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Regional cortical thickness matters in recall after months more than minutes

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The aim of this study was to determine the role of regional cortical thickness in recall of verbal material over an extended time period. MRI scans of healthy adults of varying ages were obtained. Two scans were averaged per person to achieve high spatial resolution, and a semi-automated method for continuous measurement of thickness across the entire cortical mantle was employed. Verbal memory tests assessing recall after 5 min, 30 min, and a mean interval of 83 days were administered. A general linear model (GLM) of the effects of thickness at each vertex on the different memory indices was computed, controlling for gender, age, IQ, and intracranial volume. These analyses were repeated with hippocampal volume as an additional variable to be controlled for, to assess to which extent effects of cortical thickness were independent of hippocampal size. Minute effects of cortical thickness were observed with regard to shorter time intervals (5 and 30 min). However, even when controlling for the effects of hippocampal volume, higher recall across months was associated with thicker cortex of distinct areas including parts of the gyrus rectus, the middle frontal gyrus, the parieto-occipital sulcus and the lingual gyrus of both hemispheres. In addition, hemisphere-specific associations were found in parts of the right temporal and parietal lobe as well as parts of the left precuneus. This supports a unique and critical role of the thickness of distinct cortical areas in recall after months, more than after minutes.

Introduction

New magnetic resonance (MR) imaging and neuroanatomical quantification techniques has lead to much recent interest in relating volumetric brain characteristics to human abilities. The importance of volume of different brain areas for functional decline or maintenance in normal versus degenerative conditions has now been well documented (see, e.g., Jack et al., 2004; Fischl et al., 2002). There seems to be less consistent data, however, on the importance of normal individual differences in cerebral volumetric characteristics in healthy persons. Largely, two broad classes of studies have emerged: One focuses on the role of general brain volume or cortical volume in general ability (Willerman et al., 1991; Andreasen et al., 1993; Raz et al., 1993; Harvey et al., 1994; Wickett et al., 2000; Egan et al., 1994; 1995; Flashman et al., 1998; Thompson et al., 2001; MacLullich et al., 2002, Posthuma et al., 2002; Walhovd et al., 2005). The other class of studies mainly focuses on the role of specific brain structures in prediction of specific cognitive abilities. The relationship between frontal lobe volume and neuropsychologically defined frontal lobe function has been extensively studied (see van Petten et al., 2004, for an overview of 11 such studies), as well as the role of the hippocampal volume in memory performance (e.g., Raz et al., 1998; de Toledo-Morrell et al., 2000; Hackert et al., 2002; Golomb et al., 1994, 1996; Rosen et al., 2003; Tisserand et al., 2000; Torres et al., 1997).

While the first class of studies, relating gross brain volumes to general ability, have lent support to a brain size–behavior relationship, robust relationships between specific cognitive abilities and morphometric characteristics have not been consistently established. For instance, the importance of hippocampus for mnemonic function is well documented (e.g., Scoville and Milner,

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Table 1
Characteristics of the total sample (n = 71)

	20–39 years n = 24	40–59 years n = 16	60–88 years n = 31	Total sample n = 71
Age	26.8 (4.5)	51.5 (5.9)	71.9 (6.2)	52.0 (20.6)
Gender	16 f/8 m	10 f/6 m	14 f/17 m	40 f/31 m
WASI IQ	113.5 (6.9)	115.3 (10.2)	111.7 (11.8)	113.1 (10.0)
BDI	2.8 (3.2)	2.4 (2.3)	6.1 (3.4)	4.3 (3.5)
MMS	29.1 (0.8)	29.2 (0.8)	28.5 (1.2)	28.8 (1.0)
CVLT trial 1–5	63.2 (7.1)	59.8 (8.2)	51.4 (10.8)	57.3 (10.5)
CVLT recall 5 min	14.1 (1.8)	12.5 (2.6)	10.5 (2.8)	12.2 (2.8)
CVLT recall 30 min	14.3 (1.4)	12.6 (2.6)	10.9 (3.0)	12.5 (2.9)
CVLT 10 weeks	6.1 (3.7)	4.1 (2.5)	2.2 (2.9)	3.9 (3.5)

Recall values represent number of correctly recalled items. Beck Depression Inventory (BDI) was only included in the study at a later point, so data on this inventory are presented for only 63 participants.

1957), but there is no support for a simple "bigger is better" perspective for the relationship between normal individual differences in hippocampal size and memory scores at retention intervals of an hour or less (see van Petten, 2004, for a review). Further, van Petten et al. (2004) did not find positive relationships between memory performance and several gyri of known importance for memory function in the frontal and temporal parts of neocortex. However, theoretical and empirical accounts imply that memories are strengthened and maintained across an extended time period by hippocampal–cortical interactions (Buzsaki, 1996; Kali and Dayan, 2004). Consolidation takes place over several days (Riedel and Micheau, 2001) or years (Haist et al., 2001), and while hippocampus may be involved over a prolonged interval (Buzsaki, 1996; Kali and Dayan, 2004; Ryan et al., 2001), theoretical accounts also imply that memories become increasingly cortically distributed with time. In a recent study, we found evidence for increased importance of hippocampal size across an extended retention interval with a mean of 11 weeks (Walhovd et al., 2005). However, evidence was not obtained for higher importance of cortical volume in memory across weeks independently of age, but only total cortical volume was included in that study. This poses the question whether volumetric characteristics of specific cortical areas might still be of importance in recall at such extended retention intervals. A relationship between thickness of specific cortical areas and retention may manifest itself more strongly across weeks, since some cortical areas likely are increasingly important in storage of memories with time (Buzsaki, 1996; Kali and Dayan, 2004). Further, as argued by Buckner and Wheeler (2001), it is important to determine whether cortical correlates of retrieval are dependent on characteristics of medial temporal lobe structures or not. Thus, the question whether regional cortical thickness variations is related to recall at different retention intervals was investigated also when the effects of hippocampal volume were controlled for.

