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PERGAMON

Neuropsychologia 38 (2000) 613–627

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Neuropsychology of infarctions in the thalamus: a review

Ysbrand D. Van der Werf[a, b,*], Menno P. Witter[a, b], Harry B.M. Uylings[a, c], Jelle Jolles[d]

[a]*Graduate School for Neurosciences Amsterdam, The Netherlands*
[b]*Research Institute Neurosciences Vrije Universiteit Amsterdam, Department of Anatomy and Embryology, The Netherlands*
[c]*Netherlands Institute for Brain Research, The Netherlands*
[d]*Department Biological Psychology, The Maastricht Brain and Behavior Institute, The Netherlands*

Received 25 January 1999; received in revised form 2 August 1999; accepted 3 August 1999

Abstract

From a review of the literature on the consequences of thalamic infarctions, it may be concluded that memory problems taking the form of an amnesic syndrome are dependent upon the integrity of the mammillo-thalamic tract (MTT). Memory problems incompatible with an amnesic syndrome however, appear to result from thalamic infarctions involving other areas of the thalamus but which leave MTT intact. In contrast, executive dysfunctions could not be shown so readily to depend upon a single structure of the thalamus. The results indicate that damage to the mediodorsal nucleus of the thalamus, the midline nuclei or the intralaminar nuclei, or a combined lesion of these structures may be responsible for deficits of executive functioning. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Diencephalic amnesia; Prefrontal cortex; Hippocampus; Neuropsychological tests

1. Introduction

It has long been recognized that lesions in the thalamic region, be they of either vascular, tumorous or traumatic origin, can cause cognitive disturbances [14,59,73]. Traditionally, the memory loss associated with such lesions received most attention and is usually described as 'diencephalic amnesia' [29,82]. This term suggests that there is a consistent symptomatology across patients but in fact the pattern of memory deficits can be very different among patients with thalamic lesions. In addition, in recent years reports have stressed that, following damage to the thalamus, symptoms of a dysexecutive or 'prefrontal' type can occur alone or in combination with memory loss [13,19,50,60,79]. The current article attempts to give an overview of (a) the different memory deficits and (b) the executive deficits following thalamic lesions.

The pattern of memory loss occurring in patients with lesions of the thalamic region has traditionally been thought to resemble that seen after lesions in the medial temporal lobe (MTL) region [1]. The memory problems of patients with MTL lesions typically take the form of an amnesic syndrome due to defective encoding of new information, resulting in impaired anterograde memory with intact short-term memory and normal intelligence [84]. Recent data have indicated, however, that damage to certain areas within the MTL may result in retrieval rather than encoding difficulties [1]. Nevertheless, in this article MTL functioning is taken as a whole since the functional differentiation within the MTL does not translate to a differentiation in the thalamus [86] and therefore we regard retrieval and encoding deficits as part of a thalamic MTL-like amnesia.

It should be noted that memory disturbances other than the amnesic syndrome are also frequently encoun-

* Corresponding author. Department of Anatomy and Embryology, Faculty of Medicine, Vrije Universiteit, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. Tel.: +31-20-4448040; fax: +31-20-4448054.

E-mail address: yd.van_der_werf.anat@med.vu.nl (Y.D. Van der Werf).

0028-3932/00/$ - see front matter
PII: S0028-3932(99)00104-9

Table 1
Amnesic and 'frontal' symptoms after diencephalic infarction

Study [ref]	Cases	Type of imaging	Side of the infarction	Lesion site according to the authors											
				Ant	MTT	Rt	VA	VL	Lat	MD	Midline	IML	CM	Pf	Pl
Group 1: lesions located anteriorly in the thalamus															
Archer et al. [4]	1	CT	left		+	+	+	+							
Speedie and Heilman [69]	1	CT	left							+					
Goldenberg et al. [26]	1	CT	left	+	+		+	+							
Graff-Radford et al. [28]	5	CT	case 1 left	All territory of the polar artery											
			case 3 left												
			case 5 right												
Von Cramon et al. [82]	6	CT	75% overlap of amnesics		+							+			
Bogousslavsky et al. [12]	3	CT	case 1 left	Anteriorly											
			case 2 left	Anterolaterally											
			case 3 right	Anteriorly											
Gorelick et al. [27]	1	MRI	left	+	+		+	+		+	+	+			
Stuss et al. [75]	3	CT	case 1 bilateral		+		+	+		+		+			
			case 3 left		+		+	+		+					
Sandson et al. [65]	1	MRI	left					+		+	+			+	
Cole et al. [17]	5	MRI	case 1 left	+	+					+					
Malamut [44]	1	MRI	bilateral		+	+	+					+			
Hodges and McCarthy [33]	1	MRI	bilateral		+					+		+			
Pepin and Pepin [60]	3	case 1 MRI	case 1 left		+		+	+		+	+	+			
		case 2 MRI	case 2 right		+		+				+	+			
		case 3 CT	case 3 left		+		+	+		+	+	+			
Clarke et al. [16]	1	MRI	left	+	+						+	+			
Daum and Ackermann [18]	1	MRI	bilateral		+		+	+		+		+			
Lucchelli et al. [42]	2	MRI	left	Anteroventrally											
Group 2: lesions at middle levels of the thalamus															
Graff-Radford et al. [28]	5	CT	case 4 bilateral	Territory of the paramedian artery											
Winocur et al. [85]	1	CT	bilateral		+			+		+					
Von Cramon et al. [82]	6	CT	case 5 right							+		+			
			left					+		+		+			
			case 6 left							+		+			
Mori et al. [54]	1	MRI	left		+			+				+	+	+	
Gentillini et al. [25]	8	CT	case 1 left		+			+		+	+	+			
			right		+	+	+	+		+	+	+			
			case 2 left					+		+					
			right		+	+	+	+			+	+			
			case 3 bilateral		+							+			
			case 4 bilateral		+		+	+		+	+	+			
			case 5 bilateral		+	+	+	+		+	+	+			
			case 6 left		+		+	+		+		+			
			right					+		+					
			case 7 bilateral		+		+	+		+	+	+			
			case 8 left		+					+	+				
			right		+	+	+	+		+	+	+			
Kritchevsky et al. [8]	2	MRI	case 1 right							+					
			case 2 bilateral							+					
Bogousslavsky et al. [1]	1	CT	right					+		+		+			
Fensore et al. [1]	3	MRI	left	Territory of the paramedian artery											
Nichelli et al. [56]	1	MRI	left							+	+	+		+	
			right		+		+			+	+	+			
Stuss et al. [75]	3	CT	case 2 left					+		+		+			
			right		+			+		+		+			
Graff-Radford et al. [29]	4	MRI	case 1 bilateral		+							+			
			case 2 bilateral	+	+					+		+			
			case 3 bilateral							+					
			case 4 bilateral									+			
Bogousslavsky et al. [13]	2	case 1 CT	case 1 bilateral					+		+	+	+			
		case 2 MRI	case 2 bilateral							+	+				
Barontini and Maurri [7]	1	MRI	left		+							+			
			right	+	+							+			
Mennemeier et al. [51]	1	MRI	left							+	+	+	+	+	
Calabrese et al. [15]	1	MRI	bilateral							+		+			
Daum and Ackermann [19]	1	MRI	right		+		+								
Parkin et al. [58]	1	MRI	left		+			+		+			+		
Sodeyama et al. [68]	1	MRI	left		+			+		+		+			
Van der Werf et al. [79]	1	MRI	right									+			
Group 3: extensive lesions															
Speedie and Heilman [70]	1	CT	right	+					+	+					+
Markowitsch et al. [49]	1	MRI	bilateral		+		+	+		+	+	+			
Peru and Fabbro [61]	1	MRI	bilateral	+						+					+
Amnesia		Compatible with amnesic syndrome	'Frontal' symptoms												

