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Recall deficits in stroke patients with thalamic lesions covary with damage to the parvocellular mediodorsal nucleus of the thalamus

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ABSTRACT

The functional role of the mediodorsal thalamic nucleus (MD) and its cortical network in memory processes is discussed controversially. While Aggleton and Brown (1999) suggested a role for recognition and not recall, Van der Werf et al. (2003) suggested that this nucleus is functionally related to executive function and strategic retrieval, based on its connections to the prefrontal cortices (PFC). The present study used a lesion approach including patients with focal thalamic lesions to examine the functions of the MD, the intralaminar nuclei and the midline nuclei in memory processing. A newly designed pair association task was used, which allowed the assessment of recognition and cued recall performance.

Volume loss in thalamic nuclei was estimated as a predictor for alterations in memory performance. Patients performed poorer than healthy controls on recognition accuracy and cued recall. Furthermore, patients responded slower than controls specifically on recognition trials followed by successful cued recall of the paired associate. Reduced recall of picture pairs and increased response times during recognition followed by cued recall covaried with the volume loss in the parvocellular MD. This pattern suggests a role of this thalamic region in recall and thus recollection, which does not fit the framework proposed by Aggleton and Brown (1999). The functional specialization of the parvocellular MD accords with its connectivity to the dorsolateral PFC, highlighting the role of this thalamocortical network in explicit memory (Van der Werf et al., 2003).

1. Introduction

The connectivity pattern of the medial thalamus with the medial temporal lobe (MTL) and the prefrontal cortex (PFC) suggests a pivotal role of this brain region in memory. Evidence from rodents and non-human primates highlights the importance of the anterior nuclei of the thalamus (AT) (Aggleton & Brown, 1999; Mitchell & Dalrymple-Alford, 2005; see Aggleton et al., 2010 for a review), the mediodorsal nucleus (MD) (Aggleton & Brown, 1999), the intralaminar and the midline nuclei (Vertes, Hoover, Do Valle, Sherman, & Rodriguez, 2006; Vertes, 2006).

Aggleton and Brown (1999) proposed dissociable contributions of the MD and the AT in recognition memory (Brown, Warburton, & Aggleton, 2010; Eichenbaum, Yonelinas, & Ranganath, 2007; Mandler, 1980). According to the dual process account, recognition memory is subserved by two different processes: recollection and familiarity (for the single process account on recognition memory, see Squire, Wixted, & Clark, 2007). The definitions of familiarity, recollection, and the neural systems supporting these cognitive functions are a matter of controversial debate (Ranganath, 2010). Both systems support non-associative recognition (the ability to acknowledge previous encounters with an item upon subsequent presentation), but only the recollection-network, centered on the hippocampus (HC) (Brown et al., 2010; Eichenbaum et al., 2007; Suchan, Gayk, Schmid, Koster, & Daum, 2008; Montaldi & Mayes, 2010) enables cued recall (i.e., the ability to recall, in response to an associated cue, a mental representation of an item in absence of the item itself). Montaldi and Mayes (2010) proposed that recollection is per se a form of cued recall and called it "recall/recollection". According to Aggleton and Brown (1999), the mammillothalamic tract (*mtt*) and the AT are a functional extension of the HC, subserving recall/recollection. The model predicts a selective impairment on cued recall after damage to this neural system. This prediction has received considerable support over the years (Carlesimo et al., 2007; Park et al., 2007; Rudebeck et al., 2009;

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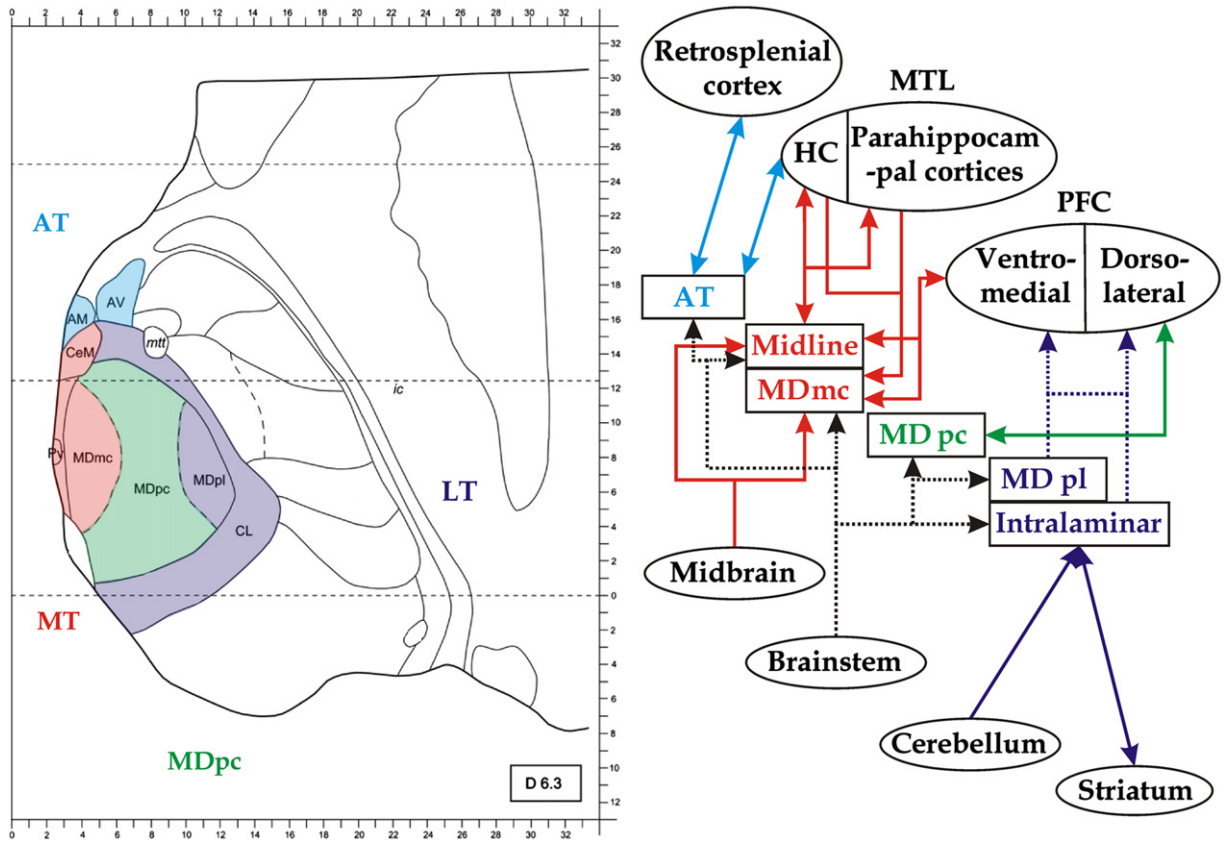

Fig. 1. Thalamo-cortical connectivity. Left panel: spatial arrangements of the AT, MT, MDpc, and LT. The section is 6.3 mm superior to the intercommissural plane. Modified from Morel (2007). Right panel: Patterns of connectivity of the groups of nuclei described. Dashed arrows indicate diffuse projections. Abbreviations: AM, anteromedial nucleus; AV, anteroventral nucleus; CeM, centromedial nucleus; CL, centrolateral nucleus; LT, lateral thalamus; MDmc, magnocellular mediodorsal nucleus; MDpc, parvocellular mediodorsal nucleus; MDpl, paralamellar mediodorsal nucleus; MT, medial thalamus; MTL, medial temporal lobe; *mtt*, mammillothalamic tract; PFC, prefrontal cortex; Pv, paraventricular nucleus.

Tsivilis et al., 2008; Vann et al., 2009; Vann, Saunders, & Aggleton, 2007; Vann & Albasser, 2009; reviewed by Aggleton et al., 2010 and Carlesimo, Lombardi, & Caltagirone, 2011).

Aggleton and Brown (1999) discussed an MD-perirhinal cortex connection (Lavenex & Amaral, 2000; Saunders, Mishkin, & Aggleton, 2005; Suzuki, 1996), and thus a role of the MD in familiarity. This part of the model would predict no impairment on cued recall after selective damage to this neural system. Carlesimo et al. (2011) and Aggleton, Dumont, and Warburton (2011), however, in their detailed reviews of the clinical evidence currently available, did not find direct support for a selective familiarity deficit in patients with MD lesions. An fMRI study found activation in the dorsomedian thalamus correlating with familiarity strength (self-assessed by the subjects; Montaldi, Spencer, Roberts, & Mayes, 2006), although no analysis was performed to identify the cluster activated as a part of the MD. The dorsomedian thalamus has been involved in recall in a functional study by De Rover et al. (2008)—no anatomical analysis was performed in this case either. Two clinical group studies (Soei, Koch, Schwarz, & Daum, 2008; Zoppelt, Koch, Schwarz, & Daum, 2003) found impairment on recall/recollection in patients with lesions in the MD and ventrolateral nucleus, although the lesion analyses did not account for *mtt* lesions (Carlesimo et al., 2011). The role of the MD in recognition memory therefore remains controversial. Aggleton et al. (2011) proposed that multiple thalamic nuclei contribute to recognition memory favoring familiarity or recall/recollection in a graded way. According to this view, the MD would underlie more familiarity-based than recall/recollection-based recognition, although supporting both to some extent. A further debated topic concerns the effects of intralaminar and midline nuclei lesions in humans, which may be involved in general operations common to familiarity and recall/recollection (Aggleton et al., 2011). Few clinical data are available on this issue (Van der Werf et al., 1999, 2003; Van der Werf, Witter, & Groenewegen, 2002).

In our view, two advancements will improve our understanding of the role of the MD, midline and intralaminar nuclei in recognition memory and recall. First, it is standard procedure to use subjective ratings upon recognition to draw inferences on the processes underlying recognition memory (recall/recollection and familiarity). The use of this procedure in clinical studies has been criticized (Brown et al., 2010; Montaldi & Mayes, 2010). The assumption that forced choice recognition tasks selectively tap recall/recollection has also been challenged (Mayes, Montaldi, & Migo, 2007; Quamme, Yonelinas, & Norman, 2007). There is agreement, instead, that cued recall is supported solely by recall/recollection, when subjects recall a unique association, rather than a source common to several items (Montaldi and Mayes, 2010). Therefore, cued recall of unique associations is a process-pure probe of recall/recollection abilities. Second, neuroanatomical evidence relates the MD, and also midline and intralaminar nuclei, to the PFC (Aggleton et al., 2011). The human PFC is involved in cued recall (Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins & Wagner, 2005; Ranganath, Johnson, & D'Esposito, 2000), especially the dorsolateral PFC (DLPFC; Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Mitchell & Johnson, 2009). The next paragraphs briefly review the thalamo-cortical connectivity of the MD, the midline and intralaminar nuclei (represented in Fig. 1).

