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Functional imaging of the thalamus in language

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ABSTRACT

Herein, the literature regarding functional imaging of the thalamus during language tasks is reviewed. Fifty studies met criteria for analysis. Two of the most common task paradigms associated with thalamic activation were generative tasks (e.g. word or sentence generation) and naming, though activation was also seen in tasks that involve lexical decision, reading and working memory. Typically, thalamic activation was seen bilaterally, left greater than right, along with activation in frontal and temporal cortical regions. Thalamic activation was seen with perceptually challenging tasks, though few studies rigorously correlated thalamic activation with measures of attention or task difficulty. The peaks of activation loci were seen in virtually all thalamic regions, with a bias towards left-sided and midline activation. These analyses suggest that the thalamus may be involved in processes that involve manipulations of lexical information, but point to the need for more systematic study of the thalamus using language tasks.

1. Introduction

The role of the thalamus in language has been enigmatic for at least half a century. Fisher (1959) was one of the first to describe aphasia in the setting of thalamic damage and Penfield and Roberts (1959) proposed a central integrating role for the thalamus in language. Despite several decades of case reports and series describing patients with thalamic lesions and aphasia, there continues to be controversy regarding the very idea that the thalamus plays any role in language at all. Where physiological models exist, they are quite varied in terms of the sub-nuclei involved and the specific operations taking place in the thalamus. The emergence of functional imaging as a tool to study brain function may permit new insights beyond what has been derived from the clinical–pathological correlative approach. To better understand the potential role of the thalamus in normal language function, the literature associating thalamic lesions with aphasia will briefly be reviewed, followed by an analysis of the literature demonstrating thalamic activation in language tasks by normal subjects.

2. Lesion evidence of thalamic involvement in language

Given the heterogeneity of thalamic nuclei in terms of function and projections to different areas of cortex, it is of interest to understand which thalamic nuclei are most likely involved with language. The thalamus projects to all areas of the neocortex, including those areas in the frontal, temporal, and parietal cortical regions that are commonly associated with language. Assigning individual thalamic nuclei to particular cortical areas is made complicated by convergence of inputs from thalamic nuclei to individual regions of the cortex. For example, restricted tracer injection into the caudal portion of the primate ventral premotor cortex, which bears at least superficial similarity to areas of the human frontal cortex important for language, produces substantial retrograde label in no fewer than 10 thalamic nuclei: ventrolateral nucleus, ventral anterior nucleus, ventral medial nucleus, centrolateral nucleus, centré-median nucleus, medial dorsal nucleus, area *X*, lateral posterior nucleus, medial pulvinar and ventral posterior nucleus (Morel, Liu, Wannier, Jeanmonod, & Rouiller, 2005). Similarly, injections of tracer into the macaque caudal superior temporal gyrus produce retrogradely-labeled neurons in multiple thalamic nuclei: the medial pulvinar, lateral posterior nucleus, suprageniculate-limitans nucleus and the medial division of the medial geniculate body (Hackett, Stepniewska, & Kaas, 1998). These data suggest that there are a number of thalamic nuclei, based on their projections to the cortex, that have a potential to be involved with language, but place a focus on ventrolateral nuclei, midline nuclei and the pulvinar which most densely project to the ventral premotor cortex and superior temporal gyrus (more extensively reviewed by Barbas et al., Lee and Bartlett, this issue).

Thalamic infarction leading to aphasia has been described in each of the four major vascular distributions of the thalamus: tuberothalamic (Bogousslavsky, Regli, & Assal, 1986; Karussis, Leker, & Abramsky, 2000; Levin, Ben-Hur, Biran, & Wertman, 2005; Raymer, Moberg, Crosson, Nadeau, & Rothi, 1997), paramedian (Bogousslavsky, Miklossy, Deruaz, Regli, & Assal, 1986; Perren,

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Clarke, & Bogousslavsky, 2005; Radanovic & Scaff, 2003), inferolateral (Karussis et al., 2000; McFarling, Rothi, & Heilman, 1982), and posterior choroidal (Neau & Bogousslavsky, 1996). Although lesions of the anterior and midline group of nuclei (ventral anterior, ventrolateral, anterior thalamic, mediodorsal and intralaminar nuclei) appear more frequently in the literature, reporting biases caused by the vagaries of vasculature have made it difficult for the early aphasiologists to assign a language "center" in the thalamus based on stroke data as they did for the cortex. For example, lesions of the pulvinar, which is extensively connected with the areas of the cortex involved with language, such as the ventrolateral prefrontal cortex and the superior temporal gyrus and sulcus (Romanski, Giguere, Bates, & Goldman-Rakic, 1997), are rarely reported, likely because (1) the pulvinar has a dual blood supply (Morandi et al., 1996; Takahashi et al., 1994); and (2) vascular lesions proximal enough in the posterior circulation to cause pulvinar infarction often cause global cognitive or arousal deficits, making it difficult if not impossible to provide a plausible cognitive decomposition of the deficits in these cases. As a result, approximately 6% of isolated thalamic infarcts are found in the posterior thalamic region (Carrera & Bogousslavsky, 2006). In this regard it should be noted that although the pulvinar is relatively protected from ischemic infarction, there are several reports of focal hemorrhage into the left pulvinar that have caused aphasic deficits (Bruyn, 1989; Crosson et al., 1986; Puel et al., 1992).