(*continued on next page*)

Table 1 (*continued*)

Study [ref]	Cases	Type of imaging	Side of the infarction	Lesion site according to the authors											
				Ant	MTT	Rt	VA	VL	Lat	MD	Midline	IML	CM	Pf	Pl
yes	no data	no data													
yes, verbal	yes	dysexecutive													
yes, verbal	no data	no data													
yes	yes	not clear because of aphasia and not enough data													
yes	yes														
yes, non-verbal	no data														
yes	no data	no data													
yes	no data	dysexecutive													
no data	no data	dysexecutive													
yes	no data	dysexecutive													
yes	yes	dysexecutive													
yes	no data	apathy, dysexecutive, confabulatory													
yes, verbal	no data	dysexecutive													
yes	no data	apathy, dysexecutive													
yes	no data	case 1: no data													
yes	yes	apathy, lack of initiative, dysexecutive improved at 3 year follow-up													
yes	yes	apathy, lack of initiative, dysexecutive													
yes, verbal	yes >	dysexecutive, distractible													
yes, mostly nonverbal	yes	dysexecutive													
yes, mostly verbal	yes	dysexecutive													
yes	yes	mildly dysexecutive, lack of initiative													
yes	no data	dysexecutive, aspontaneous													
yes, mostly verbal	no data	no evidence for frontal symptoms													
yes	yes	euphoric and delusional													
yes	yes	no data													
no	/	no data													
no	/	no data													
yes, verbal	yes	no evidence for frontal symptoms													
yes	no data no data	delusions of grandeur, disinhibited	In general: no tests of frontal function in the neuropsychological investigation												
no	no data	disinhibited													
yes	no data	apathy and irritable for 2 months postictus													
yes	no data	no data													
unknown	no data	no data													
yes, perhaps premorbid	no data	perhaps apathetic													
yes	no data	no data													
yes	no data	hallucinations and apathy													
no	/	mildly dysexecutive													
no	/	no evidence for frontal symptoms													
yes, nonverbal	no	disinhibition, dysexecutive													
yes, verbal	no data	no data													
yes	yes	not clear													
yes, mainly non-verbal	no data	dysexecutive													
yes	yes	marked personality change, mod dysexecutive													
yes	no	moderate pers change, mod. dysexecutive													
yes, mild verbal	no	moderate pers change, mod dysexecutive													
no	no	moderate pers change, mod dysexecutive													
no	no	apathy, mildly dysexecutive													
no	no	apathy, dysexecutive													
yes	not clear	no data													
yes, mild verbal	no	mildly dysexecutive													
yes	yes	not enough data													
yes, mainly nonverbal	yes	dysexecutive, disinhibited, irritable													
yes	yes	no evidence for frontal symptoms													
yes, verbal	no data	no data													
yes	no	dysexecutive, apathetic													
yes, nonverbal	yes	dysexecutive													
yes	yes	dysexecutive													
yes, moderate, verbal	no	mildly dysexecutive													

tered in thalamic-lesioned patients and other neurological patients. Such disturbances may for instance result from inattention. It is often quite difficult to distinguish between the amnesic syndrome and other memory problems with the use of neuropsychological tests.

Nevertheless, in this article, the difference between these miscellaneous forms of memory dysfunction and the amnesic syndrome (the latter to be used interchangeably with MTL-like amnesia henceforth) is thought to be of importance in the description of the role of thalamic function in memory processes and we have attempted to operationalise the differentiation between the two as described below in the section 'selection of cases'.

As mentioned above, lesions in the thalamus not only give rise to memory problems but also lead to the disruption of processes which are ascribed to the prefrontal cortex (PFC). 'Prefrontal' symptoms include disturbances of executive abilities, attention, initiative, inhibition and temporal organization of behaviour [23,24], seen in cases of patients with lesions of the PFC. In such cases, the precise pattern of deficits seems to depend on the area of the PFC that is lesioned. Dysfunctions of the medial part of the PFC result in apathy and lesions in the orbital PFC are responsible for behavioral disinhibition [20]. Structural lesions in the dorsolateral PFC affect executive functions, as evidenced by a lack of planning of behavior, an impairment of serial ordering, a deficit of attentional capacities, and severe distractibility [24].

There is evidence that the frontal cortex also actively participates in memory processes, namely the retrieval of information and the use of search strategies in the memory store [36,48,71]. Imaging studies have shown that the frontal cortex is activated during encoding [77], but it has not yet been established whether this activation is crucial for the formation of new memory traces. Therefore, memory problems may arise either as a direct consequence of prefrontal damage or secondarily as a result of prefrontal cognitive deficits, for example, inattention. The resulting 'prefrontal memory problems' can be distinguished from MTL-like amnesia by using neuropsychological tools, since recognition or aided retrieval is often spared, whereas active recall from the memory store is impaired [67]. However, it should be clear that executive dysfunctions and the amnesic syndrome can occur together in patients with extensive thalamic damage.

