

Thalamic volume predicts performance on tests of cognitive speed and decreases in healthy aging. A magnetic resonance imaging-based volumetric analysis.

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Research report

Thalamic volume predicts performance on tests of cognitive speed and decreases in healthy aging

A magnetic resonance imaging-based volumetric analysis

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Abstract

Recent studies have indicated a role for the thalamus in attention, arousal and the capacity to perform tasks of speeded information processing. The present study evaluated the role of the thalamus in age-related cognitive decline by investigating the correlations between thalamic volume, cognition and age. This was done in 57 healthy subjects ranging from 21 to 82 years of age. All subjects underwent neurocognitive testing with information processing tests and structural magnetic resonance imaging. A significant decrease in volume of the thalamus with increasing age was found, relatively stronger than and independent of the decrease of total brain volume. The decrease of thalamic volume was apparent before the onset of loss of volume of the total brain. Over the age-span studied, the thalamic decrease in volume correlated with the diminished performance on tests of cognitive speed. Additionally, in young and middle-aged, but not in old subjects, the size of the thalamus predicted performance on tasks that require cognitive speed. © 2001 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behavior

Topic: Cognition

Keywords: Thalamus; Magnetic resonance imaging; Volumetry; Mental chronometry; Aging; Attention

1. Introduction

Several functional imaging studies have shown that the thalamus in healthy young adults is activated in tasks requiring arousal, vigilance, speeded information processing and attention [24,34,36,12,22,21,46]. These capacities are at risk for the effects of aging [2,8]. It has, indeed, been argued that cognitive speed decrements with increasing age are central to impairment of cognitive functioning

[10,42,40]. It is unknown whether the thalamus plays a role in the age-related declines in cognitive performance. We therefore wanted to investigate the role of the thalamus in tasks of speeded processing, in relation to both healthy cognitive performance and age-associated decrements of cognition.

Structural magnetic resonance imaging-based volumetry in combination with neuropsychological test administration offers the possibility of assessing large cohorts of healthy subjects of different ages. This circumvents the problem inherent in clinical studies of inferring normal brain functioning from damaged brains. Functional imaging studies using healthy subjects do not have such drawbacks. On the other hand, they tend to rely only on young subjects: the functional imaging studies mentioned above

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have used subjects aged 44 years or younger. A caveat of the volumetric approach, nevertheless, lies in the fact that the nature of the data is correlational and causal inferences can therefore not be drawn.

For this study, we assembled a large cohort of normal subjects ranging from 21 to 82 years old. Care was taken to avoid inclusion of older subjects characterized by a subclinical medical condition. This was done since previous research has shown that elderly subjects considered 'gerontologically healthy' might be structurally or cognitively affected by conditions such as diabetes mellitus, mild hypertension or repeated anaesthesia [17,41,16,50]. The present study therefore uses subjects who have passed a rigorous health screening to avoid the above-mentioned confounding effects [20].

We used a set of tests selected to examine different aspects of cognitive speed. The tests used have in common the fact that they have subtests at different levels of difficulty of the mental operation, while the context of the test remains the same. In this way, the mental load of a test is varied parametrically [44]. This allows one to differentiate between speed of simple and complex information processing, respectively; in addition, the difference between the complex and simple tasks reflects the increase of mental load and can be regarded as a measure of working memory [4,33,28].

We predicted that in this population of healthy subjects the size of the thalamus was related to measures of cognitive speed regardless of age; in addition we predicted that the age-related decrements in tasks requiring speed and working memory correlated with the volume of the thalamus.

2. Materials and methods

2.1. Subjects

Fifty-seven healthy control subjects were included in this study. Written informed consent according to the declaration of Helsinki was obtained from all subjects.

Subjects were recruited via newspaper advertisements. Exclusion criteria consisted of an IQ below 80, use of psychotropic medication, depression, dementia, diabetes mellitus, liver disease, central nervous system diseases, hypertension, current or previous alcoholic beverage intake of more than 28 units per week and cardiac, pulmonary or

endocrine diseases. Subject characteristics are given in Table 1. The subjects were divided in three age groups: 21–45 years ($n=18$), 46–60 years ($n=15$) and 61–82 years old ($n=24$), respectively. By analyzing the correlations between thalamic volume and cognitive variables within the three groups as opposed to within the whole age-range, we attempted to discard the effects of age as a confounding variable. It has been shown that age explains the major part of the variance in cognitive performance in studies that use a wide age-range [48].

Of one subject in the young group, no neuropsychological data were obtained. Of one subject in the middle-aged group, no intracranial volume and total brain volume could be obtained due to motion artefacts.

2.2. Magnetic resonance imaging

Inversion recovery (IR) scans (TR 2107 ms, TE 18 ms, TI 300 ms, ETL 3, flipangle 90°, number of averages 2, FOV 230 mm, matrix 256*177, 40 consecutive slices) and three-dimensional (3D) volumetric scans (T1 weighted, fast-field echo, TR 24 ms, TE 7 ms, flipangle 30°, number of averages 2, FOV 230 mm, matrix 256*154, 124 consecutive slices) were made on a 1.5 Tesla scanner (Gyrosan ACS-II, Philips). Slice thickness of the IR scans was 3 mm and for the 3D scans 1.5 mm. The scanning axis was coronal, perpendicular to the long axis of the hippocampus. The scanned images were transferred to a SUN Ultra Sparc workstation and image analysis was performed.