Materials and methods

Sample

Volunteers were recruited by ads placed on campus and in local newspapers. Participants were required to be right-handed, feel healthy, and not suffer from diseases or conditions known to affect central nervous system functioning (e.g., hypothyroidism, multiple sclerosis, Parkinson's disease, stroke). Those satisfying these criteria were further screened for health problems and cognitive problems by a structured interview, Beck Depression Inventory (BDI; Beck and Steer, 1987), the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999). Participants included here scored $\leq$14 on the BDI, $\geq$26 on the MMSE, and $\geq$85 on the IQ test. In addition, for participants above 40 years of age, total learning score and recall scores on the California Verbal Learning Test (CVLT; Delis et al., 1987; Paolo et al., 1997[1]) were used as a screening criterion to minimize the possibility of beginning degenerative conditions influencing the results. These scores had to be less than two SDs below the population mean. The final sample in the present study consisted of 71 persons (40 F) aged 20 to 88 years, of whom a subsample of 53 was included in an earlier publication on extended retention and total cortical and hippocampal volume (Walhovd et al., 2005). To ensure equal normative function between participants of different age, IQ was correlated with age, yielding a non-significant relationship (r = −0.08, P = 0.52). Sample characteristics are shown in Table 1.

MRI scanning

A Siemens Symphony Quantum 1.5 T MR scanner with a conventional head coil was used. The pulse sequences used for morphometric analysis were: Two 3D magnetization prepared gradient echo (MP-RAGE), T1-weighted sequences in succession (TR/TE/TI/FA = 2730 ms/4 ms/1000 ms/7°, matrix = 192 × 256, FOV = 256 mm), with a scan time of 8.5 min per volume. Each volume consisted of 128 sagittal slices with slice thickness = 1.33 mm, and in-plane pixel size of 1 mm × 1 mm. The image files in DICOM format were transferred to a Linux workstation for morphometric analysis.

MRI volumetric analyses

Intracranial volume (ICV) was calculated based on proton density- (PD) weighted low-flip angle FLASH scans obtained during the same scanning session as the scans used for automatic

[1] A newer version of the CVLT has recently been published (Delis et al., 2000), with less strict norms for the normal range. Alternative norms exist for the elderly also for the version used here, so we included one person who scored marginally according to the CVLT norms (Delis et al., 1987), but who scored within the normal range according to the Paolo et al. (1997) norms, and who presented no memory complaints (Clinical Dementia Rating Scale; CDR score = 0.0; Hughes et al., 1982).

labeling. A deformable template procedure, similar to the "Shrink Wrapping" procedure described by Dale and Sereno (1993) and Dale et al. (1999), was used to obtain an estimate of the smooth surface surrounding the intracranial space (containing brain, CSF, and meninges). The procedures required for automated volumetric measurement of the entire cortical mantle are described elsewhere (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 1999a,b, 2001; Fischl and Dale, 2000; Salat et al., 2004). The measurement technique used here has been validated via histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). Thickness measurements were obtained by reconstructing representations of the gray/white matter boundary (Dale and Sereno, 1993; Dale et al., 1999) and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups (Fischl and Dale, 2000). Thickness measures were mapped on the 'inflated' surface of each participant's reconstructed brain (Dale and Sereno, 1993; Fischl et al., 1999a,b). This procedure allows visualization of data across the entire cortical surface (i.e., both the gyri and sulci) without interference from cortical folding and results in a measure of cortical thickness at each point on the reconstructed surface. General linear models (GLMs) of the effects of thickness at each vertex on different memory variables were computed, controlling for effects of age, gender and intracranial volume. All scans were also segmented as described by Fischl et al. (2002), yielding volumetric data also for a number of subcortical brain structures, including the hippocampal formation. The present segmentation of the hippocampal formation includes dentate gyrus, CA fields, subiculum/parasubiculum and the fimbria (Makris et al., 1999). The results of manual labeling using the validated techniques of the Center for Morphometric Analysis (Caviness et al., 1989; Goldstein et al., 1999; Kennedy et al., 1989; Seidman et al., 1999) are used to automatically extract the information required for automating the segmentation procedure. This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. Briefly, the segmentation is carried out as follows. First, an optimal linear transform is computed that maximizes the likelihood of the input image, given an atlas constructed from manually labeled images. Next, a nonlinear transform is initialized with the linear one, and the image is allowed to further deform to better match the atlas. Finally, a Bayesian segmentation procedure is carried out, and the maximum a posteriori (MAP) estimate of the labeling is computed. The segmentation uses three pieces of information to disambiguate labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. This latter term represents a large number of constraints on the space of allowable segmentations and prohibits label configurations that never occur in the training set (e.g., hippocampus is never anterior to amygdala). The technique has previously been shown to be comparable in accuracy to manual labeling. The present hippocampus data reflect a slightly improved version of the segmentation procedure compared to that employed in Walhovd et al. (2005). The GLMs were recomputed also controlling for the effects of hippocampal volume.