The understanding of cognitive effects of thalamic lesions has been hampered because of the small number of patients with such lesions. Most descriptions of diencephalic amnesia have been case studies, which makes it difficult to compare results because different neuropsychological tests were often used. Also, it has only recently become possible, with the advent of magnetic resonance imaging (MRI), to localize the lesion more precisely. The importance of spatial resolution in delineating the site of thalamic infarctions can be appreciated by considering the size of the various thalamic structures [35,53]. Some of the separate nuclei have volumes of only a few cubic millimeters, and since each nucleus has its own specific pattern of inputs and outputs [74], the effect of a lesion will depend upon subtle differences in its location.

This lack of neuropsychological data and of accurate anatomical localization of the thalamic lesion, means that it is not yet clear which structures are involved in the amnesic symptoms encountered following such a lesion [8]. In addition, it is unknown which thalamic structures are responsible for the disruption of typical prefrontal processes. The aim of this article is therefore to provide a detailed review of reports of the effects of selective lesions of parts of the thalamus, in order to gain an insight into the contribution of the thalamic substructures to cognitive functioning. The review focuses on the elements common to all cases described in the neurological and neuropsychological literature over the past two decades.

2. Selection of cases

Thirty-five articles involving a total of 60 patients were selected from the international literature since 1980 on the basis of three criteria. First, lesions had to be restricted to the thalamus and had to result from lacunar infarctions because the effects of these lesions are more spatially restricted than those of haemorrhages, traumata or tumors. Second, the article had to contain a description of the procedure used to delineate the structures of the thalamus that were affected by the infarction, or otherwise MRI scans had to be presented. Lastly, memory function had to be described in terms of neuropsychological test results rather than by intuitive descriptions or neurological investigation, and the raw data had to be given in the text.

The cases were grouped according to the location of the lesions. The infarctions described and depicted in the various articles were drawn on sections of the thalamus and subsequently compared. The subjects were categorized as belonging to one of three groups based on the location of the lesion on the anterior-posterior axis of the thalamus or the size of the lesion. For this purpose the thalamus was divided into three portions of equal length.

Group 1 consisted of 26 cases with lesions located anteriorly; Group 2 consisted of 32 cases in which the lesions occupied the middle portion of the thalamus; and Group 3 consisted of three cases in which the

extensive lesions could not be grouped along with one of the other groups because the infarctions encompassed regions that fell within the boundaries for both Groups 1 and 2. No articles describing lesions restricted to the posterior portion of the thalamus were found.

It is important to note that the division is arbitrary and does not follow anatomic boundaries, for example, anteriorly located does not necessarily mean that the infarction falls in the anterior nuclei but rather in the anterior one-third of the length of the thalamus.

The locations of the lesions in terms of nuclei and fiber tracts of the thalamus, according to the description of the authors, are given in Table 1. This table also shows whether the subjects had amnesic symptoms and whether these symptoms could be the result of an amnesic syndrome resembling that seen after MTL lesions. Since anterograde amnesia, as seen in the amnesic syndrome, is characterized by deficits of free recall and recognition [34], this conclusion could only be drawn when the neuropsychological assessment included free recall procedures after short and long delays and recognition variables. If recall was impaired but recognition was normal or disproportionally better, the memory deficit was likely to be the result of retrieval deficits rather than encoding deficits and hence did not resemble the amnesic syndrome [72,87]. 'No data' is indicated in the table if the neuropsychological tests used did not include recall and recognition tests, or were inadequate to arrive at this conclusion. We are aware that the inclusion of a recognition deficit in the definition of the amnesic syndrome is disputed by some researchers, but in view of the considerations mentioned in the introduction we feel that it is necessarily part of a thalamic-based amnesic syndrome.

Symptoms ascribed to the prefrontal cortex are listed in this table according to whether the subjects were dysexecutive, disinhibited or apathetic. It should be noted that the first can be deduced from the results of tests of executive functioning only, whereas the latter two are behavioral measures and are based on the description of the patient. This makes the distinction between 'apathetic' and 'disinhibited' symptoms rather subjective, and the discussion of the results will therefore focus on dysexecutive symptoms.

In the description of the functional deficits of the patients, statistical analysis on the distribution of symptoms over subgroups of patients was performed when applicable. A χ^2 analysis was done with Fisher's exact probability test (SPSS 7.5 software).

Table 2 shows the neuropsychological tools used to assess memory and executive functioning in the patients. Descriptions of the tests can be found in Lezak [40]. As a measure of immediate memory the digit or block span forward and sometimes backward was often used. There is debate about whether these are measures of memory [41], but they are nevertheless included here as such since various authors of articles reviewed here have used them for these purposes. Short-delay memory was assessed in less standardized ways: recall of a word list was usually part of the testing procedure, as were subtests of the Wechsler Memory Scale. Visual short-delay memory was investigated less often, and usually in the form of the Rey figure or Warrington's Recognition Memory Test for faces. Some authors used little-known tests or tests of local origin. The same was true for the assessment of retention: some authors used standardized methods such as the California Verbal Learning Test, Auditory Verbal Learning Test, Rey figure, whereas others relied on recall of three objects to assess retention of information.

Different tests were used to assess executive functioning, but the most often used tests were the Stroop test, some form of Card Sorting, and fluency tasks.

3. Results

3.1. Memory dysfunction after thalamic infarction

The evidence for disruption of memory and other cognitive functions is discussed on the basis of the studies listed in Table 1.

Influential reports on the nature of diencephalic amnesia [29,82] have stressed that the fiber system of the mammillo-thalamic tract (MTT) rather than nuclear structures in the thalamus is responsible for anterograde memory. Several studies have since confirmed the notion that anteriorly, but not posteriorly, located infarctions can cause a profound amnesic syndrome. Indeed, 25 out of 26 subjects in Group 1 showed symptoms of memory deficits *sensu lato* (the second case by Bogousslavsky et al. [12] could not be tested because of a lack of cooperation) (Table 1). Of these 25 patients, 10 could be classified unequivocally as suffering from an amnesic syndrome, whereas for 15 patients the neuropsychological data were insufficient to support this conclusion (indicated as 'no data' in the table). In 24 of these 25 patients, the MTT was affected by the lesion. Thus in only one amnesic patient was the MTT thought to be spared; however, from the CT image shown in the article it seems likely that the MTT was affected [69]. It can be appreciated from Table 1 that of the thalamic structures listed, lesioning of the MTT is the best predictor of the occurrence of an amnesic syndrome. In summary, all the patients in Group 1 who were tested extensively enough to allow a conclusion suffered from an amnesic syndrome. In all these patients the MTT was most likely affected by the infarction. Table 3 summarizes

