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Research Report

The functional and structural significance of the frontal shift in the old/new ERP effect

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ABSTRACT

There is a lack of studies mapping electrophysiological event-related potentials (ERPs) to structural neuroanatomical characteristics. The aim of the present study was to integrate electrophysiological memory-related activity with cortical and hippocampal volume, as well as psychometric memory performance, in a life-span sample. More specifically, we wanted to investigate the functional significance of the often-observed frontal shift of ERP amplitude with increasing age and whether neuroanatomical characteristics can explain this shift. Sixty six healthy participants (20–78 years) went through a neuropsychological examination, MRI scans, and a visual recognition ERP task with verbal stimuli. The results showed that ERPs elicited in the recognition memory task (the old/new effect) correlated significantly with cortical volume, but not with hippocampal volume. Large cortex predicted more differentiated ERP activity and not just larger amplitude in general, implying more distinct and efficient retrieval. Furthermore, ERP amplitude, cortical volume, and hippocampal volume all predicted scores on a composite memory scale. All these relationship were dependent upon the common influence of age. Finally, the participants with the most anterior distribution of activity showed the poorest recognition memory performance. Neither cortical nor hippocampal volume were related to this frontal shift. It is concluded that the distribution of activity along the anterior–posterior axis in a memory paradigm may have functional but not neuroanatomical volumetric correlates. The functional correlates need not be restricted to the older age groups.

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1. Introduction

By use of different scanning methods, studies have identified differential patterns of neural activation in older vs. younger adults (Cabeza et al., 2002; Fabiani et al., 1998). A central question regards whether such differences reflect compensatory processing, cognitive inefficiency, or, alternatively, may not be related to cognitive function. In a recent review, Friedman (2003) states that there are too few event-related potential (ERP) age-related investigations focusing on individual differences to determine whether the changes in ERP patterns can be deemed "compensatory" or "inefficient." He recommends that future electrophysiological investigations of cognitive aging include individual difference measures, so that the implication of a given neural pattern in the genesis of a given, age-related behavioral outcome can be determined. The present study is aimed at giving a contribution along these lines. By including both validated and standardized neuropsychological memory tests, as well as measures of gross neuroanatomical brain structures (cortical and hippocampal volume), in a study of the topography of the old/new ERP effect, we hope to shed light on the question of compensation vs. inefficiency in aging.

1.1. *Neuroanatomy of the old/new effect*

A considerable body of literature validates ERP as a powerful tool in memory research (for reviews, see Friedman, 2000; Friedman, 1992; Johnson et al., 1995; Kutas et al., 1988; Rugg, 1994). In a continuous string of stimuli, old recognized items elicit larger amplitude than new items in the 300 to 800 ms interval. What is sometimes referred to as the parietal old/new ERP effect typically manifests itself in this time window and is seen as a large positive deflection, often with a posterior or parietal maximum (e.g., Rugg, 1985, 1987). This effect is the focus of the present study and will be referred to as 'the old/new effect' in this article since the effect arguably does not *need* to have its maximum at parietal scalp areas. Johnson et al. (1995) argue that this old/new effect is a distinct ERP component, related to memory retrieval processes. Some recent research has indicated that the effect specifically reflects recollection rather than familiarity (e.g., Curran et al., 2001; Wilding, 2000; for reviews, see Friedman and Johnson, 2000; Mecklinger, 2000). However, the validity of such claims has been questioned (Yovel and Paller, 2004), but there is general agreement that the old/new effect indexes successful memory retrieval and is unrelated to perceptual priming. Olichney et al. (2000) found a correlation between the old/new effect and memory performance in both controls and amnesic patients and that the correlations were stronger for recall than recognition tests in the controls. While some studies have found an age decrease (Fjell et al., 2005a; Nielsen-Bohlman and Knight, 1995; Rugg et al., 1997; Wegesin et al., 2002), others have not (Friedman et al., 1993; Trott et al., 1997; Trott et al., 1999). In a recent review of ERP investigations of memory in aging, Friedman (2000) concluded that the old/new effect seems relatively spared in older persons.

Patient data (Guillem et al., 1995b; Rugg et al., 1991; Smith and Halgren, 1989) suggest that structures within the medial temporal lobe contribute to the old/new effect, either directly or through their interconnections with other structures. Intracranial recordings in patients suffering from epilepsy have shown old/new effects from the medial temporal lobe and the hippocampus (Smith et al., 1986). In a series of such studies, Guillem et al. (1995a,b, 1996, 1999) have detected the old/new effect in a number of different brain areas: hippocampus, amygdala, anterior temporal cortex, anterior cingulate cortex, lateral frontal cortex, the orbito-frontal region, and parietal cortex. Thus, it is evident that the old/new effect has widespread neural origins, including structures within the medial temporal lobe. However, when registering the old/new effect at the scalp, it is less probable that the activity from structures such as the hippocampus can be directly measured. Rather, we can assume that some of the cortical activity measurable at the scalp is dependent upon processes that originate in the medial temporal lobe.

1.2. *The frontal shift in aging*

In several different ERP paradigms, especially oddball tasks, but also recognition memory paradigms (Swick and Knight, 1997; but see Friedman et al., 1993; Rugg et al., 1997), a more even distribution of activity along the posterior–anterior axis has been found (Anderer et al., 1996; Fjell and Walhovd, 2001, 2003, 2004; Iragui et al., 1993; Pfefferbaum et al., 1984; Vesco et al., 1993; Walhovd and Fjell, 2001). In a previous publication from the present study, with a largely overlapping sample, a frontal shift of the old/new difference amplitude was found, and not only a general amplitude effect (Fjell et al., 2005a). However, it remains an open question what functional correlates this often-observed frontal shift in ERP amplitude may have and whether such a shift is related to the volume of neuroanatomical structures. Traditionally, the frontal shift has been studied in the context of the classical oddball tasks, using the amplitude to non-frequent target stimuli, or the difference between target stimuli and frequent standards. A more even amplitude distribution of ERPs (P3b) along the posterior–anterior axis in aging has previously been found to be related to poorer task performance on parts of the Wisconsin Card Sorting Test (Fabiani et al., 1998). In a PET study of source memory, however, Cabeza et al. (2002) found that low-performing older adults recruited similar right prefrontal cortical regions as young adults, but high-performing older adults engaged these regions bilaterally. Thus, these results suggested that low-performing older adults recruited a similar network as young adults but used it inefficiently, whereas high-performing older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks. This shows that age changes in neural activity, at least as measured by PET, may have important functional behavioral correlates. A topic of interest is whether or not the reduced hemispheric lateralization observed in PET studies and its association with maintained behavioral performance could have an ERP analogy in the anterior–posterior shift and associated performance level.

As Friedman (2003) states, more studies comparing the ERP topography to validated criteria variables are needed. By including a 'global' memory score in addition to the recognition memory task used during the ERP recordings, it is possible to test whether the ERP old/new effect has implications for

memory function beyond the actual task at hand. Arguably, the external validity of the old/new effect as a tool for indexing memory function will be higher if one is able to predict memory function exceeding the actual task used. Thus, even though a given ERP deflection indexes some specific neurophysiologic process, it may still be related to more global information processing abilities.

