available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Basal forebrain integrity and cognitive memory profile in healthy aging

Sandra Düzel[a], *Thomas F. Münte*[d], *Ulman Lindenberger*[e], *Nico Bunzeck*[c], *Hartmut Schütze*[b], *Hans-Jochen Heinze*[a], *Emrah Düzel*[b,c,f,*]

[a]*Department of Neurology, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany*
[b]*Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany*
[c]*Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, WC1N 3AR, UK*
[d]*Department of Psychology II, Neuropsychology Unit, Otto-von-Guericke University Magdeburg, Germany*
[e]*Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallée 94, D-14195 Berlin, Germany*
[f]*German Centre for Neurodegenerative Disorders Magdeburg, Otto-von-Guericke University Magdeburg, Germany*

ARTICLE INFO

Article history:
Accepted 16 October 2009
Available online 23 October 2009

Keywords:
Basal forebrain integrity
Verbal memory
CVLT, aging
Memory span
Attention
Psychosocial factors

ABSTRACT

Age-related dysfunctions in cholinergic and dopaminergic neuromodulation are assumed to contribute to age-associated impairment of explicit memory. Both neurotransmitters also modulate attention, working memory, and processing speed. To date, in vivo evidence linking structural age-related changes in these neuromodulatory systems to dysfunction within or across these cognitive domains remains scarce. Using a factor analytical approach in a cross-sectional study including 86 healthy older (aged 55 to 83 years) and 24 young (aged 18 to 30 years) adults, we assessed the relationship between structural integrity—as measured by magnetization transfer ratio (MTR)—of the substantia nigra/ventral tegmental area (SN/VTA), main origin of dopaminergic projections, basal forebrain (major origin of cortical cholinergic projections), frontal white matter (FWM), and hippocampus to neuropsychological and psychosocial scores. Basal forebrain MTR and FWM changes correlated with a factor combining verbal learning and memory and working memory and, as indicated by measures of diffusion, were most likely due to vascular pathology. These findings suggest that frontal white matter integrity and cholinergic neuromodulation provide clues as to why age-related cognitive decline is often correlated across cognitive domains.

1. Introduction

Age-related decline in learning and memory, often termed age-associated memory impairment (AAMI) (Crook et al., 1986), is a well-documented finding in healthy older adults (Balota et al., 2000; Cabeza et al., 2000; Craik, 1994; Salthouse, 2003), but the neurobiological correlates of this decline are still under debate. A consistent pattern of AAMI is a decrement in declarative memory (Tulving, 1985) most clearly apparent in impaired free recall and recollection (Buckner, 2004; Craik, 2006; Hedden and Gabrieli, 2004; Nilsson, 2003). Evidence from lesion studies in humans and animals indicates that

* *Corresponding author*. Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. Fax: + 44 (0)20 79168517.
E-mail address: e.duzel@ucl.ac.uk (E. Düzel).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.10.048

declarative memory is critically dependent on the integrity of the medial temporal lobe (MTL) structures, including the hippocampus and adjacent rhinal cortex (Abe et al., 2004; Mishkin et al., 1997) and the prefrontal cortex (Stuss and Levine, 2002). Therefore, recent studies have sought to investigate the relationship between structural age-related degeneration of gray and white matter in these regions and learning and recall (Brickman et al., 2007; Buckner, 2004; Craik, 2006; Mungas et al., 2005; Schiltz et al., 2006). However, it has also been pointed out that AAMI is not only a result of degeneration of prefrontal and MTL regions but also a result of age-related dysfunction in cholinergic (Mesulam, 2004b) and dopaminergic (DA) (Backman et al., 2006) neuromodulation. The focus of the present study is on these neuromodulatory influences.

An important issue in this context is the observation that, aside from declarative memory, other cognitive faculties also show age-related decline and have been shown to be correlated with learning and memory performance in aging, in particular measures of executive functions (Kray and Lindenberger, 2000; Parkin and Java, 1999), working memory (Baddeley et al., 1999), and processing speed (Salthouse, 2000). A correlated dysfunction across different cognitive domains could indicate distributed structural degeneration such that the different brain regions mediating different cognitive functions undergo correlated age-related degeneration. Another possibility that could act either in isolation or in addition to a distributed pathology could be dysfunction in neuromodulation. Major cholinergic and dopaminergic projections originate in circumscribed brain regions of the basal forebrain and the midbrain but critically modulate function in distributed brain regions and across several cognitive domains. Relatively localized structural changes in the origins of cholinergic and dopaminergic neuromodulation could thus have widespread and relatively unspecific cognitive consequences.

Both dopaminergic and cholinergic neuromodulation play a critical role in learning and recall. There is converging evidence that dopamine plays a role not only in reinforcement learning but also in hippocampus-dependent declarative memory formation (Adcock et al., 2006; Lisman and Grace, 2005; Schott et al., 2006; Wittmann et al., 2005). As in animals (Lisman and Grace, 2005), also the human SN/VTA responds to stimulus novelty even in the absence of reward (Bunzeck and Duzel, 2006). These data provide evidence in favor of a recent model suggesting a functional hippocampal–SN/VTA loop of novelty processing and encoding (Lisman and Grace, 2005). Prefrontal dopaminergic neuromodulation is also held to be critical for attention (Robbins and Roberts, 2007) and for the ability to maintain and manipulate stimulus information online in working memory (Wang et al., 2004; Williams and Goldman-Rakic, 1995). Cortical and hippocampal cholinergic innervation derives almost exclusively from the basal forebrain (medial septal nucleus, diagonal Band of Broca and Nucl. Basalis of Meynert, NBM) (Mesulam, 2004a). A number of pharmacological and lesion studies in humans and animals show that cholinergic neuromodulation is critical for learning and memory (Chudasama et al., 2004; Drachman and Leavitt, 1974; Sarter et al., 2005; Tang et al., 1997; Turchi et al., 2005; Warburton et al., 2003) and for regulating and maintaining attention possibly by enhancing the response to sensory input (Hasselmo and Giocomo, 2006; Mesulam, 2004a). Also, cholinergic neuromodulation is implicated in the ability to maintain stimulus information online in working memory (Hasselmo and Stern, 2006). Both dopaminergic and cholinergic neuromodulation undergo age-related degeneration (for reviews, see Backman et al. (2006)). Human autopsy data indicate a 3% age-related decrease in dopamine D1 (Cortes et al., 1989; Rinne et al., 1990; Seeman et al., 1987) and D2 receptors (Seeman et al., 1987) per decade. There is a 2% to 6% loss of dopaminergic neurons in the SN/VTA per decade (Fearnley and Lees, 1991), and this loss is correlated with the decrease in striatal dopamine availability (Snow et al., 1993). In older adults, behavioral deficits in episodic memory are better accounted for by D2 receptor binding than by age (Backman et al., 2000). Recently, Bunzeck et al. (2007) quantified age-related structural degeneration of the mesolimbic system in healthy elderly using magnetization transfer ratio (MTR) and correlated it with mesolimbic hemodynamic responses (HRs) to stimulus novelty. Their findings support the model of a hippocampal–SN/VTA loop of mesolimbic novelty processing by showing that the hemodynamic activation in SN/VTA and hippocampus for novelty is selectively affected by age-related degeneration of these structures. In the cholinergic system, neurons in the NBM are very prone to accumulate neurofibrillary tangles (Mesulam, 2004a,b), such that tangles in this region are also observed in healthy elderly people (Mesulam, 2004b; Sassin et al., 2000). Even in the absence of neuronal loss, the accumulation of such tangles in the NBM can be associated with a decrease in cholinergic neurotransmission as revealed by postmortem counts of cholinergic axons (Geula and Mesulam, 1989) and by in vivo SPECT mapping of cholinergic terminals (Kuhl et al., 1996). In animal studies (e.g., Weible et al., 2004; Woodruff-Pak et al., 2001) and in patients with Alzheimer's disease cognitive improvement can be achieved by nicotinergic as well as muscarinic receptor action (Oh et al., 2005; Raskind et al., 2000; Tariot et al., 2000).

To our knowledge, it is so far unclear whether in vivo age-related structural changes of cholinergic and dopaminergic projection systems provide an explanation for the unspecific nature of age-related cognitive impairment in aging. To address this issue, we investigated to what extent degeneration of SN/VTA and basal forebrain as quantified using MTR (Bunzeck et al., 2007) is related to age-associated decline in list learning and recall, working memory span, processing speed, and attention.