Memory assessment

For assessment of verbal memory, CVLT was administered in a standardized way: A list of 16 items was read five times consecutively, and each time, the participants were immediately instructed to list all items he/she could recall. After these five trials, another 16-item list was read, with instructions of immediate recall of as many items as possible, whereupon the participants were asked to recall the first list, the one that had been read five times (5 min recall). This was followed by a cued recall test. After a 30-min delay, the participants were asked, without having been forewarned, to recall this list again. In the present study, CVLT was modified so that an additional free recall test was administered by phone after a mean of 83 days[2] (range 42–241, SD = 42). The large range of intervals was caused by difficulties reaching the participants. In order to avoid rehearsal effects, they were not forewarned that they would be asked to recall the material again, and appointments for retesting could thus not be made. However, retention intervals were random and did not correlate significantly with age ($r = -0.08$, $P = 0.53$), number of correctly remembered items ($r = -0.04$, $P = 0.75$), or number of correctly remembered items minus number of intrusions/incorrectly remembered items ($r = -0.21$, $P = 0.09$). Retention intervals did, however, correlate significantly with number of intrusions ($r = 0.34$, $P < 0.01$). Thus, while intrusions do affect memory performance, the possible interpretation of such analyses here would be limited. The present analyses were performed on recall scores that were calculated as number of correctly remembered items only. This approach was chosen both in consideration of the above relationship between retention interval and intrusions and theoretical and empirical accounts viewing intrusions to be determined by partly other factors than those determining correct retrieval (Delis et al., 2000). In addition, this keeps the analysis material consistent with that presented by Walhovd et al. (2005). Descriptive data for number of hits and intrusions at the different retention intervals are shown in Table 1.

Statistics

For each hemisphere, GLMs were computed for analysis of the effect of cortical thickness at each vertex on the respective types of verbal memory scores (5 min, 30 min and several weeks), controlling for the effects of age, gender, IQ and ICV. IQ was controlled for because we were interested in investigating relationships between cortical thickness and memory independently of general ability. In the present study, there were no relationships between ICV and recall at either 5 min ($r = -0.12$, $P = 0.307$), 30 min ($r = -0.02$, $P = 0.876$), or 11 weeks ($r = 0.03$, $P = 0.833$). However, ICV varies with body size (e.g., Peters et al., 1998) and there were significant relationships between ICV and cortical

[2] For one person who took the phone test at an intermediate interval, the exact number of days was not noted.

thickness in the present sample (see Supplementary Fig. 1). ICV was therefore controlled for in the analyses. These GLM analyses were done to assess the relative power of thickness throughout the cortical mantle in predicting memory at the three retention intervals. Analyses were also performed with the same variables, controlling for the effect of hippocampal volume. The volume of the left hippocampus was controlled for in the left hemisphere cortical analyses, and the volume of the right hippocampus was controlled for in the right hemisphere analyses. These analyses were performed to assess to what extent the contribution of cortical thickness in memory prediction was independent of hippocampal volume. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 12.6 mm and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl et al., 1999a,b). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion. Statistical comparisons of global data and surface maps were generated by computing a general linear model of the effects of each variable on thickness at each vertex. Instead of using a corrected *P* value threshold, a scale with the actual *P* values is displayed in the figures. The reason for this is that the effect under investigation must necessarily be subject to considerable noise, and hence may be subtle. Normally, in a clinical or experimental setting where memory is being tested, one exerts strict control of what stimuli participants encounter during test intervals. Across several weeks, however, the participants surely must have been engaging in a number of different activities that will to varying degrees have interfered with or facilitated recall. Some may have rehearsed the list while some may not have had the list in mind at all during this interval. Since the number of participants is also somewhat limited, a harsh criterion for multiple comparisons may be too conservative. However, the distribution of number of voxels of different *P* values for the GLM is plotted, making it possible to evaluate the stability of the results in detail, and split-half analyses for effect sites are performed.

Results

In mm^3, the mean automatically labeled volume of the hippocampus was 3891 (SD = 530) for the right and 3624 (SD = 527) for the left, and mean total cortical volume measured as described by Fischl et al. (2002) was 428293 (SD = 61013). The results of the GLMs when the effects of age, gender, IQ and ICV were controlled for, without and with additional control for hippocampal volume, are shown in Figs. 1 and 2. There was little association between cortical thickness and recall at 5 and 30 min (Fig. 1). However, it was evident that higher recall across months was associated with thicker cortex of distinct areas (Fig. 2). When not controlling for the effect of hippocampal volume, this effect involved parts of the gyrus rectus, the middle frontal gyrus, the parieto-occipital sulcus, the lingual gyrus, the hippocampal gyrus and the junction of the hippocampal and parahippocampal gyrus of both hemispheres. Effects specific to the right hemisphere were seen for parts of the superior and middle temporal gyrus, the temporal pole, and the superior parietal gyrus. An effect specific to the left hemisphere was observed in parts of the precuneus and surrounding areas. When controlling for the effect of hippocampal volume, these effects remained essentially unchanged in the right hemisphere, while effects in the left hemisphere generally were modulated, and the left hippocampal and parahippocampal gyrus effects were not significant independently of hippocampal volume.

Labels were drawn around the major effect sites and regression analyses were performed with cortical thickness in specific areas predicted from memory across months. Plots are shown in Fig. 3. As seen, the correlations are quite similar across labels, all in the range 0.23 to 0.34. In order to explore possible causal mechanisms underlying these effects, we wanted to see if

