
NEUROBEHAVIORAL GRAND ROUNDS—INTRODUCTION

The thalamus and working memory

STEPHEN E. NADEAU

The Brain Rehabilitation Research Center and the Geriatric Research, Education and Clinical Center, Malcom Randall Department of Veterans Affairs Medical Center, and the Department of Neurology, University of Florida College of Medicine, Gainesville, Florida

In this issue of *JINS*, Gasparini and her colleagues (2008) report a subject with a right anterior choroidal artery territory stroke that damaged the anterior hippocampus, but likely more importantly, much of the ventral posterior limb of the internal capsule, effectively disconnecting the right thalamus from temporal cortex. Through systematic cognitive neuropsychological detective work, they provide a compelling case that the essential deficit was one of working memory. This is potentially a very important discovery. The thalamus is a phylogenetically ancient structure, and there is considerable evidence that, in human beings, much of its function has been subsumed by cortical mechanisms (Nadeau & Crosson, 1997). Consequently, there are fundamental limits to how much animal studies can inform us about human thalamic functions, and we are particularly reliant on cognitive neuropsychological studies like this one. The work of Gasparini et al. also provides a fine demonstration of the continuing value of cognitive neuropsychology in advancing our understanding of the details of brain function.

Working memory corresponds to the temporary recruitment of selected neural networks needed for task performance. The term “working memory” is a misnomer, because memory refers to stored information, whereas “working memory” refers to information that is temporarily brought out of the mental library for viewing. Other terms often used interchangeably, equally misleading, include “activation” and “attention.” Working memory corresponds neurophysiologically to several different processes, including alterations in neural firing rates, alterations in likelihood of neural firing, and selection of inputs that will produce neuronal firing in engaged networks (Desimone & Duncan, 1995; Moran & Desimone, 1985). Several years ago, we coined the less encumbered term “selective engagement” to refer to these processes (Nadeau & Crosson, 1997). Most

studies of working memory in human subjects have focused on the cortex, particularly the prefrontal cortex. Over 30 years ago, Chavis and Pandya (1976) published a landmark paper in which they demonstrated exquisitely mapped connections between the full extent of frontal cortices and posterior sensory, polymodal and supramodal association cortices. Subsequent studies have confirmed their findings and shown these connections to be reciprocal (Constantinidis & Procyk, 2004). This connectivity provides the basis for two major phenomena. Prefrontal to posterior projections provide the basis for selective engagement of particular posterior cortical networks, that is, working memory. Reciprocal posterior to frontal connections serve to fully inform the frontal cortex of what is going on posteriorly—the likely basis of the “mirror neuron” phenomenon (Rizzolatti & Craighero, 2004). In essence, the result is that whatever we perceive has immediate implications for frontally mediated plan formulation and selection. It, furthermore, seems likely that the entire cerebrum is involved in working memory and mirror neuron phenomena, broadly conceived, and that our current notions that these functions are more localized reflect the limitations of our experimental paradigms rather than the limitations of the brain substrate for these phenomena.

There is good evidence that selective engagement is also subserved by subcortical mechanisms, including the thalamus and biogenic amine systems (Nadeau, 2006; Nadeau & Crosson, 1997). We know that the thalamus functions as a gated relay, most obviously gating the transmission of visual, auditory and sensory information through the lateral and medial geniculate nuclei and the ventral posterior nucleus, respectively, to the cortex. However, it appears that these elemental sensory gating functions have largely been superseded in human beings by cortically based gating processes subserving attention, and that in human subjects, thalamic gating predominantly affects cortico-thalamo-cortical transmission. Gating though the thalamus is regulated in a more or less all or none manner *via* input from brainstem structures, most notably the midbrain reticular formation and

Correspondence and reprint requests to: Stephen E. Nadeau, Geriatric Research, Education and Clinical Center (182), Malcom Randall DVA Medical Center, 1601 SW Archer Road, Gainesville, FL. E-mail: snadeau@ufl.edu

noradrenergic and serotonergic projections. Selective gating by the thalamus is regulated in two ways: (1) *via* direct projections from overlying cortices and (2) *via* projections from prefrontal cortex, involving the thalamic reticular and intralaminar nuclei (central median and parafascicular). This frontal system, scarcely studied in animals (Bailey & Mair, 2005; Minamimoto & Kimura, 2002; Weese et al., 1999), is of particular interest because it is likely to be involved in thalamically mediated *volitional* selective engagement processes, such as those involved in language production and working memory.

Left thalamic lesions cause an aphasia marked by particular difficulty in translating semantic representations into spoken and written word representations (suggesting a problem with semantic access), but in nearly all cases, semantic knowledge, phonological sequence knowledge, and grammatic function are preserved (Nadeau & Crosson, 1997; Nadeau & Rothi, 2008). Raymer et al. (1997) argued that translating semantic into word representations makes particularly great demands on semantic engagement because there is one and only one correct response, requiring extraordinary precision of engagement. Certain left thalamic lesions can blunt this precision, leading to visual/semantic paraphasic errors and nonresponses even as semantic function is preserved. The discovery by Gasparini et al. of deficits in visual imagery and image completion from individual features or partial representations, coupled with spared perceptual processes, visual knowledge, and recognition abilities, may be evidence of an analogous loss of precision of volitional selective engagement in the right hemisphere, or impairment in a particular dimension of selective engagement mediated by the thalamus, affecting flexibility of selective engagement.

Gasparini et al. rightly point out that the hippocampal infarction could be a contributor to the deficits they found. The hippocampus supports fast Hebbian learning, encoding new information over a time span of roughly a second (the short phase of long-term potentiation). Thus, there is an overwhelming likelihood that the hippocampus contributes to many phenomena that have been subsumed under the concept of working memory, particularly when longer delays are involved (Shrager et al., 2008). For example, as Gasparini et al. point out, primacy effects in supraspan memory tasks disappear in the presence of hippocampal lesions. Thus, there is a need to replicate their findings in subjects with thalamic lesions, for example in the tuberohalamic or para-

median artery territories, which produce a pure thalamic lesion with no hippocampal involvement.

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