Another important aspect in studying the relationship between cognitive performance and brain structure is to control for non-cognitive variables related to health and lifestyle. It is possible that cognitive function and brain structure are cumulatively affected by individual health behavior, years of education, wealth, the ability to cope with stress, personality traits, and indicators of physical health such as body mass index (BMI) (Backman et al., 2006; Colcombe et al., 2003; Craik, 2006; Lindenberger and Baltes, 1997; Salthouse, 2003; Singh-Manoux et al., 2004; Smith, 2003; Springer et al., 2005). Therefore, we also examined the influence of psychosocial and physical health factors on cognitive and structural variables. We used a factor analytical approach to determine which cognitive and psychosocial functions undergo correlated changes in a group of healthy

Table 1 – Neuropsychological test scores of older and young adults (M = mean, SD = standard deviation).

	P-value	Older adults (N = 86)		Younger adults (N = 24)	
		M	SD	M	SD
Age		65.28	5.86	23.25	2.21
CVLT T1	0.000	6.78	1.96	9.56	1.72
CVLT T5	0.000	12.68	2.22	14.56	2.23
CVLT total	0.000	52.52	9.62	64.21	9.11
CVLT delayed recall	0.000	11.58	2.97	14.21	2.43
Nonverbal learning	0.000	26.68	7.85	41.54	7.87
Attention/Processing speed	0.000	359.52	66.32	493.50	83.77
Knowledge	0.010	31.98	2.68	30.47	2.72
Working memory span	0.044	6.16	1.07	6.71	1.08
Working memory manipulation	0.000	4.49	0.925	5.63	1.20
Trail making test A	0.000	38.05	11.20	24.37	9.77
Trail making test B	0.000	80.21	23.79	49.62	17.51
Verbal fluency	0.019	38.97	9.89	43.52	10.44

Legend: Compared to the older group, young participants performed significantly better in all tests. P-values are shown for all comparisons. Gray shades highlight scores in which the mean of the older group fell one standard deviation below the mean of the young group.
Abbreviations correspond as follows: CVLT T1, California verbal learning test, trial1; CVLT T5, California verbal learning test, trial5; CVLT total, California verbal learning test, total score; CVLT delayed recall, California verbal learning test, recall after 15–20 min; nonverbal learning, DCS (Diagnosticum für Cerebralschäden) total score; attention, d2 total score; vocabulary knowledge, multiple selection vocabulary test (MWT B); working memory span, digit span forward; working memory manipulation, digit span backwards; Trail making test A, Part A; Trail making test B, Part B; verbal fluency, word association test (COWA).

older adults and assessed the correlations between factor scores and regions structural integrity.

2. Results

2.1. *Health status*

None of the older and young participants had serious health problems, or obsessive alcohol or tobacco consumption, while 30% were current or former smokers. For the older adults, the mean BMI was 26.0 (SD = 3.7) and for the young adults 23.3 (SD = 3.7). For the older adults, data from the Health survey (SF12) were used to calculate mental (mean = 56.1, SD = 5.9) and physical health composite scores (mean = 47.8, SD = 7.8). The younger group had a mean of 47.5 (SD = 10.6) for the mental and a mean of 54.9 (SD = 3.9) for the physical health scores. The physical complaints of the older group (mean = 140.0, SD = 36.0) derived from the FBL questionnaire did not differ from the younger group (mean = 145.2, SD = 33.0) ($P > 0.2$).

2.2. *Mental health*

All of the older participants scored within the normal range of both, the Geriatric Depression Scale (mean GDS = 1.2, SD = 1.0) and Mini-Mental State Examination (mean 29.2, SD = 0.7).

2.3. *Individual psychosocial variables*

Within the stress-coping scores, older adults showed a mean of 12.7 for positive coping strategies (SD = 2.0) and a mean of 8.5 (SD = 2.5) for negative coping strategies. The sense of coherence (SOC) mean score was 149.3 (SD = 13.9), which is similar to previous observations in this age group (Eriksson and Lindström, 2005).

2.4. *Demographic variables*

Older adults had an average of 15 ± 4 in years of education and a job prestige average of 85 ± 40.

Table 2 – Factor loadings from principal components extraction and varimax rotation for the 11 neuropsychological and psychosocial scores.

	Factor 1	Factor 2	Factor 3	Communality
Verbal learning total			0.633	0.504
Working memory span			0.564	0.303
Knowledge (vocabulary)		0.752		0.591
Verbal fluency		0.707		0.547
Mental health			–0.794	0.634
Sense of coherence	0.529			0.496
Body mass index	0.566			0.401
Years of education	0.719			0.601
Job prestige	0.627			0.549

Legend: Factor loadings less than 0.50 are not shown. Last column shows communalities for each score.

2.5. Cognitive performance

Compared to the younger group, older participants achieved lower scores on all neuropsychological measures (Table 1). Age-related performance differences were particularly pronounced in tests of verbal (CVLT) and nonverbal (DCS) learning and memory, sustained attention and processing speed (d2) and both, motor speed and attention functions (TMT).

2.6. Factor analysis

Three factors with eigenvalues exceeding 1.0 were extracted and accounted for 22.9, 14.5, and 10.5 (sum 48%) of the total variance respectively. Singularity and multicollinearity were absent in this data set. Table 2 shows the loading coefficients of the variables with the three factors as well as the commonalities. To assist the interpretation of the factors, only coefficients greater than 0.50 were considered and only these are shown in

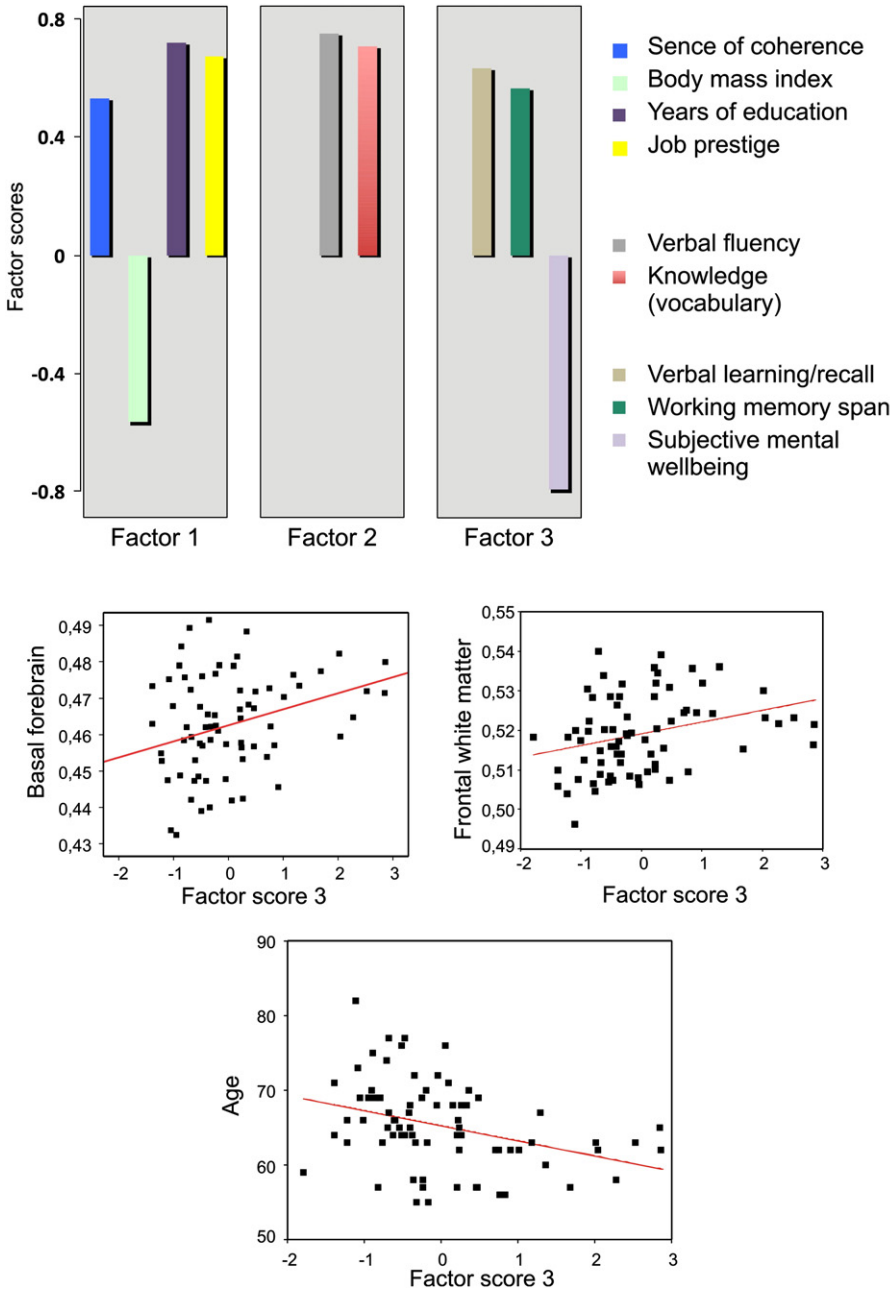

Fig. 1 – Loading coefficients of neuropsychological and psychosocial variables of the three factors from the factor analysis (see also Table 2) and their correlation with structural measures and age. Legend: the loading coefficients (higher than 0.50) are shown in the top of the figure. The left diagram in the middle displays the correlation between factor 3 (loaded on verbal learning, working memory span, and subjective mental well-being) and right basal forebrain MTR ($N = 72$). The right diagram in the middle depicts the correlation between factor 3 and left frontal white matter MTR ($N = 73$) and is depicted in the bottom of the figure. The correlation between factor 3 and age is depicted in the bottom of the figure.