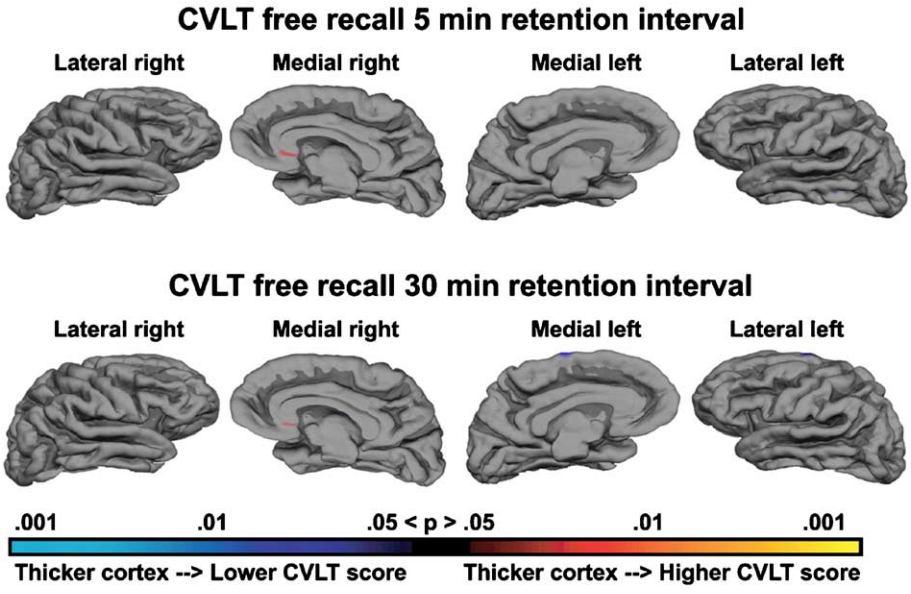

Fig. 1. The top row shows the relationships between cortical thickness and 5 min recall when the effects of age, gender, IQ, ICV, and hippocampal volume for the respective hemispheres are controlled for. The bottom row shows the relationships between cortical thickness and 30 min recall when the effects of age, gender, ICV, and hippocampal volume for the respective hemispheres are controlled for.

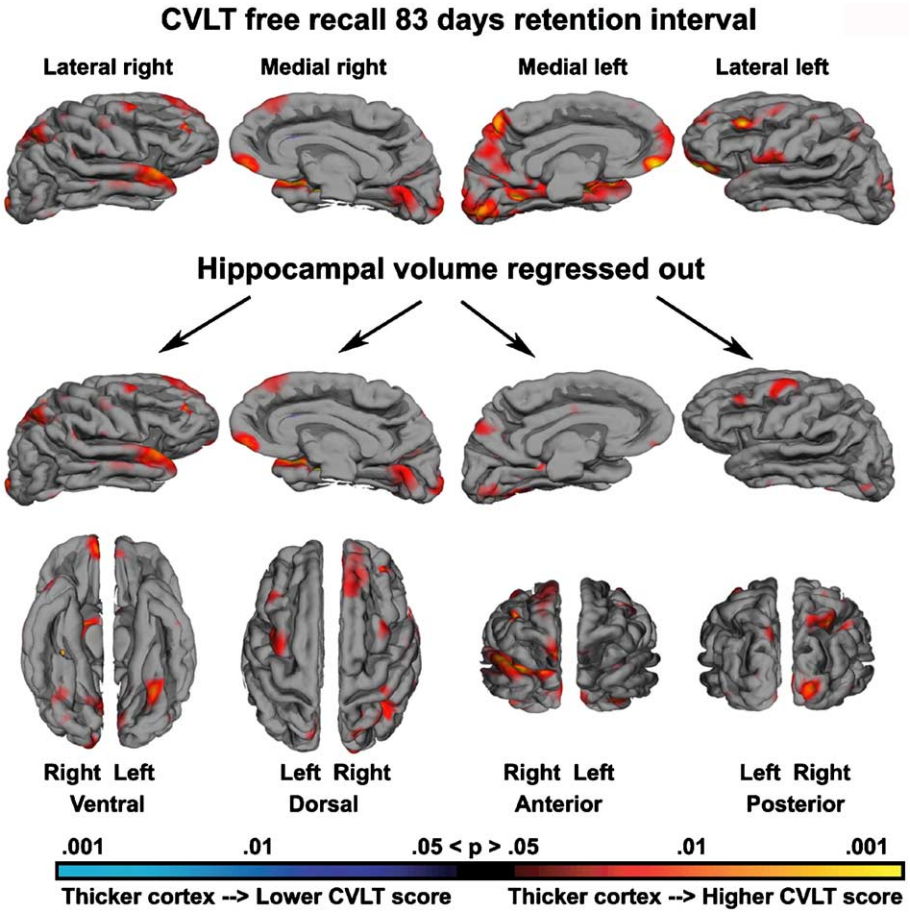

Fig. 2. The top row shows the relationships between cortical thickness and recall after months, when the effects of age, gender, IQ, and ICV are controlled for. The middle and bottom row show the relationships between cortical thickness and recall after months when the effects of age, gender, IQ, ICV, and hippocampal volume of the respective hemispheres are controlled for.

persons remembering little after months showed different age effects on cortical thickness than persons remembering much. The sample was divided in two halves based on memory score after multiple weeks: The low-memory group consisted of those remembering 0–3 items (n = 37, M = 1.2, SD = 1.2) and the high memory group consisted of those remembering 4–14 items (n = 34, M = 6.9, SD = 2.7). However, age differed significantly across these groups (low memory: range 20–88 years, M = 59.0, SD = 21.1 vs. high memory: range 21–74 years, M = 44.5, SD = 17.4, t = 3.154, P = 0.002). We therefore decided to exclude all persons from the low memory group who were older than the oldest in the high memory group, i.e., > 74 years, from the group analysis of age effects. The resulting low memory group (age M = 49.9, SD = 19.9) still had a range of remembered items from 0 to 3 (n = 25, M = 1.4, SD = 1.2), and the groups were no longer significantly different with respect to age (t = 1.112, P = 0.271). The regression plots from selected areas are shown in Fig. 4. There are some hemispheric differences, but cortical thickness in the hippocampal gyrus and gyrus rectus, as well as average thickness across all cortical effect sites, show less relationship with age in the high memory group. These differences across groups do not reach statistical significance by t tests of the Fisher z-transformed correlation coefficients. However, as mentioned, this type of test is unlikely to yield significant differences in comparing groups of this size (n = 25 and n = 34). For the right hemisphere labels, there is actually no relationship between age and average cortical thickness of the effect areas for the high memory group, whereas cortical thickness shows age decline in the low memory group.