The MD comprises at least two portions: a medial magnocellular portion (MDmc), and a more lateral parvocellular portion (MDpc). A paralamellar and a densocellular portion are regarded as part of the intralaminar nuclei (Bachevalier, Meunier, Lu, & Ungerleider, 1997; Hirai & Jones, 1989; Morel, 2007; Ray & Price, 1993; Schmahmann & Pandya, 1990). The MDmc receives afferents from the MTL, including the perirhinal and entorhinal cortex, the subiculum and the amygdala (Aggleton & Mishkin, 1984; Aggleton, Desimone, & Mishkin, 1986; Packard & Cahill, 2001; Ray & Price, 1993; Russchen, Amaral, & Price, 1987; Saunders et al., 2005). The MDmc projects almost exclusively to the ventromedial PFC (VMPFC; Bachevalier et al., 1997; Barbas, Henion, & Dermon, 1991; Contini et al., 2010; Freedman, Insel, & Smith, 2000; Preuss & Goldman-Rakic, 1987; Ray & Price, 1993; Russchen et al., 1987). The midline nuclei receive similar input from the MTL, project back and also provide input to the VMPFC. The MDmc and midline nuclei can thus be regarded as an anatomic-functional unit (Schmahmann, 2003), which we shall define as medial thalamus (MT). The MDpc receives afferents from the DLPFC and from the brainstem (Preuss & Goldman-Rakic, 1987; Russchen et al., 1987) and projects to the DLPFC (Barbas et al., 1991; Fang, Stepniewska, & Kaas, 2006; Preuss & Goldman-Rakic, 1987; Ray & Price, 1993; Russchen et al., 1987). The intralaminar nuclei diffusely project to the PFC; the most prominent projection however is the topographically organized input to the striatum (Barbas et al., 1991; Preuss & Goldman-Rakic, 1987; Sadikot, Parent, & Francois, 1992).

Hence at least three thalamic systems, aside from the HC-AT axis, can be dissociated on the basis of their connectivity patterns: the MT, including the midline nuclei and the MDmc, connected to the MTL and the VMPFC (Mitchell & Dalrymple-Alford, 2005); the MDpc, reciprocally connected to the DLPFC; and a lateral thalamic system (LT; Lopez, Wolff, & Lecourtier, 2009; Mitchell & Dalrymple-Alford, 2005) including the intralaminar nuclei and the paralamellar MD, connected to the striatum and diffusely to the PFC (Fig. 1).

We hypothesized that controversies in explaining the involvement of the MD in recognition memory and recall arise from the different connectivity and function of the MD subunits. In the present study, patients with ischemic lesions in the medial thalamus and healthy controls performed a memory task requiring recognition and cued recall of uniquely paired associates. Ischemia originated from occlusion of either the paramedian or the tuberothalamic artery. Both arteries supply the MD, but arterial territories slightly differ with respect to other thalamic regions (Pergola et al., 2012; Schmahmann, 2003). In particular, the ventral anterior nucleus, which surrounds the *mtt* (Morel, 2007) is preferentially supplied by the tuberothalamic artery, whereas the LT is preferentially supplied by the paramedian artery. Therefore, taking into account the etiology of the stroke allows for an analysis of the covert dysfunction of the thalamic areas differentially supplied. Put another way, even if no damage is evident based on the scans, the differential diagnosis (paramedian or tuberothalamic) expresses different likelihoods of dysfunction in the *mtt* or in the LT. Since we tested two groups of patients, we also assessed two age-matched control groups (paramedian matched and tuberothalamic matched).

We tested whether the recognition impairments were brought about by disruption of recall/recollection, which we probed using cued recall of unique associations. Associations featured item-scene and item-item pairs. Soei et al. (2008) found that patients with thalamic lesions showed a greater deficit in spatial than non-spatial associative memory. We tested the hypothesis that patients differently processed the content of the stimuli. We also included semantically congruent and incongruent pairs, as well as categorically homogeneous and heterogeneous pairs. The involvement of the thalamus in semantic memory is debated (Assaf et al., 2006; Kraut et al., 2002); semantic relationships between encoded items have been proposed to affect the recruitment of brain areas during encoding (Jäger, Mecklinger, & Kipp, 2006; Mayes et al., 2007). The volume loss in the territories of the MT, the LT and the MDpc was assessed and used as linear predictor for the performances of the patients. Throughout the paper we will refer to the territory of a nucleus by simply indicating its name or abbreviation, although we are aware that lesions encompass gray matter as well as passing-by fiber tracts.

Based on the thalamo-frontal connectivity pattern, the extent of damage to the MDpc was expected to covary with impairment on cued recall. Since the MT has been related to motivation (Schmahmann, 2003) and the LT to attention (Van der Werf et al., 2002) in humans, we did not expect specific recall impairments to depend on lesions to these structures, although a non-specific memory deficit could be expected (Aggleton et al. 2011).

2. Methods

2.1. Participants

Seventeen patients (10 women and 7 men) with chronic lesions in the thalamus originating from an ischemia in the paramedian ($n=9$) or tuberothalamic ($n=8$) artery participated in the study. In the following we will use the term "group" to differentiate patients from controls and the term "subgroup" to differentiate paramedian from tuberothalamic patients and controls matched to the paramedian subgroup from controls matched to the tuberothalamic subgroup. In all patients but three (two in the tuberothalamic subgroup, one in the paramedian subgroup) the lesions were unilateral. Table 1 reports the demographic data of patients and controls.

Twenty-eight healthy subjects (16 women and 12 men) matched to the patients on age, years of formal education and IQ (see Table 1) served as control group. Exclusion criteria for all subjects were history of neurological or psychiatric disorder (other than thalamic stroke in the patient group), alcohol or substance abuse, performance below the published norms for the standard neuropsychological assessment (memory scores were not used as exclusion criterion for the clinical sample), misunderstanding of task instructions and failure to complete the memory task. Only patients with a lesion-test interval >1 year participated in the study. All participants had normal or corrected-to-normal vision. The experimental procedure was approved by the ethics committee of the Faculty of Medicine at the Ruhr University Bochum. All subjects gave their informed written consent before participation and received 20 € as refund for expenses.

Two sets of analyses were performed. The first set consisted of behavioral tests comparing patients with controls and subgroups one to another, thus addressing the behavioral consequences of the ischemic episode at the group level. The second set of analyses aimed at investigating the relationship between damage to specific thalamic regions and behavior, and was performed on subsamples of patients and controls selected based on suitability of the lesions for the lesion-symptom mapping procedure.

Table 1
Demographic data of patients and controls, mean (standard deviation). All measures of time expressed in years.

Subjects	Age	Education	IQ	Age at onset	Time since lesion
Patients	62 (12)	11 (3.0)	114 (7.0)	56 (15)	5.6 (4)
Paramedian	56 (12)	12 (3.5)	117 (7)	49 (15)	7.5 (4.4)
Tuberothalamic	68 (8)	9.4 (0.9)	111 (6)	65 (9)	3.4 (1.8)
Controls	58 (16)	11.6 (2.5)	114 (7.5)	//	//
Paramedian matched	49 (17)	13 (2.7)	114 (8)	//	//
Tuberothalamic matched	67 (7)	9.9 (0.6)	115 (7)	//	//

Twelve patients and eighteen controls were included in the lesion-behavior correlations. Two patients with paramedian lesions were excluded for technical reasons (see Section 2.5); we also excluded the three patients with bilateral lesions from this analysis, hence remaining with a sample of six patients with left-sided and six patients with right-sided lesions. The control group was resized to match the demographic variables of the reduced clinical sample. The two patients excluded were in fact younger than the remainder of the clinical sample. The complete clinical sample ranged in age from 30 to 79, while the sample with 12 patients ranged from 56 to 79. Ten controls between 28 and 56 years of age were thus excluded from the lesion-behavior correlations.

Patient 7 made regular use of benzodiazepines. Patients 8 and 9 were treated with antidepressants. None of the patients had a significantly high regular alcohol intake. Patient 2 smoked.

The patients were outpatients of the Klinikum Dortmund, Germany. Two experienced neurologists (B.K. and M.S.) blind to the behavioral results evaluated the lesions and allocated all patients to the two different subgroups (tuberothalamic; paramedian) on the basis of 3 T MR images. For each patient the following images were acquired and employed for lesion localization: a T_1 (FSGPR BRAVO axial sequence, 0.9 mm × 0.9 mm × 1.2 mm voxel size; flip angle: 13, FOV=24.0, slice thickness=1.2 mm, slice spacing=0 mm, slice number=110) contrasted MRI scan; a T_2-weighted image (FLAIR axial sequence, 0.5 mm × 0.5 mm × 5.5 mm voxel size; TE=120.0, TR=8000.0, FOV=24.0, slice thickness=5.0 mm, slice spacing=0.5 mm, slice number=25). Images were obtained on the day of participation in this study or a few weeks later. The location of the necrotic tissue was used as a criterion to assess which artery underwent ischemia and hence to allocate patients to group membership. Lesions were also assessed quantitatively as a percentage of volume loss within the thalamic systems considered (Pergola et al., 2012).

2.2. Neuropsychological screening

To control for possible attention, motivation or verbal fluency deficits, patients performed standard neuropsychological tests. Visuo-spatial skills and long-term memory for non-verbal material were assessed by means of copy and delayed (30 min) recall of the Rey–Osterrieth figure (Osterrieth, 1944), respectively; immediate and delayed (30 min) Logical Memory Test from the German version of the Wechsler Memory Scale revised (Wechsler, 2004) tested immediate and delayed recall of verbal material; working memory assessment included Block Span and Digit Span (Wechsler, 1987); verbal fluency was assessed by means of the Regensburger Verbal Fluency test (including a phonemic, a semantic, an alternating subtest Daum, Reimold, & Spieker, 1994); IQ was estimated based on the Similarities and Picture Completion tests from a German short version of the Wechsler Adult Intelligence Scale (Dahl, 1972). Attention was assessed by means of a tonic- and phasic-alertness test. The task required observing a fixation spot and pressing the response button as fast as possible whenever a cue appeared on the center of the screen (Zimmermann & Fimm, 1993).

2.3. Recognition and cued recall task

The memory task was divided in 6 blocks, each including a study phase, a delay and a test phase. Administration of the task required approximately 50 min.

2.3.1. Study phase

Stimuli were nameable color photographs (minimum resolution: 400 × 400 pixels) depicting either items on a white background or scenes. The content of the pictures belonged to one of three categories: animals, objects and scenes. The content of each picture was different (see Supplementary material, Section S1).