Table 3 – Mean MTR values and their standard deviations from regions of interest for the older adults.

	M	SD
SN left	0.4606	0.012
SN right	0.4661	0.011
Hippocampus left	0.4401	0.013
Hippocampus right	0.4391	0.014
Basal forebrain left	0.4604	0.019
Basal forebrain right	0.4627	0.014
Frontal left	0.5243	0.009
Frontal right	0.5190	0.009

the table. As shown in Table 2 and also Fig. 1, factor 1 loaded with psychosocial variables (years of education, job prestige, sense of coherence) only and negatively also with BMI.

Items testing verbal fluency and vocabulary knowledge loaded on factor 2. Measures of verbal learning and memory and working memory span (DS span) loaded positively on factor 3, whereas subjective mental well-being showed a negative loading.

2.7. *Structural data*

The mean magnetization transfer ratio (MTR) values, diffusion coefficients, and anisotropy indices of the ROIs from SN/VTA, hippocampus, basal forebrain, and frontal white matter are summarized in Table 3. Within the group of older adults, none of the MTR values showed a correlation with age (all *P*-values >0.2). Note that statistical comparisons between the ROIs measures of the older adults and the young adults will be reported elsewhere as this requires matching a subsample of the older adults with our young adults for gender.

2.7.1. *Multiple regression analyses and correlations between factor scores and regional MTR*

Z-scores for each of the four factors from the factor analysis were calculated for each subject by utilizing the linear equation derived from principal components extraction. Three stepwise multiple-regression analyses were calculated with one of the three factors as dependent variables and eight MTR values from our ROIs as independent variables. Significant relationships between dependent and independent variables were followed-up by Pearson's correlations (two-tailed) between the corresponding factor score and regional MTR measure. Here, a Bonferroni correction was implemented for the number of follow-up comparisons plus additional correlations between the factors and age.

For factor 1 as independent variable, a significant model emerged ($F_{1,70}=4.1$, $P=0.044$) including the predictor right SN/VTA MTR explaining about 4% of factor 1 variance (adjusted *R*-square=0.044, standardized Beta=0.24). No significant model emerged for factor 2. For factor 3 as independent variable, a significant model emerged ($F_{2,70}=7.66$, $P=0.001$) including the predictors right basal forebrain and right FMW MTR and explaining about 18% of factor 3 variance (adjusted *R*-square=0.18, standardized Betas right basal forebrain MTR=0.26, right FWM MTR=0.27).

Follow-up Pearson's correlations were calculated using a Bonferroni correction for three follow-up correlations plus three correlations between age and the three factors (correction for 6 comparisons, $P<0.008$). Given this criterion, the relationship between right SN/VTA MTR and factor 1 was not significant ($P=0.046$, $r=0.234$, $N=73$). Right basal frontal MTR and right FWM MTR correlated significantly with factor 3 (Fig. 1; $P=0.008$, $r=0.311$, $N=72$). Age correlated negatively with factor 3 (Fig. 1; $P=0.002$, $r=-0.349$) but not with factor 1 or 2.

2.8. *Relationship between regional MTR and diffusion (ADC) and MTR and anisotropy (RA)*

In order to better understand the tissue changes underlying regional MTRs, we assessed the correlation between MTR and diffusion and anisotropy from the same individual regions of interest. In the older adults, MTR and diffusion were negatively correlated in all ROIs (Table 4) but survived Bonferroni correction (for 4 ROIs entering the correlation) only in the basal forebrain and FWM, suggesting that in those regions, MTR decreases were related to similar structural changes that also lead to increases in diffusion, which are widely held to reflect vascular pathology. Anisotropy, however, was not correlated with MTR in any of the ROIs (Table 4).

3. Discussion

We found that CVLT total performance in the older adults loaded on the same factor as working memory span (factor 3) and was distinguished from measures of verbal fluency and vocabulary knowledge (factor 2; Fig. 1). This confirms existing behavioral evidence suggesting that individual differences in long-term memory correlated with individual differences in working memory (Park et al., 2002, 1996; Verhaeghen and Salthouse, 1997). Although verbal fluency tasks are commonly used neuropsychological indicators of frontal lobe dysfunction (Bryan and Luszcz, 2000), which are particularly sensitive

Table 4 – Correlation coefficients (Pearson's correlation) for the correlations between regional measures of MTR, anisotropy, diffusion and diffusion extracted from the same region of interest (all from the left hemisphere).

	Basal forebrain MTR		Frontal white matter MTR		SN/VTA MTR		Hippocampus MTR	
	R	*P*-value	*R*	*P*-value	*R*	*P*-value	*R*	*P*-value
Anisotropy	0.176	0.151	0.214	0.073	0.074	0.543	0.066	0.585
Diffusion	–0.300	0.012*	–0.592	0.000**	–0.241	0.043	–0.253	0.031

Legend: The second column of each correlation indicates the statistical significance (*P*-value). Asterisks indicate significant correlations at $P<0.0125$ (two-tailed, Bonferroni corrected to account for 4 ROIs).

to aging (Glisky et al., 1995, 2001), they did not load on the same factor as verbal learning and memory and the respective factor (factor 2) was not correlated with frontal white matter integrity in our study.

The factor 3 (CVLT total, working memory span) correlated with right basal forebrain MTR (Fig. 1) as well as with right frontal white matter MTR (Fig. 1), suggesting that integrity in these regions affects these two cognitive functions similarly and is not selectively linked to learning and memory.

In this study, we used MTR as a measure of structural integrity. Magnetization transfer (MT) in tissue relates to the exchange of proton magnetization between mobile water protons and protons that are immobilized by macromolecules (Wolff and Balaban, 1989). In patients with multiple sclerosis, reductions in MTR can be observed even if other imaging modalities, such as T2- and T1-weighted imaging show no abnormality making it particularly sensitive in detecting early abnormalities of normal appearing tissues including white matter (Audoin et al., 2004; Fernando et al., 2005; Iannucci et al., 2000; Traboulsee et al., 2002) and cortical (Fernando et al., 2005) as well as deep gray matter (Audoin et al., 2004). MTR reductions in normal appearing white matter might be due to astrocytic proliferation, perivascular inflammation, demyelination (Rademacher et al., 1999), and loss of axonal density (van Waesberghe et al., 1999) as well as vascular insults (Fazekas et al., 2005). MTR reductions in normal appearing gray matter could be due to trans-synaptic morphological abnormality secondary to afferent demyelinating lesions (Audoin et al., 2006).

Finally, in healthy older adults, MTR of the cortex shows a negative correlation with age and the age-related reduction is stronger than that of white matter, suggesting that MTR is sensitive to age-related changes in gray matter structures (Benedetti et al., 2006; Fazekas et al., 2005). Although it is now widely acknowledged that MT imaging offers new opportunities for the assessment of structural integrity (Helms et al., 2009), data on the relationship between MTR and cognitive functioning in aging are scarce (e.g., Deary et al., 2006; Duzel et al., 2008).

