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Similar network activated by young and old adults during the acquisition of a motor sequence

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Abstract

In this functional MRI (fMRI) study, we investigated ageing effects on motor skill learning. We applied an adapted version of the serial reaction time (SRT) task to extensive groups of young ($N = 26$) and elderly ($N = 40$) subjects. Since indications have been provided for age-related shrinkage of brain regions assumed to be critical to motor skill learning, we tested the hypothesis that age effects on implicit sequence learning are larger on a neurofunctional level than on a behavioural level. The SRT task consisted of two identical scan sessions, in which subjects had to manually trail an asterisk appearing serially in one of four spatial positions by means of button-pressing. Reliable response time reductions were already found in the first session for both the young and the elderly groups, when comparing a fixed sequence condition to a random sequence, but the learning effect was greater for the young subjects. In the second session, though, both groups showed a similar degree of learning. This indicates that implicit sequence learning is still intact in elderly adults, but that the rate of learning is somewhat slower. Reliable learning-related changes in brain activity were also observed. A similar network of brain regions was recruited by both groups during the fixed compared to the random sequence, involving several regions that have been previously associated with implicit sequence learning, including bilateral parietal, and frontal regions, the supplementary motor area (SMA), cerebellum and the basal ganglia. The direct group comparison did not reveal any differences in brain activity. In addition, we did not observe any significant differences in activity when comparing the different sessions either, neither for the young nor for the elderly subjects. Hence, we did not find indications for an age-related functional reorganisation of neural networks involved in motor sequence learning. In view of earlier reports of pronounced ageing effects on the performance on declarative memory tasks, our finding of age-related sparing of processes that sustain motor skill learning, provides further support for the proposition of different memory systems relying on different brain substrates.

Keywords: Functional MRI; Procedural memory; Ageing; Basal ganglia; Skill learning; Motor; Brain activity

1. Introduction

A decline in memory function is one of the major complaints among older people. Difficulties in learning and memory can be found to some extent in all elderly adults [29]. In the past few decades, behavioural and lesion studies have provided indications that memory is not a single entity, but consists of different components relying on different brain systems [26]. It is commonly assumed that ageing differentially affects the neuroanatomical substrates of these memory systems [29]. The memory system that has typically been associated with age-related deficits is declarative memory. This type of memory involves the conscious and intentional recollection of episodes and factual information, and is dependent on the integrity of the medial temporal lobe [4,18,19]. However, it has been suggested that ageing affects other types of learning, such as procedural memory, as well, although less severely [24,27,30].

Procedural memory refers to the acquisition of skills and habits. Contrary to declarative memory, the information that is stored in procedural memory is implicitly and unconsciously retrieved by performing specific operations, which are part of a particular task [3,8,26]. Recent studies have

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indicated important roles for the basal ganglia, and the cerebellum in procedural memory, particularly in the acquisition of motor skills [16,25,28]. Although evidence has been provided for age-related shrinkage of these regions [11,17,23], very little is known about the effects age has on motor learning and the reports concerning this topic have been sparse and inconsistent. A small number of studies reported showed somewhat larger gains for younger compared to older subjects [12,27,30]. However, in other studies no apparent skill learning differences between older and young adults were observed [6,14]. These inconsistent findings indicate that, on a behavioural level, age differences in motor skill learning, if any, are very subtle.

Indications have been provided that elderly subjects use different functional networks compared with young subjects when carrying out the same cognitive task, presumably to compensate for reduced efficiency of some brain areas typically used by young adults in these tasks [1,10]. Hence, given the aforementioned findings of age-related volume reductions in brain regions assumed to be critical to motor learning, it is possible that, as a result of functional reorganisation of neural networks involved in motor skill learning, age differences are much greater on a neurofunctional level than on a behavioural level. This possibility can be tested through the use of neuroimaging techniques, such as functional MRI (fMRI), a noninvasive technique with a high spatial resolution that can safely be repeated. Previous imaging studies that examined motor skill acquisition in young subjects found support for the role of the cerebellum and the basal ganglia in this type of learning, but they also indicated the involvement of a number of other regions, including primary and premotor areas [13,21,22].

