Neuropsychologia 119 (2018) 172–181

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Size matters: Grey matter brain reserve predicts executive functioning in the elderly

M. Laubach[a,e,*,1], F. Lammers[a,e], N. Zacharias[a,e], I. Feinkohl[b], T. Pischon[b], F. Borchers[a], A.J.C. Slooter[d], S. Kühn[c,e], C. Spies[a], G. Winterer[a,e], BioCog Consortium

[a] Clinical Neuroscience Research Group, Experimental and Clinical Research Center (ECRC), Dept. of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[b] Molecular Epidemiology Research Group, Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
[c] Clinic and Polyclinic of Psychiatry and Psychotherapy, University Clinic Hamburg-Eppendorf, Hamburg, Germany
[d] Department of Intensive Care Medicine and Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, the Netherlands
[e] PharmaImage Biomarker Solutions GmbH, Biotech Park Berlin-Buch, Robert-Rössle-Str. 10, 13125 Berlin, Germany

ARTICLE INFO

Keywords:
Executive functioning
Neuroimaging
Elderly
Neuropsychology
Brain reserve
Cognitive reserve

ABSTRACT

Preserved executive functioning (EF) is crucial for daily functioning in the elderly and it appears to predict dementia development. We sought to clarify the role of atrophy-corrected cortical grey matter (GM) volume as a potential brain reserve (BR) marker for EF in the elderly. In total, 206 pre-surgical subjects (72.50 ± 4.95 years; mean MMSE score 28.50) were investigated. EF was primarily assessed using the Trail Making Test B (TMT B). Global/ lobar GM volumes were acquired with T1 MP-RAGE. Adjusting for key covariates including a brain atrophy index (i.e. brain parenchymal fraction), multiple linear regression analysis was used to study associations of GM volumes and TMT B. All GM volumes - most notably of global GM - were significantly associated with TMT B independently of GM atrophy (ß = −0.201 to −0.275, p = 0.001–0.012). Using atrophy-corrected GM volume as an estimate of maximal GM size in youth may serve as a BR predictor for cognitive decline in future studies investigating BR in the elderly.

1. Introduction

The term cognitive reserve (CR) captures the fact that an individual maintains the capability of performing cognitive tasks in the face of neurological disease with a subsequent loss of neuronal function (Stern, 2012). The model of CR states that patients with higher intelligence (IQ) or occupational attainment might have a functional advantage during late life (Stern, 2002). Analogous to the concept of CR, brain reserve (BR), in particular measures of brain structure, refers to the hypothesis that the brain is capable of minimizing clinical manifestations in the face of age-related cerebral effects or the present neuropathology (Bartrés-Faz and Arenaza-Urquijo, 2011; Chen et al., 2017). Several studies reported that subjects with larger head circumference, intracranial volume or brain weight with higher numbers of neurons are less likely to develop dementia (Katzman et al., 1988; Mori et al., 1997; Schofield et al., 1997). Furthermore, larger brain size may constitute a possible morphological advantage with regard to overall cognitive ability in the elderly (Pietschnig et al., 2015; Persson et al., 2016; Feinkohl et al., 2017; Groot et al., 2017; Vibha et al., 2017).

In both, non-demented elderly subjects and patients with mild cognitive impairment (MCI), a preserved superior level of executive functioning (EF) is associated with superior daily functioning and aging well (Schmitter-Edgecombe et al., 2011; Puente et al., 2015; Darby et al., 2017). EF reflects a range of decision-making and higher-order thinking processes like flexible problem-solving, working memory and response inhibition (Stern, 2012; Puente et al., 2015; Darby et al., 2017). In a recent long-term observation study, Chen et al. (2017) reported that subjects with low baseline EF - but notably not with low baseline memory performance - had a higher conversion rate from normal cognition to MCI. Similar observations were made by others (Royall et al., 2004; Johnson et al., 2007). Johnson et al. (2007) undertook a prospective study of 7717 elderly women (mean modified MMSE of 24.8 points), and observed that impaired EF at baseline, measured by the Trail Making Test (TMT) B, rather than global cognitive function was associated with significantly worse daily functioning both in a cross-section manner and over six years. In a three-

* Correspondence to: Department of Anesthesiology, Charité - University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany.
E-mail address: markus.laubach@charite.de (M. Laubach).
[1] www.biocog.eu.

https://doi.org/10.1016/j.neuropsychologia.2018.08.008
Received 21 February 2018; Received in revised form 7 August 2018; Accepted 9 August 2018
Available online 10 August 2018

year longitudinal cohort study of 547 non-demented elderly, Royall et al. (2004) showed that EF instead of e.g. the MMSE score was the most accurate predictor of functional status over time. Comparable results were reported by Rozzini et al. (2007), who observed an association of conversion to Alzheimer's disease (AD) with poor global cognitive performance at baseline and with worsening executive functioning, but not with worsening memory performance (one year follow-up period) in a group of amnestic MCI individuals. These findings suggest that EF is a particularly relevant constituent of CR.

Phillips et al. (2008) demonstrated that cognition and behavior in older non-demented adults are highly dependent on EF, which, in turn, is associated with prefrontal brain function. Multiple studies of elderly subjects have demonstrated that the integrity of the different brain lobes, most notably the frontal lobe, are associated with EF (Elderkin-Thompson et al., 2008; Cardenas et al., 2011; Zhang et al., 2011; Dong et al., 2015). More recently, however, Bettcher et al. (2016) reported findings that are not easily reconciled with the hypothesis of an outstanding role of the frontal lobe with respect to EF in the aging process. In their study (N = 202), cortical grey matter (GM) volume of the frontal lobe as well as additional brain lobes were not independently associated with EF performance when statistically corrected for global GM volume. Importantly, all of these studies have in common that they quantify GM volume without distinguishing whether it is the maximal brain size in youth or GM atrophy during later life that predicts EF in elderly subjects. Accordingly, any association between frontal or global GM volume and EF can be interpreted in two different ways. Low EF performance can result from age-associated cortical atrophy, small GM volumes already at a young age (BR) or both. The concept of brain reserve (BR) is mostly attributed to passive individual differences of morphological brain characteristics enduring neuropathological processes (Bartrés-Faz and Arenaza-Urquijo, 2011). Reaching a critical threshold of brain damage might result in clinical and functional deficits becoming apparent (Satz et al., 1993). A number of studies have found impaired EF preceding memory decline in the course of dementia development (Johnson et al., 2007) and the literature has pointed out the need to consider brain morphology associated with EF possibly serving as an early marker of neurodegenerative disease (Chen et al., 2017). Thus, as brain atrophy is suggested to be an early risk indicator, brain imaging might be beneficial by delivering diagnostic and prognostic information to patients in the process of individual personalized medicine (Chen et al., 2017).

In the present study, we sought to clarify, whether maximal GM volume in youth, i.e. the cortical BR, contributes to EF in the elderly. In addition, we addressed the question of whether frontal or global GM volume is associated with EF. For the neuropsychological assessment of EF the commonly used trail-making tests were applied (Reitan, 2004; Rabin et al., 2005) which have been hypothesized to reflect a wide variety of cognitive processes such as visual searching and scanning, flexibility and the ability to execute and modify a plan of action (Salthouse, 2011). In order to estimate cortical GM during youth as a BR marker in our elderly patient group, we adopted a novel strategy which - to the best of our knowledge - has not been previously applied. We calculated a brain atrophy index (brain parenchymal fraction, BPF), i.e. the ratio of the total brain parenchymal volume (BPV), which includes GM and white matter (WM), to the total intracranial volume (ICV). In the past, BPF has been used as a measure of brain atrophy, for instance by the Alzheimer's Disease Neuroimaging Initiative consortium, to predict cognitive decline in dementia patients (Callahan et al., 2015). Literature concerning the application of BPF in healthy individuals is sparse; in particular, evaluation of the course of brain atrophy in healthy adults. Vågberg et al. (2017) investigated cross-sectional data of BPF that are currently available in the literature and highlighted in a systematic review that the BPF values in healthy individuals increase until the age of 40, whereas a progressive rate of atrophy occurs along with further aging. Since ICV is stable throughout adulthood, it represents an "archeological" estimate of maximal brain size in youth (Royle et al., 2013). Thus, we used BPF in our study to correct an individual GM volume for GM atrophy, which lends this measure to the quality of a BR prediction marker even when imaging data are collected at advanced age in a cross-sectional study design. Accordingly, this strategy of data analysis extends recent work using ICV per se as a BR marker for the prediction of dementia development (Guo et al., 2013; Negash et al., 2013; Groot et al., 2017). The rationale of our approach is the well-known inter-individual variability (~ 10%) of the ratio between ICV and cortical GM volume (Ge et al., 2002).