Finally, we wanted to evaluate the stability of the presented results. Plots of the distribution of voxels along a P value axis (Supplementary Fig. 2) showed that all effects were in the same direction (i.e., there were only positive relationship between cortical thickness and recall after months). Virtually no voxels exceeded the 0.05 P value threshold for opposite effects, and the normal distribution of voxels along the P value axis was markedly skewed to the right. Even though the large number of comparisons in principle could have produced a large number of false positives, this makes it unlikely that the present results were obtained by chance. To further check the validity of these effects, the sample was divided in two halves matched as closely as possible with regard to age, gender, recall after months, IQ, and hippocampal volume. Sample characteristics are presented in Supplementary Table 1. The thickness of 8 effect areas in each hemisphere (matching those in Fig. 3) as well as the average thickness across all these areas in each hemisphere was correlated with recall score after months in both samples, and the correspondence of effects across samples was evaluated. Very similar effects were found and none of the correlations were significantly different. The correlations between recall and average thickness across all areas were

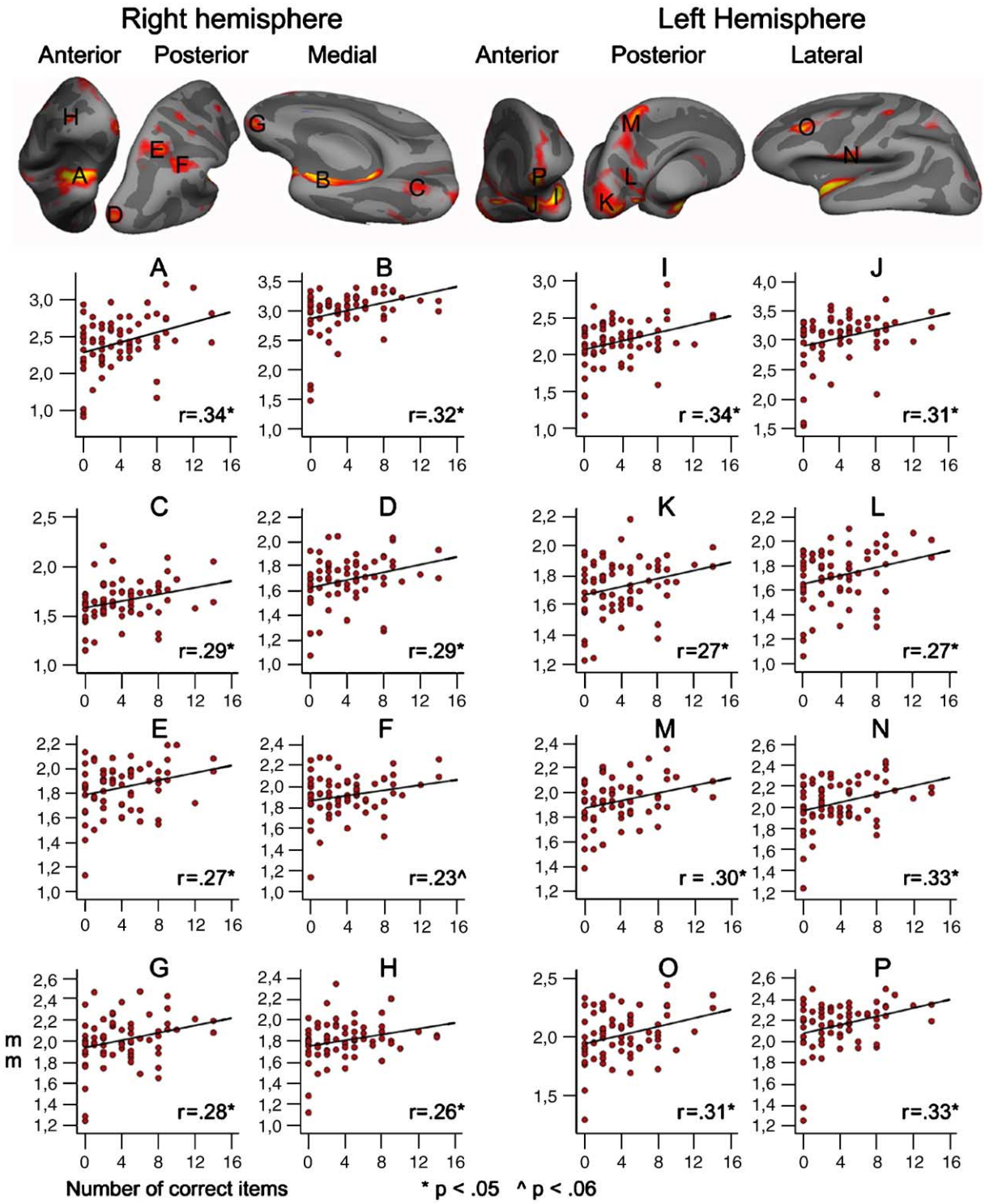

Fig. 3. The top row indicates selected effect sites on inflated template brains. The inflation allows inspection of effects that would otherwise be hidden within sulci. Labels were drawn by tracing the outer edge of the areas significantly related to memory across months. The scattergrams show mean thickness in the selected areas for each person plotted against number of correctly recalled items after months. Since the labels were drawn around effect sites, they are not restricted to conventional anatomical borders. However, the following gives a rough description of which anatomical area is the most representative for each label. Right hemisphere: (A) anterior parts of temporal lobe, stretching out to include some of the insula, (B) hippocampal gyrus, (C) lingual gyrus, (D) occipital pole, (E) superior parietal gyrus, (F) inferior parietal gyrus, (G) gyrus rectus, (H) middle frontal gyrus. Left hemisphere: (I) anterior parts of temporal lobe, stretching out to include some of the insula, (J) hippocampal gyrus, (K) occipital pole, (L) parieto-occipital sulcus, (M) postcentral sulcus, (N) subcentral gyrus, (O) middle frontal gyrus, (P) gyrus rectus.