In our study, the MTR decreases in the frontal white matter and basal forebrain were likely to be related to vascular pathology because they were negatively correlated with diffusion (ADC, Table 4), a measure that is known to be sensitive to capillary expansion, swelling of perivascular spaces, and vascular insults (Moseley, 2002; Pfefferbaum et al., 2003; Raz and Rodrigue, 2006; Wozniak and Lim, 2006). Previous studies of WM tract integrity have reported reduced FA in healthy elderly subjects most prominently in FWM and the corpus callosum (Head et al., 2004; Pfefferbaum et al., 2005; Salat et al., 2005; Sullivan et al., 2006; Sullivan and Pfefferbaum, 2006). In our study, MTR was not correlated with FA. One reason for this finding could be that the white matter ROIs, which we included in our analyses, were likely to be quite heterogeneous in terms of fiber directions. Hence, for our ROIs, ADC, by being insensitive to directionality of diffusion, may have been a more sensitive measure of pathology. Of course, our data are still well compatible with the possibility that FA in FWM shows a decline in healthy older adults. Furthermore, with respect to age-related changes in the hippocampus, Raz et al. (2005), in very elegant longitudinal studies, have reported a decline in hippocampal volumes. Although we have not observed a correlation between hippocampal MTR and age, such correlations have been weak and inconsistent also in previous cross-sectional volumetric studies of the hippocampus (e.g., Szentkuti et al., 2004). Hence, our negative cross-sectional finding of a relationship between hippocampal MTR and age (and hippocampal MTR and factor scores) does not rule out the possibility that hippocampal MTR values would decline longitudinally.

3.1. *Health and psychosocial variables*

Research on the impact of health and lifestyle factors on cognition is multifaceted and undertaken at many levels of analysis (Lovden et al., 2005). There is preliminarily evidence suggesting that age-related decrements in certain cognitive functions may be mitigated in intelligent, cognitively active individuals (Craik, 1971; Rowe and Kahn, 1987; Shimamura et al., 1995), but there is little consensus about the precise nature of the relationship between health and psychosocial variables and cognition in aging. With regard to memory, the only psychosocial variable that loaded on the same factor as CVLT total (factor 3) was the subjective mental well-being score (Fig. 1). Interestingly, subjective mental well-being loaded negatively with CVLT total. We believe that this negative relationship is due to the autobiographic nature of the questions about subjective well-being used in the health survey questionnaire, which requires recall of subjective restrictions of health and well-being over the preceding 4 months. It is conceivable that participants with good memory performance had more detailed memory about negative restrictions in their recent past and therefore reported more negative symptoms than individuals with poor memory.

Aside from this relationship, neuropsychological variables and psychosocial variables were largely separated into different factors (psychosocial = factor 1, neuropsychological = factors 2 and 3).

Factor 1 showed a relationship between years of education, job prestige, sense of coherence, and BMI (factor 1 in Fig. 1, Table 2). Sense of coherence is regarded as a stable disposition of personality (Antonovsky and Sagy, 1986; Sagy and Antonovsky, 2000) that serves as a major coping resource for the preservation of health. Together, these data suggest that education and economic success and low BMI are related to an improved sense of control over one's environment but have no direct impact on standard neuropsychological test scores. Nevertheless, it is conceivable that factors related to job prestige, years of education, and BMI would allow individuals a higher level of cognitive functioning even in the face of declining verbal learning and memory. This relationship is shown in several studies of cognitive aging (Cabeza et al., 2002; Cournot et al., 2006; Plassman et al., 1995; Potter et al., 2008, 2006). Interestingly, factors loading on verbal fluency did not correlate with frontal white matter integrity or basal forebrain integrity in our study.

3.2. *Conclusion*

Our data highlight the importance of the basal forebrain, major origin of cholinergic neuromodulatory projections, and

white matter integrity in understanding the cognitive profile of age-related memory dysfunction. They identify a neurobiological basis (basal forebrain and frontal white matter integrity) for the longstanding behavioral observation that working memory span is correlated with verbal learning and memory in age-related memory decline (Lindenberger and Ghisletta, (submitted) ; Wilson et al., 2002). An interesting avenue for the future will be to see whether such structural parameters of the integrity of neuromodulatory brain regions could motivate specific treatment strategies (e.g., using cholinergic agents). To that end, multimodal studies combining structural MRI with in vivo imaging of cholinergic (and also dopaminergic, see Duzel et al., 2008) neurotransmission could be helpful. Lifestyle and health factors such as job prestige, years of education, and sense of coherence influence cognitive aging but the impact of these factors on a number of cognitive variables including learning and recall seems weak.

4. Experimental procedures

4.1. *Participants*

Eighty-six older adults aged above 55 (mean age=65 years, age range=55–82 years, SD=5.6 years, 36 males) and 24 young adults aged between 18 and 30 (mean age=23 years, age range=21–30 years, SD=2.2 years, 8 males) participated in the study. All participants were native German speakers. Exclusion criteria for both groups were a history of neurological and psychiatric disorders, cerebral vascular disease, drug addiction, metabolic diseases like diabetes mellitus, metallic implants, tinnitus, obesity, a Geriatric Depression Scale with a depression score of more than five points (GDS ranges from 0 to 15; scores of higher than 11 indicate depression), a Mini-Mental State lower than 27 (MMSE ranges from 0 to 30; scores of lower than 25 are taken as indicators of pathology), and severe untreated hypertonia. Individuals with mild hypertonia according to the World Health Organization (WHO) and International Society of Hypertonia (ISH) classification (WHO and ISH, 1999) of hypertonia who were treated with one antihypertensive medication were eligible for participation in the study. The local ethics committee of the University of Magdeburg (Germany) approved the study. All participants gave written informed consent.

4.2. *Procedure*

Participants were recruited using local newspaper announcements. Initial screening for exclusion or inclusion criteria was done using a structured phone interview with around 120 volunteers. Eligible participants were invited for neuropsychological and psychosocial assessment including around 100 volunteers. After neuropsychological testing (duration of 90 min) participants completed psychosocial interviews and questionnaires (duration of 40 min). Four of the questionnaires were completed later at home and returned via mail. Immediately after neuropsychological and psychosocial testing, most participants underwent Doppler sonography of the extra- and intracranial vessels by a trained neurologist. Blood pressure was measured bilaterally, and a blood sample was taken for genetic studies (results are not reported here). If none of the exclusion criteria was met and audition and corrected vision was sufficient to allow neuropsychological testing, MR imaging was conducted within a week after neuropsychological and psychosocial assessment. Young participants were students or employees of Magdeburg University and contacted and selected according to the same criteria as the older adults.

4.3. *Neuropsychological testing*

The neuropsychological test battery was administered to each participant to provide an estimate of cognitive functioning including measures of learning and memory performance, attention/processing speed, working memory, verbal fluency, and vocabulary knowledge. The following neuropsychological tests were administered to all participants: The 'California verbal learning Test' (CVLT) (Delis et al., 1987); the 'Diagnosticum für Cerebralschädigung' (DCS) (Weidlich and Lamberti, 1993); the Digit Span test (digit span forward; digit span backwards); a word fluency assessment (adapted German version of the 'Controlled Oral Word Association Test' (COWAT) (Ruff et al., 1997); the 'Trail Making Test' part A and B (Reitan, 1992); the 'd2 test of Attention'; and the 'Mehrfachwahl-Wortschatztest' (MWT B, an estimate of general knowledge or 'crystallized intelligence') (Lehrl, 2005). The Mini-mental status examination (MMSE) and the Geriatric depression scale (GDS) were administered to older adults only. For a detailed description of these neuropsychological tests see Supplementary material, paragraph 1.

4.4. *Psychosocial assessment*

In a job history interview, participants reported about their educational and qualification activities (including vocational training) from school onwards. This information yielded a score for "years of education", with higher values reflecting greater education attainment. Job prestige is a global indicator to measure a person's social position. The magnitude prestige scale (MPS) (Wegener, 1984) commonly used in Germany reflects a metric scale, which measures the social prestige of jobs. Before using MPS, all occupations needed to be encoded on the basis of the International Standard Classification of Occupations 1968 (ISCO-68). It has a mean of 63.8 (SD = 30.8). The scale varies from a maximum of 186.8 for doctors to a minimum of 20 for non-educated workers. For the young participants, demographic variables were not assessed as they were still students.

4.5. *Health variables*

Self-reported history of health problems, health behavior, and social variables were assessed using a structured interview (questions adapted from the Berlin aging study, Baltes and Mayer, 1999). The Freiburg list of physical complaints (Freiburger Beschwerdeliste, FBL) was used to measure the degree of physical complaints (Hiller, 1997) as an indicator of general health status. The FBL consists of 71 complaint items that yield nine scales plus the sum of complaints as the 10th scale. A high score defines a high state of complaints. Individual

physical and mental health was assessed using the German short-form SF12 Health Survey in the standard (4-week) recall version for self-administration (for a review of the reliability and validity of the SF12, see Ware et al., 1996). Physical and mental health composite scores were calculated using the scores of twelve questions and range from 0 to 100, where 0 indicates the lowest and 100, the highest level of health. Both physical and mental health composite scales combine the 12 items in such a way that they compare to a national norm with a mean score of 50.0 (SD=10.0). Body mass index (BMI) was obtained from each participant.