2. Material and methods

2.1. Participants

In total, 206 neuropsychologically healthy adults (aged: 65–87 years), were selected as part of an interim analysis from a cohort study within the framework of the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study (www.biocog.eu). The BioCog study is a prospective 2-center (Charité University Hospital Berlin (Germany) and the University Hospital Utrecht (Netherlands)) observational cohort study with N = 1033 elderly elective surgical patients, aiming to establish valid clinical, neuroimaging and molecular biomarker panels for risk and clinical outcome prediction of postoperative delirium and postoperative cognitive deficits (Winterer et al., 2018). According to the study protocol, pre-operative data of the first 400 enrolled patients can be used for interim analyses (data from N = 291 patients in the Charité University Hospital Berlin (Germany) and N = 109 patients from the University Hospital Utrecht (Netherlands)). In the present study, only data from patients from the clinical center of Berlin, who were recruited in the entire area of the city of Berlin, were used for analyses. Since approximately 50% of all surgical interventions in the Berlin area, with roughly five million inhabitants, are conducted at the Charité University Hospital, the study cohort in Berlin ensures a good coverage of elderly surgical patients in the region (Winterer et al., 2018). The inclusion criteria comprise male and female patients aged ≥ 65 years and of European descent (Caucasian) who are scheduled for elective surgery. Study participants with ≤ 23 points in the Mini-Mental-State-Examination (MMSE), a life-time history of neuropsychiatric disorders or addiction disorders during the past five years or with centrally acting medication were excluded (complete list of eligibility criteria: https://clinicaltrials.gov/ct2/show/NCT02265263?term=biocog&rank=1). The study is registered at ClinicalTrials.gov: NCT02832193. All patients have given written informed consent after receiving spoken and written information on the study. The study was approved by the local ethics committee and conducted according to the declaration of Helsinki.

Magnetic resonance imaging (MRI) data acquisition together with clinical and neurocognitive assessments took place one day before surgery. In total, 218 MRI scans were available for this interim analysis using data from the patients from the clinical center of Berlin (N = 291). Due to the withdrawal of consent by one patient after inclusion and one case with preterm finishing of the FreeSurfer processing pipeline, as well as ten cases with gross anatomical aberrations seen while inspecting the post-processed images, 206 processed MRI scans were finally available for analysis. Of the 206 available MRI scans, TMT B data were available for 174 subjects (for demographics see Table 1).

2.2. Measures

2.2.1. Cognitive assessments

For the assessment of executive functioning, the Trail Making Test (TMT A and TMT B) was applied on the same day as the MRI investigation. The measurement of visuoperceptual abilities, which are speeded (motor) measures, is mainly reflected by part A of the TMT, whereas inhibition and set-shifting ability is reflected by part B (Arbuthnott and Frank, 2000; Strauss et al., 2006; Sánchez-Cubillo

Table 1
Cognitive and neuroimaging characteristics of participants.

Demographics	N	Mean (SD)	Range
Age (years)	206	72.50 (4.95)	65–87
Male Sex (%)	118	57.28	
Education			
ISCED 1997 Level	183	2 A/B: 23.00% 3 A/B/C: 38.20% 4 A/B: 3.20% 5 A/B: 35.60%	
Education (years)	166	13.02 (4.15)	6–24
Executive Functions Measures			
TMT A (sec)	189	50.30 (19.21)	19–132
TMT B (sec)	174	119.56 (51.01)	25–298
Intelligence Test			
IQ score	121	114.07 (14.14)	70–143
MMSE	206	28.50 (1.41)	24–30
Neuroimaging Measures			
Total intracranial volume (mm^3)	206	1.338.010 (203.127)	922.433–2.007.198
Total brain parenchymal volume (mm^3)	206	979.727 (101.958)	705.772–1.222.338
Total cortical GM volume (mm^3)[a,b]	206	310.639 (30.572)	233.497–394.180
Frontal lobe GM volume (mm^3)[a]	206	123.858 (12.543)	93.016–164.200
Parietal lobe GM volume (mm^3)[b]	206	85.802 (8.888)	66.548–111.093
Temporal lobe GM volume (mm^3)	206	61.794 (6.779)	45.140–80.615
Occipital lobe GM volume (mm^3)	206	39.185 (4.760)	28.485–52.202
BPF (BPV/ICV)	206	0.742 (0.088)	0.53–0.99
GMF (GMV/ICV)	206	0.235 (0.028)	0.16–0.30

Key: BPF, Brain Parenchymal Fraction; BPV, Brain Parenchymal Volume; GM, Grey Matter; GMF, Grey Matter Fraction; GMV, Grey Matter Volume; ICV, Intracranial Volume; IQ, Intelligence Quotient; ISCED, International Standard Classification of Education; mm, millimeters; MMSE, Mini-Mental State Examination; SD, standard deviation; sec, seconds; TMT, Trail Making Test.
[a] Excluding primary motor cortex.
[b] Excluding sensory cortex.

et al., 2009). By calculating a difference score (TMT_{Diff} = TMT B – TMT A) the variance attributable to the graphomotor and visual scanning components of the TMT A are minimized (Sánchez-Cubillo et al., 2009; Misdraji and Gass, 2010). While comparing the TMT_{Diff} score to other neuropsychological measures, correlations to memory functioning were found (Corrigan and Hinkeldey, 1987; Sánchez-Cubillo et al., 2009). However, statistically significant effects are inconsistent and more recent investigations showed that the TMT B score might be more strongly associated with working memory than the TMT_{DIFF} score (Sánchez-Cubillo et al., 2009; Fellows et al., 2017). During part A, subjects are required to connect numbers on a sheet of paper in the correct order as quickly as possible. During part B subjects have to draw lines on a sheet of paper sequentially connecting 25 encircled numbers and alternating letters (1, A, 2, B, 3, C, etc.). In the present study, the required time to finish the TMT B is used as the primary dependent variable. Due to the dependence on intelligence, visuomotor coordination and age, literature regarding standard cut-off values for the TMT is sparse (Spreen and Strauss, 1998; Tombaugh, 2004). For reference norm values across age groups, see Tombaugh (2004). For the assessment of the Intelligence Quotient (IQ) score, the multiple choice vocabulary test ("Mehrfachwahl-Wortschatz-Intelligenztest" (MWT-A)) was applied to assess crystallized cognitive ability (Lehrl, 2005). The derived IQ score correlates fairly well with global IQ in healthy adults (Lehrl et al., 1995).

2.2.2. Education

According to the International Standard Classification of Educational Degrees (ISCED-1997) (approved by the United Nations Educational Scientific and Cultural Organization (UNESCO) General Conference at its 29th session in November 1997) and following previous procedures (Kave et al., 2012), the educational level of the subjects was classified into one of seven categories: (0) preprimary education, (1) primary education, (2) lower secondary education, (3) upper secondary education, (4) post-secondary education, (5) first tertiary education and (6) second stage tertiary education. The ISCED 1997 levels of 2 and 3 are sub-classified into a,b,c and levels 4 and 5 in a,b depending on the educational level attained. The ISCED score was initially developed by the UNESO in the early 1970s as a framework to collect, illustrate and compare educational statistics on a national as well as international level.

2.2.3. Structural neuroimaging

MRI scans were obtained on a 3.0 T MRI scanner (Siemens Magnetom Trio) using a 32-channel head coil. Structural imaging yields whole head high-resolution anatomical magnetic resonance images using a 3D T1-weighted magnetization-prepared rapid gradient-echo sequence (MP-RAGE) for studying cortical volume. An axial-oblique 3D Fast Spoiled Gradient Recalled Echo (FSPGR) sequence for the T1-weighted sequence was applied (TR/TE = 2500/4.77 ms, $\alpha = 7°$). A field of view of 256 × 256 mm, with 1 × 1 mm in-plane resolution and 1 mm slice thickness was applied. After acquisition, all MRI images were checked on pathological intracranial processes by a board-certified neuroradiologist.