Table 2
Overview of Neuropsychological tests used[a]

Study [ref]	Immediate memory	Short delay recall
Archer et al. [4]	Digit span	WMS (logical memory, visual reproduction, paired associates)
Speedie and Heilman [69]	Consonant trigrams	WMS (logical memory, paired associates), RAVLT, Kimura's recurring figures, RCF
Goldenberg et al. [26]		Verbal memory, memory for associated verbal items, memory for unassociated verbal items, numeric memory, visual memory
Speedie and Heilman [70]		WMS (logical memory, paired associates, visual reproduction), RAVLT, RCF, Kimura's Recurring Figures, Milner faces
Graff-Radford et al. [28]		WMS (logical memory, paired associates), Benton VRT, RAVLT, RCF
Winocur et al. [85]	Digit span forward and backward	WMS (logical memory, paired associates, visual reproduction), Benton VRT, RCF, Kimura's Recurring Figures, Verbal learning
Von Cramon et al. [82]	Digit span, block span	Free recall of a word list, 57-unit story, Benton VRT, word-paired associates, face/name-paired associates, object paired associates, RAVLT
Bogousslavsky et al. [12]		Hebb's Recurring Digits, Corsi's Block Tapping Supraspan, RAVLT, 15 Sign of Rey
Mori et al. [54]		WMS (logical memory, paired associates, visual reproduction), Benton VRT, RCF
Gentillini et al. [25]		Story recall, Word list learning, paired associates
Kritchevsky et al. [38]		WMS (logical memory, paired associates, visual reproduction), RCF, Kimura's Recurring Figures, Benton VRT, RAVLT
Bogousslavsky et al. [11]		RCF, 10 signs of Rey
Fensore et al. [21]	Digit span forward and backward	Paired associates, logical stories, word list learning, visual memory
Gorelick et al. [27]		WMS (logical memory, visual reproduction), Benton VRT, RAVLT
Nichelli et al. [56]	Digit Span, Block Tapping test	Babcock story, Paired associates, Selective Reminding Test, Serial Position Curve, Block tapping Supraspan
Stuss et al. [75]	Digit span forward and backward	WMS (logical memory, paired associates, visual reproduction), Benton VRT, recall of 3 words
Graff-Radford et al. [29]		WMS (logical memory, paired associates), RAVLT, Craik-Tulving encoding, Benton VRT, RCF
Bogousslavsky et al. [13]	Corsi's Block Tapping	RCF, Hebb's Recurring Digits
Sandson et al. [65]	Digit span forward and backward	3 words 3 shapes test
Barontini and Maurri [7]	Digit span forward and backward	Short story, RAVLT 1 trial, RCF, verbal free recall
Cole et al. [17]		WMS, 30-word story
Mennemeier et al. [51]	Digit span forward and backward, pointing span	WMS (logical memory, visual reproduction), RCF, CVLT, Selective reminding test, Craik-Tulving encoding, Continuous Visual Memory test
Malamut et al. (44)		WMS (logical memory, paired associates, visual reproduction), RCF, spatial learning, Tactual Performance Test, CVLT, RAVLT
Calabrese et al. [15]	Digit span, Corsi Block span	RAVLT, Selective reminding test, immediate visual memory, short story, short route, RCF
Hodges and McCarthy [33]	Digit span forward and backward, Corsi Block tapping forward and backward	WMS (logical memory, paired associates), RCF
Markowitsch et al. [49]	Digit span, word span, Corsi Bock Tapping	10-item word list, RAVLT, CVLT, 57-unit story, Benton VRT, RCF, word paired associates, face/name paired associates, object paired associates, Kimura's Recuring Figures test, recurring Word test, figural Selective reminding test
Pepin and Pepin [60]	WMS (logical memory, paired associates, visual reproduction), 15-Word list	
Clarke et al. [16]	Digit span, Corsi Block tapping	RAVLT, 15 signs of Rey, Recurring words, faces, landscapes, geometrical figures, RCF
Daum and Ackermann [18]	Digit span forward and backward, Corsi Block Tapping forward and backward	WMS (paired associates), categorized and uncategorized 16-word lists, Benton VRT, visual free recall
Daum and Ackermann [19]	Digit span forward and backward, Corsi Block Tapping forward and backward	WMS (logical memory), categorized and uncategorized 16-word lists, Benton VRT
Parkin et al. [58]		WMS (logical memory, paired associates, visual reproduction), paired associates according to Leng and Parkin
Lucchelli et al. [42]	Digit span, spatial span	Story, paired associates, Selective Reminding test, RCF
Sodeyama et al. [68]	Digit span, spatial span	WMS (logical memory, paired associates, visual reproduction), visual paired associates, figural memory
Peru and Fabbro [61]	Digit span, Corsi's Block tapping	Serial position curve, Rey memory test, Picture display test, story, Selective Reminding test, 15-word list
Van der Werf et al. [79]	Digit span forward and backward, Consonant Trigrams	15-word list 5 trials, RCF, Visual Association Learning Task

