



Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions

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Abstract

The thalamus plays a crucial role in memory, executive functioning and attention. It remains, however, unclear whether thalamic structures have specific roles in each of these functions. We tested 22 cases of thalamic infarction, proven with MR imaging, using experimental and established neuropsychological tests. We performed a lesion-overlap study in standardised stereotactic space of patients sharing a certain deficit, corrected for the lesion distribution of patients without such deficits and determined the regions of interest using an atlas of the human thalamus. We checked for additional, non-thalamic, damage and for deficient comprehension and perception that would preclude interpretation of the results. Non-thalamic damage such as white matter lesions, hippocampal atrophy, sulcal widening and infarctions occur significantly more often in patients aged over 60. The patients with additional damage overlapped to a major degree with those who showed loss of orientation, or lack of comprehension of the test requirements. In the 10 patients judged 'clean', we observed a deficit of episodic long-term memory with relative sparing of intellectual capacities and short-term memory when the mammillo-thalamic tract was damaged. Lesions including the medial dorsal nucleus, midline nuclei and/or intralaminar nuclei accompany executive dysfunctioning. Reduced simple processing speed and attention are associated with age, but not with a particular structure in the thalamus. Complex attention deficits follow damage to the intralaminar nuclei.

We conclude that the analysis of structure–function relationships must take into account extra-structure damage which may explain cognitive deficits. Separate thalamic structures are involved in memory, executive functioning and attention.

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1. Introduction

Studies of patients with thalamic damage show that the thalamus plays a role in several aspects of cognition. Of these, memory has always received the greatest attention due to striking cases of diencephalic amnesia, i.e. severe memory loss due to thalamic damage (Bogousslavsky, Regli, & Uske, 1988; Castaigne et al., 1981; Ghidoni, Patacchini, Galimberti, & Aguzzoli, 1989; Graff-Radford,

Damasio, Eslinger, Yamada, & Damasio, 1985; Neau & Bogousslavsky, 1996; Partlow, Del Carpio-O'Donovan, Melanson, & Peters, 1992; Rousseaux, 1994; Rousseaux et al., 1986; Stuss, Guberman, Nelson, & Laroche, 1988; Wallesch, Kornhuber, Kunz, & Brunner, 1983). This memory deficit depends on damage to the medial and anterior portions of the thalamus (Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Von Cramon, Hebel, & Schuri, 1985); more precisely, the anterograde amnesia, reminiscent of that seen following hippocampal damage, in cases with thalamic damage appears to follow lesions of the anterior thalamic nuclei or their afferent white matter bundle, the mammillo-thalamic tract (Gentillini, De Renzi, & Crisi, 1987; Van Der Werf, Witter, Uylings, & Jolles, 2000). Severe deficits in executive functioning and attention

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have also been noted in thalamic patients, but it remains unclear which structures are involved (Bogousslavsky et al., 1988; Fukatsu, Fujii, Yamadori, Nagasawa, & Sakurai, 1997; McGilchrist, Goldstein, Jadresic, & Fenwick, 1993; Miller, Cummings, McIntyre, Ebers, & Grode, 1986; Pepin & Auray-Pepin, 1993; Sandson, Daffner, Carvalho, & Mesulam, 1991; Van Der Werf et al., 1999).

We here present a study of 22 cases of thalamic infarction, tested with a fixed battery of tests to allow comparison between cases. The selection of tests aimed to measure different aspects of memory, attention and executive functioning. We obtained MRI scans from each patient and plotted the lesion sites both in standard stereotactic space and in an atlas of the thalamus. This allowed us on the one hand to perform an analysis of the overlap of infarctions in groups of patients with similar symptoms and on the other hand, we were able to describe the location of the regions of interest in terms of nuclei and white matter tracts affected. We controlled for infarctions in subcortical areas and white matter tracts surrounding the thalamus, hippocampal atrophy and sulcal widening, factors that would confound structure–function relationships within the thalamus (De Groot et al., 2000; Houx, Vreeling, & Jolles, 1991; Scheltens et al., 1992; Visser et al., 1999). Similarly, we controlled for deficits of basal cognitive abilities, such as vigilance and understanding. In doing so, we aimed to provide more information on which thalamic structures are involved in executive functioning and attention, and to confirm previously established structure–function relationships for memory (Van Der Werf et al., 2000).

2. Methods

Neurologists from four academic centres in The Netherlands participated to recruit patients with thalamic stroke from neurology clinics, rehabilitation clinics, academic hospitals and community hospitals. In the course of 4 years, 22 patients were included.

In all patients, the diagnosis of thalamic infarction was made with the aid of structural brain images; in most cases, high-resolution MR images were obtained with a 1.5 T machine using both T1- and T2-weighted images. In case 11, no MR imaging could be performed due to the presence of a pacemaker; the MRI of case 19 was discarded because of motion artefacts. In these cases, CT scans were used to delineate the site of the lesion.

Table 1 shows demographic, personal and lesion characteristics of the group of patients studied.

2.1. Lesion localisation

Lesion sites were interpreted by two experienced neuroanatomists who were blind to the deficits of the patients. We plotted lesions in T1-weighted MR images of a single subject's brain, transformed into Talairach space (Talairach & Tournoux, 1988), using software developed in the Montreal Neurological Institute. The brain used forms the template for the software package for Statistical Parametric Mapping (SPM'99). The template consists of 1-mm isotropic voxels. After drawing, the lesions were smoothed with a 2-mm FWHM kernel. This serves to take away

Table 1
Patient characteristics

Case	Sex	Age at testing	Infarction-test delay	Side of infarction	Formal education (year)	Handedness
1	M	22	3 months	L	10	R
2	M	31	3 months	R	15	R
3	M	38	5 years	L	9	R
4	F	44	3 years and 5 months	R	11	L
5	F	46	3 months	L	10	R
6	M	47	3 months	L	15	R
7	M	50	7 months	L	>10	R
8	F	54	4 years and 5 months	Bilateral venous thrombosis	9	R
9	M	54	9 months	Bilateral	10	R
10	M	54	24 years	Bilateral	10	R
11	M	56	3–4 years	L	12	R
12	M	57	1 year and 6 months	L	>10	R
13	M	58	1 year and 3 months	Bilateral, L > R	>10	R
14	M	60	16–18 years	R	10	R
15	F	66	5–7 months	R	7	Ambidextrous
16	F	66	3 months	Bilateral	8	Ambidextrous
17	F	68	2 months	R	7.5	R
18	M	71	?	Bilateral	Unknown	R
19	M	72	3 months	L	Unknown	R
20	F	75	7 months	R	Unknown	Ambidextrous
21	F	82	2 months	L	9	R
22	F	83	3 months	L	Unknown	Ambidextrous

Abbreviations: M, male; F, female; L, left; R, right.