2.3. Structure delineation

Volumetry of the thalamus was performed using ShowImages software (developed at the Department of Clinical Physics and Informatics, Vrije Universiteit, Amsterdam, The Netherlands). The thalamus was outlined manually with fixed contrast and brightness. As reference a magnetic resonance imaging neuroanatomical atlas was used [18]. The left and right thalami were outlined on 8–12 coronal slices (average 10) using the IR scans. Volumes were calculated by summing the surfaces enclosed by the outlines multiplied by the thickness of the slice. Criteria for thalamic segmentation were as follows (see also Ref. [35]): the anterior boundary of the thalamus was defined as the first slice directly caudal to the anterior commissure. At all levels the thalamus is bordered medial-

Table 1
Subject characteristics^a

Group	<i>n</i>	M/F	Age range (years)	Mean level of education (S.D.)	Mean IQ (S.D.)
All subjects	57	32/25	21–82	2.72 (1.15)	120.3 (12.6) ($n=43$)
Young subjects	18	11/7	21–45	3.33 (0.69)	118.4 (12.2) ($n=12$)
Middle-aged subjects	15	10/5	46–60	2.40 (0.74)	120.5 (11.5) ($n=8$)
Old subjects	24	11/13	61–82	2.46 (1.44)	121.3 (13.6) ($n=23$)

^a Level of education is measured on a five-point scale, ranging from primary school to university degree.

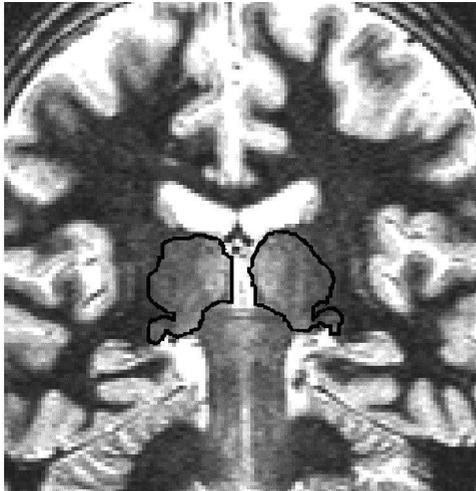


Fig. 1. Example of an inversion recovery magnetic resonance imaging scan used for measurement of the thalamus. The scan is a section through the middle level of the thalamus, where it includes the lateral geniculate and medial geniculate nucleus. Left and right thalamus are outlined separately.

ly by the third ventricle, dorsally by the lateral ventricles and laterally by the capsula interna on both sides. Ventrally, the thalamus rests upon the temporal horn of the lateral ventricle, the hypothalamus and the mesencephalon. At rostral slices, care was taken to avoid inclusion of the columnae fornicis and the mammillary bodies. At middle levels, inclusion of the nucleus subthalamicus and the nucleus ruber was avoided. The medial geniculate nucleus and the lateral geniculate nucleus were included in the outline at levels where the lateral geniculate nucleus was attached to the corpus of the thalamus and not separated from it by a white matter tract. At caudal levels, the thalamus was defined as the region below the fornix. Measurements were performed by a single experimenter who was blind to the diagnosis. The intra-rater reliability for the thalamic volumes was 0.92, calculated as Pearson's correlation coefficient over 12 remeasured images, i.e., 24 thalami (left and right). The measuring error, including instrumental and personal error, was calculated as the standard error of the mean of a 10-fold remeasurement of

two cases: this proved to be less than 1%. Inter-rater reliability of eight thalami, measured in parallel by a second rater, was 0.74. The latter error proved to be systematic, with one rater consistently showing larger estimations of thalamic volume. The relatively low inter-rater reliability did therefore not interfere with the reliability of measurement performed by the principal experimenter. Fig. 1 depicts an example of an image used to delineate the thalamus.

Intracranial volume was automatically determined from the 3D scans for all subjects using custom software developed at the Department of Medical Informatics of the Universiteit Maastricht, Maastricht, The Netherlands, running on a G3 MacIntosh workstation (Apple, Cupertino, CA, USA). This procedure generates a contour around all neural tissue, excluding the meninges and bone structures. All contours were visually inspected and where necessary manually adjusted (e.g., removal of meninges). Structures below the pons were manually excluded from the contours.

Subsequently, the total brain volume was determined from the 3D scans with an automated segmentation algorithm [32] using the program BrainImage [47]. This algorithm calculates the mean grey-level intensity of white matter, grey matter and cerebrospinal fluid, with the cut-off value between cerebrospinal fluid and grey matter indicating the separation of brain tissue from non-tissue.

2.4. Cognitive measurements

Speeded information processing was measured with the Stroop test [45] and the Paper and Pencil Memory Scanning Test (PPMST; [3,17]). These tests both contain subtests measuring simple speeded processing and subtests measuring complex speed. The difference in performance between the simple and complex task can be used as a measure of working memory. The subtests and constructs used to measure simple and complex speed and working memory are shown in Table 2.