2.2.3.1. FreeSurfer. The FreeSurfer software package was used in order to allow a direct comparison with earlier studies. Furthermore in order to process T1 MP-RAGE structural MR images, the software FreeSurfer (version 5.30) was used due to its fully automated pipeline and its free availability (http://surfer.nmr.mgh.harvard.edu), as well as a good test-retest reliability (Han et al., 2006; Jovicich et al., 2006). The steps executed were motion correction, the removal of non-brain tissue and automated Talairach transformation (Segonne et al., 2007). The pipeline of FreeSurfer conducts segmentation of the subcortical white matter and deep grey matter into structural volumes (Fischl et al., 2002), intensity normalization (Sled et al., 1998), tessellation of the grey matter into structural volumes (Fischl et al., 2002, 2004), automated topology correction (Fischl et al., 2002) and surface deformation (Dale et al., 1999; Fischl and Dale, 2000). All surfaces of each individual image data were visually inspected post-processing for the accuracy of spatial registration and grey/white matter segmentation (e.g. removal of skull and dura mater and accurate delineation of grey/white matter and pial surfaces). Since all subjects were manually checked by one researcher (M.L.), potentially differing inter-observer interpretations of the accuracy of processed images were avoided. FreeSurfer provides a 3-dimensional segmentation method in order to allocate each voxel to a neuroanatomical label. The global GM volume was calculated by summing up specific GM volumes which were segmented into 68 parcellations using the Desikan-Killiany atlas (Desikan et al., 2006). The individual parcellations were summed up to estimate the frontal, temporal, occipital and parietal lobe GM volumes (Fischl et al., 2004; Desikan et al., 2006). Since the primary motor and the sensory cortex are mainly involved in controlling motor action, respectively receiving input from peripheral mechanoreceptors (Lotze et al., 1999) by excluding the associated cortical volumes from global GM as well as specific lobar volumes, we sought to eradicate the bias of reduced dexterity and somatosensory inaccuracy with respect to the conducted tests. The same approach of excluding the primary motor and the sensory cortex from the calculations of the volumes of the frontal, respectively the parietal lobe, was chosen by Bettcher et al. (2016).

2.2.3.2. Brain parenchymal fraction. Correction for global cerebral atrophy was executed by first calculating the estimated total intracranial volume (eTIV, aka ICV) as well as the total brain parenchymal volume (global GM volume plus total WM volume

excluding ventricles). The software FreeSurfer calculates the total intracranial volume by exploiting the relationship between the ICV and the linear transform to MNI305 space and using an atlas-based spatial normalization procedure (Buckner et al., 2004). The cerebral atrophy index, i.e. the brain parenchymal fraction (BPF), was subsequently derived by dividing the total brain parenchymal volume (BPV) by the total intracranial volume (ICV) (Rudick et al., 1999; Callahan et al., 2015).

2.3. Statistical analysis

For statistical analyses, SPSS (version 25) was used. In total, three sets of analyses were executed. 1) Five separate linear multiple regression analyses for each of the four brain lobes (GM volume) and the global GM volume were executed, each time including age, the BPF and sex as additional independent variables and the TMT B score as the dependent variable (analogous calculation with the dependent variable TMT_{Diff} score). 2) In order to adjust for global GM volume, the GM volume of each of the four different lobes was divided by the global GM volume and the regression analyses with TMT B scores were repeated in the same way. Additionally, multiple regression analyses for the IQ score and the educational level as dependent variables and global GM volume, age, BPF and sex as the independent variables were conducted. Following a recent suggestion by Van Loenhoud et al. (2017), we furthermore repeated our calculations replacing the atrophy index BPF by GMF (Grey Matter Fraction) (GM/ICV). 3) Via linear regression analyses, we tested sex-specific effects on the correlation of age with the TMT B performance for small and large global GM volumes. The critical value for significance was set to $p < 0.05$.

3. Results

The 206 non-demented elderly Caucasian surgical patients investigated had a mean MMSE score of 28.50 points (range 24–30, SD 1.41) and a mean educational attainment of 13 years of education (range 6–24, SD 4.12). The effects of the different GM volumes of the four lobes and the global GM volume on the TMT B score are shown in Table 2.

All volumes of the different lobes and the global GM volume were negatively associated with the TMT B scores (see also Fig. 1).

The model shows that every increase of one standard deviation (SD) of each individual GM volume, as well as the global GM volume, significantly lowers the TMT B score. In other words, faster TMT B performance is associated with larger individual and larger global GM volumes. In detail, an increase of one SD of the frontal GM volume decreases the TMT B score by 0.229 SDs ($p = 0.006$), the increase of one SD of the parietal GM volume decreases the TMT B score by 0.263 SDs ($p = 0.002$), the increase of one SD of the temporal GM volume decreases the TMT B score by 0.263 SDs ($p = 0.002$) and an increase of one SD of the occipital GM volume decreases the TMT B score by 0.201 SDs ($p = 0.012$); also, an increase of one SD of the global GM volume decreases the TMT B score by 0.275 SDs ($p = 0.001$). The standardized coefficient (-ß-) of the global GM volume of -0.275 ($p = 0.001$) is most negatively related to the TMT B score in our model and, thus, is the most accurate predictor of all region-of-interests (GM volumes). Age also has significant explanatory power to predict TMT B performance; higher age is associated with a higher TMT B score (ß = 0.187–0.209, $p = 0.007$–0.015). No sex-specific tendencies were observed (ß = -0.085 to -0.139, $p = 0.096$–0.326). Similar results were found when including the primary motor and the sensory cortex in the calculations of the frontal, respectively the parietal lobe as well as the global GM volume (see Table 1 in the Supplement). Furthermore, we found that the TMT B - TMT A score was also accurately predicted by the global GM volume (ß = -0.269, $p = 0.002$), although the association of the temporal GM volume with the TMT_{DIFF} score was slightly more pronounced (ß = -0.284, $p = 0.001$) (see Table 2 in the Supplement).

Table 2
Associations of individual lobar and global GM volume, age, the BPF and sex with the score of the TMT B.

Independent Variable	Dependent variable	Estimate	Standard error	p-value
Frontal GM volume (mm^3)[a]	**TMT B**	-0.229	< 0.001	0.006
Age (years)		0.191	0.804	0.014
BPF (BPV/ICV)		-0.151	45.641	0.056
Sex (female)		-0.120	8.669	0.154
Parietal GM volume (mm^3)[b]	**TMT B**	-0.263	< 0.001	0.002
Age (years)		0.199	0.792	0.009
BPF (BPV/ICV)		-0.158	45.340	0.045
Sex (female)		-0.098	8.705	0.245
Temporal GM volume (mm^3)	**TMT B**	-0.263	0.001	0.002
Age (years)		0.190	0.797	0.013
BPF (BPV/ICV)		-0.146	45.368	0.065
Sex (female)		-0.095	8.805	0.270
Occipital GM volume (mm^3)	**TMT B**	-0.201	0.001	0.012
Age (years)		0.209	0.799	0.007
BPF (BPV/ICV)		-0.124	46.220	0.121
Sex (female)		-0.139	8.551	0.096
Global GM volume (mm^3)[a,b]	**TMT B**	-0.275	< 0.001	0.001
Age (years)		0.187	0.796	0.015
BPF (BPV/ICV)		-0.146	45.261	0.063
Sex (female)		-0.085	8.861	0.326

The model consists of the different grey matter volumes, age, the BPF and sex entered as independent variables and the TMT B score (sec) as a dependent variable. Estimates are standardized regression coefficients of this model. The reference of the standardized regression coefficient of sex is female.
Key: BPF, Brain Parenchymal Fraction; BPV, Brain Parenchymal Volume; GM, Grey Matter; ICV, Intracranial Volume; mm, millimeters; sec, seconds; TMT, Trail Making Test
[a] excluding primary motor cortex
[b] excluding sensory cortex

The BPF itself, except for the regression analysis including the parietal lobe ($p = 0.045$), did not contribute significantly to the prediction of EF measured by the TMT B ($p = 0.056$–0.121); however, non-significant trends were observed (see Tables 2 and 3). Of note, Fig. 2 shows only slight variance in brain atrophy across the MMSE scores (24–30 points).