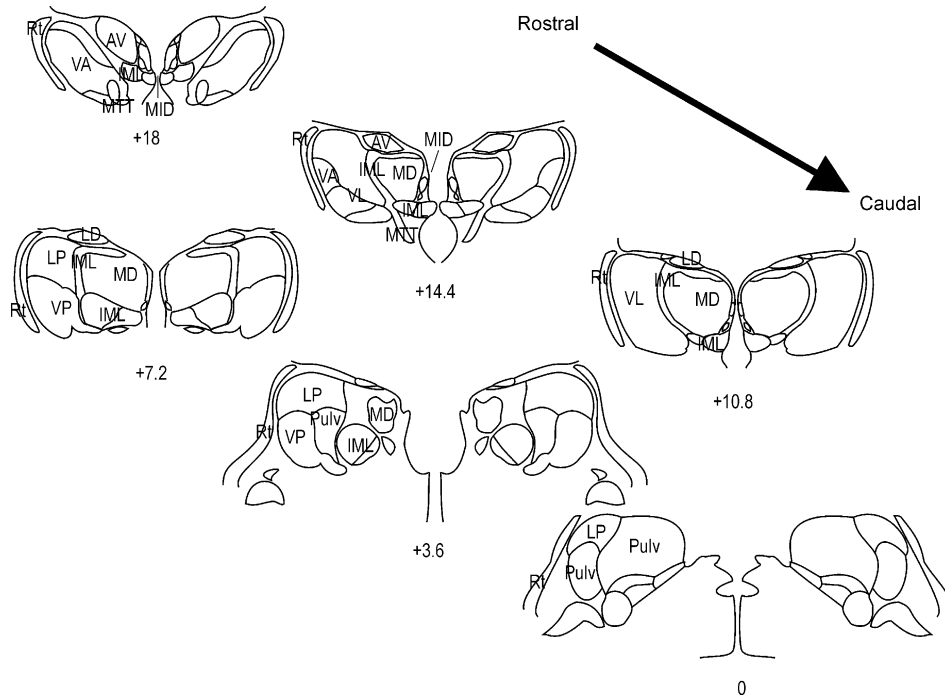


Fig. 1. Atlas of the human thalamus, used to map the site and extent of the infarctions (adapted from Morel et al., 1997). The slices shown are sections perpendicular to the line connecting the anterior commissure and the posterior commissure. The distance in millimetres to the posterior commissure is indicated. Abbreviations: Ant, anterior nuclei; IML, internal medullary lamina; LP, lateral posterior nucleus; MD, medial dorsal nucleus; Mid, Midline nuclei; MTT, mammillo-thalamic tract; Pulv, Pulvinar; Rt, reticular thalamic nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus.

sharp edges of the drawing, minimises drawing inaccuracies and the end result can be thought of as representing a probability map of the lesion localisation. We classified the infarctions according to the nuclei and white matter tracts affected, using sections of the thalamus adapted from the human thalamic atlas of Morel, Magnin, and Jeanmonod (1997) (Fig. 1). Six coronal sections perpendicular to the line connecting the anterior and posterior commissure were chosen, spaced 3.4 mm apart. The nomenclature follows that of Morel et al. (1997) and Hirai and Jones (1989).

The scans were scored by a single trained neurologist, who was blind to the outcome of neuropsychological testing, using qualitative and quantitative rating scales for the presence of cortical or subcortical abnormalities, i.e. other infarcts, white matter lesions, hippocampal atrophy and sulcal widening (Scheltens et al., 1992, 1993). The reliability of such ratings, e.g. for hippocampal atrophy, is fair to good, especially when scores are collapsed into a dichotomous score (present or absent atrophy; see Section 2.4) (Scheltens, Launer, Barkhof, Weinstein, & Van Gool, 1995).

2.2. Neuropsychological assessment: tests used

To test the different memory-related functions, we used a specially selected battery of tests following Jolles (1986) and Jolles, Houx, Van Boxtel, and Ponds (1995), used for large-scale experimental and clinical studies of neurocogni-

tion in middle-aged and elderly subjects (e.g. Bosma, Van Boxtel, Ponds, Houx, & Jolles, 2000; De Groot et al., 2000; Hofman, 2000; Moller et al., 1998; Van Boxtel et al., 1998, 2000). These addressed recall from short- and long-term memory, recognition, executive abilities and speeded information processing. Table 2 gives an overview of the tests used.

The Verbal Learning Task (VLT) was used to assess direct, delayed and recognition memory in the verbal modality (Brand & Jolles, 1985). Recognition was tested with a list containing the 15 words encountered during the learning trials and 15 distractor words. Non-verbal memory was assessed with the Rey Complex Figure Test (Meyers & Meyers, 1995), Warrington's Recognition Memory Test for Faces (Warrington, 1984), and the Visual Association Test (Lindeboom, 1989; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; Rombouts et al., 1997). Memory interference was measured using a test for recall of word triplets (Jolles, modified after Luria, 1966).

We measured attentional processes involving speeded information processing with the Brown–Peterson paradigm, digit span backward and forward (Lindeboom & Matto, 1994), the Concentration-Endurance Test (d2 test) (Brickenkamp, 1981), Concept Shifting Test (Jolles et al., 1995; a modification of the Trail Making Test, Reitan, 1958), the Stroop test (Stroop, 1935) and the Paper and Pencil Memory Scanning Test (Brand & Jolles, 1987; Houx et al., 1991; Jolles et al., 1995).

Table 2
Tests administered

Cognitive variable	Test used	Operationalisation
Memory	VLT	
	Direct recall	Number of words remembered after five trials of 15 words
	Delayed recall	Number of words remembered after a 1-h interval
	Delayed recognition	Number of words recognised (15 target words/15 distractor words)
	Rey	
	Direct recall	Number of correctly drawn elements (of 36)
	Delayed recall	Number of correctly drawn elements (of 36)
	Delayed recognition	Number of correctly recognised elements (of 24)
	VAT	Number of correctly recalled visual associations (two series of 6)
	RMTf	Number recognised (of 50)
Word triplets	Number recalled	
Attention and speeded processing	Digit span	Forward; backward
	Brown–Peterson paradigm	0-s delay; 3-s delay; 9-s delay; 18-s delay
	PPMST	% symbol subtest; 1–4 letter subtest
	Concept Shifting Task	Zero, letter, digit and alternating conditions
	Stroop	Reading and color naming conditions
d2	Total number of items crossed out; number of errors; total number of items crossed out minus errors; consistency	
Fronto-executive functions	WCST	Number of categories achieved; number of perseverative errors
	ToL	Number of trials correct; number of trial correct in minimal sequence
	Verbal category fluency	Animals; professions
	Stroop	Interference condition
Intelligence and general abilities	GIT	Three-subtest version
	DART	Number of correctly pronounced words
	CST	20 items of personal and general knowledge

Abbreviations: CST, Concept Shifting Test; DART, Dutch Adult Reading Test; GIT, Groningen Intelligence Test; MCRT, Multiple Choice Reaction Time Task; PMT, Prospective Memory Test; PPMST, Paper and Pencil Memory Scanning Test; RMTf, Recognition Memory Test for Faces; TMT, Trail Making Test; VAT, Visual Association Test; VLT, Verbal Learning Task; WCST, Wisconsin Card Sorting Test.

Executive abilities were assessed with the Tower of London test (Maastricht version of the test devised by [Shallice, 1982](#)), a computerised version of the Wisconsin Card Sorting Test ([Berg, 1948](#)), verbal category fluency ([Lezak, 1995](#)) and the colour–word interference condition of the Stroop test ([Stroop, 1935](#)).