1.3. *Rationale for the present study*

While ERP amplitude measured on the scalp is a reflection of activity in the pyramidal cortical neurons, we have at present no knowledge about how differences in neuroanatomical volumetry influence this amplitude. Larger cortex may be beneficial for cognitive functions such as memory, possibly due to a larger number of neurons or synaptic connections (Pakkenberg and Gundersen, 1997), even though straightforward relationships between brain volumes and memory functions have been hard to establish in healthy adults (van Petten, 2004; van Petten et al., 2004). A relationship between ERP amplitude in a recognition memory paradigm and the size of relevant brain structures may be found if a volumetry–memory function relationship could be established. As indicated above, a stronger relationship between old/new amplitude and cortical rather than hippocampal volume is likely. Furthermore, to understand the significance of such a possible relationship, the relationship to psychometric memory performance has to be established. In the present study, a composite score consisting of three established neuropsychological tests measuring different aspects of human memory and known to be sensitive to normal age changes (see Experimental procedures section) is used in addition to the behavioral data from the ERP task. Thus, ERPs and neuroanatomical volumes will be employed to predict global psychometric memory performance and recognition memory.

Normal aging is known to affect neuroanatomical volumes, memory function, and possibly the old/new ERP effect, and an adult life-span sample may illuminate how age influences the relationships under study. The main questions investigated are:

(1) How strong and of what nature is the relationship between volumes of cortex and hippocampus and the old/new ERP effect, with and without the influence of age accounted for? We expect a relationship between the two neuroanatomical volumes and the old/new amplitude, which is likely to be stronger for cortex than for hippocampus. Due to the expected frontal shift in aging, we further expect the relationships to be strongest at Cz and Pz. Removing the influence of age will most likely diminish the relationships because of their mutual sensitivity to age effects.
(2) Is the amplitude of the old/new effect related to psychometric memory performance? We expect that ERPs will be related to psychometric memory performance, but this has to our knowledge not been thoroughly studied with regard to the old/new effect, and, as such, this hypothesis is largely based on theoretical speculation.
(3) How do topographical changes in ERP amplitude relate to individual differences in memory capabilities and cortical/hippocampal volume? More widespread PET activity across hemispheres has been associated with maintained performance level in aging (Cabeza et al., 2002). However, based on previous ERP findings, especially those of Fabiani et al. (1998), we expect frontally distributed ERP activity to be related to poorer memory performance. If this hypothesis bears out, we expect cortical volume to mediate the relationship.

The sample in the present study largely overlaps with the samples presented in Fjell et al. (2005a,b) and Walhovd et al. (2004). The relationships between the neuroanatomical volumes and age, the relationship between the old/new effect and age, and partly the relationship between psychometric memory and age are dealt with in these publications and will not be handled in detail here. Thus, the focus of the present paper is the interrelationships between the old/new effect, psychometric memory function, and neuroanatomical structures and how these are mediated by age.

2. Results

Due to the number of different methods involved, the analyses are limited to those directly relevant for the three hypotheses. ERPs to non-word stimuli will not be analyzed, and only the trials where the participants gave a correct response are included. To assess possible confounding effects of gender, we performed ANOVAs with 3 electrodes (Fz, Cz, Pz) × gender and found no significant effects. We also performed linear regression analyses with cortical and hippocampal volume in turn as dependent variables and gender as predictor and found no significant relationships. Thus, separate analyses based on gender were not performed. When ANOVAs are used, Greenhouse–Geisser corrections are applied.

Grand average ERP curves at Pz for old and new words across three repetitions are shown in Fig. 1. Large amplitude differences between old and new words are seen in the large positive complex starting about 350 ms post-stimulus, lasting about 450 ms. The differences in activation in this complex represent the old/new effect. ANOVA with 2 types of stimuli (old, new) × 3 electrodes (Fz, Cz, Pz) yielded a main effect of stimuli ($F[1,63] = 21.647$, $P < 0.0001$). Having established the old/new effect in our data, old/new difference data will be used for the remaining analyses. ANOVA with 3 blocks of stimuli × age group yielded no significant main effects of block and no significant interaction effects for Fz, Cz, or Pz. Thus, data merged across blocks will be used for further analyses.

2.1. *Age and amplitude, volume, and memory performance*

All target variables (global memory score, recognition memory scores from the ERP task, hippocampal volume, cortical volume, and ERP amplitude at Fz, Cz, and Pz) except ERP amplitude at Fz correlated significantly with age. Cortical volume was more strongly related to age than

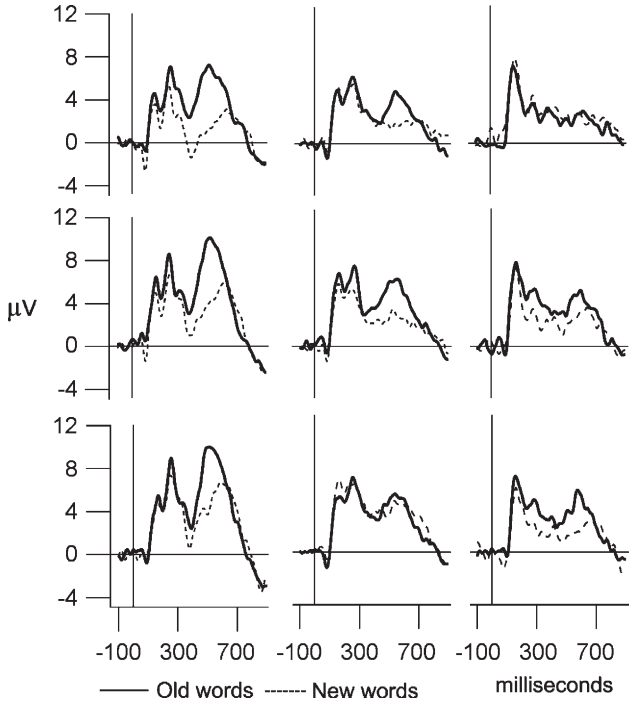

Fig. 1 – Grand average ERP curves at Pz, old and new words, over three blocks of trials. The first row represents the first block of stimuli, the second row represents the second block of stimuli, and the third row represents the third block of stimuli. The first column represents the group of young participants (20–44 years), the second column represents the group of middle-aged participants (45–69 years), and the third column represents the group of old participants (70–78 years).

hippocampal volume, and the ERP amplitudes were moderately correlated with age. Correlation coefficients are presented in Table 1.