The Stroop test consists of a reading condition in which the subject is required to read out loud as fast as possible the names of color words; a similarly administered color naming condition; and an interference condition, in which

Table 2
Tests administered to the healthy control subjects and patient groups^a

Cognitive variable	Test used	Operationalization
Speeded processing – simple	PPMST	% symbol subtest and 1 letter subtest
	Stroop	Mean of Stroop parts reading and color naming
Speeded processing – complex	PPMST	Two letter subtest
	Stroop	Stroop part interference
Working memory	PPMST	Two letter subtest minus 1 letter subtest
	Stroop	Stroop part interference minus parts reading and color naming
Intelligence	GIT	Three-subtest version

^a Abbreviations: PPMST, Paper and Pencil Memory Scanning Test; GIT, Groningen Intelligence Test.

color naming is required of color words printed in non-matching ink. The PPMST was developed as a test that employs a Sternberg paradigm modified to be used in a written version. It consists of several subtests that all require the subject to search for, and cross out, typographical characters (% symbol, 1 letter or 2 letters) on a sheet with distractor letters. The memory load is thus varied by changing the number (1 or 2) and nature (symbol or letter) of the characters to be remembered. The short form of the Groningen Intelligence Test (GIT; [27,26]) was used to obtain a measure of general intellectual functioning.

2.5. Statistical analyses

For all analyses SPSS 9.0 for Microsoft Windows software was used. Effects were judged to be significant below $P=0.05$. Since the size of the thalamus can be related to congenital factors such as head size and to developmental factors such as brain shrinkage due to age, we corrected the thalamic volumes for intracranial volume and size of the total brain. This was done by means of a linear regression analysis: expected values of thalamic volume were calculated from regression of thalamic volumes on intracranial volume and total brain size. Residuals were then calculated by subtracting the expected values from the individual thalamic volumes. Subsequently, the residuals were added to the group mean of the thalamic volumes, thereby eliminating correlations with total intracranial volume and brain size and thus possible confounding effects. To compare volumes of brain structures between the different age groups, one-way analyses of variance with Tukey's test for posthoc comparisons were used. These groups were chosen such that each group contained a sufficient number of cases to obtain statistical power for the correlational analysis within and between groups [group 1: 20–45 years ($n=18$), group 2: 46–60 years ($n=15$), group 3: 61–82 years ($n=24$)].

For the analysis of cognitive variables and thalamic size within the age groups, the volume of the thalamus was corrected for the effects of intracranial volume, brain size and age, in an attempt to avoid as many confounding variables as possible. The correction was performed in the same way as described above.

Symmetry of volume of the left and right thalami was calculated with a paired samples t -test. Differences between men and women were tested with a t -test for equality of means.

3. Results

3.1. Age and the thalamus

Total thalamic volume was found to correlate highly significantly with age; a clear downward slope was apparent over the entire age range ($r=-0.707$, $P<0.001$). When

the thalamic volumes were statistically adjusted for intracranial volume and total brain size, the Pearson's correlation coefficient for the relation between age and total thalamic volume was still significant ($r=-0.280$, $P=0.037$, Fig. 2).

Table 3 shows the summary statistics for the analyses of variance with Tukey's multiple comparisons for the different brain structures studied. Thalamic volume differed across the three age groups, the difference occurring with the transition from the young group to the middle-aged group (thalamic volume adjusted for total brain volume and intracranial volume: $F=4.563$, $P=0.015$). The brain in total also decreased in volume significantly with increasing age, whereas intracranial volume remained similar across the age range ($F=7.106$, $P=0.002$ and $F=0.743$, $P=0.480$, respectively). The relative decrease in volume of the thalamus and the total brain is given in Table 4 and shown in Fig. 3.

No gender difference appeared (thalamic volumes adjusted for intracranial volume, total brain volume and age: $n=56$, $t=-0.391$, $P=0.697$). No asymmetries were noted between the left and right thalamus ($n=57$, $t=1.294$, $P=0.201$).

3.2. The thalamus and cognitive functioning

In the whole group of healthy control subjects, the unadjusted volumes of the thalamus correlated highly significantly with performance on the different tasks of cognitive speed, i.e., the subtests of the Paper and Pencil Memory Scanning Test and the Stroop task (not shown). These significant correlations were apparent irrespective of

Total thalamic volume (mm³)

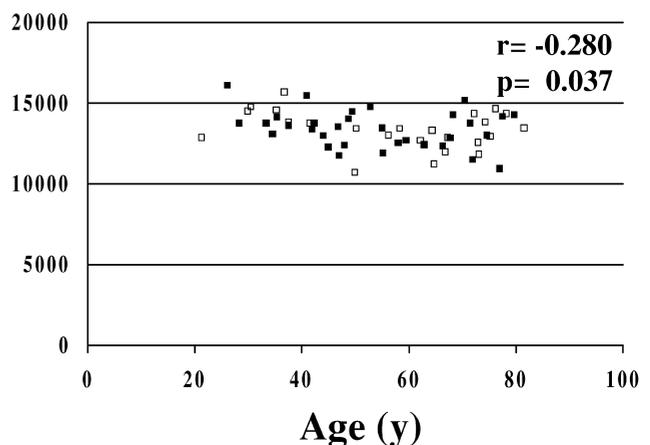


Fig. 2. Relationship between size of the thalamus, statistically adjusted for the effects of intracranial volume and brain size, and the age of the healthy subjects. Men are indicated with solid squares, women with open squares. Pearson's correlation coefficient and level of significance are given.