Implicit sequence learning as measured with the serial reaction time task (SRT) is one type of motor learning, which is thought to draw heavily upon the basal ganglia [28]. In this task, developed by Nissen and Bullemer [20], subjects view a computer monitor on which a stimulus sequentially appears at one of four positions. The four fingers of the right hand are positioned on a four-key response box, and the subjects are instructed to press the key, which corresponds to the spatial position of the stimulus. At first, the stimuli are presented according to a prearranged sequence unaware to the subjects, which is repeated several times, and then, in a separate run, the stimuli are presented at random positions. A measure of learning is obtained by comparing response times in the sequence block to the response times during the random block. Typically, response times are longer for the random sequence.

In the present study, an adapted version of the SRT [22] was applied to two extensive groups of young and elderly adults while measures of brain activity were obtained using fMRI. We tested the hypothesis that elderly subjects will show a different activity pattern in relation to implicit sequence learning than young adults, even in absence of pronounced behavioural differences.

2. Methods

2.1. Subjects

Twenty-six right-handed males between the ages of 30 and 35, and 40 right-handed males between the ages of 63 and 71 participated. They were recruited by means of advertisements in local newspapers. None of the subjects were taking psychoactive medication and they did not report any neurological or psychiatric impairment on a general health questionnaire. All elderly subjects scored 25 (out of 30) or higher (mean = 27.8, S.D. = 1.48) on the Mini Mental Status Examination (MMSE) [7], a common test for evaluating cognitive competence. In addition, structural MR images (MPRAGE: inversion time: 300 ms, repetition time (TR) = 15 ms, echo time (TE) = 7 ms, flip angle = 8°), which were acquired previous to this study, did not reveal indications for anatomical aberrations atypical for age. The subjects' informed consent was obtained according to the declaration of Helsinki and approved by the ethical committee of the "Vrije Universiteit" Medical Center. Due to technical difficulties (scanner failure and data transport problems), three elderly subjects were excluded. Three other subjects from the elderly group were excluded, because they consistently had pressed the wrong two buttons of the four-key response boxes during either one of the sessions. Therefore, demographic data and self-rated health measures are shown in Table 1 for the remaining subjects. Educational level was assessed using a 7-point scale, 0 representing no education, and 7 representing university level.

2.2. Magnetic resonance procedures

Imaging was performed on a 1.5 T Siemens Sonata (Siemens, Erlangen, Germany) scanner using a standard circularly polarised head coil. Stimuli were generated by a Pentium PC and projected on a screen at the back end of the scanner table. The projected image was seen through a mirror positioned above the participant's head. Two magnet-compatible four-key response boxes were used to record the subject's performance and reaction times. The subject's head was fixated using foam pads to reduce motion artefact and earplugs were used to reduce scanner noise. For each subject, two series of echo planar images (EPI) were

Table 1
Demographic data and self-rated health

	Young, $N = 26$ (S.D.)	Elderly, $N = 34$ (S.D.)
Age	32.4 (1.8)	66.4 (2.0)
Education (7-point scale)	5.9 (1.0)	5.5 (0.7)
Self-rated physical health (1 = bad, 5 = excellent)	4.0 (0.6)	4.0 (0.6)
Self-rated psychological health (1 = bad, 5 = excellent)	4.1 (0.7)	4.3 (0.6)

acquired sensitive to Blood Oxygenation Level-Dependent (BOLD) contrast, involving a T2*-weighted gradient echo sequence (TR = 3.6 s, TE = 60 ms, flip angle = 90°) consisting of 108 transversal whole-brain acquisitions (36 slices, $3 \times 3\,mm^2$ in-plane resolution, 3 mm slice thickness, 0.5 mm interslice gap).