4.6. *Individual psychosocial variables*

We assessed positive and negative stress-coping behavior with a standardized German short-version questionnaire (SVF 78) (Janke et al., 2002). As a multidimensional inventory of introspection, it assesses individual coping tendencies and distinguishes between stress-reducing (positive coping style) or stress-increasing (negative coping style) as well as mediating strategies (see Supplementary material, paragraph 2).

We also acquired another individual coping resource labeled the "Sense of Coherence" (SOC) (Antonovsky, 1993), which is known to indicate a stable personality disposition that serves as a major coping resource for the preservation of health (Antonovsky and Sagy, 1986; Sagy and Antonovsky, 2000). The individual benefits of a high SOC should be the successful maintenance of personal balance and health in spite of stressful events, environmental demands, and threats (Antonovsky, 1987).

4.7. *Image acquisition*

For both the young and older adults, a comprehensive structural data set was acquired in one MRI session.

4.7.1. *T1-weighted anatomical images*

For each subject, a T1-weighted sagittal 3D scan (contrast-optimized spoiled gradient-echo sequence, 124 slices, 256×256 pixel matrix, field of view (FOV)=250×250 mm, slice thickness=1.5 mm, TE=8 ms, TR=24 ms; flip angle=30°, leading to a voxel size of 0.98 mm×0.98 mm×1.5 mm) was acquired. These images were later analyzed using optimized automatic segmentation procedures (Cools et al., 2001).

4.7.2. *Combined Proton Density (PD)/T2 images*

A series of intermitting T2-weighted and proton-density-(PD)-weighted transversal slices was acquired for each subject and subsequently separated into one T2 volume and one PD volume. Each volume had a resolution of 256×256 pixels in 44 slices, voxel size=0.97 mm×0.97 mm×3.0 mm. These images were used to identify possible lesions from strokes or other brain diseases and for anatomical localization.

4.7.3. *Diffusion tensor imaging*

Diffusion-weighted images were achieved using a single-shot diffusion-weighted spin-echo-refocused EPI sequence (128×128 pixel matrix; FOV=280×280 mm; TE=70 ms; TR=10000 ms; 39 slices; slice thickness=3 mm; b-value=1000 s/mm^2), acquired in 12 non-collinear gradient orientations, each measured with the opposite diffusion gradient polarity. The orientations were chosen according to the DTI acquisition scheme proposed by Papadakis et al. (1999). The total of 24 diffusion-weighted measurements, each an average of four measurements, were divided into four blocks, each preceded by a non-diffusion-weighted acquisition. The DTI images were eddy current corrected according to the correction scheme developed by Bodammer et al. (2004), followed by a correction for head motion on the basis of the non-diffusion-weighted images using the AIR software package (Woods et al., 1998). Diffusion tensors were calculated for each voxel by singular value decomposition and then decomposed into eigenvalues and eigenvectors. Based on the eigenvalues, the apparent diffusion coefficient (ADC) and relative anisotropy (RA) were computed. This post processing resulted in transversal ADC, RA, and mean B0 volumes, each with a resolution of 256×256 pixels in 39 slices, with a voxel size of 1.09 mm×1.09 mm×3.0 mm.

4.7.4. *Magnetization transfer imaging*

MT images (see Supplementary material, paragraph 3) were acquired by using two volumes with identical settings (transversal, 256×256 pixels, 48 slices, voxel size 0.98 mm×0.98 mm×3.0 mm). The first one (MT image) with a magnetic saturation pulse (1200 Hz off-resonance, 16 ms) and the second one without (noMT) a magnetic saturation pulse resulting in a PD-like image. Subsequently, the *magnetization transfer ratio (MTR)* maps for each subject were calculated on a voxel-by-voxel basis according to MTR=(noMT-MT)/noMT.

4.8. *Regions of interests (ROIs)*

Regions of interests were defined as follows (see Fig. 2).

4.8.1. *Substantia nigra/VTA ROI (SN-ROI)*

All boundaries of the substantia nigra/VTA were selected visually based on the intense contrast change between its bright gray color and the dark gray color of the adjacent tissue in the MT image. First the SN/VTA-ROI was defined as a whole and then later was divided into a medial (mSN/VTA-ROI) and lateral part (lSN/VTA-ROI) (Fearnley and Lees, 1991). The upper limit of the SN/VTA-ROI was selected at a level of the superior colliculi where the cross sectional area of the SN/VTA appeared as an even bright gray-colored area in the MT-image, hence excluding voxels that directly flank the adjacent tissue. The anterior part of the SN/VTA-ROI was limited by the interpeduncular fossa and posterior borders were limited by the lateral side of the cerebral peduncle. The medial and lateral boundaries of the SN/VTA-ROI were extended until the contrast changed. The lower limit of the SN/VTA-ROI was identified as the last even gray-colored cross-sectional area. The total rostrocaudal extention of the ROI ranged between 3 and 4 axial slices (9–12 mm) depending on the individual size of the substantia nigra/VTA. According to the study of Fearnley and Lees (1991), the medial and lateral parts of the SN/VTA-ROI were separated by deleting a diagonal line of voxels within the SN/VTA-ROI. The junctures of the diagonal were defined by the midpoint of the ventral side of the cerebral peduncle and its intersection with an imaginary line connecting the anterior and posterior intersection of the superior

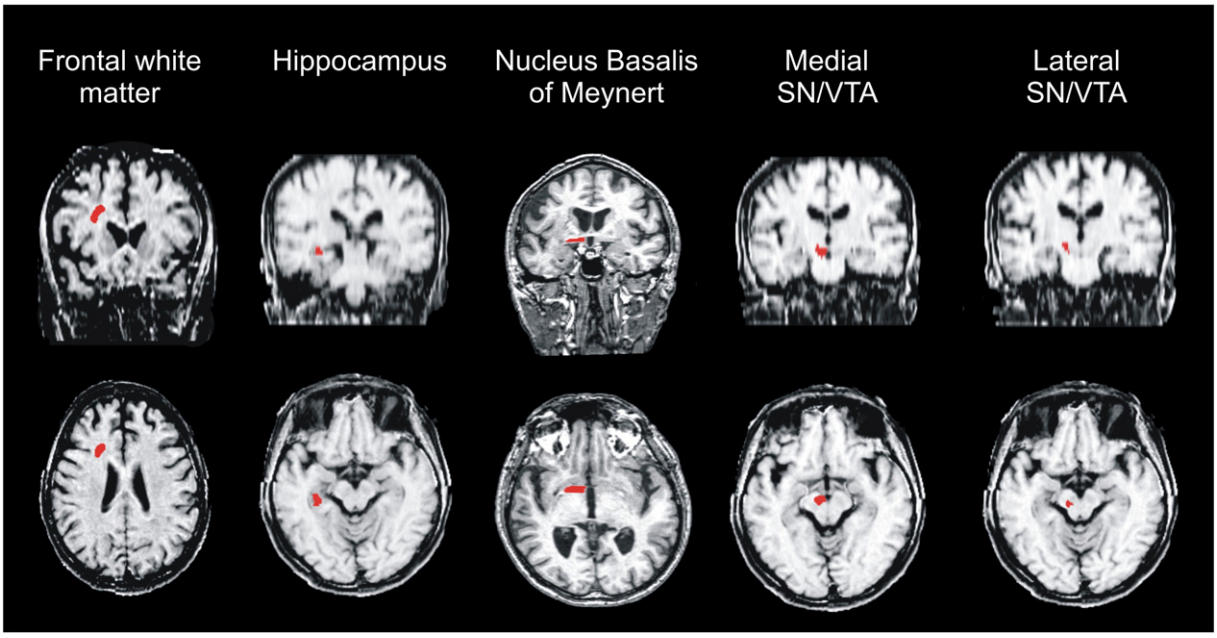

Fig. 2 – Illustration of regions of interests (ROIs) for one participant from the older group. Legend: the figure shows frontal white matter, hippocampal, basal forebrain (termed Nucl. Basalis of Meynert, T1 image) and SN/VTA (MT image) ROIs in a coronal and transversal view.

sagittal sulcus at an angle of about 45°. Note that Fearnley and Lees (1991) further subdivided into a ventral and dorsal tier, but the resolution of our MT imaging did not allow for such fine grained subdivision.