The short form of the Groningen Intelligence Test (GIT) ([Luteijn, 1966](#); [Luteijn & Van Der Ploeg, 1983](#)) was used to obtain a measure of general intellectual functioning. The Cognitive Screening Test, a Dutch modification of the Short Portable Mental Status Questionnaire ([Pfeiffer, 1975](#)), was used to obtain a measure of orientation and general knowledge.

2.3. Neuropsychological assessment: scoring

Two neuropsychologists scored the neuropsychological and observational data (JJ and JL). At the time of this assessment, both were unaware of the nature or location of the brain lesion. Before interpreting the results, the patients were judged for their ability to use language, perceive and comprehend the test instructions. The rationale for this was that for patients who were unable to understand the procedure accurately or were unable to discern or hear the stimuli, a definite conclusion about memory or other functions could not be based on the raw test data. Verbal memory

was indexed for immediate and delayed recall and delayed recognition. A separate index for visual memory was used. The patients were judged to have an amnesic syndrome if they fulfilled the criteria of anterograde amnesia with spared intellectual and attentional abilities ([Van Der Werf et al., 2000](#)). We analysed memory performance further in terms of ‘primacy’ and ‘recency’, measured as the recall of the first and the last three words in the list, respectively, summed over five trials. The number of words recalled from positions 4 to 12 in the list, summed over five trials was called ‘rest’. Delayed recall and recognition were tested after an interval of 1 h. Recall scores were expressed as total number of target words recalled, recognition scores were expressed as the number of target words minus the number of false negatives and false positives. The non-verbal recall score was the sum of the scores of the Rey direct and delayed recall measure.

Impulsivity/inhibition was judged from behaviour during the semi-structured interview preceding testing and from behaviour during test performance, e.g. from inappropriate or rash responses. Evidence for executive dysfunctions was derived quantitatively from the Wisconsin Card Sorting Test, the Tower of London test, the colour–word interference condition of the Stroop test, verbal category fluency and qualitatively from the learning strategy used in the verbal learning test. Attention and speed of information processing were judged on the basis of speed and number

of errors on tests of simple and complex processing (Houx & Jolles, 1993; Jolles, 1986; Jolles et al., 1995).

The two scoring neuropsychologists judged the performance of the patients per test variable and made use of behavioural observations made during the testing, described in the test protocol by the testing neuropsychologist (YDvdW). They used a formal scoring system in which the performance per test or observational variable was scored as either normal (scored as 0), mildly impaired (1), impaired (2) or strongly deficient (3).

2.4. Structure–function analysis

From the drawings of the lesions in stereotactic space, we established an overlap of regions affected in patients with similar symptoms, using software developed in the Montreal Neurological Institute. The degree of overlap between lesion sites does not necessarily reflect only those areas implicated in the functional deficits, but may contain areas that are damaged because of sharing arterial supply with critical regions. Such ‘innocent bystander’ regions may be excluded when the overlap plot of patients without a certain deficit is subtracted from the overlap plot of patients who share that deficit. This method has been used before in thalamic patients in determining the areas associated with neglect (Karnath, Himmelbach, & Rorden, 2002). We formed subgroups of patients on the basis of the neuropsychological scoring. We used Chi-squared analyses to verify findings from the overlap/subtraction analysis and to investigate further possible group differences (Pearson’s χ^2 , SPSS for Microsoft Windows software, version 9.0). In the analyses, we condensed the scores for test performance into a dichotomy of no/mild impairments (score 0 or 1) and evident impairments (score 2 or 3).

3. Results

3.1. Thalamic lesions

Of the 22 patients studied, 15 had unilateral lesions and 7 had lesions falling in the thalamus of both hemispheres. The latter type of infarction was more or less symmetrical in three cases, but four cases had lesions that were larger on one side or in different locations on each side. Table 3 lists the nuclei affected and Fig. 2 illustrates the location, size and shape of the lesions.

Recurring patterns occurred in the distribution of lesions: eight patients showed an elongated lesion in the rostral thalamus, seen on coronal view (Fig. 3A). This lesion was bilateral and symmetrical in patients 9 and 18, bilateral and asymmetrical in patients 10 and 20, and left-sided unilateral in patients 5, 12, 14 and 19. This type of infarction causes a lesion typically reaching the third ventricle ventral in the thalamus and coursing obliquely in the dorsolateral direction, thereby intersecting the MTT and often causing

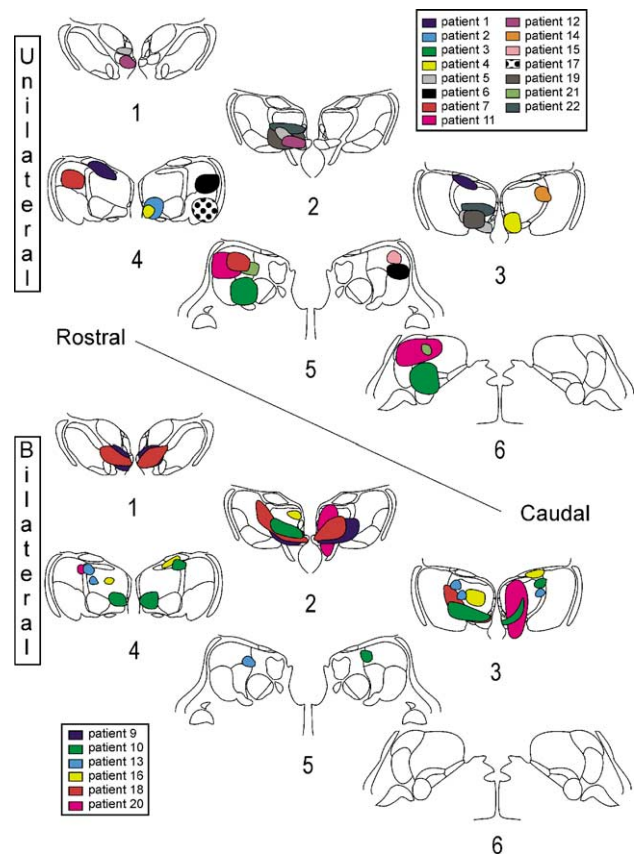


Fig. 2. Lesion sites of the patients, drawn in the atlas of the human thalamus. Patient 8 is not shown because her lesion was not the result of an infarction, but due to a venous thrombosis of the sinus rectus. Unilateral lesions are shown in the top diagram, bilateral lesions in the lower diagram. Left and right in the drawing correspond to the actual site of the infarction.

damage to the adjacent ventral IML and MD. Lesions of this type arise from embolisms or ruptures of the polar or tuberothalamic artery (Bogousslavsky, Regli, et al., 1988). In four patients, a small lacunar infarct appears in the lateral internal medullary lamina or the lateral part of the MD, approximately halfway the rostro-caudal extent of the thalamus (Fig. 3B). Cases 10, 13, 14 and 20 show such an infarction, either alone or in combination with other lesions in the thalamus. This type of lesion interferes with the integrity of the nuclei contained in the lateral IML, mainly the central lateral nucleus. This type of lesion typically occurs after an occlusion of the small arterioles of the paramedian artery.

Cases 2 and 4 had lesions encompassing the ventral part of the thalamus at a middle level bordering the third ventricle (Fig. 3C). This type of lesion lies in the region of the parafascicular and centre médian nuclei that together form the caudal IML. Again, this type of lesion follows vascular problems in the territory of the paramedian artery.