2.3. Serial reaction time task

We used a version of the SRT task that was adapted for use with fMRI by Rauch et al. [22] involving a display of four boxes, which were arranged horizontally in the middle of a screen. In one of these boxes an asterisk appeared for a duration of 1 s, then disappeared for 0.2 s, and subsequently reappeared in one of the three other boxes. This process was repeated until the end of the session. The two boxes on the left-hand side corresponded with two keys on the left-hand button box, the right-hand boxes corresponded with keys on the right-hand button-box and each key press was performed with a separate finger for each key (middle and index fingers of left and right hand). Subjects were instructed to press the corresponding key as soon as the asterisk reappeared in one of the boxes. In a sequence learning block, the stimuli were presented according to a fixed 12-item sequence (i.e. 1-2-1-4-2-3-4-1-3-2-4-3), which was repeated six times yielding 72 trials in total. In the Rauch et al. [22] study, the extensive length of this sequence was found to prevent contributions of explicit recall to task effects as assessed by a computerised debriefing procedure. A baseline block consisted of 24 stimuli in which locations were pseudorandomly determined, with the restriction that locations were not directly recurring. Each subject started with a practice session, in which they were presented with 2 min of pseudorandom sequence. This was followed by two identical scan sessions of approximately 6 min and 15 s, during which random (R) and fixed (F) sequence blocks were alternating continuously (i.e. R-F-R-F-R-F-R). The duration of the R and F blocks was 28.8 and 86.4 s, respectively. The sessions were separated by a 1-min rest period.

2.4. Analysis

Imaging data were analysed using SPM99 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). After discarding the first four volumes, time-series were corrected for differences in slice acquisition times, and realigned using sin interpolation. Next, the EPI volumes were spatially normalised into approximate Talairach and Tournoux space defined by the SPM EPI template, and resliced to 3 mm × 3 mm × 3 mm voxels. Data were smoothed using a Gaussian kernel of 8 mm.

Evoked hemodynamic responses to stimulus blocks were modelled as boxcar functions convolved with a synthetic hemodynamic response function in the context of the general linear model. A random effects analysis was employed for the calculation of group averages (one-sample *t*-test) and group interactions (two-sample *t*-test). Specific effects were tested by applying appropriate contrasts to the parameter estimates for each condition, resulting in a *t*-statistic for every voxel. We applied a threshold of $P < 0.005$, minimal cluster size = 15 voxels, corrected using a False-Discovery-Rate correction [9] for the assessment of group averages. The contrasts fixed condition versus random condition and random versus fixed were tested for significance. The regions surviving this threshold in either one of the groups were subsequently identified as regions of interest for the assessment of group interactions (i.e. young (fixed versus random) versus old (fixed versus random) and the opposite comparison) which were thresholded at $P < 0.001$, uncorrected, minimal cluster size = 5 voxels. In addition, we also tested for possible session effects at this lower threshold in both groups (i.e. session 1 (fixed versus random) versus session 2 (fixed versus random) and the opposite comparison).

3. Results

3.1. Behavioural results

Performance measures on the SRT are summarised in Table 2. Already in the first session, significant learning effects were observed. Both the young ($t(25) = 6.5$; $P = 0.001$) and the old group ($t(33) = 2.6$; $P = 0.012$) performed significantly faster during the fixed compared to the random sequence condition. However, there was a trend towards a greater improvement for the young subjects ($t(58) = 2.0$; $P = 0.056$). Significant improvements were also observed during the second session (young: $t(25) = 4.1$; $P < 0.001$; elderly: $t(33) = 6.5$; $P = 0$), but this time a

Table 2
Behavioural results

	Young		Old	
	Session 1	Session 2	Session 1	Session 2
% correct fixed sequence	97.7 (2.8)	97.3 (3.6)	96.6 (4.8)	96.5 (5.1)
% correct random sequence	96.2 (3.8)	96.0 (4.3)	92.7 (7.8)	93.9 (5.0)
Mean reaction time for fixed sequence (ms)	461 (65)	444 (76)	562 (66)	541 (70)
Mean reaction time for random sequence (ms)	489 (58)	473 (60)	576 (66)	577 (64)
Learning effect: difference in reaction time	28 (22)	29 (36)	14 (32)	36 (32)

Table 3
Maxima of regions showing significant BOLD signal rises ($P < 0.005$, FDR-corrected, extent threshold = 15) in comparison of fixed sequence vs. random sequence for the group of young subjects