As shown in Table 3, when running the multiple regression including the ratio consisting of the lobar GM volumes divided by the global GM volume, no associations of different lobar GM ratios ("adjusted lobar GM volumes") with the TMT B score were found. In this model, consisting of the "adjusted lobar GM volumes", age, BPF and sex as independent variables and the TMT B score as the dependent variable, the lobar GM ratios did not significantly predict performance at the TMT B (beta = -0.019 to 0.062, $p = 0.388$–0.789). In this model, consisting of adjusted GM volumes (see Table 3), male sex was statistically significantly negatively associated with the prediction of performance in the TMT B (ß-values: -0.222 to -0.230, $p = 0.003$–0.004). Higher age was observed to significantly predict the TMT B score positively (ß-values: 0.231–0.237, all $p = 0.002$–0.003).

Replacing the atrophy index BPF by GMF did not markedly change the obtained results (see Table 3 in the Supplement).

As part of a moderation analysis, the moderator effect of small and large global GM volume on the relation between age and the TMT B score was investigated (Fig. 3). We observed that the strength relationship of age and TMT B changes as a function of global GM volume. In the subgroup of larger global GM volume of male participants, the correlation between age and TMT B was weaker ($R^2 = 0.106$) compared to the smaller global GM volume ($R^2 = 0.154$). For female

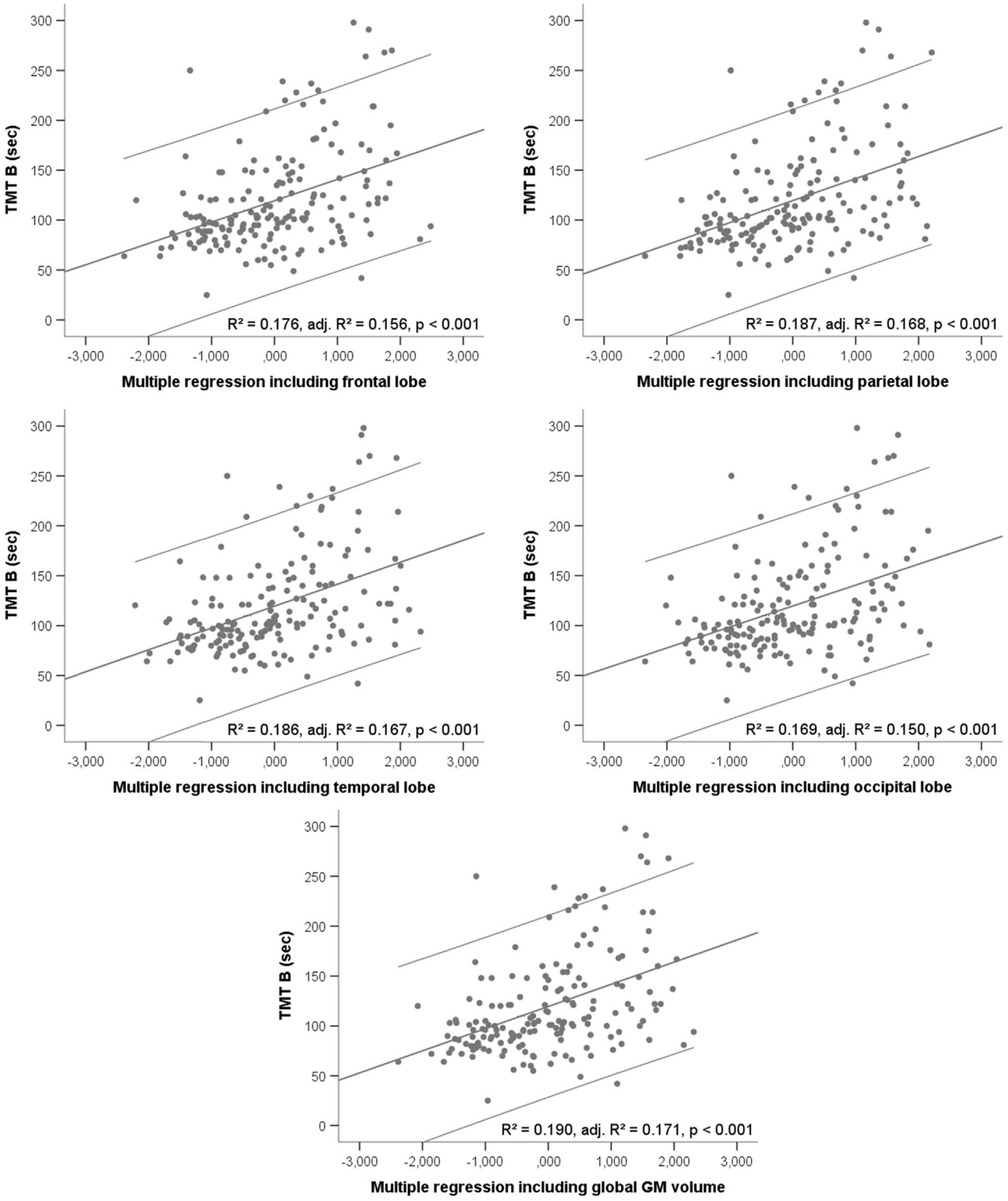

Fig. 1. Each scatterplot consists of the graph of the standardized predicted values derived from the regression equation composed of the individual GM volumes (excluding primary motor and sensory cortex) as well as the covariates age, BPF and sex (95% CI). Key: BPF, Brain Parenchymal Fraction; CI, Confidence Interval; GM, Grey Matter; sec, seconds; TMT B, Trail Making Test.

participants, however, these observations were not consistent and could not be demonstrated (see Fig. 3). For female participants, we found that the correlation of age and TMT B was weaker in the subgroup of smaller GM volume (R^2 = 0.001) compared to the subgroup of larger global GM volume (R^2 = 0.126).

Moderate negative correlations (all p values < 0.01, two-tailed) were observed for the TMT B with the IQ score (r = −0.397), and for the TMT B score with completed years of education (r = −0.354) whereas the IQ score was moderately positively correlated with completed years of education (r = 0.388). Additionally, we regressed the IQ score as well the educational attainment, reflected by the ISCED (International Standard Classification of Education) 97 Level, on global

Table 3
Associations of specific adjusted lobar volumes, age, the BPF and sex with executive functioning measured by the TMT B.

Independent Variable	Dependent variable	Estimate	Standard error	p-value
Adjusted frontal GM volume (frontal GM[a]/global GM[a,b])	**TMT B**	0.062	342.909	0.388
Age (years)		0.237	0.809	0.002
BPF (BPV/ICV)		-0.146	46.664	0.071
Sex (female)		-0.222	7.892	0.004
Adjusted parietal GM volume (parietal GM[b]/global GM[a,b])	**TMT B**	-0.029	399.303	0.689
Age (years)		0.234	0.811	0.003
BPF (BPV/ICV)		-0.155	47.019	0.059
Sex (female)		-0.230	7.845	0.003
Adjusted temporal GM volume (temporal GM/global GM[a,b])	**TMT B**	-0.026	423.045	0.717
Age (years)		0.231	0.808	0.003
BPF (BPV/ICV)		-0.150	46.675	0.064
Sex (female)		-0.227	7.885	0.003
Adjusted occipital GM volume (occipital GM/global GM[a,b])	**TMT B**	-0.019	410.687	0.789
Age (years)		0.232	0.808	0.003
BPF (BPV/ICV)		-0.147	47.449	0.075
Sex (female)		-0.229	7.857	0.003

The model consists of the adjusted specific grey matter volumes, age, the BPF and sex entered as independent variables and the TMT B score (sec) as dependent variable. Estimates are standardized regression coefficients of this model. The reference of the standardized regression coefficient of sex is female. Key: BPF, Brain Parenchymal Fraction; BPV, Brain Parenchymal Volume; GM, Grey Matter; ICV, Intracranial Volume; mm, millimeters; sec, seconds; TMT, Trail Making Test