Delayed recall	Recognition	Executive abilities
WMS (logical memory, paired associates), RCF	RAVLT	WCST
WMS (logical memory, visual reproduction), RCF	RAVLT	WCST, Serial hand positions, verbal fluency, design fluency
RAVLT	RAVLT	Verbal fluency
Verbal learning, RCF, WMS (logical memory)	RMT, letter prompt word recognition, fragmented words	
57-unit story	Facial recognition	
	15 signs of Rey	Verbal fluency, Luria's conflicting tasks, sequential rhythms and sequential geometric figures, WCST, Stroop test
WMS (logical memory, paired associates, visual reproduction)	RAVLT	WCST
Story recall		
WMS (logical memory, paired associates, visual reproduction), RCF, RAVLT		WCST, verbal fluency, design fluency
		WCST, Stroop test
	Facial recognition	
WMS (logical memory, visual reproduction), RAVLT	RAVLT	TMT
Babcock story	Word recognition	
WMS (logical memory, paired associates, visual reproduction),		TMT, WCST, Porteus Maze, color-form sorting
WMS (logical memory, paired associates), RAVLT, RCF	RAVLT, RMT words and faces	WCST, verbal fluency
		WCST, Stroop test, proverbs, Luria's conflicting tasks, sequential rhythms and sequential geometric figures
3 words 3 shapes test	3 words 3 shapes test	Verbal fluency, TMT, Stroop test, visual-verbal categorize and shift, Luria sequencing, similarities/proverbs
Short story, RCF, verbal free recall		
WMS		TMT
WMS (logical memory, visual reproduction), RCF, CVLT, rates of forgetting verbal and visual	CVLT, Milner Facial recognition	Verbal fluency, WCST, TMT
WMS (logical memory, visual reproduction), CVLT, RCF	Facial memory, CVLT, WMS (visual reproduction)	Verbal fluency, MCST, WCST, CPT, Stroop test
Short story, short route, RCF	Face recognition, word recognition	Concept formation
WMS (logical memory, paired associates), RCF	RMT words and faces	WCST, TMT, CET, verbal fluency
57-unit story, CVLT	RMT faces, recognition of 10 faces after 48 h., CVLT	TMT, Tower of Hanoi, Planning test, Concept learning, WCST, Weigl's test
RCF, 15-word list, WMS (logical memory, paired associates)	RMT faces and words.	WCST, Stroop test, verbal fluency
RAVLT, 15 signs of Rey, RCF	RAVLT, 15 signs of Rey, recognition of faces and words	WCST, verbal fluency, non-verbal fluency, Stroop test
Categorized and uncategorized 16-word lists, RCF	Recognition of words	WCST, memory for temporal order
WMS (logical memory), categorized and uncategorized 16-word lists, RCF	RMT faces	WCST, verbal fluency, memory for temporal order, list discrimination, prospective memory
	Scenes test, temporal list discrimination (verbal and non-verbal), spatial list discrimination	WCST, verbal fluency, TMT, CET
RCF	Recurring faces	CET, verbal fluency
WMS (logical memory, paired associates, visual reproduction), visual paired associates		
RCF, story	Picture display test, 15 word list recognition	Verbal fluency
15-word list, RCF, Visual Association Learning Task	RMT faces, 15-word list, RCF recognition trial	WCST, TMT, verbal fluency, Tower of London, Stroop test

[a] Abbreviations: CET, Cognitive Estimation Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; RCF, Rey Complex Figure; RMT, Recognition Memory Test; TMT, Trail Making Test; VRT, Visual Retention Test; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale.

Table 3
Distribution of amnesia, amnesic syndrome and MTT lesions across the three different groups of thalamic infarctions[a]

	No. of patients with Amnesia	No. of patients with an Amnesic syndrome	No. of patients with damage to the MTT
Group 1 ($N = 26$)	25+, 1 no data	10+, 15 no data	25 total, 10 of 10 amnesic syndrome patients
Group 2 ($N = 32$)	23+, 8−, 1 no data	8+, 5−, 10 no data	7 of 8 amnesic syndrome patients, 2 of 13 non-amnesic syndrome patients
Group 3 ($N = 3$)	3+	2+, 1−	2 of 2 amnesic syndrome patients, 0 of 1 non-amnesic syndrome patient

[a] + indicates that amnesia or amnesic syndrome was present, − indicates that it was not.

the data on memory dysfunctions of the patients in Group 1.

Of the 32 patients in Group 2 (lesions in the middle portion of the thalamus), 23 had memory problems of some kind and eight did not. No data were available for one patient. Of the 23 patients, eight could be classified as having an amnesic syndrome, five had memory problems that did not meet the criteria of an amnesic syndrome, and 10 could not be diagnosed because of insufficient data. Thus in Group 2, 13 out of 32 patients had memory problems that did not fulfil the criteria for MTL-like amnesia (five patients) or did not have any amnesic symptoms (eight patients). Eleven of these 13 patients were reported by the authors to have an intact MTT, versus two with a lesioned MTT. In the eight patients with an amnesic syndrome, seven were reported to have a lesioned MTT (Fisher exact probability: 0.000). The fiber tract in the other patient was considered by the authors to be intact [15]. In summary, as in Group 1, the patients in Group 2 with an amnesic syndrome generally had a lesion of the MTT, whereas the patients with 'other' memory problems and the non-amnesiacs had an intact MTT (Table 3).

The three patients in Group 3, in whom the infarctions extended to both the regions used to describe Groups 1 and 2, all had memory deficits. In two patients these deficits met the criteria for an amnesic syndrome. In one of these patients the infarction was reported to include the site of the MTT [49]. In the other patient the MTT was not mentioned but, based on the CT image and the fact that the nuclei surrounding the MTT were lesioned, it was inevitably involved [70]. The mild memory problems exhibited by the third patient [61] were not compatible with an amnesic syndrome, and the lesion, a rare case of venous infarction, did not appear to extend into the MTT.

In conclusion, the combined evidence from Groups 1, 2 and 3 suggests that for patients in whom damage was restricted to the thalamus, a lesion of the MTT is both a necessary and a sufficient condition for an amnesic syndrome (Table 3).

3.2. 'Frontal' symptoms after thalamic infarctions

Of the 'frontal' symptoms mentioned in the last column of Table 1, only the dysexecutive type will be discussed here, because it can be characterized with neuropsychological tests. The dysexecutive defects were assessed using the tests listed in Table 2.

The test results indicated that 15 of the 26 patients in Group 1 had disturbances of executive functioning, one patient showed no evidence of such disturbances on two different measures of executive functioning, and the remaining 10 patients were not tested adequately enough to reveal possible dysexecutive symptoms. In the one patient without evidence of disturbed executive functioning the lesion was more ventrolateral than that of the other members of the group [42]. However, the authors did not give a detailed description of the location of the lesion in terms of the nuclei affected. It can be appreciated from the MR images provided in the article that the mediodorsal nucleus (MD) and midline nuclei were spared, suggesting that these structures might be crucial for symptoms of executive dysfunctioning. In accordance with the idea that the MD is crucial for executive functioning, one article reported that selective lesion of the MD was accompanied by symptoms of executive dysfunctioning [69]. Yet, the data for three subjects in Group 1 indicate that the MD or midline nuclei may not be crucial, because these subjects did have impaired executive functioning despite sparing of the MD ([60] case 2; [16]) or of the MD and midline nuclei [44]. Instead, in these three cases the internal medullary lamina (IML) was consistently lesioned (Table 4).