Region of activation	Left/right	Brodmann area	Talairach co-ordinates (mm)			*Z*-value
			x	*y*	*z*	
Fixed > random						
Inferior frontal gyrus	L	47	−48	29	−6	5.56
Middle frontal gyrus	R	6/24	3	5	49	4.80
Superior frontal gyrus	R	6	12	9	63	4.92
	L	6	−12	15	63	4.19
Anterior cingulate	R	24	6	5	36	4.29
Precentral gyrus	L	4	−56	−15	42	4.92
	R	4	59	−10	42	4.75
Superior temporal gyrus	L	21/22	−45	−17	1	6.09
	R	21/22	50	−11	3	5.74
Putamen	R	–	24	0	0	5.92
	L	–	−12	−2	8	5.02
Caudate nucleus	L	–	−12	9	2	4.45
Globus pallidus	R	–	15	−8	9	4.41
Superior parietal lobe	L	7	−24	−56	55	4.45
	R	7	12	−55	58	4.22
Lingual gyrus	R	18	15	−79	−6	5.87
	L	18	−6	−85	−6	5.52
Cerebellum	R	–	18	−78	−15	5.80
Random > fixed						
Inferior frontal gyrus	R	47	24	22	−19	5.66
Inferior occipital gyrus	R	18	48	−70	−2	5.41
Middle occipital gyrus	L	18	−24	−99	8	5.22

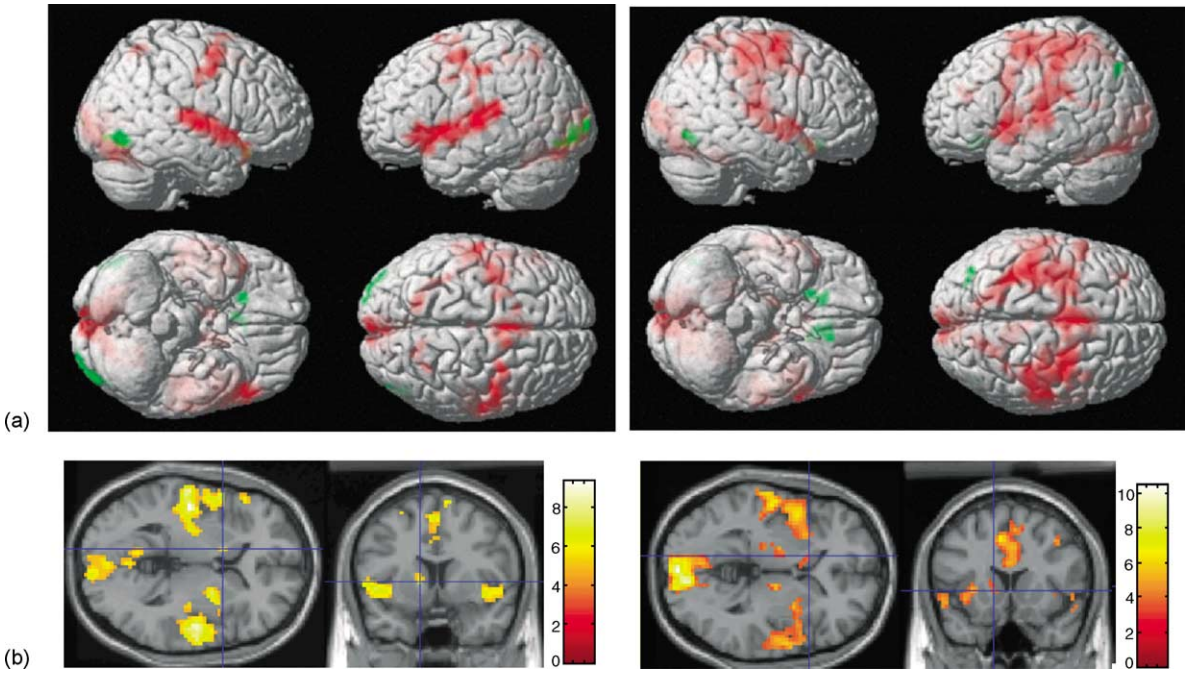

Fig. 1. (a) Normalised 3-D renderings, showing regions of the brain that were more active ($P < 0.005$, FDR-corrected, cluster = 15) during presentation of either fixed (red) or random (green) sequences. Group averages for the young subjects are shown on the left, for the elderly subjects on the right. (b) Statistical Parametric Map (SPM) overlaying a normalised T1 image, showing similar activity ($P < 0.005$, FDR-corrected, cluster = 15; colour bars represent *t* values) in the left caudate nucleus in comparison of fixed sequence vs. random sequence for the young (left-hand side) and elderly subjects (right-hand side).