Cases 3, 6, 7, 11, 17 and 21 show lesions located laterally and caudally in the thalamus, encompassing the lateral posterior nucleus, pulvinar or reticular nucleus (Fig. 3D). Such

Table 3
Lesion localisation of the patients included in this study

Case	Age	Ant	MTT	MD	Mid	IML	VA	VL	LP	VP	Pulv	Rt	White matter lesions	Hippocampal atrophy (grade)	Sulcal widening	Other lesions
1 ^a	22			L		L	L						No	No	No	Temporal cyst L
2 ^a	31				R	R							No	No	No	None
3 ^a	38									L	L		No	No	No	None
4 ^a	44				R	R							No	No	No	None
5 ^a	46		L	L	L		L						No	No	No	None
6	47					L			L		L	L	VR spaces in basal Ganglia and frontal white matter	I	Diffuse, lightly	Pontine infarct
7 ^a	50									L	L		VR spaces in basal Ganglia	No	No	None
8 ^a	54	Sinus rectus thrombosis											VR spaces	No	No	Cerebellar infarct
9 ^a	54	L/R	L/R	L/R	L/R	L/R	L/R						No	No	No	None
10 ^a	54	L	L	L/R		L/R	L		R				No	No	Fitting with age	None
11	56										L		No	No	No	Old temporal cortex infarct L
12 ^a	57		L	L	L		L						No	No	No	None
13	58			L		L/R							Periventricular + subcortical	No	Fitting with age	Basal Ganglia lacunar infarcts
14	60					R							VR spaces	II–III	Temporal	None
15	66									R	R		Parieto-occipital	I–II	Occipital	Clastrum L/R, capsula interna R infarct
16	66	R		L									No	I	Frontal	Occipital cortex infarct R
17 ^a	68									R		R	Periventricular ‘caps’	No	No	None
18	71	L > R	L/R	L	L/R	L > R	L > R						Diffuse periventricular	II	Fitting with age	Basal ganglia lacunar infarcts
19	72		L	L	L	L							Periventricular	Unclear	Diffuse	Temporo-occipital infarct R
20	75	R	R	R		L							No	II–III	Diffuse	Hypothalamic infarct R
21	82										L		No	III	Fitting with age	Caudate R, pallidum R, pontine infarcts
22	83		L	L	L	L							Diffuse	II	Temporal	Clastrum infarct R

Abbreviations: Ant, anterior nuclei; IML, internal medullary lamina; LP, lateral posterior nucleus; MD, medial dorsal nucleus; Mid, Midline nuclei; MTT, mammillo-thalamic tract; Pulv, Pulvinar; Rt, reticular thalamic nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus; L, left-sided lesions; R, right-sided lesions; VR, Virchow–Robin.

^a Patients judged ‘clean’, i.e. without significant pathology apart from the thalamic lesion.

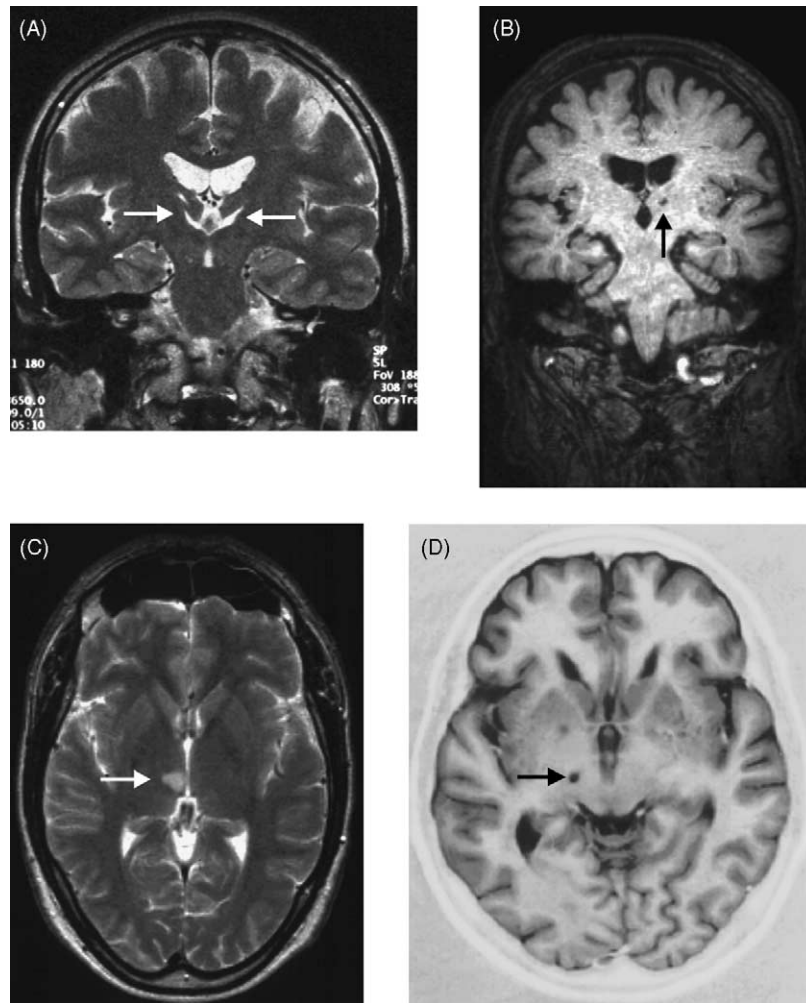


Fig. 3. (A) T2-weighted coronal MR scan of patient 10 showing a bilateral infarction of the tuberothalamic artery. The arrowheads point at the liquor-filled lacunes. Left and right are inverted, following radiological convention. (B) T1-weighted coronal MR scan of patient 13 showing a left-sided infarction in the lateral part of the medial dorsal nucleus and/or the internal medullary lamina, arising from an embolism in the paramedian artery (arrow). (C) T2-weighted axial MR image of patient 2 showing a recent right-sided medial infarction of the paramedian artery (arrow). (D) Turbo Inversion Recovery axial MR scan of patient 17, showing a right-sided ventral posterior thalamic infarction (arrow) of the posterior choroidal artery.

lesions would follow occlusions in the posterior choroidal or principal inferolateral arteries.

3.2. Other brain damage

Eleven cases showed evidence of pathology unrelated to the thalamic lesion. These included gross abnormalities like other infarctions or severe hippocampal atrophy, or subtle changes such as diffuse cortical atrophy, seen as sulcal widening (Fig. 4A–D). Some of the findings may be asymptomatic and congruent with older age, such as the presence of Virchow–Robin Spaces (e.g. cases 7 and 14) or periventricular white matter caps (case 17). Hippocampal atrophy of grade II, I or 0 is regarded as asymptomatic in the age group of 75 and older. In case 1, a cyst located in the temporal cortex was found that was judged asymptomatic. Case 8 was excluded from further analysis because

she had a venous thrombosis in the thalamus instead of an infarction. Table 3 shows the occurrence of white matter lesions, hippocampal atrophy, global cortical atrophy and evidence of other lesions as judged from visual inspection of the MR images. The table shows that most of the cases judged ‘clean’, i.e. without significant extra-thalamic damage, were 60 years of age or younger. Chi-squared analysis on the presence of significant pathology in the patients confirmed this skewed distribution ($\chi^2 = 10.145$, $P = 0.01$).