In Group 2, 12 of the 32 patients could be diagnosed as dysexecutive and three showed no evidence of such disturbances. No neuropsychological data were available for 17 patients. Of the three patients without evidence of problems with executive functioning one had a lesion that was thought to spare the MD and the greatest part of the IML, as well as the dorsal part of the midline [54]. The second patient had a bilateral lesion encompassing only 15% of the left and 5% of

Table 4
Distribution of dysexecutive symptoms and MD, IML and midline lesions across the three different groups of thalamic infarctions[a]

	No. of patients with Dysexecutive symptoms	No. of patients with damage to the MD	No. of patients with damage to the IML	No. of patients with damage to the Midline nuclei
Group 1 ($N = 26$)	15+, 1−, 10 no data	of 15 dysexecutives: 9+, 3−, 3 not clear 1 non-dysexecutive: −	of 15 dysexecutives: 9+, 3−, 3 not clear 1 non-dysexecutive: −	of 15 dysexecutives: 6+, 9− 1 non-dysexecutive: −
Group 2 ($N = 32$)	12+, 3−, 17 no data	of 12 dysexecutives: 8+, 4− of 3 non-dysexecutives: 2+, 1−	of 12 dysexecutives: 8+, 4− of 3 non-dysexecutives:1+, 2−	of 12 dysexecutives:3+, 9− of 3 non-dysexecutives: 3−
Group 3 ($N = 3$)	3+	3+	3+	3+

[a] + indicates that dysexecutive symptoms were present, − indicates they were not.

the right MD, and the proportion of lesioned midline nuclei was presumably equally small ([38] case 2). The third patient who did not show evidence of executive dysfunctioning [58] had a lesion that destroyed only a minor portion of the MD and a more substantial part of the IML, while sparing the midline nuclei.

Conversely, of the 12 patients in Group 2 who did show symptoms of executive dysfunctioning three had a lesion in a very small and specific part of the thalamus. Although these three patients had impairments of executive functioning and memory problems, they did not show evidence of memory dysfunction compatible with an amnesic syndrome. One of these patients was case 4 from the article by Graff-Radford et al. and presented with a very limited bilateral infarction of the IML, as judged by CT [29]. This patient was scored as moderately impaired on an executive control measure that included the Wisconsin Card Sorting Test and verbal fluency. The patient reported on by Mennemeier et al. [51] was shown to have a small lesion of the ventral IML close to the midline. The lesion was described by the authors to encroach upon the nucleus reuniens (medioventral nucleus), the centromedial and central lateral nuclei, the parafascicular nucleus and a negligible part of the floor of the MD. The lesion thus was mainly outside the large nuclear masses of the thalamus and was confined to the IML and midline nuclei. This patient showed mild impairments of executive functioning, that is, slowing on part B of the Trail Making Test, susceptibility to interference on the consonant trigrams and deficient recognition using low levels of encoding in the Craik–Tulving encoding task, whereas deeper levels of encoding resulted in an increasingly better recognition. The third patient showing executive dysfunctioning after a very limited infarction was described by Van Der Werf et al. [79] This patient had a minute lesion in the dorsal region of the IML and showed impaired performance on the Tower of London test, the Wisconsin Card Sorting Test, the Trail Making Test, verbal fluency measures and the Stroop test. However strongly these three cases seem to point to the involvement of the midline and/or IML in executive functioning, other cases showed the reverse pattern, namely MD lesions without reported involvement of the IML or the midline nuclei but associated with symptoms of executive dysfunctioning ([29] case 3; [38] case 1).

The three patients in Group 3 all showed evidence of impaired executive functioning. In all three the lesion encroached upon the MD, but only in one patient [49] were the IML and the midline nuclei said to be damaged. From detailed investigation of the brain images for the two other patients, however, it can be appreciated that the lesions additionally included at least a substantial portion of the midline nuclei [61,70].

In conclusion, there is less clarity about which thalamic structures are involved in symptoms of impaired executive functioning than in the case of the amnesic syndrome. The combined evidence of the three patient groups, shown in Table 4, tentatively indicates that destruction of the midline nuclei, the IML or the MD may lead to disturbances of executive functions. Lesion of one of these structures may in itself not be sufficient to produce these impairments, which instead may require the combined lesion of two or more of these structures.

4. Limitations of the data

As can be seen from Table 2, clinical memory research usually emphasizes performance in short-delay tests. Little attention has been paid to performance in long-delay tests and even less to tests of recognition memory. However, especially in patients with unilateral lesions, in whom the neuropsychological deficit is often either verbal or non-verbal, short-term retention, long-term retention and recognition should be tested in the same modality to allow a diagnosis of MTL-like anterograde amnesia. If the appropriate tests are not used, it is not possible to conclude whether an amnesic syndrome is present or not.

Some of the articles reviewed did not use a sufficient number of tests of executive control. As mentioned in the introduction the functions of the PFC are diverse and cannot be measured adequately with a single test. Administration of the Wisconsin Card Sorting Test, which is considered the standard test to detect 'frontal' dysfunction and which was frequently used as such in many of the studies reviewed, may in itself be insufficient to draw conclusions about the presence or absence of these symptoms. This is borne out by one article in which a patient displayed no deficit on the Wisconsin Card Sorting Test but showed deficits of executive processes when additional measures of strategy use, for example, the Trail Making Test and verbal fluency, were administered [51]. In addition, many tests of executive functioning are not exclusively dependent upon the functioning of the prefrontal cortex. For instance, it has been shown that posterior cortical lesions disrupt performance on the Wisconsin Card Sorting Test, and neuroimaging data indicate that other cortical areas beside the prefrontal cortex are involved in the performance of this task [10].

A further point of interest concerns the delay between the infarction and the neuropsychological testing. Secondary effects of the infarction, for example, pressure on the surrounding structures through oedema, will take weeks or months to clear. In some cases the residual cognitive deficits can even be shown to improve in the course of years after onset of the symptoms [44,61]. A particularly striking example of a change in the neuropsychological profile of a thalamic patient is given by Lucchelli et al. [42] who described a patient who recovered completely and suddenly from a dense retrograde amnesia a year after the occurrence of the stroke. It should thus be borne in mind that the differences between the cases reviewed in this article may depend at least in part on the interval between infarction and testing.

5. Discussion

5.1. Memory dysfunction after thalamic infarction

On the basis of the articles reviewed, the occurrence of an amnesic syndrome is associated with lesioning of the MTT, regardless of whether the infarction is in the anterior or middle thalamus. Only in one patient [15] was an amnesic syndrome not accompanied by destruction of this fiber tract. Conversely, nearly all the patients who did not have memory problems compatible with an amnesic syndrome had an intact MTT (11 vs 2) (Table 3).