2.2. *Volumes of cortex and hippocampus and the old/new effect*

The correlations between the old/new effect at each of the three midline electrodes and cortical and hippocampal volumes were examined. Cortical volume did not correlate significantly at Fz (r = 0.03, n.s.), but moderate relationships

Table 1 – Correlations with age

	r =	P <
Cortical volume	–0.75	0.0001
Hippocampal volume	–0.29	0.05
Recognition memory, hits	–0.00	1.000
Recognition memory, false alarms	0.38	0.01
Recognition memory, Pr	–0.37	0.01
Verbal memory	–0.50	0.0001
Visual memory	–0.54	0.0001
Global memory	–0.59	0.0001
Old/new effect Fz	–0.12	n.s.
Old/new effect Cz	–0.45	0.0001
Old/new effect Pz	–0.42	0.0001

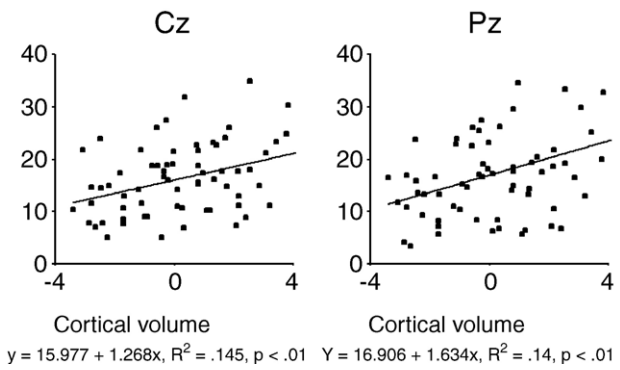

Fig. 2 – Scatterplots illustrating the relationship between ERP activity (*y* axis, μV) and volume of cortex (*x* axis, standardized residuals after regressing out intracranial volume). Cortical volume significantly predicted old/new amplitude at Cz and Pz. For hippocampal volume, none of the expressions was significant.

were found at Cz and Pz (both r = 0.37, P < 0.01). None of the correlations between the old/new effect and hippocampal volume reached significance. Scatterplots illustrating the significant relationships are shown in Fig. 2. Furthermore, to investigate the relationship between cortical volume and the different time epochs of the old/new effect, mean amplitude difference between old and new words at Pz in 50 ms time windows was correlated with cortical volume. The coefficients are presented in Fig. 3.

To investigate whether the positive correlations between cortical volume and old/new difference amplitude were a function of general, unspecific higher amplitude in participants with larger volumes, correlations between cortical and hippocampal volumes and amplitude for old and new words separately were computed. These are presented in Table 2. As can be seen, amplitude to new words correlated negatively with neuroanatomical volume at Fz. At Pz, the electrode where the old/new effect generally is best observed, no correlation between new words and cortical volume exists. Finally, multiple regression analyses showed that, when the old/new effect at Cz and Pz was predicted from cortical volume and age simultaneously, cortical volume did not contribute significantly (Table 3).

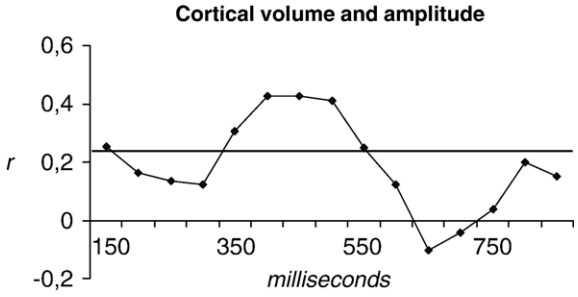

Fig. 3 – Correlations between cortical volume and amplitude at Pz to the old/new difference curves in 50 ms time windows. P < 0.05 when r > 0.24 or r < –0.24 or when r > 0.36 or r < –0.36 when Bonferroni corrections were applied.

Table 2 – Correlations between ERP peak amplitude to new and old words respectively and cortical and hippocampal volume

	Cortical volume	Hippocampal volume
New words		
Fz amplitude	**–0.34**	–0.22
Cz amplitude	–0.09	–0.16
Pz amplitude	0.09	–0.16
Old words		
Fz amplitude	**–0.33**	–0.16
Cz amplitude	0.05	0.01
Pz amplitude	**0.28**	0.00

Significant correlations ($P < 0.05$) are printed in bold characters.

2.3. *Memory performance, neuroanatomical volume, and the old/new effect*

Global memory function was significantly related to cortical volume, hippocampal volume, and the old/new effect at Cz and Pz, while the Pr and FA recognition memory scores were significantly related to cortex only. Correlation coefficients are presented in Table 4.

Multiple regression analyses showed that, when cortical volume and old/new difference amplitude at any of the electrodes Fz, Cz, and Pz were used simultaneously as predictor variables, amplitude did not give any unique significant contributions to global or recognition memory performance while cortical volume did. Additional analyses showed that neither cortical nor hippocampal volume gave significant contributions to the amount of explained variance in memory function independently of the influence from age. This is not surprising given that previous reports often have failed to find relationships between gross brain volumes and memory function (van Petten, 2004; van Petten et al., 2004). Old/new difference amplitude measures gave an age-independent contribution in two cases (Fa in recognition memory = –2.213 + 0.299 × Fz amplitude + 0.156 × age, $P < 0.001$; Pr in recognition memory = 0.931–0.005 × Fz amplitude – 0.003 × age, $P < 0.001$).

Table 3 – Multiple regression analyses

	Partial standardized beta	P of partial standardized beta	Overall R^2	F	df (regression, residual)	P of F
Dependent: Pr						
Predictors						
Age	–0.26	<0.05	0.24	9.893	2, 63	<0.0001
Topography	0.34	<0.01				
Dependent: Pr						
Predictors						
Age	–0.36	<0.05	0.25	6.951	3, 62	<0.0001
Topography	0.33	<0.01				
Cortical volume	–0.15	n.s.				
Dependent: Pr						
Predictors						
Age	–0.37	<0.05	0.20	5.141	4, 61	<0.001
Topography	0.33	<0.01				
Cortical volume	–0.17	n.s.				
Hippocampal volume	0.03	n.s.				
Dependent: global memory						
Predictors						
Age	–0.59	<0.0001	0.35	16.988	2, 63	<0.0001
Topography	0.08	n.s.				
Dependent: cortical volume						
Predictors						
Age	–0.65	<0.0001	0.40	20.570	2, 63	<0.0001
Topography	0.08	n.s.				
Dependent: hippocampal volume						
Predictors						
Age	–0.28	<0.05	0.07	2.345	2, 63	n.s.
Topography	0.11	n.s.				
Dependent: old/new amp Cz						
Predictors						
Age	–0.53	<0.0001	0.23	9.352	2, 63	<0.0001
Cortical volume	–0.09	n.s.				
Dependent: old/new amp Pz						
Predictors						
Age	–0.28	<0.01	0.20	7.935	2, 63	<0.001
Cortical volume	–0.05	n.s.				

Eight different regression analyses were performed with memory performance (Pr, global memory score) and neuroanatomical volumes (hippocampal and cortical volume) in turn as dependent variables. All analyses involving volume measures were conducted on the residuals after the variance from intracranial volume was regressed out.

Table 4 – Correlations between memory variables and neuroanatomical volumes and ERP old/new effects

	R^2
Global memory	
Cortex	**0.23**
Hippocampus	**0.07**
Fz amplitude	0.00
Cz amplitude	**0.06**
Pz amplitude	**0.05**
Pr recognition memory	
Cortex	**0.11**
Hippocampus	0.03
Fz amplitude	0.04
Cz amplitude	0.01
Pz amplitude	0.02
Hits recognition memory	
Cortex	0.01
Hippocampus	0.00
Fz amplitude	0.00
Cz amplitude	0.00
Pz amplitude	0.00
FA recognition memory	
Cortex	**0.16**
Hippocampus	0.05
Fz amplitude	0.04
Cz amplitude	0.01
Pz amplitude	0.02

Significant correlations ($P < 0.05$) are printed in bold characters. The recognition memory task is the ERP task. FA: false alarms.