4.8.2. *Hippocampal ROI (HC-ROI)*

The upper boundary of the SN-ROI served as a reference for the upper limit of the HC-ROI. The anterolateral boundaries were defined by the extensions of the lateral ventricles. The medial–posterior part of the HC-ROI was limited by the transition into the entorhinal cortex. To exclude any voxels containing cerebrospinal fluid, a safety margin of about two voxels was left between hippocampal tissue and the surrounding structures. The rostro-caudal extension of the HC-ROI comprised 3 slices (9mm).

4.8.3. *Basal nucleus ROI (BN-ROI)*

The BN-ROI was outlined on coronal T1 images, because they provided better resolution in anterior–posterior direction than the MT images. The ROIs derived from the T1 images were then coregistered with the MT images. According to Selden et al. (1998) in which basal forebrain cholinergic cell groups were delineated immunohistologically, three slices in anterior (4.5 mm) and three slices in posterior direction (4.5 mm) with the anterior commissure as starting coordinate were selected. The lateral boundary of the external globus pallidus served as lateral limit for the BN-ROI, medially the ROI was defined by the medial boundary of the internal globus pallidus.

4.8.4. *Frontal white matter (FWM-ROI)*

One common ROI was defined on the average anisotropy image of all participants. The center of the ROI was placed in the white matter junction of the superior, medial, and inferior frontal gyri just anterior of the tip of the third ventricle and lateral to the corpus callosum. The ROI extended 1 cm in anterior–posterior and superior–inferior dimensions and around 3 mm laterally and medially. Care was taken that the ROI did not include any CSF in individual participants. To that end, the location of the ROI within individual brains was checked on both the normalized AI and ADC images of each participant.

The ROI selection on individual MR data was conducted by S.S. and E.D. Both were blind with respect to age and sex of the participant. Interrater reliability could not be determined here because ROIs were not used for volumetric purposes.

4.9. *Statistical analyses*

Statistical analyses were performed using SPSS (version 11). The factor analyses were conducted for the older adults only and followed recommendations by Tabachnick and Fidel (1996). The 12 scores that were submitted to factor analysis included 6-item scores from neuropsychological assessment including data regarding verbal learning and memory (CVLT total), working memory span (DS span), working memory manipulation (DS manipulation), attention/processing speed (D2), verbal fluency, knowledge, as well as scores from the psychosocial assessment; sense of coherence, mental health, positive stress coping, job prestige, and years of education. The selection of these parameters aimed to comprehensively represent relevant cognitive and psychosocial variables while at the same time avoiding the inclusion of redundant parameters (multicollinearity).

Given the relative tendency of the Kaiser criterion (eigenvalues greater than 1) to overestimate the true number of components, we used the 'Measure of Sampling Adequacy' (MSA) to eliminate all variables that were not adequate for a factorial analysis by falling below a threshold of 0.5. This led to

the elimination of sfv78pos (0.452). We then used the Kaiser-Meyer-Olking (KMO) measure as a test of sampling adequacy and Bartlett's test of sphericity. The KMO tests whether the partial correlations among variables are small, whereas the Bartletts test shows whether the correlation matrix is an identity matrix, which would indicate that the factor model is inappropriate.

For our variables, the KMO measure was 0.669, which is satisfactory for factor analysis and the Bartlett's test of sphericity is significant. The remaining 11 scores from the older adults were submitted to principal components extraction with Varimax rotation and factors with eigenvalues exceeding 1.0 were considered for further statistical analyses.

We used multiple regression analyses to identify how much variance of factors identified in the factor analysis was explained by single or combined regional MTR values and age. Dependent (or predicted) variables were factor scores and the eight independent (or predictor) variables in each model were left and right hemispheric MTRs from SN/VTA, hippocampus, basal forebrain, FWM, and age using the stepwise method (note that the ratio between number of subjects and predictor variables was>5:1). Significant relationships between dependent and independent variables were followed-up by Pearson's correlations (two-tailed) between the corresponding factor score and regional MTR measure. Here, a Bonferroni correction was implemented for the number of follow-up comparisons plus additional correlations between the factors and age.

Statistical significance for the correlation analyses between factor scores and MTR values was based on two-tailed criteria, because it was not predictable whether psychosocial scores would correlate positively or negatively with MTR changes (a positive correlation was predicted for neuropsychological scores).

To reduce the problem of multiple comparisons, all our analyses were conducted using MTR values as a measure of structural integrity. Measures of anisotropy and diffusion were used to interpret the MTR changes rather than detecting additional correlations between cognitive and psychosocial variables and structural integrity.

REFERENCES

Abe, O., Mori, H., Aoki, S., Kunimatsu, A., Hayashi, N., Masumoto, T., et al., 2004. Periodically rotated overlapping parallel lines with enhanced reconstruction-based diffusion tensor imaging. Comparison with echo planar imaging-based diffusion tensor imaging. J. Comput. Assist. Tomogr. 28, 654–660.

Adcock, R.A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., Gabrieli, J.D., 2006. Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron 50, 507–517.

Antonovsky, A., 1987. Unraveling the mystery of health. Jossey-Bass, San Francisco.

Antonovsky, A., 1993. The structure and properties of the sense of coherence scale. Soc. Sci. Med. 36, 725–733.

Antonovsky, H., Sagy, S., 1986. The development of a sense of coherence and its impact on responses to stress situations. J. Soc. Psychol. 126, 213–225.

Audoin, B., Ranjeva, J.P., Au Duong, M.V., Ibarrola, D., Malikova, I., Confort-Gouny, S., et al., 2004. Voxel-based analysis of MTR images: a method to locate gray matter abnormalities in patients at the earliest stage of multiple sclerosis. J. Magn. Reson. Imaging 20, 765–771.

Audoin, B., Davies, G.R., Finisku, L., Chard, D.T., Thompson, A.J., Miller, D.H., 2006. Localization of grey matter atrophy in early RRMS: a longitudinal study. J. Neurol. 253, 1495–1501.

Backman, L., Ginovart, N., Dixon, A.R., Wahlin, T.B.R., Wahlin, S.A., Halldin, C., et al., 2000. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am. J. Psychiatry. 157, 635–637.

Backman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30, 791–807.

Baddeley, A., Cocchini, G., Della Sala, S., Logie, R.H., Spinnler, H., 1999. Working memory and vigilance: evidence from normal aging and Alzheimer's disease. Brain Cogn. 41, 87–108.

Balota, A.D., Dolan, P.O., Duchek, J.M., 2000. Memory changes in healthy older adults. In: Craik, E.T.a.F.I.M. (Ed.), The Oxford Handbook of Memory. Oxford University Press, Oxford.

Baltes, P.B., Mayer, K.U., 1999. The Berlin Aging Study: Aging from 70. to 100. Cambridge University Press, New York.

Benedetti, B., Charil, A., Rovaris, M., Judica, E., Valsasina, P., Sormani, M.P., et al., 2006. Influence of aging on brain gray and white matter changes assessed by conventional, MT, and DT MRI. Neurology 66, 535–539.

Bodammer, N., Kaufmann, J., Kanowski, M., Tempelmann, C., 2004. Eddy current correction in diffusion-weighted imaging using pairs of images acquired with opposite diffusion gradient polarity. Magn. Reson. Med. 51, 188–193.

Brickman, A.M., Habeck, C., Zarahn, E., Flynn, J., Stern, Y., 2007. Structural MRI covariance patterns associated with normal aging and neuropsychological functioning. Neurobiol. Aging 28, 284–295.

Bryan, J., Luszcz, M.A., 2000. Measures of fluency as predictors of incidental memory among older adults. Psychol. Aging 15, 483–489.

Buckner, R.L., 2004. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44, 195–208.

Bunzeck, N., Duzel, E., 2006. Absolute coding of stimulus novelty in the human substantia nigra/VTA. Neuron 51, 369–379.

Bunzeck, N., Schutze, H., Stallforth, S., Kaufmann, J., Duzel, S., Heinze, H.J., et al., 2007. Mesolimbic novelty processing in older adults. Cereb. Cortex.

Cabeza, R., Anderson, N.D., Houle, S., Mangels, J.A., Nyberg, L., 2000. Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study. J. Cogn. Neurosci. 12, 197–206.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 17, 1394–1402.

Chudasama, Y., Dalley, J.W., Nathwani, F., Bouger, P., Robbins, T.W., 2004. Cholinergic modulation of visual attention and working memory: dissociable effects of basal forebrain 192-IgG-saporin lesions and intraprefrontal infusions of scopolamine. Learn. Mem. 11, 78–86.

Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., et al., 2003. Aerobic fitness reduces brain tissue loss in aging humans. J. Gerontol. Ser. A., Biol. Sci. 58A, 176–180.

Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Mechanisms of cognitive set flexibility in Parkinson's disease. Brain 124, 2503–2512.