The conclusion seems wholly compatible with the ideas advanced in influential reports on diencephalic amnesia published over the last decades [29,45,47,63,82]. However, the current article shows that this hypothesis would appear to be tenable only for the memory problems associated with an amnesic syndrome. Patients in whom the MTT is intact on the other hand can have other forms of memory problems.

It should be remembered that not all authors explicitly mentioned the involvement of the midline nuclei in the lesions, although medially located infarctions inevitably affect these nuclei. This is illustrated by the article by Von Cramon et al. [82] These authors showed, on the basis of six patients and a review of the literature until 1985, that the 75% overlap area of thalamic lesions in amnesic patients involved the MTT and the adjacent IML. From the same diagram, however, it can be seen that this overlap area also involved parts of the nucleus centralis medialis (termed commissural nucleus in Von Cramon et al. [82]) and the paraventricular nucleus, grouped with the IML and midline complex of nuclei, respectively [9] In the same way, it can be argued that all infarctions located near the midline (almost all cases mentioned in group 2) include the midline nuclei and the medially located nuclei of the IML. It is possible that the involvement of these nuclei has been consistently overlooked, because of the traditional appeal of the MTT and its role in the Papez-circuit.

There is controversy about whether damage to the MD can give rise to an anterograde memory deficit. Victor et al. [80] noted that in Korsakoff patients the MD nucleus was the only nucleus together with the mamillary bodies to be affected in 100% of patients suffering from Korsakoff's syndrome or Wernicke–Korsakoff's syndrome, thereby pointing to a possible role for the MD in the memory disturbances of these patients. Some animal studies and case studies have presented data which support this view [73,88], but the hypothesis has been generally discarded [29,45,46,82]. The present analysis also does not provide evidence for the involvement of the MD in memory problems occurring after diencephalic lesions.

5.2. 'Frontal' symptoms after thalamic infarctions

Although memory deficits are among the most notable effects of a thalamic infarction, other cognitive effects also occur. These symptoms often resemble those seen after damage to the PFC. Table 4 gives an overview of the number of patients in each of the three groups showing 'frontal' defects. The 'frontal' symptoms generally occurred in combination with MTL-like anterograde amnesia, as for example in the three cases described by Pepin and Auray-Pepin [60]. However, dysexecutive and behavioral problems can also be encountered in the absence of memory problems ([13] case 2; [25]).

Conclusions about the thalamic substrate of these cognitive processes can less readily be drawn than in the case of memory deficits. This is because these faculties are often not investigated and because, when they are investigated, the tests used may not be specific or sensitive enough to detect deficits associated with prefrontal lesions. Indeed, the three different types of prefrontal dysfunction seem to be associated with different areas of the PFC [20,23], with the dorsolateral PFC being implicated in executive abilities and medial and orbital PFC being more involved in behavioral functions. Since the behavioral outcome cannot be reliably scored and compared across studies, this review focuses on the dysexecutive type of prefrontal dysfunction only.

Apart from the amnesic syndrome, other memory complaints can follow a thalamic lesion. Such memory problems result from a loss of the use of memory strategies, rather than from a deficit in the encoding of stimuli [51]. Strategy use in memory involves the PFC [32] and is considered an example of an executive function. Thus deficits of strategy use are not compatible with a formal diagnosis of amnesic syndrome because the problem is not of impaired anterograde amnesia with defective registration of incoming information, but of impaired semantic organization of memory, leading to retrieval deficits [52]. Recognition or aided recall can therefore be unimpaired [24].

Its anatomical connections make the MD ideally situated to influence prefrontal functioning (see below). Indeed, some patients show impairments of executive functioning after a selective infarction of the MD ([29] case 3; [38] case 1; [69]; [75] case 3), whereas others show similar impairments after infarctions that fall outside the MD. Conversely, there are reports of selective lesions of the MD that do not result in loss of executive control ([38] case 1). It seems therefore that the MD is not associated on a one-to-one basis with executive functioning, and that additional thalamic structures may be involved.

For example, the IML and midline nuclei appear to be involved in executive control. This is based on the three patients described in detail in the Results section who had limited infarctions confined either to the IML or both the ventral IML and adjacent part of the midline nuclei and who showed deficits of executive functioning ([29] case 2; [51,79]). Additionally, four patients who had no detectable impairments of executive functioning were found to have lesions that either completely or for the greatest part spared the midline nuclei and IML [38,42,54,58].

The number of patients with damage to the IML and midline nuclei may be underestimated because these structures are not often mentioned in the description of anatomical localization of infarctions. This might be due to their small metric dimensions, which are often below the resolution power of the imaging apparatus [35,43,53].

The results suggest that damage to each of the three structures (the MD, IML or the midline nuclei) as a result of a thalamic infarction may lead to executive dysfunctioning. It remains to be shown whether the pattern of executive dysfunctioning is similar after damage to each of these structures and in how far a combined destruction might influence the outcome in terms of cognitive incapacitation.

6. Thalamic contribution to cognition in the light of neuroanatomical data

The medial thalamus is widely regarded to be the region of the thalamus involved in the formation of memories. The medial thalamus comprises several structures, including the IML, Midline nuclei, MD, the anterior nuclei and the MTT. No conclusive evidence has been presented concerning which of these medial thalamic structures is crucial for anterograde memory [8].