similar learning effect was observed for both groups. Contrary to the elderly subjects ($t(33) = 3.8$; $P = 0.001$) the young did not show a greater learning effect in the second session than in the first session. A condition × group × session ANOVA, with session and condition as repeated measures, and response times as dependent variable, revealed significant main effects for condition ($F(1, 58) = 55.83$; $P < 0.001$), group ($F(1, 58) = 38.09$; $P = 0$), and session ($F(1, 58) = 20.7$; $P < 0.001$). In addition, a significant group × condition × session interaction ($F(1, 58) = 6.87$; $P = 0.011$) was found, indicating a slower learning rate for the elderly subjects.

Although both groups approached perfect scores, there was a small difference in accuracy on the random sequence trials across groups in favour of the young subjects (session 1: $t(58) = 2.1$; $P = 0.039$; session 2: $t(58) = 1.7$; $P = 0.090$). Since most of the errors were made directly after a shift from fixed to random sequence, this finding suggests that the elderly subjects experienced somewhat more difficulties shifting from automated to more controlled processing. Overall, these results indicate that motor skill learning abilities were still intact in the elderly adults, although it took them more time to reach a similar level of improvement.

3.2. Imaging results

Several regions were found to be more active during fixed sequence versus random sequence for both the young (Table 3, Fig. 1a) and the elderly (Table 4, Fig. 1a) subjects, including bilateral superior/inferior parietal lobe (BA 7/40), bilateral superior temporal regions (BA 21/22), the visual cortex (BA 17/18) extending into the cerebellum, the anterior cingulate gyrus (BA 24), the supplementary motor area (SMA; BA 6), left and right putamen, and left caudate nucleus (Fig. 1b). A much smaller number of regions was found to be more active in the opposite comparison. The young subjects (Table 3, Fig. 1a) showed increased activity in occipital regions, and the right inferior frontal lobe, the elderly subjects in the right occipital lobe and cerebellum, and the left middle frontal gyrus (Table 4, Fig. 1a).

No significant group interactions were found. In addition, no significant session effects were found for either one of the groups. Hence, the larger response time reduction that was observed in the elderly group comparing the second session to the first was not accompanied by additional changes in brain activity.

Table 4
Maxima of regions showing significant BOLD signal rises ($P < 0.005$, FDR-corrected, extent threshold = 15) in comparison of fixed sequence vs. random sequence for the group of elderly subjects

Region of activation	Left/right	Brodmann area	Talairach co-ordinates (mm)			*Z*-value
			x	*y*	*z*	
Fixed > random						
Inferior frontal gyrus	L	44	−59	10	24	5.64
Middle frontal gyrus	R	6	36	−4	44	6.01
	L	6	−36	6	52	5.44
	L	46	−27	39	15	3.93
Medial frontal gyrus	R	6	9	0	55	5.18
Superior frontal gyrus	R	6	30	−17	62	5.68
	L	6	−6	3	63	5.13
Anterior cingulate	L	24	−3	2	39	6.41
Precentral gyrus	L	4	−39	−29	54	6.34
	R	4	36	−4	44	6.01
Postcentral gyrus	L	40	−50	−20	18	6.21
	R	1/2/3	45	−29	54	5.75
Superior temporal gyrus	R	42	59	−20	12	5.56
	L	22	−48	6	−5	5.35
Lingual gyrus	–	17/18	0	−90	5	6.92
Caudate nucleus	L	–	−12	6	11	3.97
Putamen	L	–	−18	−8	6	5.25
	R	–	27	3	3	4.90
Inferior parietal lobe	R	40	36	−33	38	5.22
	L	40	−56	−28	24	4.79
Central parietal lobe	R	7	3	−41	63	5.00
Middle occipital gyrus	R	18	15	−95	19	5.02
Cerebellum	L	–	−18	−73	−11	5.56
	R	–	24	−50	−18	5.01
Random > fixed						
Medial frontal gyrus	L		−9	23	−11	5.29
Middle occipital gyrus	R		45	−67	−4	5.22
Cerebellum	R		18	28	−14	5.67