The pictures were sorted in 4 pair classes according to the content: item-item pairs were either homogeneous (animal-animal and object-object: Condition HOII), or heterogeneous (animal-object: Condition HEII); the item-scene associations were either semantically congruent (e.g., a toothbrush and a bathroom: Condition COIS) or incongruent (no semantic link: Condition INIS). Fig. 2 illustrates an example for each condition.

Subjects were asked to encode picture pairs for a later memory test. Before starting the experiment training stimuli were presented. Subjects were told that the task required first recognition of a probe item, then recall of the paired item. They were also asked to report which category the paired item belonged to, even if they did remember the item.

Sixteen picture pairs were shown per block, 96 overall. The blocks were always presented in the same order. The order of picture presentations in each block varied randomly across subjects. In each block, 4 pairs belonged to each condition. All pictures were displayed on a computer screen. The 2 pictures together spanned a visual angle of approximately 22°. Each pair was shown for 5000 ms, followed by an interval displaying a fixation cross for a time randomly varying between 500 ms and 2000 ms. The interstimulus interval varied to reduce predictability of stimulus delivery and thereby improve attention.

2.3.2. Delay

Between the study and the test phase there was an interval of approximately 2–3 min, during which the experimenter asked the subjects general questions, not related to the pictures subjects had just seen. This procedure was followed in order to prevent active rehearsal of the stimulus material.

2.3.3. Test phase

Single pictures were presented in the center of the screen. Thirty-two pictures were shown per block, half of which were old (a single picture per pair), the other half consisting of new pictures (shown neither in the preceding study phase, nor in previous blocks). In each block the 16 old pictures were equally distributed across conditions: HOII (4 pictures), HEII (4), COIS (4) and INIS (4). The balanced design prevented between-blocks effects of condition. The proportion of animals, objects and scenes was matched between old and new stimuli. The order of presentation was random.

Subjects were asked to press a button to determine whether pictures were old or new. A failure to respond within 15 s was followed by a message in red font, asking subjects to respond faster. If the subject classified the stimuli as new, the test continued, showing a fixation cross for 1000 ms and then the next stimulus.

If the stimulus was classified as old, regardless of the correctness of the assessment and without receiving any feedback, the subject was asked to verbally declare the pair-picture, and also the category it belonged to—even if the item itself was not recalled.

2.4. Behavioral analysis

Neuropsychological background tasks were analyzed by means of Analyses of Variance (ANOVA; Greenhouse–Geisser correction was applied where appropriate) including the factors GROUP (17 patients; 28 controls) and SUBGROUP (tuberothalamic; paramedian). Since the two subgroups (tuberothalamic patients and respective controls; paramedian patients and respective controls) differed with respect to age, we included age as a covariate. All statistics were computed

Fig. 2. Examples of the stimuli as they were shown in the study phase (a single pair per trial). Pair HOII is an example of a categorically homogeneous pair (animal-animal); Pair HEII is an example of a categorically heterogeneous pair (animal-object); Pair COIS depicts a congruent item-scene pair; Pair INIS depicts an item and an incongruent scene.

Table 2
Classification of the responses and conditions of the task.

Response	Abbreviation	Definition
Hits		Responses successfully classifying an old item as old
Correct rejections		Responses successfully classifying a new item as new
Complete recall	$\mathbf{H^+}$	Hits followed by correct cued recall of the unique picture associate
Partial recall	$\mathbf{H^{0+}}$	Hits followed by no or incorrect cued recall of the associate, but correct retrieval of the category to which the associate belonged
No recall	$\mathbf{H^{00}}$	Hits followed neither by correct cued recall, nor by correct category recall
No response		The subject failed to respond within the given time
Condition (example)		
Object/object	**HOII**	Homogeneous item-item pair
Animal/object	**HEII**	Heterogeneous item-item pair
Lion/savanna	**COIS**	Congruent item-scene pair
Crab/airplane	**INIS**	Incongruent item-scene pair

using the Statistical Package for the Social Sciences statistics engine (SPSS Statistics 20, IBM, Chicago, Illinois).

2.4.1. Recognition and cued recall task

Due to the complexity of the task, a number of different types of responses had to be considered separately. The classification of the responses is summarized in Table 2.

The memory performance index (Pr) and the bias index of the Two-High-Threshold Model were calculated to estimate recognition accuracy (Snodgrass & Corwin, 1988; Soei et al., 2008).

$$\mathrm{Pr} = \mathrm{Hit\text{-}rate} - \mathrm{False\text{-}alarms\ rate}$$

$$\mathrm{Bias\ index} = \mathrm{False\ alarms\ rate}/(1-\mathrm{Pr})$$

Recall/recollection abilities were estimated by cued recall rate (see equation below). Non-associative recognition performance was estimated using hit trials in which neither the correct associated item, nor the correct category were named, meaning that the recognition judgment was only based on the item at hand. We refer to this measure as non-associative hit-rate (see equation below). This is not a familiarity estimate (see the Discussion, Section 4.1). The task was designed to allow isolation of recall/recollection trials and did not focus on familiarity. Non-associative hit-rate and cued recall rate were computed separately for each condition as follows:

$$\text{Cued recall rate} = \mathrm{H^+}/(\text{total old} - \text{no response trials})$$

$$\text{Non-associative hit-rate} = \left(\mathrm{H^{00}}\right) \Big/ \left[(\text{total old} - \text{no response trials}) - \left(\mathrm{H^+} + \mathrm{H^{0+}}\right)\right]$$

In this formula the abbreviation H^+ indicates the number of hits followed by recall of the uniquely paired associate. H^{0+} is the number of hits followed by no or incorrect recall of the uniquely paired associate, but correct recall of the category to which the paired associate belonged. H^{00} is the number of hits followed by no recall at all. "Total old" indicates the overall number of old items shown during the test phase and equals 96. "No response trials" indicates the number of trials in which the subject failed to respond within the allowed time. This implies that the divisor of the cued recall rate is the total number of valid responses. In the equation defining non-associative hit-rate, the number of hits followed by recall of either the item or the category is subtracted from the total number of valid responses, so that only trials not yielding associative information are analyzed.

Note that the computation used for the cued recall rate indexes the probability of recalling a priori with respect to the recognition judgment. An alternative way of computing recall performances would be H^+/hits, which indexes the probability of recalling the paired associate given that the item has been recognized. In this case detection of a cued recall impairment would imply a disproportionate deficit on recall compared to recognition. We chose the above reported expression for two reasons. First, the metric adopted is easily comparable with the non-associative hit-rate because both refer to the probability of success upon the presentation of the item, a priori with respect to successful recognition. Second, a concurrent decrease in H^+ and hits may go unnoticed in the computation H^+/hits. However, a concurrent impairment is what one would expect if recall/recollection were impaired. On the other hand, the index H^+/hits has the advantage to discount the possibility that low cued recall scores are obtained due to a selective decrease in hits. For this reason in the following analyses we additionally report a test on H^+/hits whenever a significant effect of GROUP is detected on the cued recall rate as above defined.

Patients (2 subgroups according to the affected artery: tuberothalamic or paramedian) and Controls (2 subgroups formed to match the patients' subgroups for Age, Education and IQ) were compared on Pr and bias index using ANOVAs applied on the whole stimulus set.

We compared patients and controls on cued recall rate and non-associative hit-rate separately across different conditions (HOII: HEII; COIS; INIS) by means of ANOVA. We also compared the performances on category retrieval (partial recall), merging the H^+ and H^{0+} responses.

Response times were compared through ANOVA for Hits vs. Correct Rejections—and for H^+ vs. H^{00}. The response times for each subject were computed on data pooled from the 4 conditions. The factors GROUP, SUBGROUP and the covariate Age were included in the analysis. The factor RESPONSE distinguished Hits from Correct Rejections in the first analysis and H^+ from H^{00} in the second.

2.5. Lesion assessment

Two experienced neurologists blind to the behavioral performances inspected the brain scans of the patients to determine the thalamic substructures affected and eventual extrathalamic damage. This procedure has been consistently used in the field (Bellebaum, Daum, Koch, Schwarz, & Hoffmann, 2005; Perren, Clarke, & Bogousslavsky, 2005; Peterburs et al., 2011; Van der Werf et al., 2003). Figs. 3 and 4 illustrate the lesions for all patients in T2 contrast (axial sections) and T1 contrast (coronal sections).

The quantitative assessment procedure, which was performed by a third rater, is described in detail elsewhere (Pergola et al., 2012). Brain images were coregistered to the atlas (Morel, 2007) through rigid body transformation in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Axial sections were exported in separate slices 1 mm away from each other and matched onto the atlas based on anatomical landmarks. This step involved a manual normalization of the images to the atlas. The lesions were manually traced and the surface of the lesioned area was computed for each lesioned structure in each slice using the software CellˆP^{TM}. The same software served to estimate the total volume of the thalamic nuclei depicted on the atlas. The volume of the necrotic tissue in each nucleus was computed based on the surface measurements. Additional surface measurements performed on the atlas drawings served to provide an estimation of the volumes of the target structures. The damage to single nuclei was merged according to the connectivity pattern (for the nomenclature, see Morel, 2007):

- MT: Included the midline nuclei and the MDmc. The midline nuclei included the Central Medial, Paraventricular and Medioventral nuclei. Estimated volume: 172 mm^3.
- LT: Included the intralaminar nuclei and the paralamellar MD. The intralaminar nuclei included the Centre Médian, Parafascicular, Subparafascicular, Central Lateral nuclei. Estimated volume: 573 mm^3.
- MDpc: Estimated volume: 383 mm^3.

The AT was damaged in only two of the fifteen patients included in the analysis, and the volume loss was negligible (P 14: 3.4 mm^3 i.e., 1.9%; P 15: 0.20 mm^3 i.e., 0.14%). The row lesion size in mm^3 was divided by the estimated volume of the same structures based on the atlas to obtain the percentage of volume loss due to the ischemia. Finally, the relationship of thalamic damage with behavior was statistically tested.

In case of bilateral lesions, the volume loss for each structure on both sides was assessed. Only the lesion on the side with greatest damage is reported; these data did not enter the linear fits with behavior because of the difficulty of comparing bilateral with unilateral lesions and are reported as a descriptive index of the lesions.

The procedure used allows evaluation of damage to the thalamic nuclei with an image resolution (i.e., the minimal error detectable based on the quality of the scans used) of 2.2 mm^3 (Pergola et al., 2012). Supplementary material (Section S2.3) includes a standard lesion-symptom mapping analysis (overlap/subtraction). The two procedures yielded consistent results.