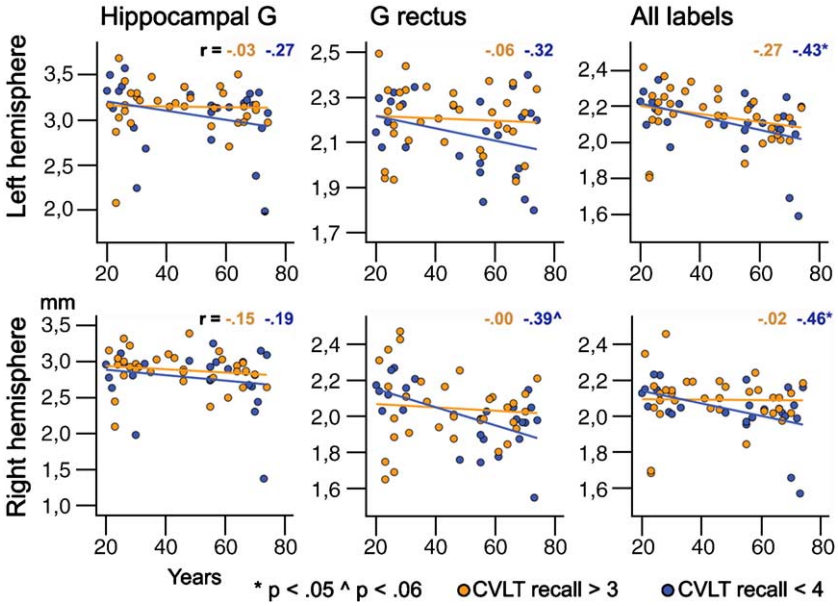

Fig. 4. The scatterplots illustrate the relationship between cortical thickness and age according to memory function for two groups: blue circles signify the low memory group (those who remembered 0–3 items after an extended interval), yellow circles signify the high memory group (those who remembered 4–14 items after an extended interval). As can be seen, a steeper relationship between age and cortical thickness is found in the low memory group than in the high memory group. The cortical areas were chosen based on sites showing an association between cortical thickness and recall after months. The labels were drawn within the hippocampal gyrus [rh: label B, lh: label J] and the gyrus rectus [rh: label H, LH: label P] in both hemispheres. In addition, mean thickness across 8 effect site labels in each of the hemispheres is plotted (for location of these labels, see Fig. 3).

0.39 and 0.33 for right, and 0.41 and 0.35 for the left hemisphere (P for all <0.05).

Discussion

The present results support a critical role of thickness of distinct cortical areas in verbal recall. For recall after shorter retention intervals, that is, 5 and 30 min, virtually no effect of cortical thickness was seen. However, more pronounced effects were seen across weeks or months. These effects were relatively widespread and extended to include the junction of the hippocampal and parahippocampal gyrus of both hemispheres when the effect of hippocampal volume was not controlled for. However, thickness of distinct cortical areas was significantly associated with recall after months also independently of hippocampal volume. Thicker cortex in parts of the gyrus rectus, the middle frontal gyrus, the parieto-occipital sulcus and the lingual gyrus of both hemispheres was uniquely associated with higher recall rate after months. In addition, hemisphere-specific associations were also found independently of same-side hippocampal volume. Specifically, this included parts of the hippocampal gyrus and the junction between the hippocampal and parahippocampal gyrus, the superior and middle temporal gyrus, the temporal pole, and the superior parietal gyrus and parietal transversal sulcus of the right hemisphere, as well as parts of the precuneus of the left hemisphere. It is noteworthy that hippocampal volume seemed to have little to do with the association between cortical thickness and extended verbal recall in the right hemisphere, whereas this association seemed more mediated by hippocampal volume in the left hemisphere. Controlling for IQ did not substantially weaken the observed cortical thickness relationships, which appear specific to recall after months.

Based on the present data, it seems that individual differences in regional cortical thickness become a more valuable memory predictor at a longer retention interval. This is likely related to a temporally graded consolidation process depending partly on regional neuroanatomical differences, as discussed above. It is generally accepted that memories become more cortically distributed with increasing time, but it remains to be understood how the cortical maintenance of memory traces can be grounded or reflected in cortical thickness, as it seems here. At least two related explanations may be possible: First, thicker cortex of these areas may be a general sign of cognitively beneficial neuroanatomical characteristics. This may not necessarily be specifically related to memory function, but appears to be here, since IQ was regressed out. There is evidence that larger brains have more neurons (Pakkenberg and Gundersen, 1997), and neuroanatomical volumes are partly genetically determined (e.g., Thompson et al., 2001). Thickness may signify the number of neurons or functional connections with associated cortical and subcortical areas important in cognitive processes, including memory. That is, thicker cortex may positively affect recall after several weeks by improving the hippocampal–neocortical dialogue that maintains or strengthens the memory-traces over time (Buzsaki, 1996; Kali and Dayan, 2004). Second, memory processing – learning and rehearsal – may possibly also affect cortical thickness. Draganski et al. (2004) recently presented evidence for training-induced cortical thickening in adult persons. One may then reason that persons who generally tend to engage the most in memory-maintaining activities such as rehearsal have developed thicker cortex in relevant areas. If this is true, it remains unclear what the microscopic changes behind such thickening could be. As Draganski and colleagues state, macroscopic dynamic cortical alterations could be based on changes at synaptic level or they might include increased glial of neuronal cell genesis. Neuro-

genesis in adult mammals certainly exists, but likely only in a few regions (Kempermann et al., 2004), and the functional significance of this in higher order cognition may be limited. During our evolutionary history, neurogenesis has decreased (Rakic, 2004) while central nervous system complexity, and hence, cognitive ability, has increased.

The present study is based on a cross-sectional life span sample, so other causal mechanisms may be at play here than in a young sample. However, as seen from Fig. 3, the present findings do not indicate that high memory performers have thicker cortex in young age. Rather, the high and low memory performers seem to become different across the adult life span, with those remembering well maintaining cortical thickness, and those remembering less well showing cortical thinning with age. This does not exclude the possibility of a neurogenesis-mechanism in the high memory group that may compensate for degenerative thinning, but whatever the causal mechanism and microstructural basis is, it seems from these cross-sectional data that the end product is preservation of cortical thickness, not thickening per se.