Table 3
Volumes of brain structures for the three age groups

Variable	Young subjects (<i>n</i> =18) Mean (S.D.)	Middle-aged subjects (<i>n</i> =14) Mean (S.D.)	Old subjects (<i>n</i> =24) Mean (S.D.)	<i>F</i>	<i>P</i>
Thalamic volume unadjusted measurements (in 10 ³ mm ³)	15.29 (1.32)	13.41 (1.97)	12.22 (0.94)	25.213	<0.001 ^{a,b,c}
Thalamic volume adjusted for intracranial volume and total brain volume (in 10 ³ mm ³)	14.01 (1.01)	13.00 (1.12)	13.11 (1.14)	4.563	0.015 ^{a,b}
Total brain volume (in 10 ⁶ mm ³)	0.86 (0.06)	0.84 (0.08)	0.78 (0.07)	7.106	0.002 ^b
Intracranial volume (in 10 ⁶ mm ³)	1.04 (0.08)	1.03 (0.09)	1.01 (0.09)	0.743	0.480

^a Significant difference between young and middle-aged subjects (Tukey, *P*<0.05).

^b Significant difference between young and old subjects (Tukey, *P*<0.05).

^c Significant difference between middle-aged and old subjects (Tukey, *P*<0.05).

Table 4
Relative sizes of the thalamus adjusted for intracranial volume and total brain size and of the total brain volume for the three age groups^a

	Young (S.E.M.)	Middle-aged (S.E.M.)	Old (S.E.M.)
Thalamus unadjusted measurements	100 (2.0)	87.7 (3.3)	79.9 (1.3)
Thalamus adjusted for ICV and total brain size	100 (1.7)	92.8 (2.1)	93.5 (1.7)
Total brain	100 (1.7)	96.9 (2.6)	90.4 (1.7)
ICV	100 (1.7)	99.2 (2.4)	96.9 (1.8)

^a ICV, Intracranial volume; S.E.M., standard error of the mean.

statistically adjusting for total brain volume and/or intracranial volume. However, when the thalamic volumes were additionally adjusted for the effects of age, all correlations with performance on the tests disappeared (Table 5).

When the data were analyzed for the three different age-groups separately, several cognitive variables in the group of young subjects (20–45 years) proved to correlate significantly with thalamic volume, when adjusted for intracranial volume, total brain volume and age. These variables were the speed of completing both the simple and

complex subtests of the Paper and Pencil Memory Scanning Test. Significant correlations were also found for the Stroop test working memory. The relationship was such, that subjects with bigger thalami performed better on each task than subjects with smaller thalami. Fig. 4 shows the relationship between thalamic volumes and the performance on a task for simple cognitive speed, the % subtest of the Paper and Pencil Memory Scanning Test for the young subject group.

In the group of middle-aged subjects (46–60 years) a significant relation showed up between all measures of the Stroop test and the volume of the thalamus, adjusted for intracranial volume, total brain volume and age. In the old group of subjects (61–82 years), no significant relations could be detected.

Performance data of the subjects on the tasks administered are given in Table 6. In general, the variance of test results increased from the young to the middle-aged and old subjects.

4. Discussion

We have shown here, using a correlational approach in a group of healthy subjects, that a decrease in volume of the thalamus occurs with increasing age. The relation between age and thalamic atrophy is strongly significant and can only in part be explained by volume changes of the whole brain. The specific loss of volume of the thalamus with increasing age has to our knowledge not been described before. An earlier study using structural MRI showed no significant differences between thalamic volumes of young and old men [30], but this could be due to the smaller

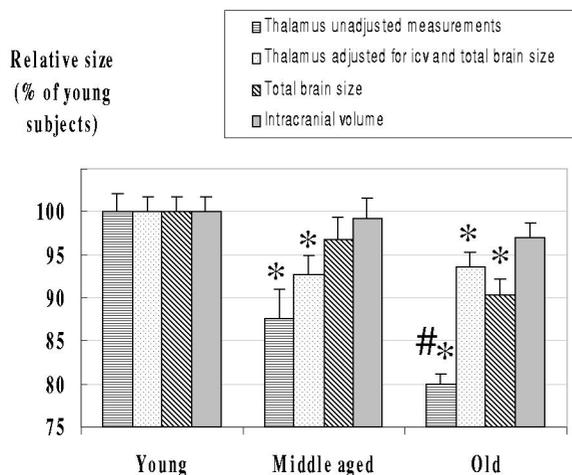


Fig. 3. Relative sizes of the thalamus; the thalamus adjusted for the effects of total brain volume and intracranial volume; the total brain size; and the intracranial volume for each of the three age groups. Error bars indicate standard errors of the mean. Abbreviation: ICV, intracranial volume. * denotes significant differences at the *P*<0.05 level with the group of young subjects, # denotes significant difference at the *P*<0.05 level with the group of middle-aged subjects.