4. Discussion

In the present fMRI study, we compared brain activity patterns in young and elderly adults while they were performing and adapted version of the SRT task developed by Rauch et al. [22]. Although behavioural studies have reported very modest age differences in motor skill learning, we examined the possibility that differences are larger on a neurofunctional level in view of age-related shrinkage of brain regions assumed to be critical to motor learning [23].

Significant learning effects were already observed in the first session of the SRT for both the young and the old adults. Both groups showed a clear reduction in response times for the fixed relative to the random sequence condition, but the learning effect was greater for the young subjects. However, in the second session the learning effect remained approximately at the same level for the young subjects, whereas the elderly subject showed a greater response time reduction compared to the first session. Furthermore, both groups attained approximately the same degree of implicit learning in the second session. These results are in line with studies indicating that motor skill learning is still intact in elderly adults but that the rate of learning is somewhat slower [12,27].

A similar network of brain regions was recruited by both groups during the fixed compared to the random sequence, involving several regions that have been previously associated with implicit sequence learning, including bilateral parietal and frontal regions, the SMA, cerebellum and the basal ganglia [13,21,22]. Additional activity was observed in the superior temporal lobe. This region has been associated with the acquisition of smooth pursuit eye movements [2]. During the SRT, subjects are required to visually scan the four spatial positions for the target. The learning-related activity observed in the superior temporal lobe may, therefore, reflect the acquisition of a fixed sequence of eye movements. Hence, besides manual motor skills primarily mediated by the SMA, this finding may indicate that implicit sequence learning as measured with the SRT also involves a visuomotor component mediated by superior temporal regions.

The direct group comparison did not reveal any differences in brain activity. Hence, these results are not in line with the idea that elderly subjects are recruiting a different functional network than young subjects do. In addition, we did not observe any significant differences in activity between sessions 1 and 2, neither for the young nor for the elderly subjects. This was not due to a lack of statistical power, since highly comparable activity patterns were obtained from sessions 1 and 2 for both groups, which greatly resembled the overall average (data not shown). The absence of session effects in the elderly group is surprising, because, on a behavioural level, we did find a session effect for the elderly subjects, indicating a significantly larger response time reduction in the second session. This suggests that there is no straightforward relation between degree of learning on the adapted version of the SRT that we used and the fMRI measures that were obtained in this study.

Our results were somewhat different from those obtained in a previous fMRI study using the same version of the SRT [22]. In this study, mostly left-lateralised activity was reported, except for right-lateralised activity in the striatum, whereas in our study, mostly bilateral activity was observed. Furthermore, we observed additional activity in the left and right superior temporal gyrus, which was not reported in the Rauch et al. study. These differences may be due to differences in sample size (small ($N = 10$) versus extensive ($N \geq 26$)), and data analysis procedures (fixed effects versus random effects).

Finally, the finding of highly similar patterns of widespread brain activity for young and old adults is intriguing, since indications have been provided for an age-related change in the coupling between the BOLD fMRI signal and neural activity. A slight age-related decrease in the signal-to-noise ratio of the BOLD signal has been observed during both visual [15] and motor [5] stimulation tasks. The results of the present study, in which extensive groups of young and old subjects were compared, underline that this decrease is very subtle and is not necessarily associated with substantial group differences in brain activity. This indicates that fMRI can be an effective tool for investigating effects of ageing on cognition, although some caution in interpretation seems appropriate.

Resuming, although we found a slight difference in learning rate between elderly and young adults, the eventual degree of learning was similar across groups. Furthermore, we did not find indications for an age-related functional reorganisation of neural networks involved in motor sequence learning. In view of earlier reports of pronounced ageing effects on the performance on declarative memory tasks, our finding of age-related sparing of processes that sustain motor skill learning, provides further support for the proposition of different memory systems relying on different brain substrates.