[a] excluding primary motor cortex
[b] excluding sensory cortex

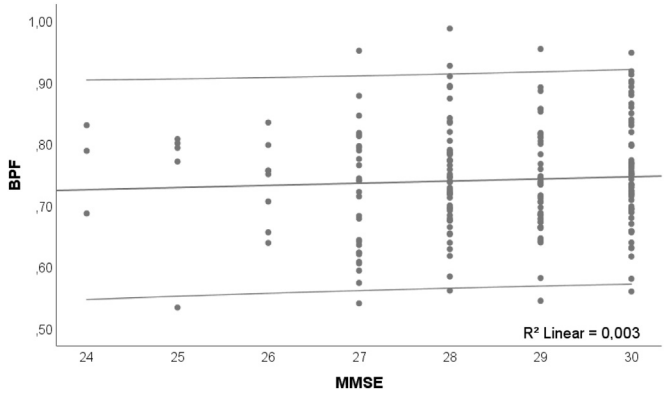

Fig. 2. The scatter plot consists of the brain parenchymal fraction (BPF) shown on the y-axis which is derived by dividing the total brain parenchymal volume (BPV) by the total intracranial volume (ICV). The MMSE score is shown on the x-axis (95% CI). **Key: CI, Confidence Interval; MMSE, Mini-Mental-State-Examination.**

GM volume as well as the covariates of age, the BPF and sex. Thereby, we observed that global GM volume could neither significantly predict the IQ score (beta = 0.179; p = 0.088) nor the ISCED 97 Level (beta = 0.093; p = 0.245).

4. Discussion

In this study, the associations of different lobar GM volumes and global GM volume with EF as well as the approach of using an atrophy-corrected global GM volume as a BR prediction marker were examined. We observed that global GM volume was most strongly associated with EF, i.e. patients with a larger GM volume demonstrated superior TMT B performance. The second strongest associations were observed for the parietal and temporal lobe followed by the frontal lobe, whereas the occipital lobe was the least correlated with EF. Since we corrected GM volume for brain atrophy as part of the multiple regression analyses, our measures of "corrected GM volume" can be considered an "archeological" estimate of the maximal brain size in youth (Royle et al., 2013). The neuropsychological and neuroimaging tests were conducted on the same day; thus, confounding factors such as day-to-day physiological variations of brain volumes (Duning et al., 2005) were minimized. We corrected the global GM volume for cerebral atrophy; accordingly, despite adopting a cross-sectional study design, the latter is applicable as a predictor of EF even in advanced aged subjects. Global GM volume also was a relevant predictor of TMT_{Diff} score, but we observed a stronger relationship for the temporal GM volume. Associations of the TMT_{DIFF} score with memory functioning are described in literature (Corrigan and Hinkeldey, 1987; Sánchez-Cubillo et al., 2009); thus, our observations are in line with several prior studies which showed that the temporal GM volume was most accurately related to working memory (Bailey et al., 2013; Bettcher et al., 2016). However, there is also literature indicating that the TMT B – TMT A score might rather be a relatively pure indicator of EF (Sánchez-Cubillo et al., 2009); further studies are needed to evaluate the significance and distinct interpretations for the TMT_{DIFF} score. Notably, our observations point in the same direction as previous studies showing a morphological advantage, e.g. larger ICV protects against dementia development (Guo et al., 2013; Negash et al., 2013; Groot et al., 2017). In any case, since it is suggested that CR and BR have independent and synergistic contributions to compensate for brain pathology (Stern, 2012) which may reciprocally influence each other (Persson et al., 2016) global GM volume at least appears to be a reasonable quantitative reserve marker in the elderly. In this way, both global GM volume and the associated EF can be used as reserve markers for the prediction of transition to MCI (Chen et al., 2017), transition of MCI to Alzheimer's disease (Albert et al., 2001) or to address the question of whether the clinical manifestation of existing Alzheimer pathology is concealed (Darby et al., 2017), which in turn may help to disentangle the heterogeneity of brain aging, including age-related changes to brain function (Burzynska et al., 2012).

In order to correct for possible age-related brain atrophy, we used the BPF as an independent variable in our regression analyses. Synek and Reuben (1976) first proposed the correlation of the ventricular to brain area (VBR) as an index based on a structure's area, whereas the introduction of the ratio BPV to ICV (BPF) is first referred to Rudick et al. (1999). By applying FreeSurfer, the reliability of measures is improved and the particular structure as well as the cerebral size is less subject to error compared to measurement results from earlier decades. Due to the improved reliability and reproducibility, we expected to introduce a lower error, consequently achieving a higher reliability of the BPF. In our study, the BPF did not, except for the parietal lobe, show a statistically significant effect on EF – although this was a non-significant trend. This is likely due to the sample composition in our study with clearly non-demented patients and only a slight variance of the MMSE score (see Fig. 2), as reflected by a median score of > 28.

As part of the moderation analyses, we showed a sex-specific buffer effect of global GM volume on the TMT B performance in the elderly (see Fig. 3). For male participants a positive influence of larger global GM volume, by means of a "buffering" effect, on the correlation between age and TMT B was observed. For female participants, however, contrasting observations were made. The subgroups were rather small (female = 73, male = 101), with a fairly large distribution of data values; therefore, interpretation of the prior moderation analyses are limited. However, it is conceivable that in a larger cohort, there might be a stronger, sex-independent effect of brain size, i.e. an age dependency of smaller GM volume being associated with worse EF. In

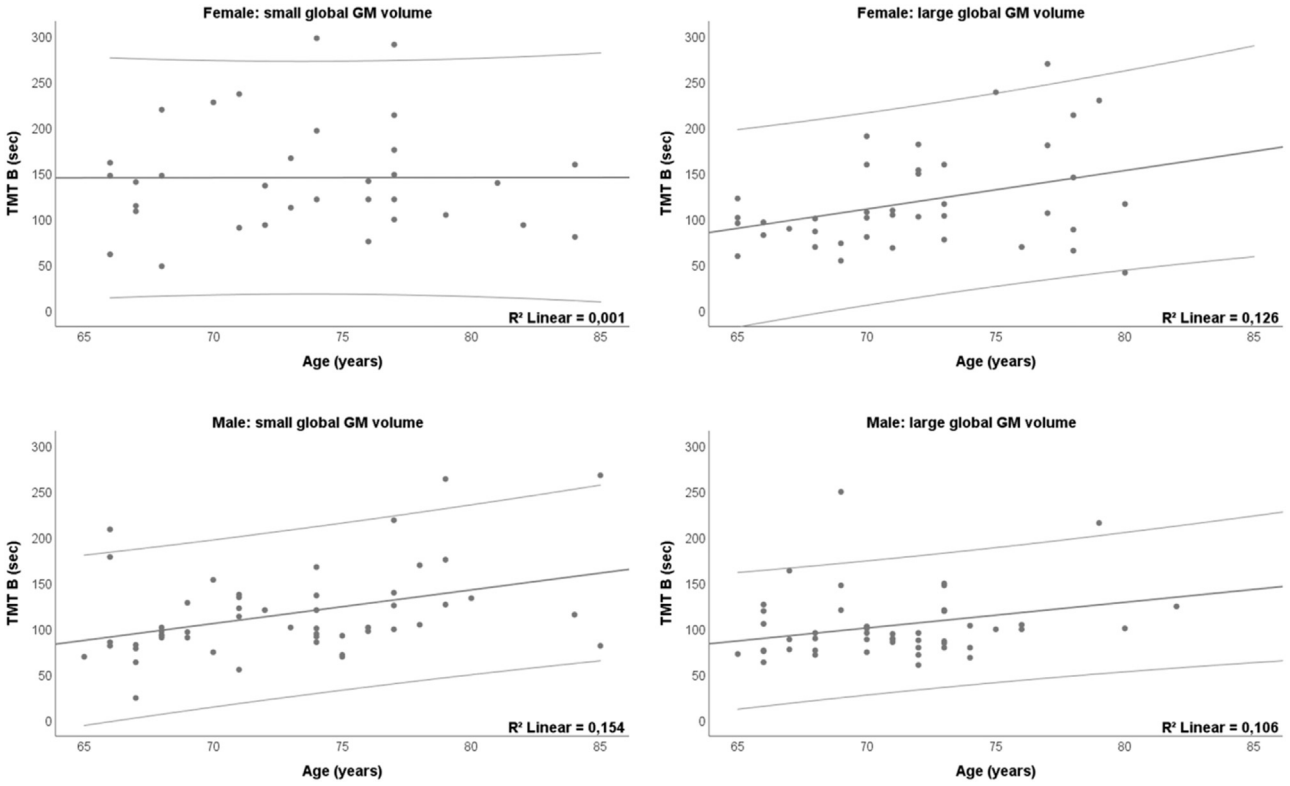

Fig. 3. To assess the effects of GM volume on the TMT B score, we assigned the subjects into four groups. This was done by a median split of the global GM volume (primary motor and sensory cortex are excluded) for the female and the male subjects separately. On the top of this figure, displayed for female participants (N = 73), the TMT B is regressed onto age and shown as dichotomized into small global GM volume (N = 33) on the left and into large global GM volume on the right side (N = 40). The lower part of this figure shows the regression of the TMT B onto age for male participants (N = 101). Displayed in the lower part, for male participants, is the global GM volume split into small (N = 51) on the left and large (N = 50) on the right side (95% CI). **Key: CI, Confidence Interval; GM, Grey Matter; sec, seconds; TMT B, Trail Making Test B.**

other words, the negative influence of age on EF might be moderated by global GM volume.