Table 5

Correlations between statistically adjusted thalamic volumes with measures of cognitive performance^a

Test variable	Adjusted for ICV and BV,		Adjusted for ICV, BV and age		
	All subjects (n=55)	All subjects (n=55)	Young subjects (n=17)	Middle-aged subjects (n=14)	Old subjects (n=24)
<i>Simple speed</i>					
Stroop (I/II)	-0.105	0.006	0.368	-0.553*	0.063
PPMST (% subtest)	-0.383**	-0.186	-0.577*	-0.184	-0.396
PPMST (1 letter)	-0.326*	-0.166	-0.614**	-0.229	-0.118
<i>Complex speed</i>					
Stroop (III)	-0.168	-0.081	-0.180	-0.626*	0.109
PPMST (2 letter)	-0.293**	-0.142	-0.628**	-0.213	0.032
<i>Working memory</i>					
Stroop (III-I/II)	-0.198	-0.130	-0.508*	-0.606*	0.108
PPMST (2-1 letter)	-0.208	-0.093	-0.359	-0.185	0.045

^a ICV, Intracranial volume; BV, brain volume. * $P < 0.05$, ** $P < 0.01$.

number of subjects investigated than in the current study. Additionally, in the former study the slices used had thicknesses of 7 mm and were oriented in the axial plane, both of which reduce the number of slices on which the thalamus is visible and thereby lead to a decrease in accuracy of the measurement. The present investigation employed 3-mm thick slices in the coronal plane.

Based on our results, thalamic size decreases with higher age following a linear relationship starting reasonably early during the life-span. Middle-aged healthy sub-

jects, i.e., 45–60 years of age, already show a significant decrease in thalamic size as compared to young healthy subjects. Total brain volume, on the other hand, only starts to decrease significantly in the group of old subjects. Apparently, the size of the thalamus is vulnerable to the effects of aging and is affected more pronouncedly than the brain as a whole. This means that the thalamic volume decrease does not follow cortical atrophy as a cause of deafferentation, or loss of target area, but is independent of – and possibly precedes – cortical change. Support for the notion of relatively selective effects of age on the thalamus comes from a structural brain imaging study in aging and dementia [23], using T2 weighted relaxometry as a measure of atrophy. It was shown that the thalamus has an increased T2 relaxation time that is related to age rather than the presence of dementia, whereas the hippocampal and amygdalar relaxation times are unrelated to age but increase in dementia. From the current data it cannot be derived whether the age-related thalamic loss of volume is related to the degeneration of other areas, e.g., the prefrontal cortex. This area shows the greatest age-related size decrements of the different cortical fields [37]. Studies in which the relation of thalamic atrophy with that of other brain structures is investigated are currently underway in our group.

We predicted that the reduced capacity of elderly people to perform speeded tasks would be related to decrease of volume of the thalamus. Indeed, after adjusting for intracranial volume and total brain size, the volume of the thalamus correlates significantly with the performance on a variety of tasks in the domains of speeded processing and working memory. After additionally partialling out the effects of age, thalamic volume does not explain the decrease in cognitive performance anymore. Apparently, thalamic volume, as a separate factor on top of the age-related effects on cognition, is not related to cognitive functioning across the age range. This concurs with previous studies that could not find such a relation with

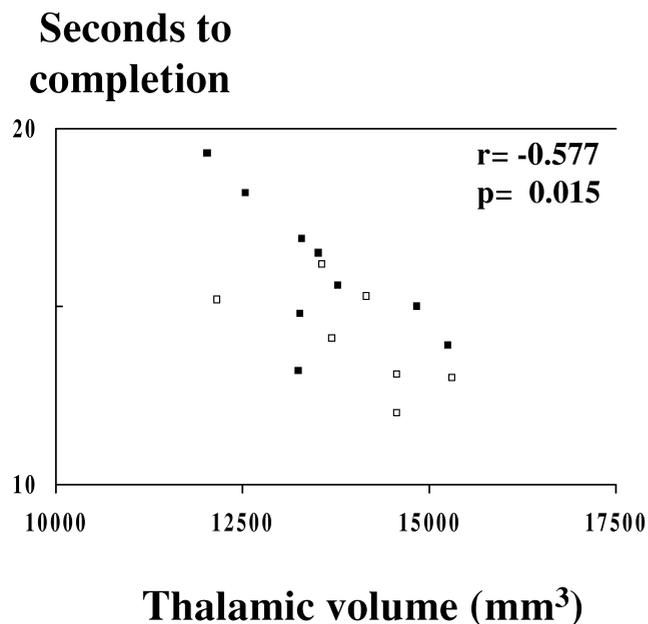


Fig. 4. For the young subjects ($n=17$, 21–45 years), the relationship between level of performance on a task of cognitive speed and volume of the thalamus adjusted for intracranial volume, brain volume and age is shown. The test score is the duration of the search of a target item (a %-sign) amidst distractor items (letters). Men are indicated with solid squares, women with open squares. Pearson's correlation coefficient and level of significance are given.