3.3. Neuropsychological data

Ten patients showed impaired understanding of the test instructions, had an impairment of reasoning or formal thought processes, had perceptual problems or visuo-constructive deficiencies that would hamper the interpretation of the test

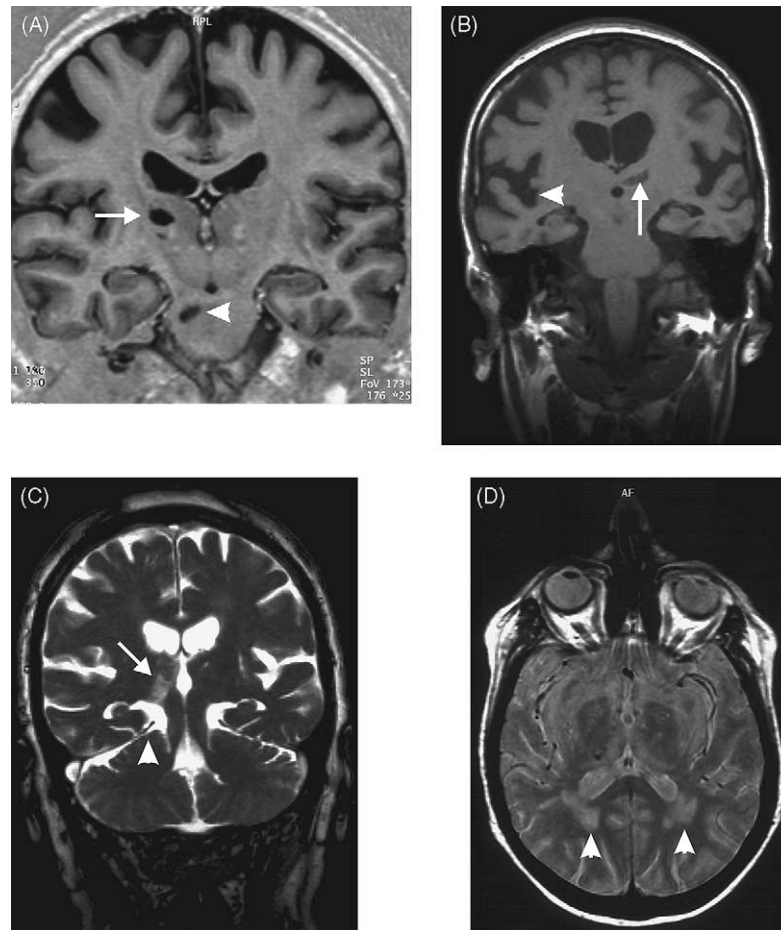


Fig. 4. (A) T1-weighted coronal MR image of patient 6 showing a right posterior thalamic infarction (arrow). Note the pontine infarction (arrowhead). (B) T1-weighted coronal MR image of patient 22. The left sided tuberothalamic artery infarction is indicated with an arrow. Note the pronounced cortical atrophy (arrowhead). (C) T2-weighted MR image of patient 20, showing the medial thalamic infarction extending into the hypothalamus (arrow). The arrowhead indicates the grade III hippocampal atrophy. (D) T2-weighted MR scan of patient 15, showing the bilateral parieto-occipital subcortical white matter hyperintensities (arrowheads).

of memory and executive functioning. The conclusion of impaired understanding was made by the two scoring neuropsychologists, at the time of scoring blind to the imaging data of the patients.

Patients were excluded from interpretation of the memory test scores on the basis of any of the following: scores of 2 or 3 on language, perception or visuo-construction; an orientation score below 17; an IQ score of more than one standard deviation below the mean (i.e. 85 or lower). The latter criterium was not applied for case 3 since he is a non-native Dutch speaker which lowered his IQ score. This left a group of 12 patients judged sufficiently cognitively adequate (i.e. sufficiently able to use language, perceive the test stimuli, understand the instructions, etc.). This is shown in Table 4.

From this group of 12 selected patients, 10 also fulfilled the criterium of having no significant additional brain damage. The neuropsychological test results of all patients included in this study are given in Table 5.

3.3.1. Memory

In the whole group of patients, memory performance varied from intact to severely impaired. The verbal recall, verbal recognition and visual recall impairments were distributed randomly over both age groups (younger than 60 or 60 and older) and over the two groups of patients, those judged 'clean and cognitively adequate' and those not ($\chi^2 = 1.316$, $P = 0.251$ and $\chi^2 = 1.473$, $P = 0.225$, respectively, for the verbal recall scores).

In the 'clean and cognitively adequate' group, consisting of 10 patients, three cases matched the criteria for an amnesic syndrome. Of these, cases 9 and 10 showed a memory deficit in both the verbal and non-verbal modality, whereas in case 12 the deficit was observed only in verbal memory tasks. The other cases showed either mild or no memory problems. In the remaining group of patients, those with extra-thalamic lesions and/or a lack of cognitive adequacy, cases 15, 18 and 20 had memory problems compatible with an amnesic syndrome. Cases 19 and 22 had a dense amnesia

Table 4

Prerequisites for interpretation of performance on the tests of memory, speeded processing, attention and executive deficits

Case	Language skills (0–3)	Orientation (1–20)	Understanding (0–3)	IQ	Perception (0–3)	Visuo-construction (0–3)
1 ^a	0	19.5	0	103	0	0
2 ^a	0	18	0	114	0	0
3 ^{a,b}	0	18	1	79	0	0
4 ^a	0	No data	0	107	0	0
5 ^a	0	17	1	103	0	0
6 ^a	0	19.5	0	114	0	0
7 ^a	0	18.5	0	132	0	0
8	0	19	2	110	0	2
9 ^a	0	No data	0	93	0	0
10 ^a	0	19	1	119	0	0
11	0	18	2	86	0	0
12 ^a	0	18	0	114	0	0
13	0	20	2	No data	0	0
14	0	19	0	58	0	2
15	0	19.5	2	56	0	2
16	0	20	2	No data	2	2
17 ^a	0	20	0	114	0	0
18	0	7	2	No data	0	3
19	0	15	2	68	0	No data
20	0	6	2	No data	0	No data
21 ^a	0	20	1	100	0	0
22 ^b	0	16	2	61	0	3

Use of language, orientation, understanding, perception and visuo-construction are scored on the basis of consensus between two independent neuropsychologists on a scale of 0 (normal) to 3 (severely impaired). Orientation is measured with the CST, a Dutch modification of the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). IQ is measured with the short version of the Groningen Intelligence Test (GIT; Luteijn, 1966).

^a Patient judged 'cognitively adequate', i.e. sufficiently oriented and able to understand the tests, enabling the experimenters to validly interpret the test results.

^b Non-native speaker.