The observed associations of different brain volumes with EF are in line with reports from earlier studies. Elderkin-Thompson et al. (2008) manually masked the prefrontal cortex of MRIs of 23 healthy elderly individuals which were subsequently segmented automatically; different regions of the prefrontal GM volume were computed as ratios of intracranial volume. They found that specific prefrontal sub-regions are correlated with EF (Elderkin-Thompson et al., 2008). Using an explorative voxel-based morphometry approach, Zhang et al. (2011) reported associations of EF with four different brain lobes (frontal, temporal, parietal, and occipital) in 326 subjects. By applying deformation-based morphometry (DBM), Cardenas et al. (2011) showed that impaired EF is associated with smaller frontal lobe volumes (N = 71). The limitations of these three studies are mainly due to the applied image processing approaches that are accompanied by a compelling inter-observer variance. By applying the FreeSurfer software package, Dong et al. (2015) overcame these limitations and observed associations between GM volumes and cognitive performance in a large sample (N = 813) from the Northern Manhattan Study (NOMAS). Superior EF performance was primarily associated with greater frontal lobe volume (Dong et al., 2015). However, patients of different ethnicities with neurocognitive disorders such as dementia were not excluded, which impedes a direct comparison with our findings. In contrast, in the study of Bettcher et al. (2016), a sub-cohort of the NIH Aging and Cognition study (neurologically healthy older adults of undisclosed ethnicity), participants with neurocognitive disorders were not included and FreeSurfer was used for processing of the MR images with little inter-observer variance. In line with our findings, they found associations between EF performance and global as well as lobar structures, including frontal GM volumes. Accordingly, the study of Bettcher et al. (2016) and our study suggest that an isolated view on particular cortical volumes may not be sufficient to fully grasp association with EF in elderly non-demented subjects – in fact, our study results suggest that global GM volume is the best predictor. Most importantly, none of these studies specifically addressed BR; rather, the focus was on brain atrophy.

It is important to acknowledge that brain atrophy trajectories might be non-linear across different brain tissues, e.g. there is evidence that WM volume decline is significantly greater than GM volume decline in old age, particularly in the 9th decade (Royle et al., 2013). Since this is not entirely elucidated, in the future long-term data on changes in the grey/white matter ratio are needed to account for any divergence of trajectories; subsequently, the influence on the strategy to apply GM volume as a BR marker using BPF for brain atrophy correction will need to be carefully evaluated. From longitudinal measures acquired throughout the life span, it is known that regional brain volume does change in healthy adults (Raz et al., 2005). Neuroimaging in vivo data could demonstrate that there are global and spatially-localized relationships of normal ageing and brain morphology (Sowell et al., 2003; Fjell et al., 2013). Ubiquitous longitudinal cortical grey matter volume losses were observed in multiple studies (Scahill et al., 2003; Sowell et al., 2003), in particular in the prefrontal (Pfefferbaum et al., 1998; Resnick et al., 2003; Sowell et al., 2003) and parietal regions (Sowell et al., 2003). Fjell et al. (2013) found an accelerated decline for total brain volume at the end of the 20 s as well as from the age of 60 onwards. Pfefferbaum et al. (2013) described a cubic function for frontal lobe volume changes longitudinally, likewise indicating two points of accelerated decline - the first occurring in the late 20 s and the second after 60 years of age. One explanation might be that regions which

mature late contain more thin myelinated fibers and are consequently more vulnerable to age-related decline in terms of primary degenerative events in the early period of the 20s (Raz et al., 2000; Bartzokis, 2004). Furthermore, late critical ages accompanied by the demyelination of larger connections occurring in the late 60 s (Fjell et al., 2013). Hippocampal shrinkage was found to be substantial and accelerate with age (Scahill et al., 2003; Raz et al., 2005) following a slight increase in volume until the age of 50 (Pfefferbaum et al., 2013). Furthermore, the choice of post-processing method for brain volume quantification of longitudinal as well as cross-sectional data also impairs the opportunity for the direct comparability of data in general and in particular of the BPF (Vågberg et al., 2017), as well the ICV estimation (Nordenskjold et al., 2013). Also, the dehydration-rehydration status of each patient has a physiological effect on brain volume (Duning et al., 2005); thereby complicating the quantification of longitudinal change (Scahill et al., 2003). In the present study, the BPF index was applied to calculate the potential BR marker of atrophy-corrected grey matter volume. Since the literature indicates that the BPF varies throughout the individual's lifetime (Vågberg et al., 2017), further studies with multiple measurement time points investigating individual healthy subjects longitudinally, aiming to establish normative age-related values, are needed. As a further limitation to interpretation, it is prudent to highlight that TMT was the sole indicator of executive functions applied. Next to extensive neuroimaging assessments, additionally to the measured EF we also conducted many neuropsychological tests of other cognitive functions; thus, adding further EF domains could have led to higher dropout rates, and the tests might be ecologically less valid in an unfamiliar environment such as the laboratory (Luis et al., 2003). However, covering more extensive executive processing data is important to evaluate various EF domains and might therefore reduce bias. Future studies may want to include a more detailed characterization of executive functions (e.g. the Miyake's conceptual framework for executive functions (Miyake et al., 2000)) to validate the role of atrophy-corrected grey matter volume as potential reserve marker for EF in late life. For all of the conducted multiple regression analyses, rather small adjusted R-squared values were observed, ranging from 0.157 (occipital lobe) to 0.181 (parietal lobe and global GM volume). Thus, an essential part of residual variation between individuals in EF cannot be referred to cortical GM volume (corrected for key predictors) and the latter might have been operationalized in a rather simplified manner. This is in line with prior large-scale investigations observing that only 33% of the variance in cognition is explained by brain volumetrics (adjusted for ethnicity, age, education, and sex) (Gupta et al., 2015). Further investigations are needed to address the large gap in the knowledge regarding variables to explain the variation in cognition. To fulfill the need for an explanation of variations in cognitive performance, adding further neuroimaging and molecular variables (e.g. WM microstructure, neurotransmitter function or network connectivity) might also contribute to a more complete picture (Hedden and Growdon, 2015).

Nonetheless, in summary, our study suggests for the first time that GM brain volume, corrected for brain atrophy, predicts EF in the elderly. Thus, atrophy-corrected global GM volume appears to be a promising quantitative brain reserve marker. In addition, several prior studies reported an association of global and prefrontal cortical volume with executive function in the elderly population (Elderkin-Thompson et al., 2008; Cardenas et al., 2011; Zhang et al., 2011; Dong et al., 2015). Our findings strengthen the view that global GM volume is stronger associated with EF than lobar GM volumes.

Acknowledgements

The research leading to these results has received funding from European Union funded Seventh Framework Research Program [FP7/2007–2013], under grant agreement No. HEALTH-F2-2014-60246, BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly), www.biocog.eu. Additional (internal) funding was obtained from the Berlin Institute of Health (BIH).