Table 6
Performance data of the subjects on the tests of cognitive speed

Subject		Simple speed			Complex speed		Working memory	
		Stroop 1/2(I/II)	PPMST 1 letter	PPMST %-symbol	Stroop III	PPMST 2 letter	Stroop III-1/2(I+II)	PPMST 2-1
Young (<i>n</i> = 17)	Mean	46.7	22.9	15.6	83.4	34.0	36.8	11.1
	S.D.	8.4	4.2	2.6	15.8	5.8	11.7	3.0
	Variance	70.2	17.4	6.7	248.4	33.6	136.2	9.0
Middle-aged (<i>n</i> = 15)	Mean	49.1	26.8	20.5	83.6	42.9	35.4	16.0
	S.D.	7.8	6.9	4.7	14.9	15.8	9.6	9.7
	Variance	60.4	47.5	21.9	221.4	249.0	91.4	93.1
Old (<i>n</i> = 24)	Mean	56.9	37.3	32.6	108.2	59.1	51.4	21.8
	S.D.	10.6	6.7	7.1	24.9	12.6	18.9	8.8
	Variance	111.8	44.7	51.1	622.0	159.1	357.2	76.6
All (<i>n</i> = 56)	Mean	51.7	30.2	24.2	94.1	47.1	42.8	17.0
	S.D.	10.2	8.8	9.3	23.3	16.1	16.5	8.9
	Variance	104.5	77.5	86.8	541.4	260.2	273.0	79.3

cognitive speed for other structures in the brain, using similar methodologies [48].

Nevertheless, evidence from studies of the thalamic contributions to arousal mechanisms described in the introduction, led us to predict that thalamic volume would be related to measures of information processing under time-constrained conditions regardless of age. The results show that this prediction is supported for healthy young subjects and to a lesser degree for middle-aged, but not old subjects. The significant effects pertain to both measures of simple speed and complex speeded processing. The relationship was such, that subjects with larger thalamic performed faster on completing these tasks. This concurs with the view of Shulman et al. [43], who in a review of subcortical activations in visual tasks indicate that thalamic activation is related to arousal and attention processes.

The relative paucity of significant relations between the thalamus and cognitive performance in the middle-aged group and the absence of such relations in the old group of subjects might be explained by increased heterogeneity in these groups, compared with the young subjects. Aging effects that take place above the age of 45 may affect individuals to a different degree or at different stages. Such aging effects can for instance include small lesions outside the thalamus, such as white matter infarctions, undetected by MR imaging [9]. These would act to confound the role of the thalamus in predicting cognitive outcome. The interindividual differences are reflected in the greater variance observed in the neurocognitive test data in middle-aged and old subjects, obscuring the correlation between the thalamus and cognition. In the young group on the other hand, aging effects have not yet taken place and thalamic volume is correlated with cognitive performance.

It needs to be stressed that the smaller size of the thalamus is not necessarily associated with worse cognitive functioning in the elderly. Johansson et al. [19] describe

thalamic activation in elderly subjects in paradigms of divided attention. Recent functional magnetic resonance imaging data have shown that elderly subjects in fact show greater thalamic activation than young subjects in performing a task requiring intact working memory capacities [31]. The latter data show that the thalamic activation was correlated with the amount of errors of commission in the task and possibly reflect effort or monitoring processes. Increased effort has been described in elderly subjects in order to maintain the same level of cognitive performance [15] and in such compensatory processes, the thalamus may play a role [6].

A few limitations of the current study have to be kept in mind when interpreting the data: the only structure measured here is the thalamus and the volumes can therefore not be compared with those of other brain structures. It remains to be shown whether the declines in speeded processing and working memory with higher age are specifically related to the involution of the thalamus, or that structures other than the thalamus play an additional role. Candidate structures are the prefrontal cortex [37,38,29,14,5,7,11,39,49], other association cortices [13], the basal ganglia [30] or the subcortical white matter, where age-related lesions might lead to slowing of cognitive processes [9]. The prefrontal cortex, thalamus and basal ganglia are involved in parallel and segregated circuits that are involved in, amongst others, the processes of speeded processing that we describe here [1]. Interruptions of these circuits at either level might underlie the reduced speed of processing in the elderly. Another issue that deserves mention is the number of cognitive variables used here: a large number of correlations increases the likelihood of occurrence of type I errors (false positives). Nevertheless, the fact that relations proved to be quite consistent across the different tasks shows the robustness of our findings.

In conclusion, we have shown on the basis of a structural magnetic resonance imaging based volumetric analysis, that there is a correlation between the volume of the thalamus in healthy young adults and performance on tasks of speeded information processing. In addition, the observed decrease in volume of the thalamus that occurs with increasing age is stronger than that of the brain as a whole and starts earlier. The age-associated decrease in thalamic volume thus might be correlated with the decreased capacity of elderly subjects to perform tasks of cognitive speed.