We sought to account for the thalamic shrinking secondary to the lesion (Kraemer et al., 2004), but this attempt was not successful in each individual patient. P1 and P4, in fact, presented with thalamic rearrangements difficult to evaluate (see Supplementary material, Section S2.2) and were therefore excluded. Patients with bilateral lesions were also excluded. We also restricted the control sample in order to match it for Age, Education and IQ to the patient sample. The remaining subjects entailed 12 patients and 18 controls.

2.6. Lesion data analysis

We considered in the subsequent analysis those variables for which patients showed impairments at group level (see Results, Section 3.2). A *Z*-transformation of controls' performances (the restricted sample including 18 subjects) was computed after checking the normality of the distribution by means of Smirnow–Kolmogorov tests. Then we extracted the *Z*-scores of the patients based on this distribution. These scores do not only provide a description of patients'

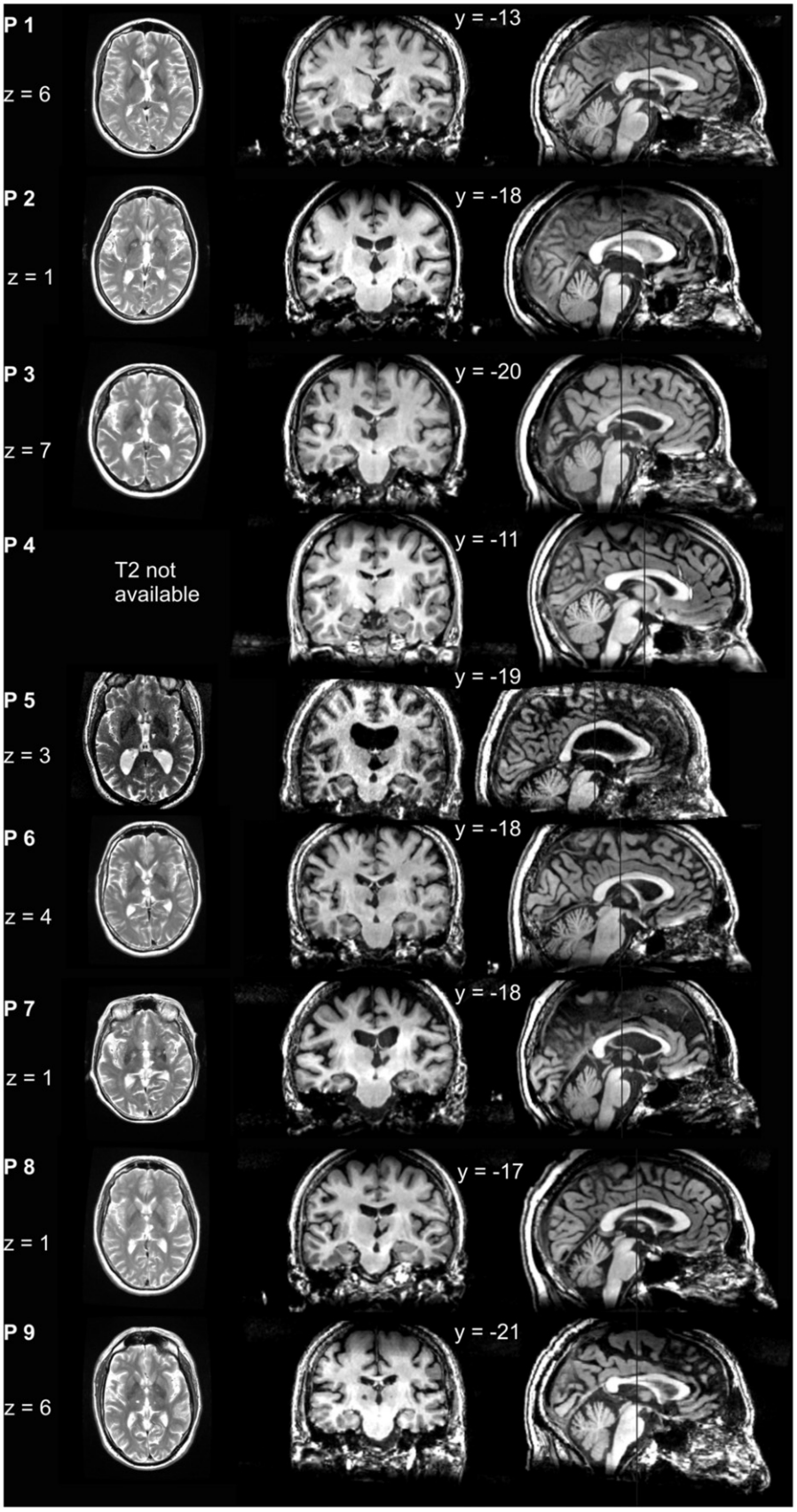

Fig. 3. Brain images of the patients with paramedian lesions. The first column shows T_2 contrasted axial sections of the brains of patients 1 through 9. The second column shows T_1 contrasted coronal sections of the respective patients. The third column shows the coronal section localization. The origin is set on the anterior commissura. Coordinates are expressed in mm.

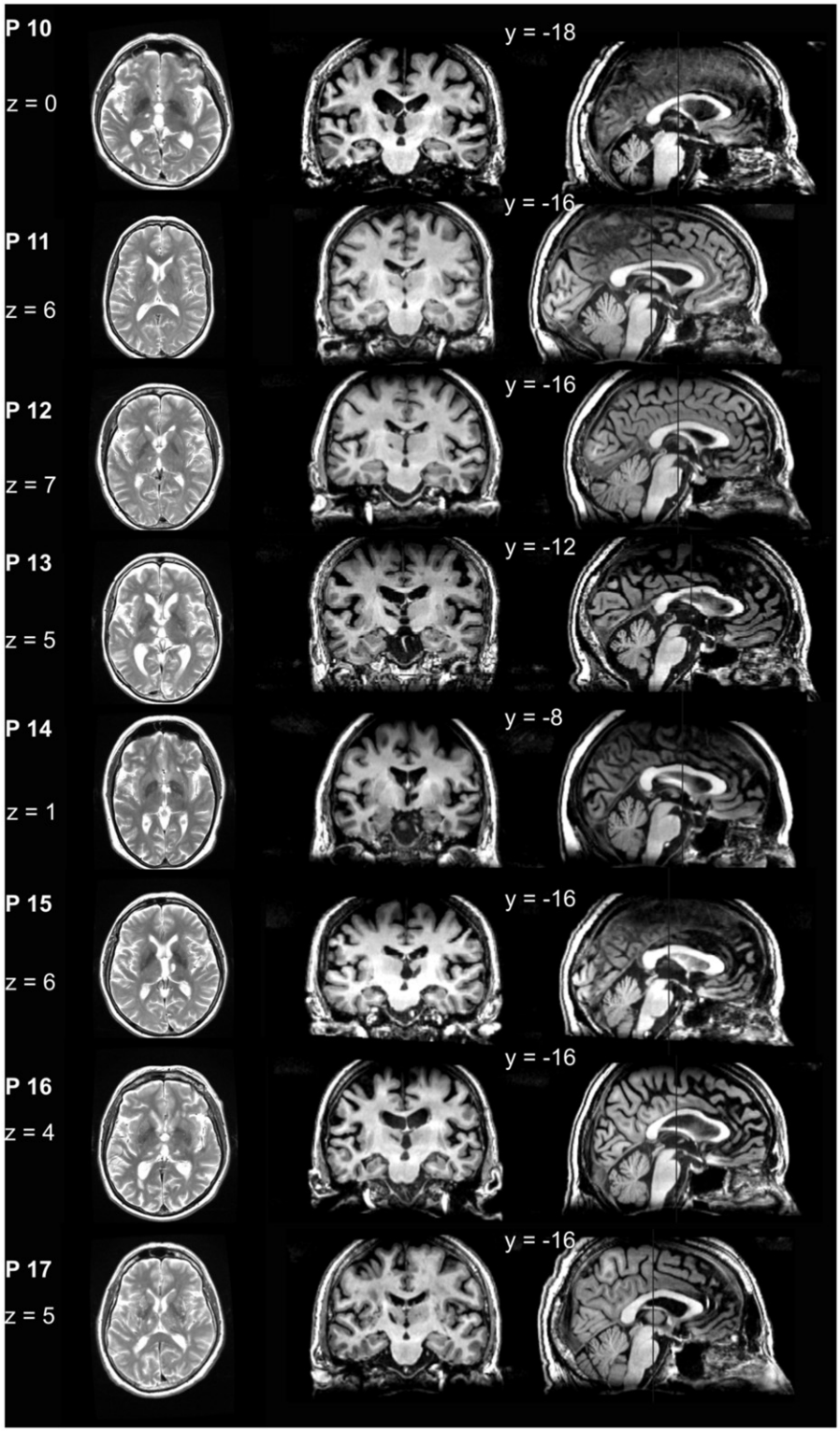

Fig. 4. Brain images of the patients with tuberothalamic lesions. The first column shows T2 contrasted axial sections of the brains of patients 10 through 17. The second column shows T1 contrasted coronal sections of the respective patients. The third column shows the coronal section localization. The origin is set on the anterior commissura. Coordinates are expressed in mm.

performances, but also express the impairment of patients relative to controls. On the basis of the *Z*-scores the effect of the lesion side was analyzed by means of *t*-tests. Patients were divided in two subgroups (left-sided, right-sided; not to be confounded with the subgroups above reported based on vascular diagnosis). Behavioral variables related to memory were analyzed: delayed verbal recall (Logical Memory test); delayed non-verbal recall (Rey–Osterrieth Figure); the indices of interest based on the group analyses (see Results, Section 3.2) were also analyzed.

We evaluated a Pearson's correlation table between the proportions of tissue loss in the regions of interest (MT, MDpc, LT). There was no significant correlation between damage to the three regions, meaning that damage was not bound to co-occur in these structures (data not shown). For this reason, and considering the size of the sample (12 subjects), which in statistical terms is small, a multivariate analysis (including marginalization for covariates before the inference) was not considered suitable.

Table 3
Means and standard errors for all neuropsychological tests divided per subtest, group and subgroup.