The clinical lesion data thus strongly suggest that thalamic lesions impair language function. A recent formal meta-analysis of patients with either ischemic or hemorrhagic thalamic infarction, found that the most common deficit among patients was in naming, with relative preservation of repetition (De Witte, Brouns, Kavadias, Engelborghs, & De Deyn, 2011). Other commonly noted features in patients with thalamic aphasia are a high frequency of semantic paraphasic errors (Demeurisse et al., 1979; Ebert, Vinz, Görtler, Wallesch, & Herrmann, 1999; Karussis et al., 2000; Radanovic & Scaff, 2003; Raymer et al., 1997) and perseverations (Bell, 1968; Bogousslavsky, Regli et al., 1986; Bruyn, 1989; Demeurisse et al., 1979; Graff-Radford, Eslinger, Damasio, & Yamada, 1984; Levin et al., 2005; McFarling et al., 1982; Puel et al., 1992).

While the meta-analysis from De Witte et al. provided a general overview of the thalamic contribution to language, a more detailed examination of individual patients may provide different insights. Note, that that several challenges exist when examining the pooled clinical literature to attempt to gain insights into language function. One difficulty is the variability of exact location and size of the infarctions. This suggests that there may be a role for detailed description of clinical–pathological correlations in small numbers of patients. Another potential difficulty that arises in describing the detailed language performance in aphasic patients is how these deficits are defined. Herein, we will use the term 'lexical' to describe the processes that involve processes that involve manipulation of word forms. The term 'semantic' will be used to describe processes that involve the manipulation of word meaning.

The language deficits of two thalamic stroke patients were described in great detail by Raymer et al. (1997) and later by Crosson (1999). These patients had strokes in different distributions: one patient with a left tuberothalamic ischemic stroke (damaging the ventrolateral, ventral anterior, centré-median and thalamic reticular nuclei) and a second with a slightly larger left paramedian ischemic stroke (damaging ventral anterior, ventrolateral, mediodorsal, centré-median, parafascicular and thalamic reticular nuclei). In both cases, the authors found that subjects had difficulty with oral picture naming, written picture naming and oral naming to auditory definition. However, tasks that involved direct orthographic output to phonologic input (writing to dictation), or phonologic output from orthographic input (reading aloud) were intact. The subjects also did well on auditory word – picture matching, as well as written word – picture matching. Furthermore, the majority of the naming errors took the form of semantically-related words. These suggested to the authors that the core deficit was one of retrieval of lexical items from semantic input. Further supporting the idea that the thalamus may be involved in the use of semantic information to facilitate lexical retrieval, are the findings of category-specific naming deficits in patients with thalamic infarcts and deficits (Crosson, Moberg, Boone, Gonzalez Rothi, & Raymer, 1997; Levin et al., 2005) and demonstrations that the thalamus may be involved in object recall (Segal, Williams, Kraut, & Hart, 2003; Slotnick, Moo, Kraut, Lesser, & Hart, 2002; Wahl et al., 2008).

Analysis of the effects on language of thalamotomy or thalamic deep brain stimulation can avoid the limitations imparted by the idiosyncrasies of the thalamic vasculature, though the ability to make inferences about thalamic structure-function relationships via this approach is limited by the small range of thalamic targets employed (typically ventrolateral nucleus, pulvinar and intralaminar nuclei). For example, Ojemann, Fedio, and van Buren (1968) and Ojemann and Ward (1971) studied the effects of deep brain stimulation in both the ventrolateral nucleus and pulvinar in separate populations of patients with extrapyramidal movement disorders. In the naming paradigm used in these studies, the subject read aloud a plate on which was printed: "This is a _ " followed by a line drawing of an object. By requiring motor output by the subject, this paradigm was designed to capture dysnomia that could not be accounted for by motor speech deficits. The investigators observed naming problems after stimulation of the anterior superior pulvinar (5/8 patients on left, 1/7 on right), and in the posterior inferior medial ventrolateral nucleus (6/13 patients on left, 0/12 on right), but not in other areas of the ventrolateral nucleus that were more anterior or superior. The sites producing naming errors were contiguous across the ventrolateral nucleus and pulvinar and there were no qualitative differences in the types of errors produced. More than half of the errors in both series were substitution errors, rather than omissions. This is in contrast to the types of naming errors seen in the same study with stimulation outside of the thalamus, in the subcortical parietal white matter, which produced >80% omission errors (Ojemann et al., 1968). Note that these studies are reviewed in more detail in Hebb and Ojemann (this issue). In addition, Fedio and Van Buren found predominantly substitution error during stimulation of the left pulvinar, but not in adjacent areas outside the pulvinar or in the right pulvinar (Fedio & Van Buren, 1975). Similarly, Vilkki and Laitinen (1976) found decreases in word fluency and token test performance in those undergoing left ventrolateral thalamotomy, and trends towards worsening token test performance and naming for patients undergoing pulvinotomy (Vilkki & Laitinen, 1976). The findings are by bolstered by the known connectivity data, which would suggest that all of the structures described above (ventral lateral thalamus, pulvinar and intralaminar nuclei), project to areas of the cortex important for language (Jones, 2007).

Another commonly reported feature of patients with thalamic lesions, either due to stroke to electrolytic lesion, is a relatively rapid recovery from language deficits. When recovery has been described, most patients recover to a significant degree within 6 months of the ictus (Archer, Ilinsky, Goldfader, & Smith, 1981; Graff-Radford et al., 1984; McFarling et al., 1982; Raymer et al., 1997; Vilkki & Laitinen, 1976), though several patients with persistent aphasic deficits after focal thalamic lesions have been described (Bell, 1968; Demeurisse et al., 1979; Graff-Radford et al., 1984; Karussis et al., 2000; Puel et al., 1992; Radanovic & Scaff, 2003). Recovery of language function after small strokes has also been described in the cortex (Mohr et al., 1978), and the mechanisms for this are not known. It is certainly possible that resolution of edema or microscopic hemorrhage may play a role. It is also