Disclosure statement

This publication is part of the doctorate of Markus Laubach and Florian Lammers. Prof Winterer is the coordinator of the BioCog Consortium and chief executive of the company PharmaImage Biomarker Solutions GmbH. The company is one of the partners of the BioCog Consortium. The remaining authors declare no conflict of interest and all authors have no conflicting financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.08.008.

References

Albert, M.S., Moss, M.B., Tanzi, R., Jones, K., 2001. Preclinical prediction of AD using neuropsychological tests. J. Int. Neuropsychol. Soc. 7, 631–639.
Arbuthnott, K., Frank, J., 2000. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. J. Clin. Exp. Neuropsychol. 22, 518–528.
Bailey, H.R., Zacks, J.M., Hambrick, D.Z., Zacks, R.T., Head, D., Kurby, C.A., Sargent, J.Q., 2013. Medial temporal lobe volume predicts elders' everyday memory. Psychol. Sci. 24, 1113–1122.
Bartrés-Faz, D., Arenaza-Urquijo, E.M., 2011. Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. Brain Topogr. 24, 340–357.
Bartzokis, G., 2004. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol. Aging 25 (5–18), 49–62 (author reply).
Bettcher, B.M., Mungas, D., Patel, N., Elofson, J., Dutt, S., Wynn, M., Watson, C.L., Stephens, M., Walsh, C.M., Kramer, J.H., 2016. Neuroanatomical substrates of executive functions: beyond prefrontal structures. Neuropsychologia.
Buckner, R.L., Head, D., Parker, J., Fotenos, A.F., Marcus, D., Morris, J.C., Snyder, A.Z., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage 23, 724–738.
Burzynska, A.Z., Nagel, I.E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S.-C., Lindenberger, U., Heekeren, H.R., 2012. Cortical thickness is linked to executive functioning in adulthood and aging. Hum. Brain Mapp. 33, 1607–1620.
Callahan, B.L., Ramirez, J., Berezuk, C., Duchesne, S., Black, S.E., 2015. Predicting Alzheimer's disease development: a comparison of cognitive criteria and associated neuroimaging biomarkers. Alzheimer's. Res. Ther. 7, 68.
Cardenas, V.A., Chao, L.L., Studholme, C., Yaffe, K., Miller, B.L., Madison, C., Buckley, S.T., Mungas, D., Schuff, N., Weiner, M.W., 2011. Brain atrophy associated with baseline and longitudinal measures of cognition. Neurobiol. Aging 32, 572–580.
Chen, Y., Denny, K.G., Harvey, D., Farias, S.T., Mungas, D., Decarli, C., Beckett, L., 2017. Progression from normal cognition to mild cognitive impairment in a diverse clinic-based and community-based elderly cohort. Alzheimer'S. Dement. J. Alzheimer's. Assoc. 13, 399–405.
Corrigan, J.D., Hinkeldey, N.S., 1987. Relationships between parts A and B of the trail making test. J. Clin. Psychol. 43, 402–409.
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9, 179–194.
Darby, R.R., Brickhouse, M., Wolk, D.A., Dickerson, B.C., 2017. Effects of cognitive reserve depend on executive and semantic demands of the task. J. Neurol., Neurosurg. Psychiatry 88, 794–802.
Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968–980.
Dong, C., Nabizadeh, N., Caunca, M., Cheung, Y.K., Rundek, T., Elkind, M.S.V., Decarli, C., Sacco, R.L., Stern, Y., Wright, C.B., 2015. Cognitive correlates of white matter lesion load and brain atrophy: the northern Manhattan study. Neurology 85, 441–449.
Duning, T., Kloska, S., Steinsträter, O., Kugel, H., Heindel, W., Knecht, S., 2005. Dehydration confounds the assessment of brain atrophy. Neurology 64, 548–550.
Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., Kumar, A., 2008. Executive function and MRI prefrontal volumes among healthy older adults. Neuropsychology 22, 626–637.
Feinkohl, I., Winterer, G., Spies, C.D., Pischon, T., 2017. Cognitive Reserve and the Risk of Postoperative Cognitive Dysfunction. Dtsch. Arzteblatt Int. 114, 110–117.
Fellows, R.P., Dahmen, J., Cook, D., Schmitter-Edgecombe, M., 2017. Multicomponent analysis of a digital trail making test. Clin. Neuropsychol. 31, 154–167.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. In: Proceedings of the National Academy of Sciences of the United States of America, 97, 11050–11055.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.
Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatically parcellating the human cerebral cortex. Cereb. Cortex 14, 11–22.
Fjell, A.M., Westlye, L.T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Holland, D., Dale, A.M., Walhovd, K.B., 2013. Critical ages in the life course of the adult brain: nonlinear subcortical aging. Neurobiol. Aging 34, 2239–2247.
Ge, Y., Grossman, R.I., Babb, J.S., Rabin, M.L., Mannon, L.J., Kolson, D.L., 2002. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am. J. Neuroradiol. 23, 1327–1333.
Groot, C., Van Loenhoud, A.C., Barkhof, F., Van Berckel, B.N.M., Koene, T., Teunissen, C.C., Scheltens, P., Van Der Flier, W.M., Ossenkoppele, R., 2017. Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. Neurology.
Guo, L.-H., Alexopoulos, P., Wagenpfeil, S., Kurz, A., Perneczky, R., 2013. Brain size and the compensation of Alzheimer's disease symptoms: a longitudinal cohort study. Alzheimer's. Dement.: J. Alzheimer's Assoc. 9, 580–586.
Gupta, M., King, K.S., Srinivasa, R., Weiner, M.F., Hulsey, K., Ayers, C.R., Whittemore, A., Mccoll, R.W., Rossetti, H.C., Peshock, R.M., 2015. Association of 3.0-T brain magnetic resonance imaging biomarkers with cognitive function in the Dallas heart study. JAMA Neurol. 72, 170–175.
Han, X., Jovicich, J., Salat, D., Van Der Kouwe, A., Quinn, B., Czanner, S., Busa, E., Pacheco, J., Albert, M., Killiany, R., Maguire, P., Rosas, D., Makris, N., Dale, A., Dickerson, B., Fischl, B., 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. NeuroImage 32, 180–194.
Hedden, T., Growdon, J.H., 2015. Challenges and opportunities in linking brain-based biomarkers to person-specific variation in cognition: pumping up the volume. JAMA Neurol. 72, 149–151.
Johnson, J.K., Lui, L.-Y., Yaffe, K., 2007. Executive function, more than global cognition, predicts functional decline and mortality in elderly women. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 62, 1134–1141.
Jovicich, J., Czanner, S., Greve, D., Haley, E., Van Der Kouwe, A., Gollub, R., Kennedy, D., Schmitt, F., Brown, G., Macfall, J., Fischl, B., Dale, A., 2006. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. NeuroImage 30, 436–443.
Katzman, R., Terry, R., Deteresa, R., Brown, T., Davies, P., Fuld, P., Renbing, X., Peck, A., 1988. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann. Neurol. 23, 138–144.
Kave, G., Shrira, A., Palgi, Y., Spalter, T., Ben-Ezra, M., Shmotkin, D., 2012. Formal education level versus self-rated literacy as predictors of cognitive aging. J. Gerontol. B Psychol. Sci. Soc. Sci. 67, 697–704.
Lehrl, S., 2005. Manual zum MWT-B: [Mehrfachwahl-Wortschatz-Intelligenztest], Balingen, Spitta-Verl.
Lehrl, S., Triebig, G., Fischer, B., 1995. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol. Scand. 91, 335–345.
Lotze, M., Montoya, P., Erb, M., Hulsmann, E., Flor, H., Klose, U., Birbaumer, N., Grodd, W., 1999. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. J. Cogn. Neurosci. 11, 491–501.
Luis, C.A., Loewenstein, D.A., Acevedo, A., Barker, W.W., Duara, R., 2003. Mild Cognitive Impairment. Dir. Future Res. 61, 438–444.
Misdraji, E.L., Gass, C.S., 2010. The trail making test and its neurobehavioral components. J. Clin. Exp. Neuropsychol. 32, 159–163.
Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn. Psychol. 41, 49–100.