	Controls		Patients		Significant effects
	Paramedian	Tuberothalamic	Paramedian	Tuberothalamic	
Rey–Osterrieth					DELAY ($p=.004$)
Immediate	35.3 ± 0.4	34.7 ± 0.7	33.4 ± 1.7	33.8 ± 1.1	
Delayed	21 ± 1.5	18 ± 1.3	19 ± 2.0	16 ± 2.2	
Logical memory					DELAY ($p=.015$), GROUP ($p<.001$)
Immediate	35 ± 1.6	31 ± 1.6	22 ± 3.6	18 ± 3.1	
Delayed	32 ± 1.9	26 ± 1.8	19 ± 3.7	14 ± 3.0	
RWF correct					SUBTEST ($p<.001$), SUBTEST*AGE ($p=.005$)
Phonematic	11 ± 1.4	11.8 ± 1.0	8.6 ± 1.0	7.4 ± 0.8	
Semantic	20 ± 1.0	19 ± 1.3	18 ± 1.7	17 ± 1.7	
Alternate	13.4 ± 0.75	15 ± 1.5	13 ± 0.8	11 ± 1.3	
RWF errors					SUBTEST*GROUP ($p=.021$)
Phonematic	0.21 ± 0.15	0.09 ± 0.09	0.6 ± 0.3	0.9 ± 0.3	
Semantic	0.86 ± 0.18	0.73 ± 0.30	0.3 ± 0.3	1.0 ± 0.5	
Alternate	0.86 ± 0.18	0.45 ± 0.25	0.7 ± 0.7	0.3 ± 0.2	
Block span					AGE ($p=.004$)
Forward	8.6 ± 0.5	$8.1 \pm 0.$	7.0 ± 0.9	7.6 ± 0.5	
Backward	7.9 ± 0.4	6.5 ± 0.5	5.7 ± 0.5	6.4 ± 0.5	
Digit span					
Forward	7.6 ± 0.5	8.9 ± 0.6	7.1 ± 0.6	7.9 ± 1.0	
Backward	7.6 ± 0.7	7.6 ± 0.5	5.9 ± 0.5	5.8 ± 1.1	
Alertness					
Tonic	337 ± 14	360 ± 21	430 ± 57	371 ± 17	
Phasic	322 ± 12	340 ± 20	380 ± 47	340 ± 20	

A linear model was used to fit the data, featuring the proportions of tissue loss in the different structures as independent variables (MT, MDpc, LT) and the *Z*-scores achieved by patients as dependent variables. We removed from each linear fit the patients showing no damage in the target territory because these patients are the least informative with respect to the role of the target territory in memory. The model was defined as follows:

$$\text{behavior} = \text{coefficient} \times \text{lesion}$$

We used *Z*-transformed behavioral scores as a proxy for behavior, and the quantitative lesion assessment as an estimator of the proportion of tissue loss in each territory examined. This model assumes that the patients would perform the task not differently from controls, if they had no damage in the target territory, thereby allowing for separate assessments of the contribution of each territory to the deficits. The coefficient was calculated based on a simple linear regression through the origin, with a single predictor, i.e., the percentage of volume lost. This model was chosen because of the a priori hypothesis that the deficit was induced by damage in the thalamic structures examined and also because the paucity of data points (in statistical terms) warrants a parsimonious approach. It may well be that the relationship between lesion and behavior is a non-linear one, but this is the simplest possible model. The significance level was based on the distance between the data points and the regression line (see Eisenhauer, 2003 for a discussion). α was adjusted for multiple comparisons by using the Bonferroni correction. This correction is important for the linear fits performed here, because patients with no lesion in one territory (e.g., in the MDpc) still have lesions in other thalamic areas (e.g., in the LT). Since this may undermine the assumption that there is no deficit when there is no lesion in the target territory, we adopted a stricter test for the effects detected. In order to increase the power of the analysis we merged data from the different conditions (HOII, HEII, COIS, INIS). Note that the COIS condition, which featured associations between semantically related animals/objects and scenes, might elicit different cognitive processes compared to the other conditions. Correct recall of the uniquely paired associates may be facilitated by memory for pre-existent, overlearned semantic associations. To rule out this interpretation, we additionally fit the data on cued recall after excluding the COIS condition. The results of this analysis are reported in Supplementary material (Section S2.4.4.1). Additionally, we checked the results obtained through the linear fits by means of nonparametric correlations between lesions and behavioral scores (Spearman's Rho).

3. Results

3.1. Neuropsychological screening

As far as the neuropsychological assessment is concerned, we only report those tests in which a significant effect of GROUP or SUBGROUP emerged. See Supplementary material (Section S2.1) for the complete statistics. Table 3 reports the scores obtained by patients and controls and the significant effects. The neuropsychological assessment included 17 patients and 28 controls.

Patients of both subgroups (tuberothalamic; paramedian) performed poorer than controls (two subgroups: paramedian match and tuberothalamic match) in both subtests of the Logical Memory test [main effect of GROUP, $F(1,39)=27$, $p<.001$]. The ANOVA on the number of errors in the Regensburger Verbal Fluency task yielded a significant SUBTEST $\times$ GROUP interaction [$F(1.9,38)=4.2$, $p=.021$]. Patients committed significantly more errors than controls only in the phonemic subtest of the Regensburger Verbal Fluency test [$t(44)=2.8$, $p=.009$; $p>.1$ in the other two subtests].

3.2. Recognition and cued recall task

Fig. 5 shows the mean Pr for the patient and control groups. The analyses in this section included 17 patients and 28 controls. ANOVA on Pr with the factors GROUP (patients; controls) and SUBGROUP (tuberothalamic; paramedian) including Age as a covariate yielded a significant main effect of GROUP [$F(1,39)=4.2$, $p=.048$] and a significant main effect of Age [$F(1,39)=8.0$, $p=.007$]. No significant effects of SUBGROUP were found. ANOVA on the bias index with the same factors and covariates did not yield significant results.

Separate repeated measures ANOVAs with factors GROUP, SUBGROUP, CONDITION (HOII; HEII; COIS; INIS) and the covariate Age were performed for cued recall rate and non-associative hit-rate.

On cued recall rate we found main effects of CONDITION [$F(2.1,85)=12$, $p<.001$], Age [$F(1,40)=12$, $p=.001$] and GROUP [Patients performing poorer than controls, see Fig. 6a; $F(1,40)=12$, $p=.001$]. Except for a CONDITION $\times$ GROUP trend [$F(2.1,85)=2.9$, $p=.059$], no significant interactions were found (all $p>.1$). The CONDITION main effect is further analyzed in Supplementary material (Section S2.4.1). No significant effects of CONDITION or GROUP with respect to non-associative hit-rate were found [all $F<2.0$, $p>.1$] (Fig. 6b). The alternative computation of the cued recall rate as H^+/hits yielded a significant CONDITION $\times$ GROUP interaction [$F(2.1,85)=3.1$, $p=.047$] and significant main effects of

CONDITION [$F(2.1,85)=10$, $p<.001$], Age [$F(1,40)=13$, $p=.001$], and GROUP [$F(1,40)=13$, $p=.001$]. The main effects of CONDITION and GROUP mirrored the effects described above. In order to resolve the interaction, we pooled data over the factor SUBGROUP and performed four t-tests (independent samples, unequal variances after Levene's test for equality of variance, two-tailed) with the factor GROUP (one test per condition). Patients performed poorer than controls in every condition: HOII [$t(41)=3.3$, $p=.002$], HEII [$t(38)=3.8$, $p<.001$], COIS [$t(27)=2.8$, $p=.008$], INIS [$t(42)=4.6$, $p<.001$]. The t-values show that the difference between patients and controls was maximal in the INIS condition and minimal in the COIS condition.

To summarize, patients were impaired on recognition accuracy. Patients were impaired on cued recall rate (computed either ways), but not on non-associative hit-rate.

We also compared performance on category recall. Successful category recall rate was calculated as the sum of H^{+} and H^{0+} responses over total of old items shown, i.e., all the cases in which *at least* category information was available. Fig. 6c plots the results. Repeated measures ANOVA including successful category recall rate across different experimental conditions using the factors GROUP, SUBGROUP (paramedian; tuberothalamic), and CONDITION (HOII, HEII, COIS, INIS), and Age as a covariate, yielded main effects of GROUP [$F(1,40)=7.7$, $p=.008$] and Age [$F(1,40)=23$, $p<.001$], mirroring those found on cued recall rate. Older subjects achieved lower performances than younger ones. Patients showed poorer overall performance. The effect of the factor CONDITION was not significant [$F(1,40)<1$, $p>.1$].

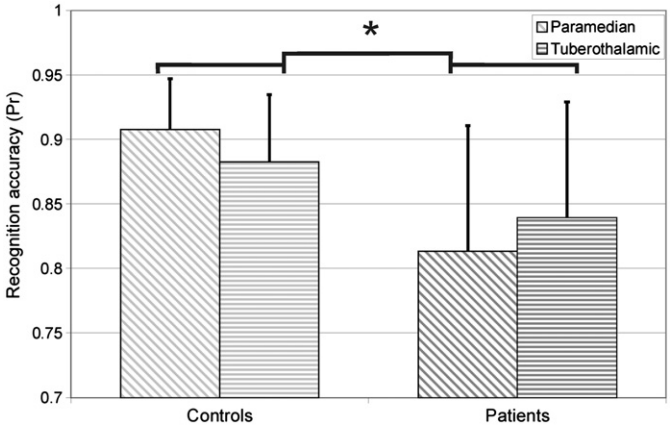

Fig. 5. Patients' and control subjects' performance in the recognition accuracy index (Pr; see definition in Section 2.4.1). This analysis included 17 patients and 28 controls. Perfect performance corresponds to 1. One asterisk indicates a significant difference ($p<.05$, two-tailed).

3.3. Response times

In the following we report the main results of the response times analysis, performed on 17 patients and 28 controls. Significant effects of GROUP are plotted in Fig. 7. The supplementary material reports the complete statistics (Section S2.4.2, Table SII). A repeated measures ANOVA comparing the response times on Hits and Correct Rejections, with the factors RESPONSE, GROUP, SUBGROUP and the covariate Age yielded a significant main effect of Age [$F(1,40)=7.1$, $p=.011$]. Patients were overall slower than controls, but this effect did not reach significance [$F(1,40)=3.3$, $p=.078$].

A repeated measures ANOVA comparing response times on H^{+} and on H^{00}, with the factors RESPONSE, GROUP, SUBGROUP, and the covariate Age yielded a significant RESPONSE × GROUP interaction [$F(1,40)=6.6$, $p=.014$]. We performed 2 post-hoc t-tests (independent samples, unequal variances after Levene's test, two-tailed) comparing the response times between groups for each type of response. Patients were significantly slower on H^{+} responses [$t(21)=2.5$, $p=.019$], but not on H^{00} responses [$t(44)=1.1$, $p=.30$].

Overall, the 17 patients tested showed a poorer performance on recognition accuracy and cued recall as compared to the 28 matched controls. There was no significant effect involving the subgroups. Patients differed from controls on the processing of the different stimulus material and on the response times, but these effects only reached significance with respect to cued recall.