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References

[1] Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol 2001;42:277–86.
[2] Chou IH, Lisberger SG. Spatial generalization of learning in smooth pursuit eye movements: implications for the coordinate frame and sites of learning. J Neurosci 2002;22:4728–39.
[3] Corkin S. Acquisition of motor skill after bilateral medial temporal lobe excision. Neuropsychologia 1968;6:255–65.
[4] Corkin S. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. Semin Neurol 1984;4:249–59.

[5] D'Esposito M, Zarahn E, Aguirre GK, Rypma B. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. Neuroimage 1999;10:6–14.
[6] Durkin M, Prescott L, Furchtgott E, Cantor J, Powell DA. Performance but not acquisition of skill learning is severely impaired in the elderly. Arch Gerontol Geriatr 1995;20:167–83.
[7] Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–98.
[8] Gabrieli JE. Cognitive neuroscience of human memory. Ann Rev Psychol 1998;49:87–115 [review].
[9] Genovese CR, Nichols T, Lazar N. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 2002;15:772–86.
[10] Grady CL. Brain imaging and age-related changes in cognition. Exp Gerontol 1998;33:661–73.
[11] Gunning-Dixon FM, Head D, McQuain J, Acker JD, Raz N. Differential aging of the human striatum: a prospective MR imaging study. Am J Neuroradiol 1998;19:1501–7.
[12] Gutman GM. The effects of age and extraversion on pursuit rotor reminiscence. J Gerontol 1965;20:346–50.
[13] Hazeltine E, Grafton ST, Ivry R. Attention and stimulus characteristics determine the locus of motor-sequence encoding—a PET study. Brain 1997;120:123–40.
[14] Howard DV, Howard JH. Age differences in learning serial patterns: direct versus indirect measures. Psychol Aging 1989;4:357–64.
[15] Huettel SA, Singerman JD, McCarthy G. The effects of aging upon the hemodynamic response measured by functional MRI. Neuroimage 2001;13:161–75.
[16] Laforce R, Doyon J. Differential role for the striatum and cerebellum in response to novel movements using a motor learning paradigm. Neuropsychologia 2002;40:512–7.
[17] Matochik JA, Chefer SI, Lane MA, Woolf RI, Morris ED, Ingram DK, et al. Age-related decline in striatal volume in monkeys as measured by magnetic resonance imaging. Neurobiol Aging 2000;21:591–8.
[18] Milner B. Amnesia following operations on the medial temporal lobes. In: Whitty CWM, Zangwill OL, editors. Amnesia. London: Butterworth; 1966.
[19] Milner B. Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 1972;19:421–46.
[20] Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. Cogn Psychol 1987;19:1–32.
[21] Rauch SL, Savage CR, Brown HD, Curran T, Alpert NM, Kendrick A, et al. A PET investigation of implicit and explicit sequence learning. Hum Brain Mapp 1995;3:271–86.
[22] Rauch SL, Whalen PJ, Savage CR, Curran T, Kendrick A, Brown HD, et al. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. Hum Brain Mapp 1997;5:124–32.
[23] Raz N, Gunning-Dixon F, Head D, Williamson A, Acker JD. Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. Am J Neuroradiol 2001;22:1161–7.
[24] Raz N, Williamson A, Gunning-Dixon F, Head D, Acker JD. Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. Microsc Res Tech 2000;51:85–93.
[25] Salmon DP, Heindel WC, Butters N. Semantic memory, priming, and skill learning in Alzheimer's disease. In: Memory functioning in dementia. Amsterdam: Elsevier; 1992.
[26] Squire L. Mechanisms of memory. Science 1986;247:301–5.
[27] Tumin FJ. Reminiscence as a function of chronological and mental age. J Gerontol 1962;17:393–6.
[28] Vakil E, Kahan S, Huberman M, Osimani A. Motor and non-motor sequence learning in patients with basal ganglia lesions: the case of serial reaction time (SRT). Neuropsychologia 2000;38:1–10.
[29] Woodruff-Pak DS. The neuropsychology of aging. Oxford: Blackwell Publishers Ltd.; 1997.
[30] Wright BM, Payne RB. Effects of aging on sex differences in psychomotor reminiscence and tracking proficiency. J Gerontol 1985;40:179–84.