Mori, E., Hirono, N., Yamashita, H., Imamura, T., Ikejiri, Y., Ikeda, M., Kitagaki, H., Shimomura, T., Yoneda, Y., 1997. Premorbid brain size as a determinant of reserve capacity against intellectual decline in Alzheimer's disease. Am. J. Psychiatry 154, 18–24.
Negash, S., Xie, S., Davatzikos, C., Clark, C.M., Trojanowski, J.Q., Shaw, L.M., Wolk, D.A., Arnold, S.E., 2013. Cognitive and functional resilience despite molecular evidence of Alzheimer's disease pathology. Alzheimer's. Dement. J. Alzheimer's Assoc. 9. pp. e89–e95.
Nordenskjold, R., Malmberg, F., Larsson, E.M., Simmons, A., Brooks, S.J., Lind, L., Ahlstrom, H., Johansson, L., Kullberg, J., 2013. Intracranial volume estimated with commonly used methods could introduce bias in studies including brain volume measurements. Neuroimage 83, 355–360.
Persson, N., Ghisletta, P., Dahle, C.L., Bender, A.R., Yang, Y., Yuan, P., Daugherty, A.M., Raz, N., 2016. Regional brain shrinkage and change in cognitive performance over two years: the bidirectional influences of the brain and cognitive reserve factors. NeuroImage 126, 15–26.
Pfefferbaum, A., Rohlfing, T., Rosenbloom, M.J., Chu, W., Colrain, I.M., Sullivan, E.V., 2013. Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. Neuroimage 65, 176–193.
Pfefferbaum, A., Sullivan, E.V., Rosenbloom, M.J., Mathalon, D.H., Lim, K.O., 1998. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Arch. Gen. Psychiatry 55, 905–912.
Phillips, L.H., Henry, J.D.A., Vicki, Jacobs, R., Anderson, P.J., 2008. Executive Functions and the Frontal Lobes: A Lifespan Perspective. Neuropsychology, Neurology, and Cognition. US: Taylor & Francis, Philadelphia, PA, pp. 57–79 (xxxiii, 541 pp.).
Pietschnig, J., Penke, L., Wicherts, J.M., Zeiler, M., Voracek, M., 2015. Meta-analysis of associations between human brain volume and intelligence differences: how strong are they and what do they mean? Neurosci. Biobehav. Rev. 57, 411–432.
Puente, A.N., Lindbergh, C.A., Miller, L.S., 2015. The relationship between cognitive reserve and functional ability is mediated by executive functioning in older adults. Clin. Neuropsychol. 29, 67–81.
Rabin, L.A., Barr, W.B., Burton, L.A., 2005. Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members. Arch. Clin. Neuropsychol. 20, 33–65.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.
Raz, N., Williamson, A., Gunning-Dixon, F., Head, D., Acker, J.D., 2000. Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. Microsc. Res. Tech. 51, 85–93.
Reitan, R., 2004. The trail making test as an initial screening procedure for neuropsychological impairment in older children. Arch. Clin. Neuropsychol. 19, 281–288.
Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J. Neurosci. 23, 3295–3301.
Royall, D.R., Palmer, R., Chiodo, L.K., Polk, M.J., 2004. Declining executive control in normal aging predicts change in functional status: the freedom house study. J. Am. Geriatr. Soc. 52, 346–352.
Royle, N.A., Booth, T., Valdés Hernández, M.C., Penke, L., Murray, C., Gow, A.J., Maniega, S.M., Starr, J., Bastin, M.E., Deary, I.J., Wardlaw, J.M., 2013. Estimated maximal and current brain volume predict cognitive ability in old age. Neurobiol. Aging 34, 2726–2733.
Rozzini, L., Chilovi, B.V., Conti, M., Bertoletti, E., Delrio, I., Trabucchi, M., Padovani, A., 2007. Conversion of amnestic mild cognitive impairment to dementia of Alzheimer type is independent to memory deterioration. Int. J. Geriatr. Psychiatry 22, 1217–1222.
Rudick, R.A., Fisher, E., Lee, J.C., Simon, J., Jacobs, L., 1999. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple sclerosis collaborative research group. Neurology 53, 1698–1704.
Salthouse, T.A., 2011. What cognitive abilities are involved in trail-making performance? Intelligence 39, 222–232.
Sánchez-Cubillo, I., Periáñez, J.A., Adrover-Roig, D., Rodríguez-Sánchez, J.M., Ríos-Lago, M., Tirapu, J., Barceló, F., 2009. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J. Int. Neuropsychol. Soc. JINS 15, 438–450.
Satz, P., Morgenstern, H., Miller, E.N., Selnes, O.A., Mcarthur, J.C., Cohen, B.A., Wesch, J., Becker, J.T., Jacobson, L., D'elia, L.F., et al., 1993. Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). J. Acquir Immune Defic. Syndr. 6, 503–511.
Scahill, R.I., Frost, C., Jenkins, R., Whitwell, J.L., Rossor, M.N., Fox, N.C., 2003. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. Arch. Neurol. 60, 989–994.
Schmitter-Edgecombe, M., Parsey, C., Cook, D.J., 2011. Cognitive correlates of functional performance in older adults: comparison of self-report, direct observation, and performance-based measures. J. Int. Neuropsychol. Soc. JINS 17, 853–864.
Schofield, P.W., Logroscino, G., Andrews, H.F., Albert, S., Stern, Y., 1997. An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia. Neurology 49, 30–37.
Segonne, F., Pacheco, J., Fischl, B., 2007. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. IEEE Trans. Med. Imaging 26, 518–529.
Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans. Med. Imaging 17, 87–97.
Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., 2003. Mapping cortical change across the human life span. Nat. Neurosci. 6, 309–315.
Spreen, O., Strauss, E., 1998. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford Univ. Press, New York.
Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. JINS 8, 448–460.
Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 11, 1006–1012.
Strauss, E., Sherman, E.M.S., Spreen, O., 2006. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford Univ. Press, Oxford.
Synek, V., Reuben, J.R., 1976. The ventricular-brain ratio using planimetric measurement of EMI scans. Br. J. Radiol. 49, 233–237.
Tombaugh, T.N., 2004. Trail making test A and B: normative data stratified by age and education. Arch. Clin. Neuropsychol. Off. J. Natl. Acad. Neuropsychol. 19, 203–214.
Vågberg, M., Granåsen, G., Svenningsson, A., 2017. Brain parenchymal fraction in healthy adults—a systematic review of the literature. PLoS One 12, e0170018.
Van Loenhoud, A.C., Wink, A.M., Groot, C., Verfaillie, S.C.J., Twisk, J., Barkhof, F., Van Berckel, B., Scheltens, P., Van Der Flier, W.M., Ossenkoppele, R., 2017. A neuroimaging approach to capture cognitive reserve: application to Alzheimer's disease. Hum. Brain Mapp. 38, 4703–4715.
Vibha, D., Tiemeier, H., Mirza, S.S., Adams, H.H.H., Niessen, W.J., Hofman, A., Prasad, K., Van Der Lugt, A., Vernooij, M.W., Ikram, M.A., 2017. Brain volumes and longitudinal cognitive change: a population-based study. Alzheimer Dis. Assoc. Disord.
Winterer, G., Androsova, G., Bender, O., Boraschi, D., Borchers, F., Dschietzig, T.B., Feinkohl, I., Fletcher, P., Gallinat, J., Hadzidiakos, D., Haynes, J.D., Heppner, F.,

Hetzer, S., Hendrikse, J., Ittermann, B., Kant, I.M.J., Kraft, A., Krannich, A., Krause, R., Kuhn, S., Lachmann, G., Van Montfort, S.J.T., Muller, A., Nurnberg, P., Ofosu, K., Pietsch, M., Pischon, T., Preller, J., Renzulli, E., Scheurer, K., Schneider, R., Slooter, A.J.C., Spies, C., Stamatakis, E., Volk, H.D., Weber, S., Wolf, A., Yurek, F., Zacharias, N., 2018. Personalized risk prediction of postoperative cognitive impairment - rationale for the EU-funded BioCog project. Eur. Psychiatry 50, 34–39.

Zhang, H., Sachdev, P.S., Wen, W., Kochan, N.A., Zhu, W., Crawford, J.D., Brodaty, H., Slavin, M.J., Reppermund, S., Kang, K., Trollor, J.N., 2011. Neuroanatomical correlates of cognitive performance in late life. Dement. Geriatr. Cogn. Disord. 32, 216–226.