2.4. *Functional and anatomical correlates of the frontal shift*

The sample was divided in two halves based on age (young group <50 years, $n = 31$, old group >50 years, $n = 35$), and all participants were assigned a number based on whether they had their largest old/new difference at Fz (1), Cz (2), or Pz (3). The mean of the old and the young group was 1.77 (standard error = 0.09) and 1.44 (standard error = 0.12), respectively. ANOVA yielded a main effect of age group on peak topography ($F[1,66] = 7.586$, $P < 0.05$), confirmed by a 3 electrodes × 2 age groups interaction on data not converted into a single 3-value variable ($F[2,128] = 6.964$, $P < 0.05$). The result was further confirmed by running analyses on amplitude normalized data, both by a 3 electrodes × 2 age groups interaction ($F[2,128] = 10.029$, $P < 0.05$) and by converting the topographical distribution into a single 3-value variable as described above ($F[1,66] = 6.939$, $P < 0.05$). These analyses validate the frontal shift with increasing age in the current sample. As in other analyses, the topography was determined based on old/new difference data. To test the functional and structural significance of anterior vs. posterior peaks, regression analyses with age and topography (as a single 3-value variable) as simultaneous predictors and global memory score, Pr, cortical volume (ICV regressed out), and hippocampal volume (ICV regressed out) in turn as criteria variables were performed, and the results are presented in Table 3. Both topography and age uniquely predicted Pr score. Including cortical volume as an additional predictor in this regression analysis did not render topography or age insignificant. However, the three other variables were uniquely predicted by age only, not topography. It is evident from Fig. 4 that frontal peaks (Fz) are associated with lower recognition memory performance for both older and younger adults.

To assess the effect of topography for each of the two age groups separately, four ANOVAs with topography (1–3) × global memory score, Pr, cortical volume, and hippocampal volume, in turn, were calculated for both age groups. In the young group, 5 participants had their maxima at Fz, 10 at Cz, and 16 at Pz, while the corresponding numbers for the old group were 17, 8, and 10. A significant relationship between Pr recognition memory scores and topography was found for the old and marginally for the young group (Young group: $F[2,31] = 2.637$, $P = 0.089$, old group: $F[2,35] = 7.482$, $P < 0.01$), but not for the other variables. The relationship between age groups, memory function, and old/new difference amplitude is illustrated in grand average curves (Fig. 5) and voltage maps in the time window 450–600 ms (Fig. 6). As can be seen from the figures, especially in the old age groups, poorer Pr memory score is associated with a more frontal distribution of old/new difference activity.

From the analyses above, a theoretically less interesting explanation for the relationship between topography and memory function cannot be ruled out: lower memory accuracy results in attenuation of the old/new effect, and this attenuation is probably smaller at more anterior locations where the old/new effect is less pronounced. However, an additional multiple regression analysis with age, topography, and old/new difference amplitude at Fz, Cz, and Pz simultaneously as predictors, and Pr as the dependent variable, showed that topography ($P < 0.01$) and marginally age ($P = 0.057$) still gave unique contributions to the explained variance in Pr ($R^2 = 0.27$), while none of the other variables did.

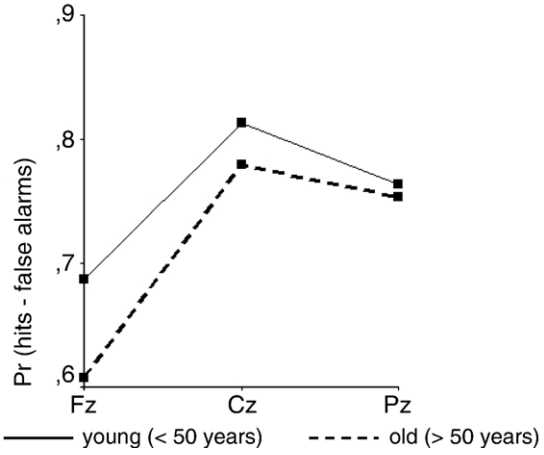

Fig. 4 – The relationship between the topography of the old/new effect (*x* axis) and recognition memory performance (*y* axis). In both age groups, the persons with old/new effects peaking at Fz were those showing the lowest recognition memory scores.

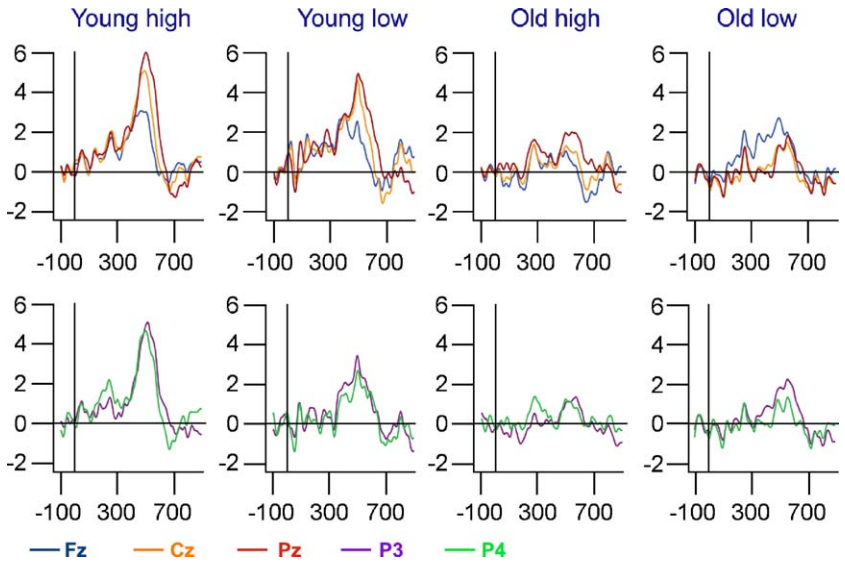

Fig. 5 – Grand average old/new difference ERP curves as a function of age and memory performance. The sample was divided by the median age (50 years) and by the median Pr score. The young groups had a Pr and global memory score of 0.66/53.9 and 0.84/55.9, while the corresponding numbers for the old groups were 0.57/44.2 vs. 0.80/48.7. As can bee seen from the curves, lower memory performance is associated with a more frontal distribution of old/new difference activity.

2.5. *Path analyses*

Finally, we constructed two path models based on our initial speculations regarding the distribution of variance between the different variables topography, old/new difference amplitude, cortical volume, hippocampal volume, Pr, and global memory score. Amplitude was operationalized as the maximum old/new difference at any of the midline electrodes. In the first model, age was not included. In the second, age was included as the only exogenous variable. The path diagrams are shown in Figs. 7A–D. The first model yielded a minimal value of discrepancy (chi-square) of 14.034 with 6 degrees of freedom, yielding a relative chi-square of 2.384, which implies that the model fits the data reasonably well. Still, in this model, only the paths between global memory score and cortical volume, topography and Pr, cortical and hippocampal volume, and cortical volume and old/new difference amplitude were significant. Thus, we constructed an alternative, reduced model, where the non-significant paths were removed. This model is shown in Fig. 7B. Chi-square now was 17.420 with 11 *df*, thus yielding a relative chi-square of 1.584, which is a very good fit to the data.

