and Kotz et al., which would be expected if this loop's involvement in biasing word production toward one of many possibilities generalizes to other aspects of language.

Crucian and colleagues have used a mental object rotation task to assess visuospatial deficits in PD. The impairment in male PD patients relative to male controls affirms the visuospatial nature of a deficit that has long been known to exist for PD patients (e.g., Cummings & Huber, 1992; Growdon & Corkin, 1986; Stern & Mayeux, 1986). Clower et al. (2002) recently confirmed a basal ganglia loop in primates with parietal cortex (area 7b) as its target, and speculated that this loop might be the source of spatial deficits in PD. However, the lack of such a difference between Crucian's female PD patients and controls in the mental object rotation task brings a specific methodological problem into relief. Both female groups showed near-chance levels of performance. Apparently, normal older women have enough difficulty with the mental rotations task that it obscured the investigators' ability to determine whether a real difference exists between the two groups. The implications are twofold: First, female controls and PD patients should be assessed on a version of this task that produces above chance levels of performance in female controls so that the test is sensitive to potential between group differences. Second, an important clinical implication is that it would be easy to mistake a normal age-related decline for a disease-related deficit if an appropriate, gender-specific normative group was not used.

Finally, the paper by Elsinger et al. has used fMRI of paced finger tapping, which assesses motor timing, to study response to dopamine replacement therapy in PD, long considered a disease model for striatal dysfunction. The findings are rich with implications. For example, the reduced activity in the sensorimotor cortex of PD patients relative to normal controls indicated that loss of dopaminergic afferents to the striatum resulted in reduced activation of sensorimotor cortex during paced movement. However, one particularly relevant finding for the work represented in this symposium was the normalization of activity in the SMA–putamen–thalamic loop for paced finger tapping "on" as compared to "off" dopamine replacement when PD patients rely on internal as opposed to external pacing. In contrast, while the Crosson et al. study also reported activation of a medial corticostriate circuit, the activated circuit was different. In both studies (respectively) the medial frontal (SMA, pre-SMA), striatal (putamen, dorsal caudate), and thalamic (ventral lateral, ventral anterior) components of the basal ganglia loops showed increased activity, but the pallidal component of the loops demonstrated no significant change. Importantly, the cortical connections of SMA are largely with motor and lateral premotor cortices, while the cortical connections of pre-SMA are primarily with prefrontal cortex (Matsuzaka et al., 1992; Picard & Strick, 1996). Such connectivity suggests these two loops perform different functions, and traditionally the SMA loop has been linked to motor functions while the pre-SMA loop has been linked to more explicitly cognitive functions (Picard & Strick, 1996). While the results of these studies are consistent with this notion, the SMA activation for the motor timing task appears to be associated with some aspect of the time representation rather than to motor requirements *per se* suggesting that this dichotomy may be too simplistic.

CONCLUSIONS

As readers peruse some or all of the work from this symposium, it is worth asking what these papers collectively tell us that we would not have known otherwise. The work by Kraut, Hart, and colleagues takes a large step in defining the role of thalamic nuclei in semantic functions. For a long time, errors in thalamic aphasia suggested this structure is involved in semantic processing (e.g., Cappa & Vignolo, 1979; Crosson, 1984; Raymer et al., 1997). Nadeau and Crosson (1997) suggested thalamic mechanisms, under the

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guidance of frontal cortex, selectively engage elements of neural nets necessary to perform a semantic task. The conceptual framework of Kraut, Hart, and colleagues clearly represents an advance over this position. On the basis of converging evidence, they suggested that the pulvinar is involved in binding together the semantic features that define an object. As the authors and others continue work in this area, the nature of the anatomical system involved in feature binding should become clearer.