Table 5

Neuropsychological test performance after an infarction in the thalamus

Case	Recall verbal	Recognition verbal	Visual memory	Amnesic syndrome	Fronto-executive functions		Speeded information processing	
					Planning	Impulsivity/inhibition	Simple	Complex
1 ^a	0	0	2	No	2	2	2	0
2 ^a	1	2	1	No	2	2	0	0
3 ^a	0	0	2	No	2	2	0	0
4 ^a	0	0	1	No	2	2	2	2
5 ^a	2	2	2	No	2	2	2	2
6	0	0	0	No	1	0	0	1
7 ^a	2	0	0	No	0	2	0	0
8	0	0	1	No	2	1	0	2
9 ^a	3	3	3	Yes	3	2	0	2
10 ^a	3	3	3	Yes	2	0	0	2
11	2	0	2	No	1	0	2	0
12 ^a	3	3	0	Yes, verbal	1	0	2	1
13	2	1	2	No	1	0	2	2
14	3	1	2	No	3	0	3	3
15	3	3	3	Yes	3	0	3	3
16	2	0	3	No	2	0	1	1
17 ^a	0	0	0	No	0	0	2	0
18	3	3	3	Yes	3	3	3	3
19	3	No data	3	Insufficient data	3	3	3	3
20	3	3	3	Yes	3	2	3	No data
21	0	0	0	No	2	0	2	2
22	3	0	3	Insufficient data	2	2	3	2

Test results are scored qualitatively from 0 (intact) to 3 severely impaired.

^a Patient judged both 'clean' and 'cognitively adequate'.

Table 6
Profile of memory performance

Case	Primacy (0–15)	Recency (0–15)	Rest (0–45)	Delayed recall (0–15)	Recognition (0–15)	Non-verbal recall (0–72)	Memory interference
1 ^a	12	7	25	7	14	17.5	None
2 ^a	15	0	27	6	10	26	Proactive
3 ^a	12	11	25	9	15	29	Global
4 ^a	12	10	23	11	15	31	No data
5 ^a	12	5	11	6	12	35	Proactive
6	11	9	22	9	14	42.5	None
7 ^a	13	7	16	8	13	47	Proactive
8	14	4	24	8	12	30.5	Global
9 ^a	1	8	12	0	8	4.5	No data
10 ^a	7	11	10	0	8	18	None
11	8	10	11	6	14	14	Global
12 ^a	13	9	6	0	0	55	Retroactive
13	7	4	8	0	8	21	Proactive
14	5	7	11	4	9	20	No data
15	11	6	9	2	7	8.5	Global
16	10	8	20	4	13	5.5	Global
17 ^a	14	11	22	11	14	38	No data
18	2	2	2	0	No data	No data	No data
19	5	7	8	No data	No data	17.5	None
20	0	2	0	0	3	No data	Global
21	13	12	24	9	12	38	Global
22	1	8	10	2	12	7	Global

^a Patients judged both 'clean' and 'cognitively adequate'.

presumably caused by an amnesic syndrome, but clouding of consciousness precluded such a diagnosis.

Table 6 presents a closer look at the memory performance of the patients. It shows that two of the patients judged 'clean and cognitively adequate' with an amnesic syndrome (cases 9 and 10) had low primacy scores (1 and 7, respectively) and variable recency scores of verbal learning. Such a pattern indicates a failure to encode new verbal stimuli. In contrast, the patients in this group who did not have an amnesic syndrome all had good primacy scores (12 or higher). Interestingly enough, case 12 who had an amnesic syndrome in the verbal modality only, did show a high primacy score. In view of his markedly deficient delayed recall and recognition scores, his memory deficit seems more a problem of rapid forgetting than of deficient encoding. His deficit cannot be attributed to retrieval problems and, therefore, remains compatible with an amnesic syndrome. In addition, this case was the only one to show retroactive interference in the word triplets test.

In the group of patients that were judged to have additional lesions and/or cognitive dysfunctions precluding test administration, four of five patients with a probable amnesic syndrome (cases 18, 19, 20 and 22) had the same profile of low primacy scores. Case 15, on the other hand, showed a relatively good primacy score.

3.3.2. Frontal-like dysfunctions

Executive dysfunctions frequently characterised our thalamic patients and were found regardless of whether the patients were considered 'clean and cognitively adequate' and regardless of age ($\chi^2 = 0.069$, $P = 0.793$ and $\chi^2 = 2.006$,

$P = 0.157$, respectively). Impulsivity or disinhibition on the other hand, appeared to cluster in the group of patients considered 'clean and cognitively adequate' but showed no relationship with age. This was confirmed by statistical analysis ($\chi^2 = 2.933$, $P = 0.087$ and $\chi^2 = 0.188$, $P = 0.665$, respectively). Executive deficits could be associated with severe memory disorders (e.g. case 9) or be encountered alone (e.g. case 8).

3.3.3. Speeded information processing

These functions were tested both with simple and complex information processing tests and included aspects of attention. Speeded information processing is frequently impaired in patients with thalamic lesions. Here too, the deficits were found regardless of whether or not the cases were judged 'clean and cognitively adequate' (for the simple tasks: $\chi^2 = 1.473$, $P = 0.225$; for the complex tasks: $\chi^2 = 2.291$, $P = 0.130$). Impairments on tasks of simple speed, however, tended to cluster with the group of patients aged 60 or older ($\chi^2 = 4.197$, $P = 0.040$). Complex attentional deficits, on the other hand, did not show a relationship with age ($\chi^2 = 1.683$, $P = 0.195$).

3.4. Structure–function relationships

3.4.1. Overlap/subtraction analysis

As an initial screening, we performed the overlap and subtraction image analysis on the group of subjects with any kind of memory problem (scores of >2 on any of the memory variables: verbal recall, verbal recognition, visual memory, and/or amnesic syndrome, see Table 6) minus the group

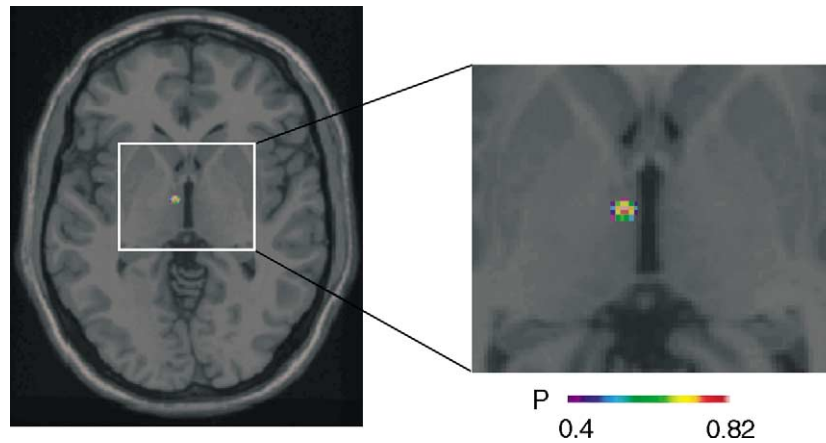


Fig. 5. Amnesic syndrome corresponds to lesions of the MTT. The figure shows the degree of overlap of lesions of patients with an amnesic syndrome, corrected for the lesion distribution of patients who do not show such deficits, in the group of 10 'clean' patients. The data are displayed on a template in standardised space ($z = -2$) (Scheltens et al., 1995). The image is thresholded between $P = 0.4$ and 0.82 .