Amnesia due to thalamic damage has classically been regarded as a disconnection syndrome [83], taken as a disconnection of the temporal cortex from the frontal cortex. On the basis of the articles reviewed, we argue that the thalamic structure most evidently involved in the occurrence of amnesic syndrome is the MTT. However, anatomically, the MTT cannot be considered simply as a pathway from temporal to frontal regions. The MTT connects the mammillary bodies to the anterior nuclei of the thalamus, which in turn project to the cingulate cortex [55]. The latter cortex projects both to other parts of the PFC and the MTL. Structures within the MTL project via the fornix to the mammillary bodies, thus completing the circuit. This circuitry was considered by Papez [57] to be the anatomical substrate of emotion, but has subsequently been considered crucial for long-term memory [1]. Tracing studies in mammals have indicated that within the MTL, it is the hippocampal formation, and in particular the subicular regions, that projects through the fornix to the medial and lateral mammillary nuclei [3,66]. These nuclei provide differential input to the anteromedial, anteroventral and anterodorsal thalamic nuclei. In addition to the route via the mammillary bodies, the subiculum and pre- and parasubiculum also send monosynaptic projections to the anterior thalamic nuclei [2]. The four anterior thalamic nuclei then project onto the limbic cortex, that is, the anterior and posterior cingulate, retrosplenial and subicular areas. However, the density of innervation varies: the anteromedial nucleus preferentially sends input to anterior portions of the cingulate, the anterodorsal nucleus to the retrosplenial cortex and the anteroventral nucleus

primarily to the posterior cingulate cortex. The lateral dorsal nucleus sends its fibers to both cingulate and retrosplenial cortices. The thalamocortical projections are reciprocal. Thus, the corticothalamic and thalamocortical connections between the limbic cortex and anterior thalamic nuclei show considerable overlap [22,53,62,76,81]. In the light of these neuroanatomical data, it seems unlikely that either the MTT or the anterior nuclei of the thalamus serve as an intermediate between temporal and frontal cortical regions. Amnesia after damage to the thalamus is therefore not the result of a simple disconnection between frontal and temporal areas. Rather, it appears that the role of the thalamus is an active one, for which the MTT is relevant. Based on the evidence reviewed above that the MTT contains fibers bound for the anterior nuclei, it is to be expected that infarctions affecting the anterior nuclei produce the same deficits as damage to the MTT. However, these types of infarctions are rarely encountered. Rousseaux et al. (1991) describe a patient with a reported rightsided lesion that damaged the anteroventral nucleus mainly and the MTT only partially [64]. This patient had an anterograde verbal and visuospatial memory deficit that produced a persistent amnesia seemingly consistent with an amnesic syndrome. Due to the partial lesion of the MTT, however, it cannot be made out whether damage to the anterior nuclei is sufficient to result in an amnesic syndrome.

The midline and intralaminar nuclei of the thalamus would appear to have a role in frontal cognitive functions. These nuclei, somewhat inappropriately called the non-specific nuclei, in fact receive very distinct patterns of input and in turn influence functionally segregated circuits in the forebrain [31]. Positron emission tomographic studies support the notion that the intralaminar nuclei serve as relay stations for the activating effects of the brainstem reticular formation on the cerebral cortex [37]. The intralaminar nuclei are divided into a rostral group (centromedial, paracentral, central lateral and rhomboid nuclei) and a caudal group (centre médian and parafascicular nuclei). The densest projections of the intralaminar nuclei seem to involve the striatum, but there are also widespread projections to the cerebral cortex. These cortical afferents show topographical specificity, such that practically every cortical area receives input from at least one of the intralaminar nuclei. The midline nuclei have fewer and more restricted cortical termination fields than the intralaminar nuclei. These include the frontal cortex, medial temporal cortex and amygdala [9]. Although projection and innervation patterns need to be determined in more detail to allow speculation on the role of each of the separate intralaminar and midline nuclei, the clinical data indicate that these thalamic structures are capable of influencing prefrontal functioning.

Although we have suggested above that it is unlikely that an amnesic syndrome occurs following lesions of the MD, it is still of interest to summarize the major connections of the MD in view of the hypothesis that amnesic disorders resulting from thalamic damage are caused by a disconnection between temporal and frontal cortices. The prefrontal cortex is defined in all mammals as the area having the relatively densest reciprocal connections with the MD compared to other thalamic nuclei [78]. The connections between the prefrontal cortex and the MD are topographically organized [30]. The medial (magnocellular, fibrosa) part of the dorsomedial nucleus connects with the orbital and rostral parts of the prefrontal cortex, and the lateral (parvocellular, fascicular) part is connected to dorsal and dorsolateral prefrontal areas. Lesions in the MD are associated with a decrease in cerebral blood flow in cortical areas, most notably the dorsolateral prefrontal cortex [5,6,39,65].

However, a minor non-fornical, projection from the entorhinal cortex to MD has been observed in monkeys [2]. Nevertheless, the projection appears too weak for the MD to mediate the transfer of neural information from temporal to frontal cortices. Taken together, the anatomical evidence indicates that lesions to the MD, like the MTT or anterior nuclei of the thalamus, do not simply produce a disconnection between the temporal and frontal cortical fields. Amnesia due to thalamic lesions as a disconnection syndrome thus seems untenable and the role of the thalamus in memory should be reinterpreted.

However, the MD might be involved in the dysexecutive problems observed in patients with thalamic lesions. Yet, in the literature reviewed, lesions of the MD are not always related to executive dysfunctioning on a one-to-one basis. Impairments of executive functioning can be found in the absence of MD lesions and, conversely, MD lesions can occur without there being such impairments.

7. Conclusions

It is clear from the reviewed literature that the thalamus participates in many brain circuits involved in the processing of old information and new stimuli, which allows it to influence behavior, complex cognitive skills, and memory processes. Although we now have some insight into which structures of the thalamus, both nuclei and fiber tracts, are involved in these faculties, a full picture has not yet emerged. This is in part due to the variable quality of neuropsychological testing of patients with thalamic lesions, and to the problems of localizing thalamic damage.

Nevertheless, the following conclusions seem warranted. Memory disturbances after thalamic lesions

can take different forms. The data summarized in this article support the opinion held by Rousseaux [63], who noted attentional disorders and cognitive slowing following paramedian thalamic infarctions in contrast to 'pure' amnesia after anteriorly located infarctions. It is shown here that the structure crucial for this 'pure' amnesia, which we define as an amnesic syndrome, observed in patients with thalamic infarctions seems to be the MTT. Lesions of the MTT are a sufficient and necessary condition for the development of amnesic syndromes after the thalamus has been damaged. Thus, other memory deficits and disturbances of executive function, which may underlie these miscellaneous memory deficits, are caused by damage to structures other than the MTT. Candidate structures are the midline nuclei, the intralaminar nuclei and the MD, which we propose to act in concert to influence frontal functioning, but more studies are needed to verify this. In particular, the dissociation between the role of fiber systems passing through the thalamus and the thalamic nuclei is an area that deserves to be studied. A combination of animal- and clinical experimental data is needed to unravel the contribution of thalamic structures to the various forms of cognition that seem to be affected in patients with lesions of the thalamus.

Acknowledgements

This study was supported by a grant from the Netherlands Organization for Scientific Research (NWO), grant number 970-10-012.

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