Earlier work indicated that basal ganglia infarcts alone do not cause classical symptoms of aphasia (Nadeau & Crosson, 1997; Weiller et al., 1993). Yet, the recent work of Copland et al. (2000c) clearly showed that nonthalamic subcortical lesions of the language-dominant hemisphere affect complex language functions. The three studies that address the role of the dominant basal ganglia in language provide converging evidence that the basal ganglia are involved in those functions. Both Copland and Kotz et al. have shown that the basal ganglia are involved in controlled linguistic processing, that is, the type of processing in which attention can be deliberately focused on relevant stimuli, whether during priming of single words or making grammatical judgments. All three of these studies implicated the basal ganglia in semantic processing of words or sentences. In addition to semantic processing, the Kotz et al. study implicated the basal ganglia in syntactic processing, and the Crosson et al. study implicated the basal ganglia in lexical processing. An unresolved issue is the degree to which the processing mechanisms at the lexical and semantic levels overlap with processing mechanisms at the syntactic level. Another commonality between the paradigms of Copland and Crosson et al. is that the systems were driven to respond to or to select one of multiple choices. Crosson et al. suggested that the basal ganglia maintain across time a bias toward selection of a specific item as opposed to its competitors.

The findings of Elsinger, Rao, and colleagues indicate that dopaminergic deafferentiation of the striatum affects participation of the SMA–putamen–thalamic loop for movements that depend upon the utilization of an internal representation for time. Rao et al. (1997) found this loop to be active during the same task in neurologically normal subjects. As noted above, an interesting question is what parallels can be drawn between the role of basal ganglia loops in this paced finger tapping paradigm and their role in the word generation paradigm of Crosson et al. On the other hand, such reductionism may not be the best representation of reality. The cortical connectivity of the SMA-basal ganglia loop involved in the former study is primarily to motor and premotor cortices, and the cortical connectivity of the pre-SMA–basal ganglia loop implicated in the latter study is primarily to prefrontal cortices. As the basal ganglia and frontal cortices have evolved to accomplish new functions, it is likely that the relationships between the underlying anatomic components have evolved as well. Although the components of basal ganglia loops activated in the Elsinger et al. and Crosson et al. studies were striking in their similarities, the authors' respective functional interpretations were quite different. Elsinger et al. as well as Rao et al. (1997) suggested that the SMA–putamen–thalamic loop is involved specifically in internal timing mechanisms, not just in internal guidance of movements. In contrast, Crosson et al. suggested that the basal ganglia components of the pre-SMA–caudate–thalamic loop were involved in maintaining a bias toward one of multiple responses across time so that biases could influence controlled processes. While these two studies superficially support the distinction between the SMA circuit's importance for movement and the pre-SMA circuit's importance for cognitive processing, the interpretations offered by Elsinger et al. and Crosson et al. suggest that this dichotomy may be too simplistic. A procedural learning study in PD supports this conclusion by showing that motor learning was impaired in PD patients when the patients were required to switch from one response to another but learning was normal when switching was not required (Haaland et al., 1997). In addition, future research efforts and conceptual models must not only look for functional parallels between the various basal ganglia loops, they also must take into account the likelihood that basal ganglia functions have evolved along with the cortical units to which they are so intimately linked.

Finally, as the answers to such questions become clearer in the realms of language, semantics, and psychomotor functions, it will become necessary to expand the scope of our inquiry into other realms of cognition. From the standpoint of basal ganglia functions, the findings of Crucian et al. suggest that visuospatial functions would be a fruitful area for the development of new paradigms that draw on what we have learned in these other areas. From the standpoint of the thalamus, the unique work of Kraut, Hart, and colleagues will be illuminating for future investigators, though there will be limits in the degree to which the concept of feature binding can act as a model for other cognitive systems. Importantly, this symposium is an excellent example of how hypothesis-driven research, which relies on the integration of behavioral data in brain-damaged patients and functional imaging in patients and healthy adults can extend the sophistication of the questions we can ask and *sometimes answer*. To be sure, the work represented by this symposium, as well as by the work of many other investigators, will lead to new understandings regarding the contribution of subcortical structures to cognition.

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