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References

- [1] G.E. Alexander, M.D. Crutcher, M.R. DeLong, Basal ganglia–thalamocortical circuits: parallel substrates for motor, oculomotor, ‘prefrontal’ and ‘limbic’ functions, *Prog. Brain Res.* 85 (1990) 119–146.
- [2] J.E. Birren, K.W. Schaie, *Handbook of the Psychology of Aging*, 3rd Edition, Van Nostrand Reinhold, New York, 1990.
- [3] N. Brand, J. Jolles, Information processing in depression and anxiety, *Psychol. Med.* 17 (1987) 145–153.
- [4] T.S. Braver, J.D. Cohen, L.E. Nystrom, J. Jonides, E.E. Smith, D.C. Noll, A parametric study of prefrontal cortex involvement in human working memory, *NeuroImage* 5 (1997) 49–62.
- [5] R. Cabeza, A.T. McIntosh, C.L. Grady, L. Nyberg, S. Houle, E. Tulving, Age-related changes in neural interactions during memory encoding and retrieval: a network analysis of PET data, *Brain Cogn.* 35 (1997) 369–372.
- [6] R. Cabeza, A.R. McIntosh, E. Tulving, L. Nyberg, C.L. Grady, Age-related differences in effective neural connectivity during encoding and recall, *Neuroreport* 8 (1997) 3479–3483.
- [7] R. Cabeza, N.D. Anderson, S. Houle, J.A. Mangels, L. Nyberg, Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study, *J. Cogn. Neurosci.* 12 (2000) 197–206.
- [8] F.I.M. Craik, T.A. Salthouse, *The Handbook of Aging and Cognition*, Lawrence Erlbaum, Hillsdale, NJ, 1992.
- [9] J.C. De Groot, F.E. De Leeuw, M. Oudkerk, J. Van Gijn, A. Hofman, J. Jolles, M.M. Breteler, Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study, *Ann. Neurol.* 47 (2000) 145–151.
- [10] J.L. Earles, T.A. Salthouse, Interrelations of age, health, and speed, *J. Gerontol.: Psychol. Sci. Soc. Sci.* 50 (1995) 33–41.
- [11] G. Esposito, B.S. Kirkby, J.D. Van Horn, T.M. Ellmore, K.F. Berman, Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation, *Brain* 122 (1999) 963–979.
- [12] P. Fiset, T. Paus, T. Daloz, G. Plourde, P. Meuret, V. Bonhomme, N. Hajj-Ali, S.B. Backmann, A.C. Evans, Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study, *J. Neurosci.* 19 (1999) 5506–5513.
- [13] C.L. Grady, J.M. Maisog, B. Horwitz, L.G. Ungerleider, M.J. Mentis, J.A. Salerno, P. Pietrini, E. Wagner, J.V. Haxby, Age-related changes in cortical blood flow activation during visual processing of faces and location, *J. Neurosci.* 14 (1994) 1450–1462.
- [14] C.L. Grady, A.R. McIntosh, B. Horwitz, J.M. Maisog, L.G. Ungerleider, M.J. Mentis, P. Pietrini, M.B. Schapiro, J.V. Haxby, Age-related reductions in human recognition memory due to impaired encoding, *Science* 269 (1995) 218–221.
- [15] C.L. Grady, A.R. McIntosh, F. Bookstein, B. Horwitz, S.I. Rapoport, J.V. Haxby, Age-related changes in regional cerebral blood flow during working memory for faces, *NeuroImage* 8 (1998) 409–425.
- [16] P.J. Houx, J. Jolles, Age-related decline of psychomotor speed: effects of age, brain health, sex, and education, *Percept. Mot. Skills* 76 (1993) 195–211.
- [17] P.J. Houx, F.W. Vreeling, J. Jolles, Rigorous health screening reduces age effect on memory scanning task, *Brain Cogn.* 15 (1991) 246–260.
- [18] G. Jackson, J. Duncan, *MRI Neuroanatomy. A New Angle on the Brain*, Churchill Livingstone, New York, 1996.
- [19] P. Johannsen, J. Jakobsen, P. Bruhn, S.B. Hansen, A. Gee, H. Stodkilde-Jorgensen, A. Gjedde, Cortical sites of sustained and divided attention in normal elderly humans, *Neuroimage* 6 (1997) 145–155.
- [20] J. Jolles, F.R. Verhey, W.J. Riedel, P.J. Houx, Cognitive impairment in elderly people. Predisposing factors and implications for experimental drug studies, *Drugs Aging* 7 (1995) 459–479.
- [21] N. Kajimura, M. Uchiyama, Y. Takayama, S. Uchida, T. Uema, M. Kato, M. Sekimoto, T. Watanabe, T. Nakajima, S. Horikoshi, K. Ogawa, M. Nishikawa, M. Hiroki, Y. Kudo, H. Matsuda, M. Okawa, K. Takahashi, Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep, *J. Neurosci.* 19 (1999) 10065–10073.
- [22] S. Kinomura, J. Larsson, B. Gulyas, P.E. Roland, Activation of the human reticular formation and thalamic intralaminar nuclei, *Science* 271 (1996) 512–515.
- [23] M.P. Laakso, K. Partanen, H. Soininen, M. Lehtovirta, M. Hallikainen, T. Hanninen, E.L. Helkala, P. Vainio, P.J. Riekkinen Sr., MR T2 relaxometry in Alzheimer’s disease and age-associated memory impairment, *Neurobiol. Aging* 17 (1996) 535–540.
- [24] D. LaBerge, M.S. Buchsbaum, Positron emission tomographic measurements of pulvinar activity during an attention task, *J. Neurosci.* 10 (1990) 613–619.
- [25] F. Luteijn, A new abbreviated Groninger IntelligenceTest (in Dutch), *Ned. Tijdschr. Psychol. Haar Grensgebieden* 21 (1966) 675–682.
- [26] F. Luteijn, F.A.E. Van Der Ploeg, *De Groninger Intelligentie Test (The Groningen Intelligence Test)*, Swets and Zeitlinger, Lisse, 1983.
- [27] D.S. Manoach, G. Schlaug, B. Siewert, D.G. Darby, B.M. Bly, A. Benfield, R.R. Edelman, S. Warach, Prefrontal cortex fMRI signal changes are correlated with working memory load, *Neuroreport* 8 (1997) 545–549.
- [28] J.M. McDowd, D.M. Oseas-Kreger, D.L. Filion, Inhibitory processes in cognition and aging, in: F.N. Dempster, C.J. Brainard (Eds.), *Interference and Inhibition in Cognition*, Academic Press, San Diego, CA, 1995.
- [29] D.G.M. Murphy, C. DeCarli, M.B. Schapiro, S.I. Rapoport, B. Horwitz, Age-related differences in volumes of subcortical nuclei, brain matter, and cerebrospinal fluid in healthy men as measured with magnetic resonance imaging, *Arch. Neurol.* 49 (1992) 839–845.
- [30] K.A. Nielson, H. Garavan, S.A. Langenecker, S.M. Rao, Inhibitory control in young and older adult subjects as measured by event related fMRI, *Soc. Neurosci. Abstr.* 25 (1999) 1139.
- [31] N. Otsu, A threshold selection method from gray-level histograms, *IEEE Trans. Systems Man Cybernetics* 9 (1979) 62–66.
- [32] A.M. Owen, The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging, *Eur. J. Neurosci.* 9 (1997) 1329–1339.