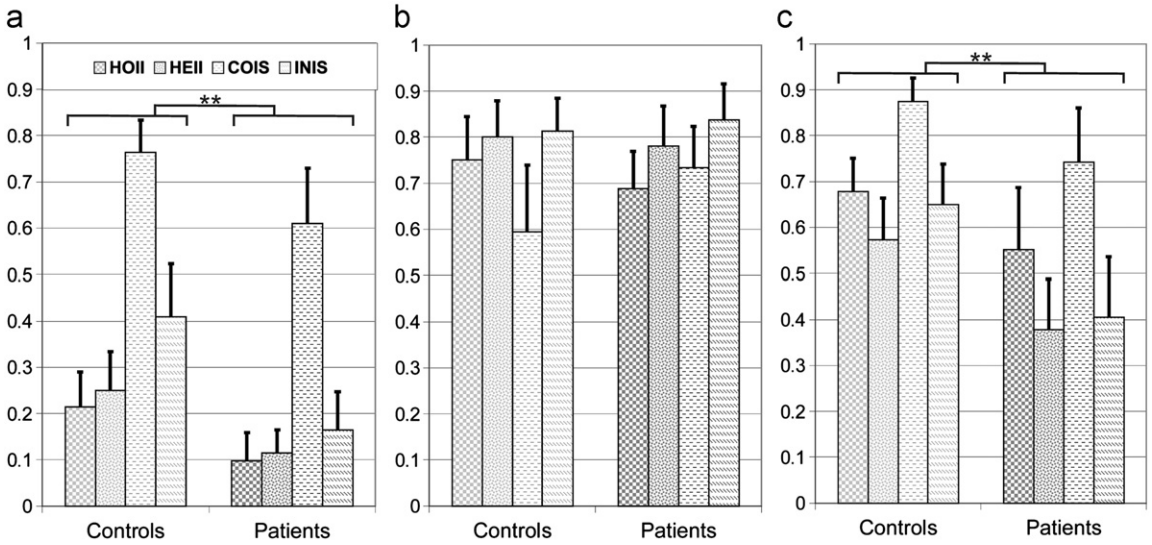

Fig. 6. Comparison of patients and controls on the memory task. The experimental conditions differ in the content of the pairs: HOII are homogeneous item-item pairs (e.g., two animals or two objects); HEII are heterogeneous item-item pairs (e.g., one animal and one object); COIS are congruent item-scene associations (e.g., lion and savannah); INIS are incongruent item-scene associations (e.g., zebra and bathroom). Note that two asterisks mark a highly significant difference ($p<.01$, two-tailed). Perfect performance corresponds to 1. These analyses included 17 patients and 28 controls. Indices are defined in Section 2.4.1. (a) Performance of patients and controls on cued recall rate (complete cued recall of the unique picture associate) separately for each condition. (b) Performance of patients and controls on non-associative hit-rate (item recognition rate in absence of correct recall). (c) Performance of patients and controls on category recall rate (proportion of old items correctly recognized as old and correctly associated to partial or complete recall of the unique paired associate).

3.4. Lesions

Table 4 summarizes the structures chiefly affected in the present patient sample according to the assessment performed through radiologic inspection by two neurologists blind to the behavioral results. Patients 1 to 9 constitute the paramedian group. Patients 10 to 17 form the tuberothalamic group. The extrathalamic damage detected in some patients was considered upon radiologic inspection typical of samples drawn from a relatively old population and was not further analyzed.

Table 5 shows the results of the estimation of the proportion of tissue loss for the patients included in the quantitative lesion assessment. Note that the analyses reported in this and the following sections included 12 unilateral patients and 18 controls. It is noteworthy that the quantitative assessment revealed a more extensive damage, compared to the radiologic inspection. This point has been discussed elsewhere (Pergola et al., 2012).

3.4.1. Z-transformation

We *Z*-transformed patients' scores on the variables on which they were impaired based on the performances of the control sample. In each case the resulting distribution did not significantly differ from the normal distribution based on Smirnow–Kolmogorov tests (including the alternative ways of computing cued recall performance; all *p*-values $>.1$).

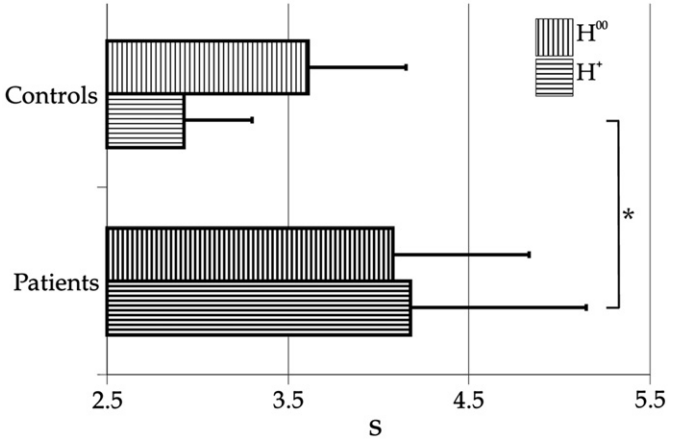

Fig. 7. Significant group effect in the response times analysis. This analysis included 17 patients and 28 controls. One asterisk indicates a significant difference ($p<.05$, two-tailed). Abbreviations: H^{00}: hit trials followed by no recall; H^{+}, hit trials followed by cued recall of the unique picture associate.

3.4.2. Role of the lesion side

To address the role of the lesion side in the observed behavioral performances, the 12 patients with unilateral lesions were divided in two subgroups according to the lesioned side. Six patients belonged to the "left subgroup" and six to the "right subgroup". The analysis yielded no significant effects of lesion side and is reported in the Supplementary material (Section S2.4.3). Following this analysis, the lesion side was not considered in the lesion-behavior correlations.

3.4.3. Lesion-behavior correlation

The volume losses of the MDpc, the MT and the LT were used as predictors for patients' performance on the *Z*-scores of Pr, cued

Table 5
Quantitative lesion description in the patients entering the lesion-behavior correlation analysis. The table reports the extent of the lesion within each considered thalamic area and, in brackets, the percentage of the volume loss in the given structure. The bottom row reports the volumes of the target structures estimated on the atlas (Morel, 2007). Patients with bilateral lesions are indicated in italic font. For these patients the table reports the lesions on the side in which the lacuna was larger. Abbreviations: MDpc, parvocellular mediodorsal nucleus; MT, medial thalamus; LT, lateral thalamus.

	MT	LT	MDpc
P2	41 mm^3 (24%)	37 mm^3 (6.5%)	18 mm^3 (4.7%)
P3	28 mm^3 (17%)	186 mm^3 (32%)	46 mm^3 (12%)
P5	61 mm^3 (36%)	64 mm^3 (11%)	12 mm^3 (3.1%)
P6	19 mm^3 (11%)	36 mm^3 (6.3%)	17 mm^3 (4.5%)
P7	3.7 mm^3 (2.2%)	39 mm^3 (6.8%)	65 mm^3 (17%)
P8	19 mm^3 (11%)	75 mm^3 (13%)	21 mm^3 (5.5%)
P9	0 mm^3 (0%)	19 mm^3 (3.4%)	0 mm^3 (0%)
P10	0 mm^3 (0%)	7.4 mm^3 (1.3%)	0 mm^3 (0%)
P11	26 mm^3 (15%)	20 mm^3 (3.4%)	38 mm^3 (9.9%)
P12	0 mm^3 (0%)	15 mm^3 (2.7%)	0 mm^3 (0%)
P13	33 mm^3 (19%)	58 mm^3 (10%)	100 mm^3 (26%)
P14	12 mm^3 (7.0%)	0 mm^3 (0%)	0 mm^3 (0%)
P15	87 mm^3 (51%)	96 mm^3 (17%)	40 mm^3 (10%)
P16	20 mm^3 (12%)	91 mm^3 (16%)	73 mm^3 (19%)
P17	0 mm^3 (0%)	19 mm^3 (3.3%)	9.3 mm^3 (2.4%)
Estimated volume	172 mm^3	573 mm^3	383 mm^3

Table 4
List of all patients with lesion locations. This table reports the result of a consensus assessment performed by two radiologists blind to the behavioral scores obtained by patients in the neuropsychological and experimental tests. Patients P1 through P9 constitute the paramedian subgroup. Patients P10 through P17 constitute the tuberothalamic subgroup. Abbreviations: ILN, intralaminar nuclei; MD, mediodorsal nucleus; VL, ventrolateral nucleus; VA, ventral anterior nucleus; VPL, ventroposterior lateral nucleus.

Subject	Thalamic nuclei	Additional damage
P1	Right VA, MD	3° ventricle enlargement
P2	Right MD	Microangiopathic changes in the basal ganglia
P3	Left MD and ILN	
P4	Left MD	Virchow–Robin spaces in the basal ganglia
P5	Right MD	Proportional brain shrinking
P6	Left MD	
P7	Right MD	Homolateral lacunae in the corona radiata
P8	right MD	
P9	Left VL, right VL, VA	
P10	Left VL	Small bilateral hippocampal sclerosis; bilateral sulcal widening, especially in the insula
P11	Left VA, VL; right VL	Microangiopathic changes in the caudatus; Virchow–Robin spaces in the basal ganglia
P12	Left VL	Microangiopathic changes in the basal ganglia
P13	Left VA, VL, MD	Proportional bilateral brain shrinking; Virchow–Robin spaces; Marklager lacunae in the basal ganglia
P14	Right VA	Small lacunae in the basal ganglia
P15	Right VL, VA, MD	
P16	Left MD, bilateral VPL	Proportional bilateral brain shrinking; Virchow–Robin spaces; Marklager lacunae in the basal ganglia
P17	Left VL	Microangiopathic changes in the basal ganglia

recall rate, response times (H^+). Patients with unilateral lesions and evidence of damage to the target area were included in these analyses. Applying Bonferroni correction for testing behavioral scores in three areas α was set to.017. Therefore, we considered the linear fits significant whenever p-values were smaller than .017; $p=.033$ was considered the threshold for non-significant trends. Fig. 8 shows the statistically significant regression plots regarding the MDpc and also includes the unstandardized coefficients of the regression. In the statistics we report the standardized coefficients (Beta). All the Z-transformed behavioral scores that we used are reported in Supplementary Table SIII.

Damage to the MDpc showed a trend towards predicting Pr [Beta$=-.71$, adjusted $R^2=.43$, $t(8)=-2.8$, $p=.023$]; significant fits were obtained with respect to cued recall rate [Beta$=-.82$, adjusted $R^2=.63$, $t(8)=-4.1$, $p=.004$] and response times (H^+) [Beta$=.79$, adjusted $R^2=.57$, $t(8)=3.6$, $p=.007$]. Damage to the MDpc predicted cued recall performance also when it was corrected for hits [Beta$=-.81$, adjusted $R^2=.62$, $t(8)=-4.0$, $p=.004$].