In the second model, including age, chi-square and *df* were 65.024 and 8, giving a relative chi-square of 7.003. Thus, this model did not fit the data well. We followed the same procedure as for model 1, removing all insignificant paths (keeping the path between topography and Pr which was only

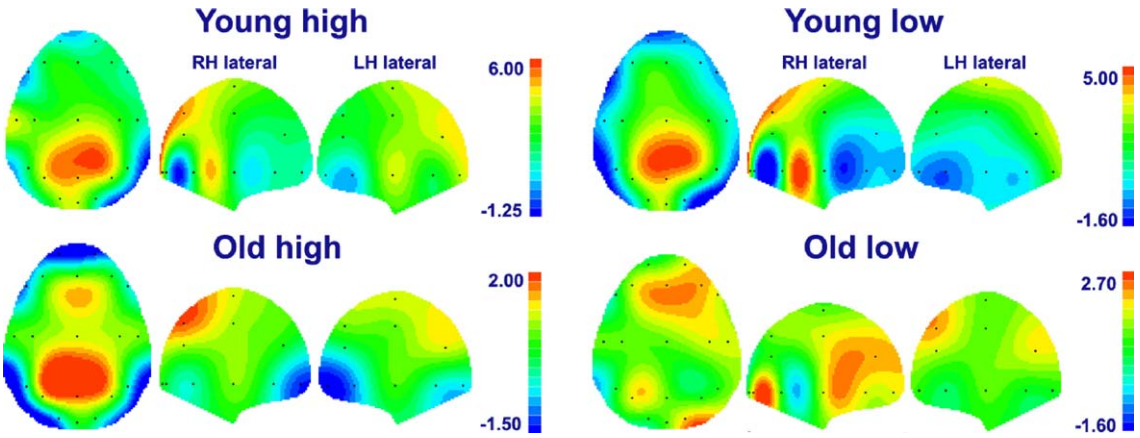

Fig. 6 – Voltage maps as a function of age and memory performance. The voltage maps show the mean distribution of old/new difference activity in the 450–600 ms time window. The older group with a lower than median score on Pr has a markedly more frontal distribution of old/new difference amplitude. The color bars are fitted to each group, such that extremes of the scales represent the highest and lowest value of the grand average of each group of participants. RH: right hemisphere; LH: left hemisphere.

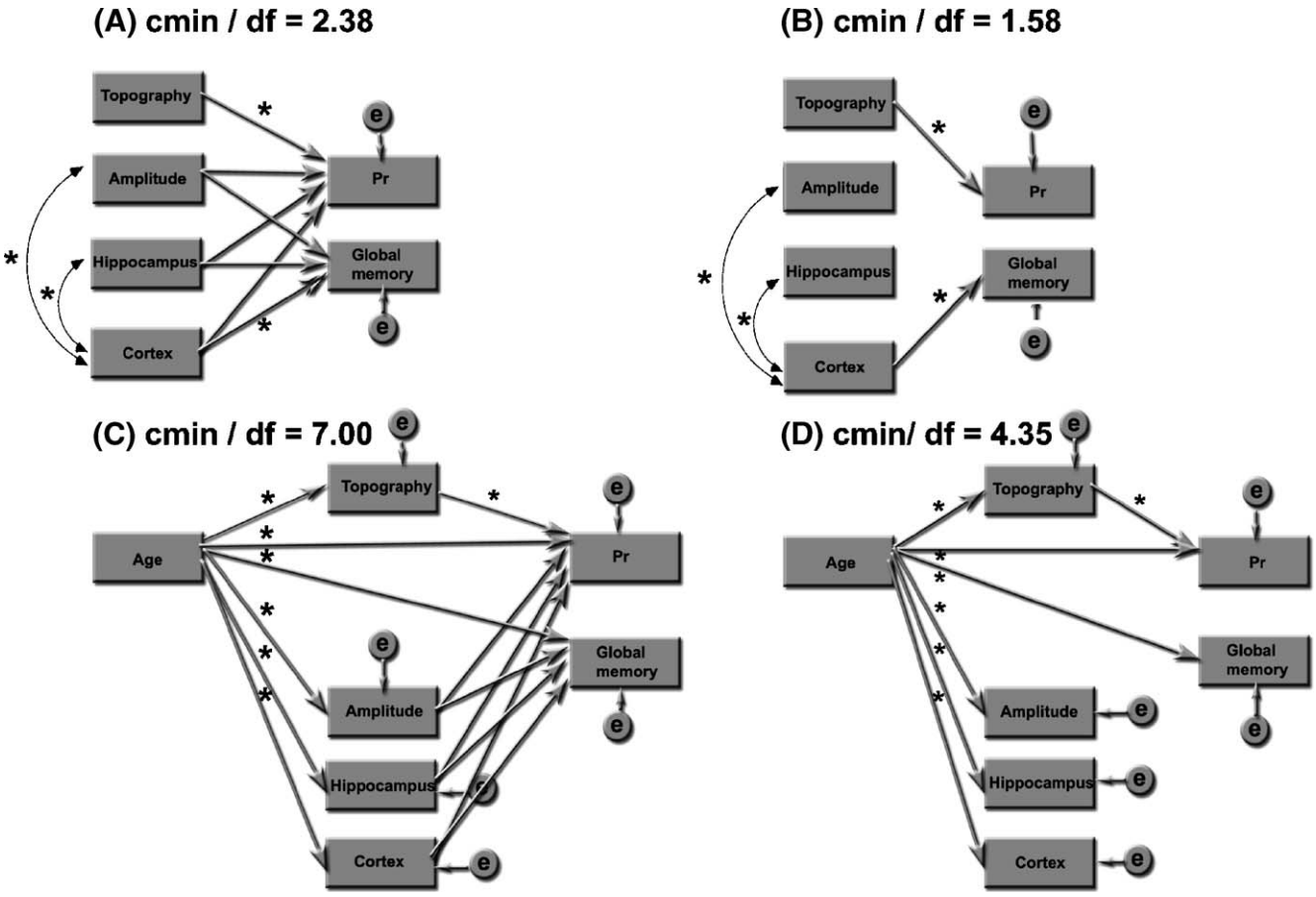

Fig. 7 – Path analyses. Path analyses showing the distribution of effects between different variables. In panel A and B are the relationships between the variables shown without age included in the model, while in panels C and D, age is included as the single exogenous variable. *$P < 0.05$.

marginally significant, $P = 0.073$). In the reduced model, chi-square and *df* were 60.898 and 14, giving a relative chi-square of 4.350. This represent a much better fit between the model and the data but still is far from perfect. However, all the paths were now significant.

3. Discussion

3.1. *Age and amplitude, volume, and memory performance*

The ERP data show a clear old/new effect, spanning a wide time window from 300 to 700 ms after word presentation. The reductions in cortical and hippocampal volume with increasing age correspond to previous reports (e.g., Courchesne et al., 2000; Walhovd et al., 2004). Furthermore, the significant reduction of global memory function fits well with numerous studies showing age-dependent decreases in most types of memory tasks (Lezak, 1995; Parkin et al., 1993). Also, the old/new effect was moderately related to age (see Fjell et al., 2005a for more thorough analyses of age effects). This has not consistently been found in previous studies (see Friedman, 2000 for a review). In the present study, a simple recognition memory ERP task was used, so responses based on familiarity judgments vs. recollection cannot directly be separated. However, previous research has established that older people tend to depend more on familiarity-based judgments in recognition tasks (Parkin et al., 1993), and this may have diluted the old/new effect.