of people without memory problems (scores of <2 on all of the memory variables). This analysis shows that memory problems may occur after lesion of different widespread areas of the thalamus. The subtraction of the area damaged in subjects without memory problems from that of patients with, does not reveal a single area of high probability (not shown). To analyse further the involvement of thalamic structures in specific functions, we made separate overlap/subtraction plots for the amnesic syndrome, for simple and complex speeded processing, for impulsivity/disinhibition and deficits of executive functioning. For the overlap of areas associated with the amnesic syndrome minus the overlap of the lesions of patients without, two regions emerged in the left and right ventral anterior thalamus, coinciding with the location of the mammillo-thalamic tract, or MTT ($P = 0.52$ and 0.46 , respectively). When the analysis was restricted to the patients judged 'clean', a single circumscribed region emerged with high probability ($P = 0.82$; Fig. 5; Table 7). The peak lies in the left thalamus, due to the lesion distribution of the three patients that contribute to this overlap; in cases 9 and 10, the lesion damaged the thalamus on both sides, in case 12 the lesion was found in the left thalamus only. The probability does not reach 1, because one patient (case 5) did not show an amnesic syndrome in spite of left unilateral damage in the region of

the MTT. Statistical analysis confirmed that the clustering of an amnesic syndrome with lesions of the MTT in the group of 10 selected patients was significant ($\chi^2 = 6.429$, $P = 0.011$).

For deficits of executive functioning, there was no single region in the thalamus that shows a high degree of association with the deficits. Rather, two areas showed up with equal likelihood of involvement ($P = 0.40$ and 0.39) in the group of 'clean' patients only: these are a right medial ventral region corresponding to the ventral MD, midline nuclei and medial intralaminar nuclei, and a region lying ventrally and anteriorly in the left thalamus. At first glance, this area seems to correspond to that found for the amnesic syndrome, but it lies lateral, posterior and dorsal to it, and, therefore, would correspond to the anterior portion of the intralaminar nuclei that is located adjacent to the MTT (Fig. 6; Table 7). For complex speeded processing, a peak indicating a probability of involvement of 0.69 arose in the left ventral anterior portion of the thalamus, with the same coordinates as the presumed ventral intralaminar peak found for executive dysfunctioning. This was evident in the group of 'clean' patients only. For impulsivity/inhibition and simple speeded processing, no overlaps were found with probabilities greater than 0.35 in either the groups of 'clean' patients or all patients (not shown).

Table 7
Peak values from the overlap/subtraction analysis

Function	X	Y	Z	Probability	Corresponding structure
Amnesia—all patients	-6	-9	-1	0.5135	Left MTT
	8	-11	1.5	0.4644	Right MTT
Amnesia—clean patients	-6	-9	-2	0.8195	Left MTT
Complex speed—clean patients	-7	-10	0	0.6935	Left vIML
Executive dysfunctioning—clean patients	5	-19	-1	0.4025	Right vIML/MD
	-8	-10	1	0.3852	Left vIML

X, Y and Z coordinates of local maxima are given in stereotactic space. Only overlaps with $P > 0.35$ are shown.

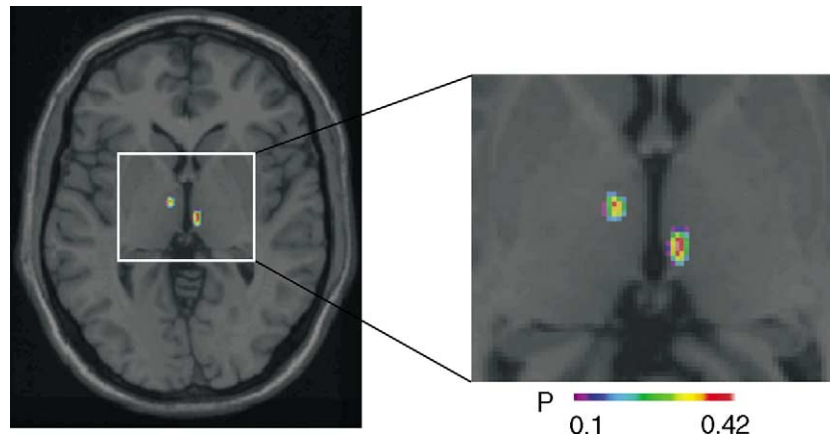


Fig. 6. Executive disorders correspond to damage to the ventral IML and ventral MD/midline. Shown in the figure is the degree of overlap of lesions in patients with executive dysfunction, corrected for the lesion distribution of patients without such deficits, within the group of 10 'clean' patients. The data are displayed on a template in standardised space ($z = +1$) (Scheltens et al., 1995). The degrees of overlap are thresholded between $P = 0.1$ and 0.42 . Note the more lateral and dorsal position of the anterior thalamic peak, compared to Fig. 5.

3.4.2. Case-wise description of the data

In the group of 10 patient judged 'clean and cognitively adequate', all three cases that showed memory deficits so severe as to qualify as an amnesic syndrome, had sustained damage to the MTT. In cases 9 and 10, the damage to the MTT was found on both sides; in case 12, the lesion was found on one side only. One case, however, which had unilateral damage to the MTT showed memory problems but not strong enough to fulfil the criteria of an amnesic syndrome (case 5). In the remaining 12 patients, a similar picture emerged although definite conclusions could not be drawn due to the structural pathological or cognitive factors complicating test interpretation. Thus, patients 18 and 20 had lesions encompassing the MTT and were diagnosed with an amnesic syndrome. Patients 19 and 22 had also sustained damage to their MTT and suffered from a dense amnesia, although they were too disoriented to obtain sufficient test results for a diagnosis of an amnesic syndrome. Patient 15 did not have a lesion encompassing the MTT, a finding that would not agree with the fact that her memory deficit might lead to the diagnosis of an amnesic syndrome. Nevertheless, at closer observation, the profile of her memory performance was characterised by a good primacy score compared to her recency score, as evident from Table 7. Apparently, her severe memory deficits are not so much a result of an amnesic syndrome but due to a lack of efficient use of memory strategies. This would be the result of her extensive white matter lesions and additional infarcts.

The executive deficits were at first sight not found to be strongly related to the site of the infarction in the thalamus. They could be observed after large anterior lesions (e.g. case 5), middle lesions (e.g. case 4) or large posterior lesions (e.g. case 3). Since executive dysfunctions were so frequent and seemingly a-specific, we decided to look at the cases that did not display signs of deficits on these measures, to see if they had a common denominator. There were five cases without gross defects in the performance on tasks of executive func-

tions. These had lesions falling postero-laterally (cases 6, 11 and 17), a small lesion lying anteriorly without interfering with the IML and barely touching the MD (case 12) or a small lesion falling in the lateral MD (case 13). These five lesions, thus, tended to either avoid the main masses of the MD, midline nuclei and the lateral part of the IML, or be so small as to affect only a small portion of these nuclei.

No relation between the attentional or information processing deficits and damage to thalamic structures was apparent. These seemed to be scattered over the group regardless of whether the lesions were found anterior, posterior, lateral or medial. Four cases showed no evidence of such deficits; these had lesions falling posteriorly (cases 3, 6 and 7) or in the ventral midline (case 2).

4. Discussion

We aimed to find relationships between thalamic structures and memory, executive functions and attention. We performed a lesion-overlap and subtraction study in stereotactic space to investigate associations between thalamic structures and cognitive functions across our group of subjects, followed by a case-wise analysis of the pattern of deficits in each subject. A clear relationship between a specific kind of memory disorder, i.e. the amnesic syndrome, and structural damage to the MTT was found. No such simple relationships showed up for executive functioning and attention.