The areas in which thickness was associated with recall after months have previously been conceptualized as parts of a neural network underlying episodic memory. This is evident from both patient and functional imaging studies. For instance, in a review, Buckner and Wheeler (2001) point to predominantly left-sided parietal areas activated during retrieval success and frontal–polar and more posterior frontal areas that seem involved in implementation and monitoring during retrieval attempt. These areas are close to the areas of the gyrus rectus, the middle frontal gyrus, the left precuneus and the parieto-occipital sulcus identified here. Broad areas including the junction of the hippocampal and parahippocampal gyrus, as well as parts of the superior and middle temporal gyrus and the temporal pole, was significantly associated with recall in the right hemisphere only. The parahippocampal gyrus' importance in recall has been well established (e.g., Weniger et al., 2004). Further, increased activity in the right temporal pole has been associated with both item encoding and retrieval in a PET study (Persson and Nyberg, 2000). Function and structure must undoubtedly somehow be related, but a straight-forward correspondence between the two should not be assumed. Functional imaging data can, however, inform us on the tasks the cortical areas here are involved in, and point to their importance in memory performance. Buckner and Wheeler (2001) argue that an important task for future studies is to determine whether the significance of cortical correlates of retrieval success, e.g., left parietal and associated cortex, are dependent upon medial temporal structures. At a structural level, the present data informs us that regional cortical thickness seem to matter more in recall after months than minutes, and that this relationship is independent of general ability and hippocampal volume.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2006.01.011.

References

Andreasen, N.C., Flaum, M., Swayze II, V., O'Leary, D.S., Alliger, R., Cohen, G., Ehrhardt, J., Yuh, W.T., 1993. Intelligence and brain structure in normal individuals. Am. J. Psychiatry 150, 130–134.

Beck, A.T., Steer, R., 1987. Beck Depression Inventory Scoring Manual. The Psychological Corporation, New York.

Buckner, R.L., Wheeler, M.E., 2001. The cognitive neuroscience of remembering. Nature 2, 624–634.

Buzsaki, G., 1996. The hippocampal–neocortical dialogue. Cereb. Cortex 6, 81–92.

Caviness, V.S., Filipek, P.A., Kennedy, D.N., 1989. Magnetic resonance technology in human brain science: blueprint for a program based upon morphometry. Brain Dev. 11, 1–13.

Dale, A.M., Sereno, M.I., 1993. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J. Cogn. Neurosci. 5, 162–176.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis I: segmentation and surface reconstruction. NeuroImage 9, 179–194.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test. The Psychological Corporation, San Antonio, TX.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 2000. California Verbal Learning Test, 2nd ed. The Psychological Corporation, San Antonio, TX.

de Toledo-Morrell, L., Dickerson, B., Sullivan, M.P., Spanovic, C., Wilson, R., Bennett, D.A., 2000. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. Hippocampus 10, 136–142.

Egan, V., Chiswick, A., Santosh, C., Naidu, K., Rimmington, J.E., Best, J.K., 1994. Size isn't everything: a study of brain volume, intelligence and auditory evoked potentials. Pers. Individ. Differ. 17, 357–367.

Egan, V., Wickett, J.C., Vernon, P.A., 1995. Brain size and intelligence: erratum, addendum, and correction. Pers. Individ. Differ. 19, 113–115.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97, 11050–11055.

Fischl, B., Sereno, M.I., Dale, A.M., 1999a. Cortical surface-based analysis: II. Inflation, flattening, and a surface-based coordinate system. NeuroImage 9, 195–207.

Fischl, B., Sereno, M.I., Tootell, R.B., Dale, A.M., 1999b. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8, 272–284.

Fischl, B., Liu, A., Dale, A.M., 2001. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans. Med. Imaging 20, 70–80.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation. Automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Flashman, L.A., Andreasen, N.C., Flaum, M., Swayze, V.W., 1998. Intelligence and regional brain volumes in normal controls. Intelligence 25, 149–160.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. J. Psychiatr. Res. 12, 189–198.

Goldstein, J.M., Goodman, J.M., Seidman, L.J., Kennedy, D.N., Makris, N., Lee, H., Tourville, J., Caviness, V.S., Faraone, S.V., Tsuang, M.T., 1999. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. Arch. Gen. Psychiatry 56, 537–547.

Golomb, J., Kruger, A., De Leon, M.J., Ferris, S.H., Mittelman, M., Cohen, J., George, A.E., 1994. Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. Learn. Mem. 1, 45–54.

Golomb, J., Kluger, A., de Leon, M.J., Ferris, S.H., Mittelman, M., Cohen, J., George, A.E., 1996. Hippocampal formation size predicts declining memory performance in normal aging. Neurology 47, 810–813.

Hackert, V.H., T. Heijer, T., Oudkerk, M., Koudstaal, P.J., Hofman, A., Breteler, M.M.B., 2002. Hippocampal head size associated with verbal memory performance in nondemented elderly. NeuroImage 17, 1365–1372.

Haist, F., Gore, J.B., Mao, H., 2001. Consolidation of human memory over decades revealed by functional magnetic resonance imaging. Nat. Neurosci. 4, 1139–1145.

Harvey, I., Persaud, R., Ron, M.A., Baker, G., Murray, R.M., 1994. Volumetric MRI measurements in bipolars compared with schizophrenics and healthy controls. Psychol. Med. 24, 689–699.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. Br. J. Psychiatry 140, 566–572.

Jack Jr., C.R., Shiung, M.M., Gunter, J.L., O'Brien, P.C., Weigand, S.D., Knopman, D.S., Boeve, B.F., Ivnik, R.J., Smith, G.E., Cha, R.H., Tangalos, E.G., Petersen, R.C., 2004. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 62, 591–600.