3.2. *Volumes of cortex and hippocampus and the old/new ERP effect*

While the above results fit well with established knowledge of the biology and workings of the human memory system, the analyses of the relationship between the electrophysiological, volumetric, and psychometric variables go beyond previous research. In coherence with our theoretical speculations, a positive relationship between the old/new ERP effect and cortical volume was found. This implies that larger cortical volume generates enhanced activity to incoming stimuli. This activity is selective to certain classes of stimuli since higher amplitude was elicited to old relative to new words. Thus, selective processing of stimuli is implied as a neurocognitive correlate of larger cortical volume. As discussed in Introduction, the variations in cortical volume are hardly explainable by neuron number alone (Peters et al., 1998), and the link between the old/new

effect and cortical volume may therefore be a result of differences in other brain characteristics, such as synaptic efficiency. Thus, efficient processing of incoming information due to a well-developed neuronal network with a large number of interconnections and synapses may be reflected in enhanced ERP amplitude to relevant types of stimuli. It is worth noticing that, since the analyses are done after the volumetric variables are regressed on intracranial volume, it is large relative volume that has beneficial effects, not larger structures per se.

Only data from the correct response trials were included in statistical analyses, so the correlations are probably not a direct result of the fact that participants with larger cortical size recognize more old words. It is possible that the participants with the largest volumes of cortex may have the best potential for establishing memory traces, and this is why they show more activity to recognized words than participants with smaller cortical volumes. This can be interpreted within a framework of the old/new effect as an index of the strength of the memory trace (Bentin and Moscovitch, 1990; Bentin et al., 1992; Johnson et al., 1985, 1998; Paller et al., 1987). In any case, the data indicate that larger cortical volume is beneficial for memory retrieval as indexed by the old/new ERP effect. The relationships with ERP amplitudes were stronger for cortex than for hippocampus, which may reflect the more direct relation of cortex to amplitude deflections observed at the scalp. In studies using intracerebral recordings, the old/new effect is demonstrated in cortical areas as well as in the hippocampus (Guillem et al., 1995a,b; 1996, 1999). However, to the extent that hippocampal volume and activity are related, it seems that the old/new effect recorded at the scalp only can be indirectly related to hippocampal activity.

As the multiple regression analyses showed, the relationships between cortical volume and amplitude were dependent on age. This is not surprising since the main source of variance in well-screened life-span samples is age. Still, this does not invalidate the current conclusions regarding the relationships between neuroanatomical volume and ERP amplitude but makes inferences with regard to causation more difficult. Our finding of a relationship between neuroelectrical memory-related activity and cortical volume must at present be restricted to adult life-span samples. A study using a large, age-homogenous sample, with more inter-individual variance in memory abilities, may be able to replicate the results. In the opposite case, the old/new effect and cortical volume may be related through the cognitive, neurophysiological, and neuroanatomical changes that take place during the normal adult life-span, but not through normal individual variations within a given age cohort.

3.3. *Memory performance, neuroanatomical volume, and the old/new effect*

The second question of investigation regarded the relationship between actual memory performance and the neuroscientific measures. Positive relationships were established, but all of these were dependent on the influence from age. Cortical and hippocampal volume both predicted global memory performance, and cortical volume in addition predicted Pr and FA in the recognition memory task (see Fjell et al., 2005b; Walhovd and Fjell, 2001 for more detailed analyses of neuroanatomical volume in relation to memory performance). Furthermore, ERP amplitude at Cz and Pz predicted global memory scores. Interestingly, number of hits in the recognition memory task was not related to any of the physiological measures, while number of FA's was. This is probably related to the phenomenon that older participants are known to produce more false positives than younger participants (Parkin et al., 1993). Functional scanning studies have demonstrated that memory-related cognitive processing draws on cortical structures, and the present results indicate that the volumetric characteristics of such structures also are related to memory processing. The differential electrophysiological activity to old relative to new stimuli in the participants with larger cortical volume may also contribute to explain why this is so. Larger cortical volume may enable more efficient resource allocation and stimulus processing by means of more targeted cortical activity. Since volumetric measures of large brain sections generally are more strongly related to mental ability than are measures of specific structures (MacLullich et al., 2002; Wickett et al., 2000), it is not surprising that cortical volume is a better predictor than hippocampal volume for global memory performance, whereas uncovering a role for the hippocampus requires more targeted tasks or conditions.

To our knowledge, it has not been shown previously that the amplitude of the old/new effect is related to performance on a battery of well-validated memory tests in healthy individuals. However, Olichney et al. (2000) found such a relationship in amnesic patients and concluded that a link existed between what they called the late positive repetition effect and conscious memory. Neuropsychological memory tests are different from, and more complex than, the ERP task and are related to both visual and verbal, semantic and non-semantic, and recognition and recall abilities. Thus, the ERP amplitude elicited to old vs. new words in the ERP recognition task is related to more general memory capabilities. This may give hope that ERP measures can be used also in clinical settings where measuring of memory deficits is important. The lack of relationship between the old/new amplitude and the behavioral results from the ERP task may be explained by the recognition memory format, known to be less age-sensitive than recall formats. It seems likely that some of the processes yielding qualitatively "stronger" memories, but not necessarily better performance in a recognition task, e.g., contextual recall, are at play for the young, but not the old participants. This differential processing may again be captured by ERPs, but not behavioral task scores. Furthermore, the reliability and stability of the test scores in one task are obviously less than that of the composite score of three broad neuropsychologically validated memory tests, and this may further contribute to diminish the correlations.

It must again be stressed, however, that the relationships described here are largely dependent upon the influence from age. However, the differential correlational patterns and the fact that the observed results correspond reasonably well to what could be expected from previous research and theoretical speculations give some credibility to the findings.

3.4. *Functional and anatomical correlates of the frontal shift*

The main purpose of the study was to investigate functional and structural correlates of the often-observed frontal shift in aging. More elderly had their maxima at Fz or Cz, rather than Pz, and this validated the frontal shift in the present sample. Significant functional correlates were identified, in that an effect of topography was found, especially for the old participants, for Pr in the recognition memory task. Thus, as Figs. 4, 5, and 6 show, frontal activation in the continuous performance recognition paradigm is related to lower recognition memory capabilities. Thus, the frontal shift may indicate inefficiency rather than compensatory processing. However, counteracting the hypothesis of the frontal shift as a marker of inefficient processing with increasing age, the same tendency was attained in the youngest half of the sample. Thus, anterior maxima seem detrimental for memory processing throughout the adult life-span, not just in higher age. Even though a frontal shift typically comes with age, the degree to which activation is anteriorly focused seems related to poorer memory performance no matter the age of the participant. In the path analyses, the same conclusion was supported, in that the topography was related to Pr. both when age was included in the model and when it was not.

It is interesting that this result was obtained for the behavioral results from the ERP task only, and not for the composite memory score. Thus, it seems that the behavioral correlates of an electrophysiological memory-associated activation are related to topography and distribution of activity more than strength of activation (i.e. amplitude) per se. Thus, amplitude correlated with global memory performance, while topographical characteristics correlated with more specific recognition memory performance from the ERP task.