We checked the results of the linear fits through the origin also using a nonparametric correlation measures (Spearman's Rho; we used $\alpha=.05$). Lesion in the MDpc predicted cued recall rate, when it was computed over the total number of items shown [$n=9$, Rho$=-.75$, $p=.02$] and also when it was computed over the number of hits [$n=9$, Rho$=-.75$, $p=.021$]. The relationships between MDpc damage and memory deficits did not reach significance when ordinary least squares regressions were computed (data not shown); also the constant term of the regressions did not provide a significant fit, which is important for the reliability of the regressions through the origin dispayed in Fig. 8 (Eisenhauer, 2003).

Damage to the MT did not significantly correlate with Pr [Beta$=-.19$, adjusted $R^2=-.085$, $t(8)=-0.54$, $p=.60$], cued recall rate [Beta$=-.42$, adjusted $R^2=.073$, $t(8)=-1.3$, $p=.23$] and response times (H^+) [Beta$=.17$, adjusted $R^2=-.092$, $t(8)=0.49$, $p=.64$]. The MT did not show significant linear relationships with cued recall performance after hit rate correction [Beta$=-.41$, adjusted $R^2=.064$, $t(8)=-1.3$, $p=.24$].

Damage to the LT did not significantly correlate with Pr [Beta$=-.31$, adjusted $R^2=.004$, $t(11)=-1.0$, $p=.33$] and response times (H^+) [Beta$=.33$, adjusted $R^2=.020$, $t(11)=1.1$ $p=.30$], but showed a trend towards predicting cued recall rate [Beta$=-.65$, adjusted $R^2=.42$, $t(11)=-2.7$, $p=.022$]. The LT also showed a trend towards predicting cued recall corrected for hits [Beta$=-.65$, adjusted $R^2=.37$, $t(11)=-2.7$, $p=.022$].

Supplementary material (Section S2.4.4.1) reports the same tests performed on cued recall rates in which the condition featuring a semantic link between the components of a pair (COIS) was excluded. The finding that MDpc predicts a deficit in cued recall remained robust when alternative methods to compute recall/recollection performances were probed.

4. Discussion

To our knowledge this is the first study using a quantitative lesion assessment to evaluate the memory performance of a group of patients with focal lesions of the thalamus. Our aim was threefold. First, we tested recognition memory in 17 patients with thalamic lesions. Patients showed significantly poorer recognition accuracy than controls. Second, we predicted that the recall/recollection component of recognition memory would be impaired. The results on cued recall performance supported the hypothesis. There was no significant non-associative hit-rate impairment. This suggests that the impairment detected on recognition memory is related to a recall/recollection deficit. Third, we fit patients' deficits as linear functions of the damage to thalamic regions defined based on connectivity. Evidence from cued recall rate and response times converged to indicate that the behavioral impairments covary with the damage to the MDpc. This finding was even valid when a number of alternative ways to compute recall performance was employed.

We controlled for deficits in other cognitive domains by using standard neuropsychological tests. The patient sample was selectively impaired on verbal recall. Patients also committed more errors in the phonemic subtest of the Regensburger Verbal Fluency test, which might suggest impaired executive function, or might relate to concurrent impairment on verbal recall, since most errors were perseverations.

The present results extend previous experimental evidence by separately assessing the contribution of the MD subunits, by

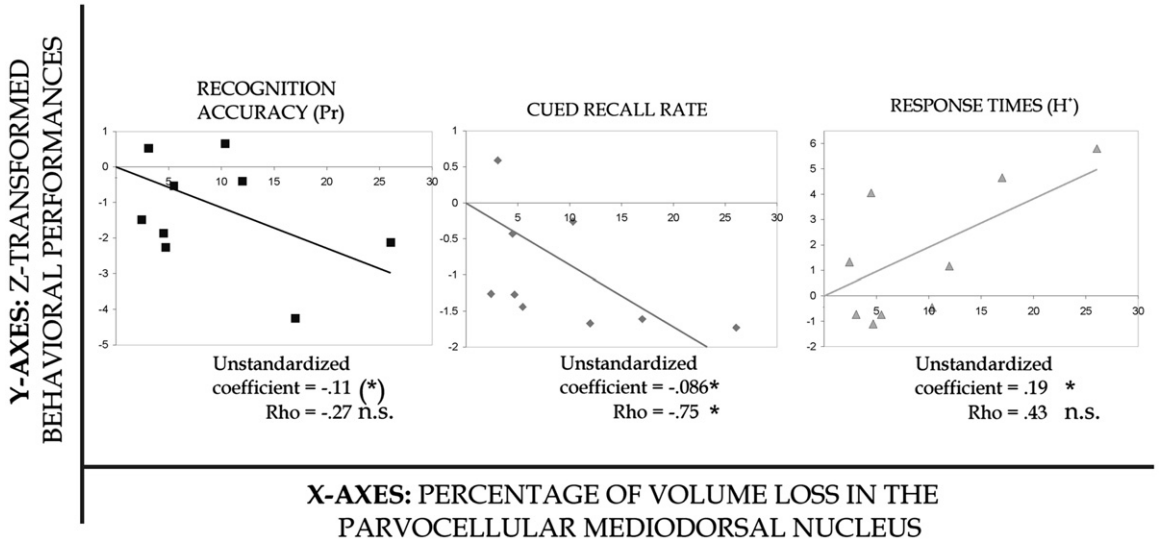

Fig. 8. Relationship between the volume loss in the parvocellular mediodorsal nucleus, expressed in percentage and shown on the horizontal axis, and patients' performance, expressed in Z-scores and shown on the vertical axis. One asterisk indicates a significant fit ($p<.017$ after correction for multiple comparisons, two-tailed, for the linear fits; $p<.05$, two-tailed, for Spearman's Rho), one asterisk between brackets labels a non-significant trend ($p<.033$, two-tailed, for the linear fits). This analysis included 9 patients, after exclusion of bilateral patients and patients with no damage in the parvocellular mediodorsal nucleus. Z-scores were computed based on the distribution on the behavioral measures of a sample of 18 controls matched with the patients. Behavioral indices are defined in Section 2.4.1. The unstandardized coefficient represents the slope of the regression line; rho is Spearman's correlation coefficient. Abbreviations: Pr, performance index; H^+, trials in which a hit was followed by cued recall of the unique picture associate.

testing a larger group of patients, by using a process-pure method for probing recall/recollection and a quantitative analysis of the lesions (Cipolotti et al., 2008; Giovanello, Verfaellie, & Keane, 2003; Soei et al., 2008; Van der Werf et al., 2003; Zoppelt et al., 2003).

4.1. Multiple neural systems support recognition memory: The value of recall as a probing task

The single-item old/new assessment is a standard task to probe recognition (see Montaldi & Mayes, 2010 and Wixted, Mickes, & Squire, 2010, for a methodological review). The cued recall task allowed directly probing the recall/recollection abilities of the participants independently of subjective ratings. Subjects could not perform forced choices, so they could solely rely on the recall/recollection system to perform the task. Non-associative hit-rate was assessed using those trials in which recognition was performed without retrieving associated information, which do not strictly require the recall/recollection system. Patients showed no deficit in non-associative hit-rate, and this finding is consistent with the thesis that the MDpc participates in recall/recollection processing. It should be pointed out that the non-associative hit-rate is not a pure familiarity measure, because recognition without retrieval of associated information may still be based on single item recall/recollection (non-criterial recollection: see Yonelinas, Aly, Wang, & Koen, 2010). However, hits followed by cued recall of the unique paired associates are most likely based on recall/recollection (Montaldi & Mayes, 2010).

The question stands whether recall might be effectively cued in patients by showing the whole pair and avoiding naming of the items. This possibility was discounted by Soei et al. (2008), who found that patients with medial thalamic lesions were impaired in a forced choice relational memory assessment. Another interpretation of the present findings alternative to a specific involvement of MDpc in cued recall is that the greater impairment shown by patients on cued recall, as compared to non-associative recognition, is a consequence of greater representational complexity (Cowell, Bussey, & Saksida, 2010). We took this argument into account, and therefore asked subjects to retrieve the category to which the associate belonged. Partial cued recall also relies on recall/recollection, as suggested by evidence that the HC is involved in performance of cued recall of categories (Ryan, Cox, Hayes, & Nadel, 2008). This task does not require naming the stimuli (the experimenter provided the categories) and, similarly to forced choice, it does require associated information, but not the ability to retrieve a full visual representation of the item. Patients were impaired also in this case: task complexity alone does not satisfactorily account for the patients' impairment (see also Giovanello et al., 2003).

Controls, but not patients, responded faster in H^{+} trials than they did in H^{00} trials, i.e., when they were able to recall the unique association. The present findings accord with the available evidence (Dewhurst, Holmes, Brandt, & Dean, 2006). Subjects were explicitly asked to refrain from trying to recall the pair before the old/new assessment. We suggest that the selective impairment found on H^{+} trials reflects slowing down of recall/recollection processing in patients.

We sought to gain further insight about more fine-grained aspects of recall processing by sorting stimuli so that different conditions were generated. One condition (COIS) featured a strong semantic link relating the two components of a pair. Both patients and controls performed significantly better on cued recall in the COIS condition as compared to all three other conditions (Fig. 6a), possibly due to more efficient unitization based on semantic memory (Mayes et al. 2007; Quamme et al., 2007). It was therefore important to demonstrate that the linear relationships established between lesion localization and behavior were not driven by performance in this condition: tests not including the COIS condition showed that our findings persist when this condition is excluded (Supplementary material, Section S2.4.4.1). Patients performed significantly poorer than controls also in the COIS condition. These results suggest that selective impairment on recall/recollection is related to impaired recall of any material, including "unitized pairs". Critically, in the test phase subjects were not presented pairs, but single items, which is different from the procedure used by Quamme et al. (2007).

4.2. Methodological issues concerning the lesion assessment

We provided quantitative estimates of the damage to the structures we focused on. The resolution offered by this method is critical for the reliability of our key finding—the specific involvement of MDpc in recall/recollection. The procedure applied can reach a theoretical resolution of 2.2 mm^3 (Pergola et al., 2012). For the present study, however, it was not critical to precisely assess the volume lost in each thalamic substructure—which could only be done with post-mortem analyses (Gold & Squire, 2006; Harding, Halliday, Caine, & Kril, 2000). What was crucial was ranking the extent of the damage across the patient sample in order to relate it with behavior. This depends on the structures analyzed and on the patient sample. Based on the image resolution, the minimal measureable percentages of volume loss were 1.3% for the MT, 0.38% for the LT, 0.57% for the MDpc. The median patient-to-patient difference was one order of magnitude greater: 12% for the MT, 6.6% for the LT, 7.0% for the MDpc. Of all the patient-to-patient differences, over 91% fell within the resolution of the assessment. These numbers support the reliability of the quantitative assessment used.