Cortes, R., Gueye, B., Pazos, A., Probst, A., Palacios, J.M., 1989. Dopamine receptors in human brain: autoradiographic distribution of D1 sites. Neuroscience 28, 263–273.

Cournot, M., Marquie, J.C., Ansiau, D., Martinaud, C., Fonds, H., Ferrieres, J., et al., 2006. Relation between body mass index and

cognitive function in healthy middle-aged men and women. Neurology 67, 1208–1214.
Craik, F.I., 1971. Age differences in recognition memory. Q. J. Exp. Psychol. 23, 316–323.
Craik, F.I.M., 1994. Memory changes in normal aging. Curr. Dir. Psychol. Sci. 3, 155–158.
Craik, F.I., 2006. Brain–behavior relations across the lifespan: a commentary. Neurosci. Biobehav. Rev. 30, 885–892.
Crook, T., Bartus, R.T., Ferris, S.H., 1986. Age associated memory impairment: proposed diagnostic criteria and measures of clinical change: report of a National Institute of Mental Health Work Group. Dev. Neuropsychol. Rev. 2, 261–276.
Deary, I.J., Bastin, M.E., Pattie, A., Clayden, J.D., Whalley, L.J., Starr, J.M., et al., 2006. White matter integrity and cognition in childhood and old age. Neurology 66, 505–512.
Delis, D., Kramer, J., Kaplan, E., Ober, B., 1987. California Verbal Learning Test: Adult Version. The Psychological Corporation, San Antonio, TX.
Drachman, D.A., Leavitt, J., 1974. Human memory and the cholinergic system. A relationship to aging. Arch. Neurol. 30, 113–121.
Duzel, S., Schutze, H., Stallforth, S., Kaufmann, J., Bodammer, N., Bunzeck, N., et al., 2008. A close relationship between verbal memory and SN/VTA integrity in young and older adults. Neuropsychologia 46, 3042–3052.
Eriksson, M., Lindström, B., 2005. Validity of Antonovsky's sense of coherence scale: a systematic review. J. Epidemiol. Community Health 59, 460–466.
Fazekas, F., Ropele, S., Enzinger, C., Gorani, F., Seewann, A., Petrovic, K., et al., 2005. MTI of white matter hyperintensities. Brain 128, 2926–2932.
Fearnley, J.M., Lees, A.J., 1991. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5), 2283–2301.
Fernando, K.T., Tozer, D.J., Miszkiel, K.A., Gordon, R.M., Swanton, J.K., Dalton, C.M., et al., 2005. Magnetization transfer histograms in clinically isolated syndromes suggestive of multiple sclerosis. Brain 128, 2911–2925.
Geula, C., Mesulam, M.M., 1989. Cortical cholinergic fibers in aging and Alzheimer's disease: a morphometric study. Neuroscience 33, 469–481.
Glisky, E.L., Polster, M.R., Routhieaux, B.C., 1995. Double dissociation between item and source memory. Neuropsychology 229–235.
Glisky, E.L., Rubin, S.R., Davidson, P.S.R., 2001. Source memory in older adults: an encoding or retrieval problem? J. Exp. Psychol. Learn. Mem. Cogn. 27, 1131–1146.
Hasselmo, M.E., Giocomo, L.M., 2006. Cholinergic modulation of cortical function. J. Mol. Neurosci. 30, 133–135.
Hasselmo, M.E., Stern, C.E., 2006. Mechanisms underlying working memory for novel information. Trends Cogn. Sci. 10, 487–493.
Head, D., Buckner, R.L., Shimony, J.S., Williams, L.E., Akbudak, E., Conturo, T.E., et al., 2004. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb. Cortex 14, 410–423.
Hedden, T., Gabrieli, J.D., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5, 87–96.
Helms, G., Draganski, B., Frackowiak, R., Ashburner, J., Weiskopf, N., 2009. Improved segmentation of deep brain grey matter structures using magnetization transfer (MT) parameter maps. Neuroimage 47, 194–198.
Hiller, W., 1997. Die Freiburger Beschwerdenliste (FBL), Form FBL-G und revidierte Form FBL-R. Z. klin. Psychol. Psychother. 26, 309–311.
Iannucci, G., Tortorella, C., Rovaris, M., Sormani, M.P., Comi, G., Filippi, M., 2000. Prognostic value of MR and magnetization transfer imaging findings in patients with clinically isolated syndromes suggestive of multiple sclerosis at presentation. AJNR Am. J. Neuroradiol. 21, 1034–1038.
Janke, W., Erdmann, G., Kallus, K.W., 2002. Stressverarbeitungsfragebogen (SVF mit SVF 120 und SVF 78). Hogrefe, Göttingen.
Kray, J., Lindenberger, U., 2000. Adult age differences in task switching. Psychol. Aging 15, 126–147.
Kuhl, D.E., Minoshima, S., Fessler, J.A., Frey, K.A., Foster, N.L., Ficaro, E.P., et al., 1996. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann. Neurol 40, 399–410.
Lehrl, S., 2005. Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. 5. Spitta Verlag, Aufl. Balingen.
Lindenberger, U., Baltes, P.B., 1997. Intellectual functioning in old and very old age: cross-sectional results from the Berlin Aging Study. Psychol. Aging 12, 410–432.
Lindenberger, U., Ghisletta, P., Cognitive decline in old and very old age: evidence for a common cause. (submitted)
Lisman, J.E., Grace, A.A., 2005. The hippocampal–VTA loop: controlling the entry of information into long-term memory. Neuron 46, 703–713.
Lovden, M., Ghisletta, P., Lindenberger, U., 2005. Social participation attenuates decline in perceptual speed in old and very old age. Psychol. Aging 20, 423–434.
Mesulam, M.M., 2004a. The cholinergic innervation of the human cerebral cortex. Prog. Brain Res. 145, 67–78.
Mesulam, M.M., 2004b. The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? Learn Mem. 11, 43–49.
Mishkin, M., Suzuki, W.A., Gadian, D.G., Vargha-Khadem, F., 1997. Hierarchical organization of cognitive memory. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 352, 1461–1467.
Moseley, M., 2002. Diffusion tensor imaging and aging—a review. NMR Biomed. 15, 553–560.
Mungas, D., Harvey, D., Reed, B.R., Jagust, W.J., DeCarli, C., Beckett, L., et al., 2005. Longitudinal volumetric MRI change and rate of cognitive decline. Neurology 65, 565–571.
Nilsson, L.G., 2003. Memory function in normal aging. Acta. Neurol. Scand. Suppl. 179, 7–13.
Oh, M.M., Wu, W.W., Power, J.M., Disterhoft, J.F., 2005. Galantamine increases excitability of CA1 hippocampal pyramidal neurons. Neuroscience.
Papadakis, N.G., Xing, D., Houston, G.C., Smith, J.M., Smith, M.I., James, M.F., et al., 1999. A study of rotationally invariant and symmetric indices of diffusion anisotropy. Magn. Reson. Imaging. 17, 881–892.
Park, D.C., Smith, A.D., Lautenschlager, G., Earles, J.L., Frieske, D., Zwahr, M., et al., 1996. Mediators of long-term memory performance across the life span. Psychol. Aging 11, 621–637.
Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K., 2002. Models of visuospatial and verbal memory across the adult life span. Psychol. Aging 17, 299–320.
Parkin, A.J., Java, R.I., 1999. Deterioration of frontal lobe function in normal aging: influences of fluid intelligence versus perceptual speed. Neuropsychology 13, 539–545.
Pfefferbaum, A., Adalsteinsson, E., Sullivan, E.V., 2003. Replicability of diffusion tensor imaging measurements of fractional anisotropy and trace in brain. J. Magn. Reson. Imaging 18, 427–433.
Pfefferbaum, A., Adalsteinsson, E., Sullivan, E.V., 2005. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. Neuroimage 26, 891–899.
Plassman, B.L., Welsh, K.A., Helms, M., Brandt, J., Page, W.F., Breitner, J.C., 1995. Intelligence and education as predictors of cognitive state in late life: a 50-year follow-up. Neurology 45, 1446–1450.
Potter, G.G., Plassman, B.L., Helms, M.J., Foster, S.M., Edwards, N.W., 2006. Occupational characteristics and cognitive performance among elderly male twins. Neurology 67, 1377–1382.
Potter, G.G., Helms, M.J., Plassman, B.L., 2008. Associations of job demands and intelligence with cognitive performance among men in late life. Neurology 70, 1803–1808.