The present data correspond well to the finding by Fabiani et al. (1998) that stable frontal maxima of P3s in an older group of participants were associated with poorer performance on WCST (Wisconsin Card Sort Test). However, the present result stands in contrast to the finding by Cabeza et al. (2002) that changes of activation in old age indicated compensatory processing. However, the latter results were obtained for hemispheric lateralization, not anterior–posterior activity distribution. Furthermore, in the Cabeza et al. study, PET was used, which is sensitive to fundamentally different neurophysiological characteristics, at a much larger time scale, than ERPs.

The frontality of the activity was not mediated by cortical or hippocampal volume in the present data. Thus, in this sample, it is no reason to conclude that the frontal shift is a result of neuroanatomical degeneration or volume decrease. However, the present results are limited in that only total cortical volume was calculated. Thus, one cannot exclude the possibility that selective volume loss in specific cortical areas may be of significance in this respect, e.g., in frontal or prefrontal areas. While selective prefrontal volume loss with age has been found by some (Raz et al., 1997), however, others have observed the greatest age effects in the parietal region (Resnick et al., 2000). Furthermore, even if specific frontal volume loss in aging exists in the present sample, it would still be likely that some sort of correlation between regional volume loss and global cortical volume existed. Thus, even though more studies certainly are needed, the present data do not point to neuroanatomical correlates of the distribution of activity along the anterior–posterior axis.

3.5. *Limitations*

Some limitations in the present study must be taken into consideration when the conclusion is evaluated. First, the present paradigm is not suited to distinguish between the contributions from familiarity and recollection, which are two different fundamental cognitive processes. At least two other memory-related processes may exist within the 350–800 ms time window analyzed. The first is the negative FN400, and the second is the repetition effect which may be seen in the 350–500 ms segment. The paradigm in the present study was not suitable for distinguishing between these different neurocognitive processes, making interpretations regarding the exact cognitive nature of the component studied harder. Furthermore, the paradigm used, with repeated blocks of stimuli, is not standard in ERP memory research. The use of blocks of repeated stimuli may have influenced the reliance upon recollection and familiarity differentially for different age groups. However, since statistical analyses showed that repetition did not exert any main effects or interaction effects with age, there is reason to believe that this aspect has not influenced the data in a substantial way.

4. Experimental procedures

4.1. *Sample*

The participants were recruited by newspaper ads. All participants gave their informed consent to the study, according to the Declaration of Helsinki, and The Regional Committee for Research Ethics in Norway has approved the project. Participants were given a moderate sum of money to refund possible costs related to their participation. All participants were right-handed community dwellers, screened for diseases and traumas known to affect central nervous system (CNS) function by a set of health-related questions. Criteria for exclusion were neurological conditions or use of medication known to influence CNS functioning. All participants were told to wear their glasses if using such. Participants were examined with the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler et al., 1999). Participants with an IQ score below 85 were excluded. In addition, all participants were examined with neuropsychological tests. Participants scoring below 2 standard deviations from the population mean on the immediate and delayed free recall measures of a verbal memory test were excluded [California Verbal Learning Test; 10, for elderly persons (>65 years), norms from Paolo et al. (1997) were used], as were participants with a Mini Mental State (Folstein et al., 1975) score of less than 26 or a Beck Depression Inventory (Beck et al., 1987) score of 15 or more. After applying a final exclusion criterion based on the performance in the ERP task, Pr (*P*(hits) – *P*(False Alarms: Fa))

of >0.40 (see Results section), which lead to the exclusion of 5 participants, the total *n* was 66. Sample characteristics are presented in Table 5.

4.2. *ERP stimuli*

The stimuli in the ERP task were meaningful words and phonotactically correct but semantically meaningless words (legal pseudowords), here referred to as non-words. One list of 80 words and one list of 80 non-words were created. From each of these lists, 20 words and 20 non-words were drawn to constitute the to-be-remembered material, while the rest served as distractors. The non-words were constructed by making up pronounceable strings of letters of comparable length to the regular words. All the non-words were checked against a large database from the University of Oslo, containing all Norwegian words (http://www.dokpro.uio.no/ordboksoek.html). The mean number of letters in the target word list was 4.6 (range 3–7), and the mean number of syllables was 1.45 (1–2). The corresponding numbers for the non-target word list were 4.6 (2–7) and 1.5 (1–3). None of these differences were statistically significant (number of letters: $t = -0.057$, $df = 78$, $P = 0.954$; number of syllables: $t = -0.349$, $df = 78$, $P = 0.728$). For the non-word targets, the mean number of letters was 5.3 (4–7) and the mean number of syllables was 1.75 (1–2), while the corresponding numbers for the non-targets were 5.5 (4–7) and 1.85 (1–2). None of these differences turned out statistically significant (number of letters: $t = -0.889$, $df = 78$, $P = 0.377$; number of syllables: $t = -1.013$, $df = 78$, $P = 0.314$). Frequency norms were found by searching for number of occurrences a given word had in the Oslo Corpus of Tagged Norwegian Texts database containing 18.5 million words, provided by the Text Laboratory at the Institute of Linguistics at the University of Oslo, database (http://www.tekstlab.uio.no/norsk/bokmaal/english.html). For word targets, the mean frequency was 408.85 (6–4147), while the mean frequency for the distractor words was 999.85 (1–12204), a non-significant difference (Levene's Test for Equality of Variances $F = 4.341$, $P = 0.04$, thus, non-equal variances assumed, $t = -1.751$, $df = 72.39$, $P = 0.084$).

Table 5 – Sample characteristics

Total sample, *n* = 66	Mean	Range	SD
Age	49.9	20–78	19.8
Gender females/males	38/29		
IQ	114	91–133	9.1
Education in years	15.4	9–20	2.3
MMS	29.0	26–30	0.9
Beck DI	4.0	0–14	3.5
Cortex 1000 mm^3	467	332–595	61
Hippocampus 1000 mm^3	7.4	5.6–10.9	0.8
Recognition memory false alarms	10.21	1–35	7.69
Recognition memory hits	53.74	37–60	5.51
Recognition memory (Pr)[a]	0.73	0.42–0.97	0.13
Global memory (mean *t* score)	50.5	25.2–61.3	7.7

Beck Depression Inventory was included in the study at a later point and only administered to 59 participants.
[a] Pr = proportion hits–proportion false alarms.

Each participant completed two successive ERP tasks. First, in the discrimination task, 20 words and 20 non-words were presented randomly on a computer screen. Each word was presented for 1 s, and the inter-stimulus interval was 2 s. The participants were asked to press one button if a presented word was meaningful and another button if the word was nonsense (non-words). They were also told that they would be required to remember the words and non-words in the subsequent task. The lexical decision task was included in order to secure a certain level of stimuli processing depth for each participant. The second task, the memory task, consisted of 3 blocks of stimuli. In each block, the 20 words and the 20 non-words from the discrimination task were repeated. In addition, 20 new words and 20 new non-words were presented in each block, making the total number of stimuli in each block 80. The order of the presentation of the old stimuli was randomized within each block. All ERP analyses were done on data collapsed across these three blocks of stimuli to increase the number of trials in each average and thus enhance the stability of the results. A substantial number of trials may be especially important in older age groups where latency jitter may contribute to diminish the peaks, and the reliability probably is lower (Walhovd and Fjell, 2002). The participants were told to press one button whenever a word or a non-word was repeated and another button whenever they saw a word or a non-word presented for the first time. This task was designed to be relatively easy with a high hit rate to be able to compare groups that would differ on more challenging tasks. Both Pr (Proportion hits–Proportion Fa), Fa (Fa), and Hits (number of hits) were used as measures of memory function in addition to the composite memory score.