It proved necessary to distinguish between patients with pure lesions of the thalamus and those in which additional damage obscured the interpretation of test results; the association between functional deficits and structural damage in our image analysis was invariably higher when considering only the pure cases of thalamic damage.

The occurrence of such subtle additional brain lesions in older age is a common phenomenon and explains a large

proportion of the differences between subjects. Indeed, the variance in cognitive capacities increases with older age, causing structure–function relationships between e.g. thalamic volume and performance on cognitive tasks in healthy subjects to attain significance in young subjects only (Houx & Jolles, 1993; Van Der Werf et al., 2001).

The data confirm our previous finding that no single area in the thalamus appears to account for memory problems in the broad sense of the word (Van Der Werf et al., 2000). Damage to several and distinct areas contribute to amnesia, although the nature of the memory deficit may be different. These areas include large areas in the anterior and medial parts of the thalamus, including the anterior nuclei, MD, midline and intralaminar structures. Posterior and lateral lesions can evolve without any memory problem, showing some degree of functional specificity in the thalamus. When considering memory problems consistent with an amnesic syndrome, however, only one area proved to associate highly: a ventral area that overlaps the location of the MTT. It has to be noted that this peak spreads into the adjacent sector of the ventral MD and IML. It cannot be ruled out that these lesions contribute to the development of an amnesic syndrome. The data would, therefore, concord with the views of Graff-Radford et al. (1990) and Aggleton and Brown (1999), who state that a combined lesion to the MTT and adjacent IML white matter carrying fibres from the medial temporal lobe cortices to the MD is necessary for the development of a dense amnesia, characterised by both deficient recall and recognition. According to Aggleton and Brown (1999), damage to the MD and afferent fibres carried in the IML alone would be sufficient to produce a recognition deficit. The cases that had IML and/or MD lesions but no damage to the MTT/anterior nuclei (cases 1, 4, 6 and 16), however, did not have such recognition deficits. The claim of a role for the MD in recognition memory can, therefore, not be supported on the basis of our data, nor those of other reports of lesions in the MD with spared recognition (Edelstyn, Jenkinson, & Sawyer, 2002; Kritchevsky, Graff-Radford, & Damasio, 1987).

One case had a lesion to the left MTT, which was not associated with an amnesic syndrome (case 5). Memory problems were unmistakable and strong but the deficits of this patient were not as severe as those seen in patients with typical dense amnesias following thalamic damage. Instead, she showed a deterioration of strategic abilities hampering memory performance, as indicated by the combination of a depression of recall scores with relatively intact recognition scores. The profile is, therefore, more reminiscent of a frontal amnesia. In this case, the lesion was confined to the left thalamus only and the right side might have been able to provide some compensation. At present, however, this case remains an anomaly.

Executive deficits frequently follow thalamic lesions. An interpretative problem here is that most tests used to determine the integrity of the executive functions draw on several functions: they require the subject to perform set shifting or

to access semantic knowledge, but may also tap memory, working memory and attentive processes. Executive functioning as such can, therefore, not be ascribed solely to the integrity of the prefrontal cortices, but also make use of other areas. This can be appreciated in functional imaging variants of the tests used here, for instance in the Wisconsin Card Sorting Test (Berman et al., 1995), the Stroop test (Taylor, Kornblum, Lauber, Minoshima, & Koeppel, 1997) and the Tower of London test (Baker et al., 1996) that activate parietal, temporal and occipital cortices in addition to prefrontal areas. This is reflected in the absence of a strong association between a restricted thalamic structure and executive deficits. Rather, two areas have moderate degrees of association as seen from the overlap of subjects showing substantial deficits on the executive tasks: these are a ventral anterior region including the ventral IML adjacent to, but lateral and dorsal to the MTT, and a more posterior region in the ventral medial part of the MD that might also include part of the adjacent midline nuclei and IML. This indicates that diverse areas in the thalamus might account for executive deficits, but that the combination of lesioned structures likely contains the ventral IML or the ventral MD. In accord with this, Mennemeier and coworkers (Mennemeier, Fennell, Valenstein, & Heilman, 1992; Mennemeier et al., 1997) have published a detailed analysis of a case with a small but strategically located infarction encompassing the left ventral IML and MD, and described deficits of executive aspects of memory.

Deficits of simple speeded processing and attention do not seem to be associated with a certain structure in the thalamus. This might be caused by the fact that inattention is a general feature of thalamic lesions, irrespective of where the damage is found. This would follow the findings of Castaigne et al. (1981) and Rousseaux (1994), who noted that a loss of attention was a common denominator in patients with thalamic infarctions. Rather, performance on simple tasks of attention tended to be associated with increasing age across the whole group of patients. This indicates that in higher age, processes of attention become more vulnerable to disruption due to thalamic lesions. This would fit with correlation data in both healthy and diseased subjects, showing that age-related volume decreases of the thalamus correlate with reduced simple speeded processing (Van Der Werf et al., 2001). More complex forms of attention, as measured here with the same tests for simple speeded processing but with more complex demands, appear to be related to an area in the ventral IML, similar to that associated with executive dysfunctions.

The following remarks on subject selection and interpretation of the data are warranted: our study group likely suffered from an inclusion bias, i.e. patients with evident cognitive impairments were probably more likely to be included, whereas patients with asymptomatic thalamic infarctions may have gone relatively unnoticed. Although not necessarily corrupting the structure–function relationships found here, this might lead to an overestimation of the

likelihood that any thalamic infarction leads to cognitive deficits. Our data, nevertheless, do indicate which are the regions where infarctions remain ‘silent’ in terms of specific cognitive deficits; infarctions falling laterally or posteriorly in the thalamus seem unrelated to both memory problems and executive dysfunctioning. In addition, infarctions of limited size that fall in the MD do not necessarily result in memory or executive dysfunctions. This indicates that a critical mass of tissue in the MD needs to be damaged before functioning is disturbed, agreeing with a previously published report of normal memory and frontal functions despite a small lesion to the MD (Kritchevsky et al., 1987). Such reports of asymptomatic thalamic infarctions would increase further our understanding of the relationship between thalamic structures and cognition.

The present investigation of thalamic involvement in cognition focused on memory, executive functions and cognition; other functions, such as those in the domain of language, were not addressed. Given the fact that none of the subjects in the study was excluded from the analyses because of inadequate language skills, we are confident that we did not miss any cognitive deficits that might be mediated by language disturbances.

In conclusion, our study: (a) shows that in studies of patients with thalamic damage, special attention needs to be paid to the occurrence of additional brain damage that might influence the cognitive outcome in these patients. This, sometimes subtle, damage occurs especially in patients aged 60 and older; (b) confirms that dense memory deficits compatible with the criteria of an amnesic syndrome are associated with lesions of the MTT; (c) suggests that executive deficits cannot be attributed as readily to lesions of a certain structure in the thalamus, but may arise from combined lesioning of several structures including the MD, IML and midline nuclei; (d) shows that simple attentional deficits seem a rather general trait of thalamic lesions and occur more frequently with higher age, whereas complex attentional processes draw upon structures overlapping those associated with executive processes.

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