Kali, S., Dayan, P., 2004. Off-line replay maintains declarative memories in a model of hippocampal–neocortical interactions. Nat. Neurosci. 7, 286–294.

Kempermann, G., Wiskott, L., Gage, F.H., 2004. Functional significance of adult neurogenesis. Curr. Opin. Neurobiol. 14, 186–191.

Kennedy, D.N., Filipek, P.A., Caviness, V.S., 1989. Anatomic segmentation and volumetric calculations in nuclear magnetic resonance imaging. IEEE Trans. Med. Imaging 8, 1–7.

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60, 878–888.

MacLullich, A.M.J., Ferguson, K.J., Deary, I.J., Seckl, J.R., Starr, J.M., Wardlaw, J.M., 2002. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. Neurology 59, 169–174.

Makris, N., Meyer, J., Bates, J., Yeterian, E.H., Kennedy, D.N., Caviness, V.S., 1999. MRI-based parcellation of human cerebral white matter and nuclei. Part II: rationale and applications with systematics of cerebral connectivity. NeuroImage 9, 18–45.

Pakkenberg, B., Gundersen, H.J.G., 1997. Neocortical neuron numbers in humans: effect of sex and age. J. Comp. Neurol. 384, 312–320.

Paolo, A.M., Tröster, A.I., Ryan, J.J., 1997. California verbal learning test: normative data for the elderly. J. Clin. Exp. Neuropsychol. 19, 220–234.

Persson, J., Nyberg, L., 2000. Conjunction analysis of cortical activations common to encoding and retrieval. Microsc. Res. Tech. 51, 39–44.

Peters, M., Jäncke, L., Staiger, J.F., Schlaug, G., Huang, Y., Steinmetz, H., 1998. Unsolved problems in comparing brain sizes in homo sapiens. Brain Cogn. 37, 254–285.

Posthuma, D., De Geus, E.J., Baaré, W.F.C., Pol, H.E.H., Kahn, R.S., Boomsma, D.I., 2002. The association between brain volume and intelligence is of genetic origin. Nat. Neurosci. 5, 83–84.

Rakic, P., 2004. Neuroscience: immigration denied. Nature 427, 685–686.

Raz, N., Torres, I.J., Spencer, W.D., Millman, D., Baertschi, J.C., Sarpel, G., 1993. Neuroanatomical correlates of age-sensitive and age-invariant cognitive abilities: an in vivo MRI investigation. Intelligence 17, 407–422.

Raz, N., Gunning-Dixon, F.M., Head, D., Dupuis, J.H., Acker, J.D., 1998. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology 12, 95–114.

Riedel, G., Micheau, J., 2001. Function of the hippocampus in memory formation: desperately seeking resolution. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25, 835–853.

Rosas, H.D., Liu, A.K., Hersch, S., Glessner, M., Ferrante, R.J., Salat, D.H., van der Kouwe, A., Jenkins, B.G., Dale, A.M., Fischl, B., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58, 695–701.

Rosen, A.C., Prull, M.W., Gabrieli, J.D., Stoub, T., O'Hara, R., Friedman, L., Yesavage, J.A., de Toledo-Morrell, L., 2003. Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. Behav. Neurosci. 117, 1150–1160.

Ryan, L., Nadel, L., Kiel, K., Putnam, K., Schnyer, D., Trouard, T., Moscovitch, M., 2001. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance in neurologically intact people. Hippocampus 11, 707–714.

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S.R., Busa, E., Morris, J.C., Dale, A.M., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 14, 721–730.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol., Neurosurg. Psychiatry 20, 11–21.

Seidman, L.J., Faraone, S.V., Goldstein, J.M., Goodman, J.M., Kremen, W.S., Toomey, R., Tourville, J., Kennedy, D., Makris, N., Caviness, V.S., Tsuang, M.T., 1999. Thalamic and amygdala–hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. Biol. Psychiatry 46, 941–954.

Thompson, P.M., Cannon, T.D., Katherine, L., Narr, K.L., van Erp, T., Veli-Pekka Poutanen, V.-P., Huttunen, M., Lönnqvist, J., Standertskjöld-Nordenstam, C.-G., Kaprio, J., Khaledy, M., Dail, R., Zoumalan, C.I., Toga, A.W., 2001. Genetic Influences on brain structure. Nat. Neurosci. 4, 1253–1258.

Tisserand, D.J., Visser, P.J., van Boxtel, M.P.J., Jolles, J., 2000. The relation between limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiol. Aging 21, 569–576.

Torres, I.J., Flashman, L.A., O'Leary, D.S., Swayze, V.I., Andreasen, N., 1997. Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. Biol. Psychiatry 42, 1087–1096.

van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 42, 1394–1413.

van Petten, C., Plante, E., Davidson, P.S.R., Kuo, T.Y., Bajuscak, L., Glisky, E.L., 2004. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia 42, 1313–1335.

Walhovd, K.B., Fjell, A.M., Reinvang, I., Lundervold, A., Quinn, B.T., Dale, A.M., Makris, N., Fischl, B., 2005. Cortical volume and speed-of-processing are complementary in prediction of performance intelligence. Neuropsychologia 43, 704–713.

Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio, TX.

Weniger, G., Boucsein, K., Irle, E., 2004. Impaired associative memory in temporal lobe epilepsy subjects after lesions of hippocampus, parahippocampal gyrus, and amygdala. Hippocampus 14, 785–796.

Wickett, J.C., Vernon, P.A., Lee, D.H., 2000. Relationships between factors of intelligence and brain volume. Pers. Individ. Differ. 29, 1095–1122.

Willerman, L., Schultz, R., Rutledge, J.N., Bigler, E.D., 1991. In vivo brain size and intelligence. Intelligence 15, 223–228.