Rademacher, J., Engelbrecht, V., Burgel, U., Freund, H., Zilles, K., 1999. Measuring in vivo myelination of human white matter fiber tracts with magnetization transfer MR. Neuroimage 9, 393–406.
Raskind, M.A., Peskind, E.R., Wessel, T., Yuan, W., 2000. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 54, 2261–2268.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., et al., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.
Raz, N., Rodrigue, K.M., 2006. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 30, 730–748.
Reitan, R.M., 1992. The Trail Making Test: Manual for Administration and Scoring. Neuropsychology Laboratory, Tucson.
Rinne, J.O., Lonnberg, P., Marjamaki, P., 1990. Age-dependent decline in human brain dopamine D1 and D2 receptors. Brain Res. 508, 349–352.
Robbins, T.W., Roberts, A.C., 2007. Differential regulation of fronto-executive function by the monoamines and acetylcholine. Cereb Cortex 17 (Suppl. 1), i151–i160.
Rowe, J.W., Kahn, R.L., 1987. Human aging: usual and successful. Science 237, 143–149.
Ruff, R.M., Light, R.H., Parker, S.B., Levin, H.S., 1997. The psychological construct of word fluency. Brain Lang. 57, 394–405.
Sagy, S., Antonovsky, H., 2000. The development of the sense of coherence: a retrospective study of early life experiences in the family. Int. J. Aging Hum. Dev. 51, 155–166.
Salat, D.H., Tuch, D.S., Greve, D.N., van der Kouwe, A.J., Hevelone, N.D., Zaleta, A.K., et al., 2005. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiol. Aging 26, 1215–1227.
Salthouse, T.A., 2000. Aging and measures of processing speed. Biol. Psychol. 54, 35–54.
Salthouse, T.A., 2003. Memory aging from 18 to 80. Alzheimer Dis. Assoc. Disord. 17, 162–167.
Sarter, M., Hasselmo, M.E., Bruno, J.P., Givens, B., 2005. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res. Brain Res. Rev. 48, 98–111.
Sassin, I., Schultz, C., Thal, D.R., Rub, U., Arai, K., Braak, E., et al., 2000. Evolution of Alzheimer's disease-related cytoskeletal changes in the basal nucleus of Meynert. Acta. Neuropathol. (Berl) 100, 259–269.
Schiltz, K., Szentkuti, A., Guderian, S., Kaufmann, J., Munte, T.F., Heinze, H.J., et al., 2006. Relationship between hippocampal structure and memory function in elderly humans. J. Cogn. Neurosci. 18, 990–1003.
Schott, B.H., Seidenbecher, C.I., Fenker, D.B., Lauer, C.J., Bunzeck, N., Bernstein, H.G., et al., 2006. The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J. Neurosci. 26, 1407–1417.
Seeman, P., Bzowej, N.H., Guan, H.C., Bergeron, C., Becker, L.E., Reynolds, G.P., et al., 1987. Human brain dopamine receptors in children and aging adults. Synapse 1, 399–404.
Shimamura, A.P., Berry, J.M., Mangels, J.A., Rusting, C.L., Jurica, P.J., 1995. Memory and cognitive abilities in university professors: evidence for successful aging. Psychol. Sci. 271–277.
Singh-Manoux, A., Ferrie, J.E., Lynch, J.W., Marmot, M., 2004. The role of cognitive ability (intelligence) in explaining the association between socioeconomic position and health: evidence from the Whitehall II Prospective Cohort Study. Am. J. Epidemiol. 161, 831–839.
Smith, J., 2003. Stress and aging: theoretical and empirical challenges for interdisciplinary research. Neurobiol. Aging 24 (Suppl. 1), S77–S80 discussion S81-2.
Snow, B.J., Tooyama, I., McGeer, E.G., Yamada, T., Calne, D.B., Takahashi, H., et al., 1993. Human positron emission tomographic [18F]fluorodopa studies correlate with dopamine cell counts and levels. Ann. Neurol. 34, 324–330.
Springer, M.V., McIntosh, A.R., Winocur, G., Grady, C.L., 2005. The relation between brain activity during memory tasks and years of education in young and older adults. Neuropsychology 19, 181–192.
Stuss, D.T., Levine, B., 2002. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu. Rev. Psychol. 53, 401–433.
Sullivan, E.V., Pfefferbaum, A., 2006. Diffusion tensor imaging and aging. Neurosci. Biobehav. Rev. 30, 749–761.
Sullivan, E.V., Adalsteinsson, E., Pfefferbaum, A., 2006. Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. Cereb. Cortex 16, 1030–1039.
Szentkuti, A., Guderian, S., Schiltz, K., Kaufmann, J., Munte, T.F., Heinze, H.J., et al., 2004. Quantitative MR analyses of the hippocampus: unspecific metabolic changes in aging. J. Neurol. 251, 1345–1353.
Tabachnick, B.G., Fidel, L.S., 1996. Using Multivariate Statistics, 3rd Ed. HarperCollins Publishers Inc., New York.
Tang, Y., Mishkin, M., Aigner, T.G., 1997. Effects of muscarinic blockade in perirhinal cortex during visual recognition. Proc. Natl. Acad. Sci. U. S. A. 94, 12667–12669.
Tariot, P.N., Solomon, P.R., Morris, J.C., Kershaw, P., Lilienfeld, S., Ding, C.A., 2000. 5-Month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 54, 2269–2276.
Traboulsee, A., Dehmeshki, J., Brex, P.A., Dalton, C.M., Chard, D., Barker, G.J., et al., 2002. Normal-appearing brain tissue MTR histograms in clinically isolated syndromes suggestive of MS. Neurology 59, 126–128.
Tulving, E., 1985. Memory and consciousness. Can. Psychol. 26, 1–12.
Turchi, J., Saunders, R.C., Mishkin, M., 2005. Effects of cholinergic deafferentation of the rhinal cortex on visual recognition memory in monkeys. Proc. Natl. Acad. Sci. U. S. A. 102, 2158–2161.
van Waesberghe, J.H., Kamphorst, W., De Groot, C.J., van Walderveen, M.A., Castelijns, J.A., Ravid, R., et al., 1999. Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. Ann. Neurol. 46, 747–754.
Verhaeghen, P., Salthouse, T.A., 1997. Meta-analyses of age-cognition relations in adulthood: Estimates of linear and nonlinear age effects and structural models. Psychol. Bull. 122, 231–249.
Wang, M., Vijayraghavan, S., Goldman-Rakic, P.S., 2004. Selective D2 receptor actions on the functional circuitry of working memory. Science 303, 853–856.
Warburton, E.C., Koder, T., Cho, K., Massey, P.V., Duguid, G., Barker, G.R., et al., 2003. Cholinergic neurotransmission is essential for perirhinal cortical plasticity and recognition memory. Neuron 38, 987–996.
Ware, J.E., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med. Care 34, 220–233.
Wegener, B., 1984. Gibt es ein Sozialprestige? Konstruktion und Validität der Magnitude-Prestigeskala. ZUMA-Arb. Ber. 84.
Weible, A.P., Oh, M.M., Lee, G., Disterhoft, J.F., 2004. Galantamine facilitates acquisition of hippocampus-dependent trace eyeblink conditioning in aged rabbits. Learn. Mem. 11, 108–115.
Weidlich, S., Lamberti, G.D.C.S., 1993. Diagnosticum für Cerebralschädigungen. Hans Huber, Bern, Switzerland.
WHO, ISH, 1999. WHO/ISH-Guidelines-Subcommittee: World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. J. Hypertens. 151–183.

Williams, G.V., Goldman-Rakic, P.S., 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 376, 572–575.

Wilson, R., Beckett, L., Barnes, L., Schneider, J., Bach, J., Evans, D., et al., 2002. Individual differences in rates of change in cognitive abilities of older persons. Psychol. Aging 17, 179–193.

Wittmann, B.C., Schott, B.H., Guderian, S., Frey, J.U., Heinze, H.J., Duzel, E., 2005. Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron 45, 459–467.

Wolff, S.D., Balaban, R.S., 1989. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. Magn. Reson. Med. 10, 135–144.

Woodruff-Pak, D.S., Vogel III, R.W., Wenk, G.L., 2001. Galantamine: effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning. Proc. Natl. Acad. Sci. U. S. A. 98, 2089–2094.

Woods, R.P., Grafton, S.T., Holmes, C.J., Cherry, S.R., Mazziotta, J.C., 1998. Automated image registration: I. General methods and intrasubject, intramodality validation. J. Comput. Assist. Tomogr. 22, 139–152.

Wozniak, J.R., Lim, K.O., 2006. Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. Neurosci. Biobehav. Rev. 30, 762–774.