A more important difficulty relates to demarcating the borders of a lesion on an MR-generated grayscale image. This applies to any lesion assessment and may be particularly challenging for the analysis of periventricular MT lesions. MR imaging, however, is considered reliable for ischemic lesions assessment (Flossmann, Redgrave, Briley, & Rothwell, 2008; Stoffel et al., 2004). The procedure most likely results in an underestimation of the damage (Kraemer et al., 2004). It cannot be excluded that non-apparent lesions to adjacent regions contribute to the observed behavior (Aggleton et al., 2011). The fact remains that the core area of the lesion is most likely dysfunctional, hence there is a higher likelihood that impairments depend on apparent – rather than non-apparent – damage.

Current findings are supported by the outcome of an established overlap/subtraction analysis, which is reported in Supplementary material (Section S2.3): a cluster of voxels in the MDpc was significantly related to recall deficits. Note that the overlap/subtraction analysis was conducted using an automated whole-brain normalization and subsequent transformation of the coordinates into the atlas space. Therefore, the spatial processing of the brain images was independent from the quantitative assessment. As briefly mentioned in the introduction, it is possible that white matter lesions located in the territory of a thalamic nucleus contribute to the observed impairments (Aggleton et al., 2011). The quantitative analysis performed here bears a conceptual advancement, compared to the overlap/subtraction procedure. The overlap/subtraction procedure reveals voxels damaged in impaired but not in unimpaired patients; yet the origin of the impairment may lie in the gray or white matter. The quantitative analysis instead relates behavior to damage in any region of the target nucleus, and not necessarily in a specific location eventually including white matter tracts, thereby reducing the probability of a spurious lesion-behavior correlation. Although in principle this limitation remains, the consistent results obtained with the two techniques support the involvement of the MDpc in the recall deficits observed in this clinical sample.

Based on these observations, we conclude that the quantitative procedure used reliably ranks damage to given structures across the patient sample. The use of parametric statistics to address ranking scores may be questioned. Even though we examined a relatively large number of patients, the sample size is hardly suitable for nonparametric tests. We decided to use linear fits to provide a more sensitive test of the relationship between tissue loss and behavioral scores. However, the association between damage in the MDpc and cued recall performance persisted when a nonparametric index was used (Spearman's Rho). The overlap/subtraction analysis also relied on nonparametric statistics. The relationship between tissue loss in the MDpc and recall impairments was very robust in the present investigation.

The lesion side did not affect results significantly—although the sample size (12) may be too small to allow conclusive results in this respect. Moreover, the heterogeneity of lesion etiologies may hinder attempts to address laterality effects on the deficits shown by the present clinical sample. It should be noted, however, that Carlesimo et al. (2011), in their meta-analysis including a total of 83 patients, also found weak evidence supporting an effect of the lesion side on recognition memory performance.

The assessment of the lesion-behavior relationship in bilateral patients remains a further problematic issue. In order to ensure that our results were not driven by this potentially confounding factor, we excluded the three patients with bilateral lesions from the sample for the linear fits and the nonparametric correlations.

4.3. Significance of the present results in light of the anatomy of the thalamus

We found that impairments of the patients on cued recall and response times covaried with damage to the MDpc; the association between deficits on recognition accuracy and damage to the MDpc fell short of significance. There was also a trend associating damage to the LT with deficits on cued recall. The literature relating LT with memory is controversial. Lopez et al. (2009) reported intact acquisition, but impaired remote retrieval in rats with LT lesions on a spatial memory task. Notably, the lesions also included the MDpc. Savage, Sweet, Castillo, and Langlais (1997) found that impairment on acquisition and retention of a spatial memory task in rats with intralaminar nuclei/midline nuclei lesions were at least in part due to concurring cell degeneration in the AT. The case reported by Van der Werf et al. (1999), based on the sections provided in the article, displayed a selective intralaminar nuclei lesion, but the impairments were unselective, involving memory as well as attention, executive function, and IQ. With respect to the present results, lesions involving the LT may also have damaged the MDpc or its efferents. Another possible explanation is that the LT contributes to accessory operations which are important for recognition memory (Aggleton et al., 2011). Indeed, in the present sample also some patients with little or no detectable damage in the MDpc showed recall deficits. The trend we found with respect to the LT agrees with the multi-effect multi-nuclei model of the thalamic contribution to recognition and recall/recollection (Aggleton et al., 2011).

Limited volume losses in the MD correlated in the present study with significant impairment, in contrast to previous studies (Kritchevsky, Graff-Radford, & Damasio, 1987). Notably, the case reported by Kritchevsky et al. (1987) displayed a medial lesion, thus it is possible that most of the damage was sustained by the MDmc. Failure to observe memory impairments after MD lesions may partly relate to the different thalamo-frontal connectivity of the MD subunits.

Five patients showed damage in the putative region of the *mtt*, which may be relevant with respect to the interpretation (Carlesimo et al., 2011). The *mtt* is too small to allow quantitative assessment of lesions based on MR images. However, it is visible as a white area on T1 scans, when intact, so that we could qualitatively evaluate its involvement in the lesion. In particular, we checked slice by slice whenever the lesion encroached on the *mtt*, based on its location on the anatomical atlas used (Morel, 2007). Whenever the lacuna trespassed the borders of the *mtt*, we considered it as being damaged. Note that this is a conservative procedure, because partial damage may not disrupt the function of the *mtt*.

We tested whether the pattern of impairments above described applied to the subset of patients who did *not* present with a lesion to the *mtt* (Patients 2, 3, 5, 6, 7, 8, 9, 10, 12, 16) by comparing them to the control group (18 subjects; the analysis is reported in Supplementary material, Section 2.4.5.1). With respect to this subset of patients it is important to highlight that all patients were tested in the chronic phase of the disease (minimum lesion-test interval was 12 months for patient P12; patients P10 and P15 were tested, respectively, 15 and 20 months after infarction, all other patients after at least 2 years). Therefore it is unlikely that the lesion could affect the functionality of the surrounding non-lesioned tissue due to edema or inflammation. We additionally tested whether the subgroups of patients with and without overt damage to the *mtt* differed in the key variables assessed (Supplementary material, Section S2.4.5.2). The rationale for this analysis is that according to other reports it may be hypothesized that the subgroup of patients with lesioned *mtt* performed poorer than the patient sample without evident *mtt* lesion (Carlesimo et al., 2007; Cipolotti et al., 2008; Van der Werf et al., 2003).

Patients with no evidence of *mtt* damage performed poorer on recognition accuracy and cued recall compared to controls. Notably, these patients only displayed a trend towards impairment on category recall and on response times. Restricting the sample also reduces statistical power, which may explain the reduced significance of the findings on category recall and response times. However, the impairments on recognition accuracy and cued recall rate remained significant in this subset of patients. Moreover, the subgroups of patients with or without apparent damage in the *mtt* did not significantly differ with respect to recognition accuracy, cued recall rate and reaction times (Supplementary material, Section S2.4.5.2). Control variables such as age, age at lesion onset, time passed since lesion onset and performance in the Logical Memory test were also matched between subgroups. Besides, we could not detect differences between patients with tuberothalamic ischemia (in whom the lesion has a higher probability to encroach on the *mtt*: Schmahmann, 2003) and patients with paramedian ischemia (in whom the probability of damage in the LT is higher, but the probability of damage to the *mtt* is lower). Indeed, the inter-individual variability of the thalamic arterial supply is high (Carrera & Bogousslavsky, 2006), and a larger sample size may be needed to differentiate the two subgroups of patients. Several nuclei are supplied by both arteries, including the MD, which may partly account for the homogeneity of cognitive deficits across the two clinical subgroups.

Based on this evidence we cannot conclude that damage to the *mtt* biased current results towards a falsely positive involvement of the MDpc in the deficits we measured. It is still likely that this factor affected the data, and particularly the group comparisons with controls, but there is no evident reason why it should inflate the statistics on the MDpc, and not on the MT and the LT involvement.

At first sight there is discrepancy between our findings and the findings by Van der Werf et al. (2003), who located in the *mtt* the area related to amnesia in a clinical group study. In the overlap/subtraction analysis reported in the Supplementary material (Section S2.3) we used the same statistical tools used by Van der Werf et al. (2003). The authors performed the analysis on 10 "cognitively clean" patients by selecting the subsamples of affected vs. unaffected patients based on the diagnosis of amnesic syndrome (Van der Werf et al., 2003, page 1340). We used performance on the

cued recall task to allocate patients to subgroups (instead of diagnosis of amnesia) and found that the MDpc was the key region for the behavioral deficit at hand (Supplementary material, Fig. S2). It is therefore possible that damage to the MDpc causes milder memory impairments, which need a more sensitive assessment to be detected, compared to lesion to the *mtt*.

We conclude that the present results do not undermine the importance of the integrity of the *mtt* and of other thalamic regions, such as the MT and the LT for cued recall performance, but rather highlight the role of damage in the MDpc in originating recall/recollection impairments.

4.4. Putative functions of the MD and its network

Based on the present data, lesion to the MDpc impairs cued recall and thus the recollection component of recognition memory. This evidence is not in agreement with the dichotomic framework proposed by Aggleton and Brown (1999). The hypothesis put forward by Aggleton et al. (2011) about a graded involvement of several thalamic nuclei in recall/recollection is more consistent with the current findings. However, these results suggest that the MDpc is critical for recall/recollection, rather than generally contributing to recognition memory. Based on further evidence, it is possible to hypothesize that the MDpc is involved in different cognitive tasks requiring binding of sensory representations: episodic cued recall, semantic object activation and future thinking (Assaf et al., 2006; Mottaghy et al., 1999; Weiler, Suchan, Koch, Schwarz, & Daum, 2011), although none of these studies analyzed differentially the MD subunits. The operations above mentioned may be crucial for memory function (Aggleton et al., 2011). The MT is not selectively connected to the perirhinal cortex, but to many areas in the MTL and the VMPFC, so that it may be discussed on what neuroanatomical basis a selective impairment on familiarity should be predicted. However, a recent study on rodents suggested a role of the amygdala in familiarity-based recognition (Farovik, Place, Miller, & Eichenbaum, 2011). The amygdala heavily projects to the MDmc, and current results do not rule out the possibility that this area contributes to recognition based on familiarity. These findings instead suggest that recall/recollection in humans requires integrity of the MDpc, likely due to its connections to the DLPFC (Van der Werf et al., 2003).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2012.06.019.

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