4.3. *ERP procedures*

Subjects were seated in a reclining chair within a sound attenuating and electrically shielded recording chamber, about 100 cm from a 21-in. computer screen. The letters were 2 ('a', 'c', etc.) or 3 ('b', 'd', etc.) cm in height, about 15 cm wide, and were white, presented on a black background, and a small blue cross appearing between the stimuli was used as a fixation point. The visual field varied from about 1.7° × 2.6° to 1.7° to 6.0°. The electrodes were placed in accordance with the international 10–20 system. A total of 20 electrodes (Ag/AgCl) were used for recording; Fp1, Fp2, F7, F3, Fz, F8, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, and O2, referred to the left mastoide. Statistical results will be presented for Fz, Cz, and Pz only in this article. A VEOG channel was obtained by placing one electrode above and one below the left eye, and ground was placed anteriorly on the right side. Ideally, an additional HEOG channel should have been used to remove artifacts resulting from saccadic eye movements. However, as preliminary data ($n = 10$) from another project in our laboratory using the same stimuli parameters have shown, correlations between HEOG-corrected and non-corrected amplitudes are in the range of $r = 0.99$ to $r = 0.98$ at the central electrode. Thus, it is very unlikely that the lack of HEOG correction will have any substantial impact on the data presented in this article. Inter-electrode impedance was generally measured to be less than 10 kΩ. For the recording of EEG activity, A/D rate was

500 Hz, and filter setting was 0.10 Hz (high pass) and 70 Hz (low pass). In addition, a 50 Hz notch filter was applied. The signals were amplified by a SynAmp DC amplifier (Neuroscan Inc.). Epochs were rejected from averaging if amplitude exceeded ±110 μV, and eye blinks were corrected for statistically in accordance with Semlitsch et al.'s (1986) recommendations. Averaging was performed for correctly identified old and new words and non-words. EEG was segmented in epochs of 1000 ms duration (–100 ms to 900 ms relative to stimulus onset). All data average files were digitally filtered (20 Hz low pass) and baseline-corrected before statistical measures of component latency or amplitude were made. Neuroscan software was used to present stimuli, record, and analyze EEG activity. The old/new effect was defined as the most positive point constituting a peak between 350 and 800 ms. In addition, we used mean amplitude in time windows of 50 ms post-stimulus as measures of ERP activity for some analyses. Analyses of topographical differences between age groups were done both on raw data and on amplitude-normalized data, according to procedures recommended by McCarthy and Wood (1985). That is, for each data point, the minimum group value for that variable was subtracted, and the resulting number was divided by the range of the group.

4.4. *Memory tests*

In addition to the recognition ERP task, the participants went through three neuropsychological memory tests. These tests consist of several subtests and provide measures of verbal and non-verbal recognition and recall, at different time intervals, from a few seconds and up to 30 min. The scores of several subtests from each of the broad tests (described below) were standardized relative to the sample (*t* scores), and a composite score of all the sub-scores was computed (mean *t* scores). The reason for this was that we wanted a broad and reliable measure of global memory function, in addition to the more specific recognition memory test from the ERP task. All the memory tests are neuropsychologically validated and widely used. Below is a short description of the tests. For a broader account, see Lezak (1995) and Cabeza et al. (2002).

4.4.1. *California Verbal Learning Test (CVLT; Delis et al., 1987)*

A list of 16 items was read five times consecutively, and, each time, the participant was immediately instructed to list all items he/she could recall and a total learning score was computed (equals the total number of remembered words, trials 1–5). After these five trials, another 16-item list was read, with instructions of immediate recall of as many items as possible, whereupon the participant was asked to recall the first list, the one that had been read five times (5 min recall). After a 30-min delay, the participant was asked, without having been forewarned, to recall this list again (30-min recall). In addition, a recognition test was provided in which the participant was required to identify the 16 target words in a list of 32 words (30 min recognition). The scores analyzed here are calculated as number of hits minus false alarms (FA) remembered.

4.4.2. *Continuous Visual memory Test (CVMT; Trahan and Larrabee, 1988)*

The CVMT is comprised of 112 complex, ambiguous drawings (e.g., 12-point polygons, etc.) and irregular nonsense figures. The drawings are printed on 5 × 8 in. white cards and organized in 7 blocks of 16 stimuli. The drawings are presented successively to the participant and exposed for 2 s each. Stimuli in the first block by definition are new and different and represent the input stimuli. Seven of these drawings appear once in each of the remaining six blocks and are "old" drawings whenever they reappear. The other nine drawings in each block are entirely new stimuli that never reappear in the task. However, seven of the "new" drawings in each of the last six blocks have similar stimulus characteristics (e.g., 12-point polygons, 7-point polygons, etc.) as the "old" drawings, one from each category. These drawings are perceptually quite similar to the corresponding "old" drawings. The other two "new" stimuli in each block belong to other stimulus classes. Because no "old" stimuli are presented in the first block, analysis of performance is based on responses given in the last six blocks, which together contain 42 "old" and 54 "new" stimuli. Scores employed in the current study included a learning score (number of hits + 54-number of false alarms). After this learning trial, a delayed recognition test is administered after 30 min. The participant is shown 7 sheets with 7 figures from the learning trial, and the task is to decide which of the figures were shown 7 times.

4.4.3. *Rey–Osterrieth complex figure test (Osterrieth, 1944; Rey, 1941)*

Participants are shown a complex drawing and are asked to copy it. They are not told to memorize the figure. When they have finished the drawing, the figure is removed, and they are asked to reproduce it by memory (immediate recall). The same procedure is repeated after 30 min. The recall drawings are scored according to standardized criteria.

The composite memory score made consisted of the mean sample-standardized scores of 4 CVLT variables (total learning score, recall after 5 min, recall after 30 min, recognition after 30 min), 2 CVMT scores (total learning score, recognition after 30 min), and 2 Rey–Osterrieth scores (immediate recall and recall after 30 min). Each participant got a composite score consisting of the mean of all the *t* values of the sub-scores. This composite memory score is seen as a broad measure of general memory capability and is hereafter termed 'global memory function'.

4.5. *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.

4.6. MRI volumetric analyses

The automated procedures for volumetric measures of the different brain structures are described by Fischl et al. (2002). 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 labelled images. Next, a non-linear 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 (for example, hippocampus is never anterior to amygdala). The technique has previously been shown to be comparable in accuracy to manual labeling. In the present paper, volumes for cortical gray matter and hippocampus are reported. 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 labeling. A deformable template procedure, similar to the "Shrink Wrapping" procedure described by Dale and colleagues (Dale et al., 1999; Dale and Sereno, 1993), was used to obtain an estimate of the smooth surface surrounding the intracranial space (containing cerebrum and cerebellum, CSF, meninges, and brainstem to a level immediately below the pons). All volumes were regressed on ICV, and the standardized residuals were used in all analyses.

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