- [34] T. Paus, R.J. Zatorre, N. Hofle, Z. Caramanos, J. Gotman, M. Petrides, A.C. Evans, Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task, *J. Cogn. Neurosci.* 9 (1997) 392–408.
- [35] C.M. Portas, J.M. Goldstein, M.E. Shenton, H.H. Hokama, C.G. Wible, I. Fischer, R. Kikinis, R. Donnino, F.A. Jolesz, R.W. McCarley, Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging, *Biol. Psychiatry* 43 (1998) 649–659.
- [36] C.M. Portas, G. Rees, A.M. Howsemann, O. Josephs, R. Turner, C.D. Frith, A specific role for the thalamus in mediating the interaction of attention and arousal in humans, *J. Neurosci.* 18 (1998) 8979–8989.
- [37] N. Raz, F.M. Gunning, D. Head, J.H. Dupuis, J. McQuain, S.D. Briggs, W.J. Loken, A.E. Thornton, J.D. Acker, Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter, *Cereb. Cortex* 7 (1997) 268–282.
- [38] N. Raz, F.M. Gunning-Dixon, D. Head, J.H. Dupuis, J.D. Acker, Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging, *Neuropsychology* 12 (1998) 95–114.
- [39] P.A. Reuter-Lorenz, J. Jonides, E.E. Smith, A. Hartley, A. Miller, C. Marshuetz, R.A. Koeppel, Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET, *J. Cogn. Neurosci.* 12 (2000) 174–187.
- [40] S. Rubichi, M. Neri, R. Nicoletti, Age-related slowing of control processes: evidence from a response coordination task, *Cortex* 35 (1999) 573–582.
- [41] J.A. Salerno, D.G.M. Murphy, B. Horwitz, C. DeCarli, J.V. Haxby, S.I. Rapoport, M.B. Shapiro, Brain atrophy in hypertension. A volumetric magnetic resonance imaging study, *Hypertension* 20 (1992) 340–348.
- [42] T.A. Salthouse, The processing-speed theory of adult age differences in cognition, *Psychol. Rev.* 103 (1996) 403–428.
- [43] G.L. Shulman, M. Corbetta, R. L. Buckner, J.A. Fiez, F.M. Miezin, M.E. Raichle, S.E. Petersen, Common blood flow changes across visual tasks: I. Increases in subcortical structures and cerebellum but not in nonvisual cortex, *J. Cogn. Neurosci.* 9 (1997) 624–647.
- [44] S. Sternberg, Memory scanning: new findings and current controversies, *Q. J. Exp. Psychol.* 27 (1975) 1–32.
- [45] J.R. Stroop, Studies of interference in serial verbal reactions, *J. Exp. Psychol.* 18 (1935) 643–662.
- [46] W. Sturm, A. De Simone, B.J. Krause, K. Specht, V. Hesselmann, I. Radermacher, H. Herzog, L. Tellmann, H.W. Müller-Gärtner, K. Willmes, Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere, *Neuropsychologia* 37 (1999) 797–805.
- [47] B. Subramaniam, J.G. Hennessey, M.A. Rubin, L.S. Beach, A.L. Reiss, Software and methods for quantitative imaging in neuroscience: The Kennedy Krieger Institute Human Brain Project, in: S.H. Koslow, M.F. Huerta (Eds.), *Neuroinformatics: An Overview of the Human Brain Project*, Elsevier, Mahwah, NJ, 1997, pp. 335–360.
- [48] D.J. Tisserand, P.J. Visser, M.P. Van Boxtel, J. Jolles, The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range, *Neurobiol. Aging* 21 (2000) 569–576.
- [49] D.J. Tisserand, M.P. Van Boxtel, J. Jolles, Age-related volume reductions of prefrontal regions in healthy individuals are differential, *Brain Cogn.*, in press.
- [50] M.P. Van Boxtel, F. Buntinx, P.J. Houx, J.F. Metsemakers, A. Knottnerus, J. Jolles, The relation between morbidity and cognitive performance in a normal aging population, *J. Gerontol.: Biol. Sci. Med. Sci.* 53 (1998) M147–154.