Aus der Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Associations between executive functioning and cortical grey matter volume in the elderly

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Assoziationen zwischen exekutivem Funktionieren und dem Volumen der kortikalen grauen Substanz bei Älteren

zur Erlangung des akademischen Grades
Doktor medicinae (Dr. med.)

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List of Abbreviations

α	alpha
3D	three-dimensional
BioCog	Biomarker Development for Postoperative Cognitive Impairment in the Elderly
BPF	Brain Parenchymal Fraction
BPV	Brain Parenchymal Volume
BR	Brain Reserve
CR	Cognitive Reserve
Diff	Difference
DTI	Diffusion Tensor Imaging
EF	Executive Functioning
eTIV	estimated Total Intracranial Volume
Fig	Figure
FSPGR	Fast Spoiled Gradient Recalled Echo
GM	Grey Matter
ICV	Intracranial Volume
IQ	Intelligence Quotient
ISCED	International Standard Classification of Education
MCI	Mild Cognitive Impairment
mm	millimeter
MMSE	Mini-Mental-State-Examination
MP-RAGE	Magnetization-Prepared Rapid Gradient-Echo
MRI	Magnetic Resonance Imaging
ms	milliseconds
MWT-A	Mehrfachwahl-Wortschatz-Intelligenztest
NMB	Nucleus Basalis of Meynert
PFC	Prefrontal Cortex
SD	Standard Deviation
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
ß	beta
TE	Echo Time
TMT	Trail Making Test

TR	Repetition Time
WM	White Matter

Abstract (English)

Introduction: Preserved executive functioning (EF) promotes superior daily functioning in the elderly and protects against dementia development. In this study, 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.

Methods: In total, 206 pre-surgical subjects without any evidence for neuropsychiatric disorders (72.50 ± 4.95 years; mean MMSE score 28.50) from the BioCog cohort study (www.biocog.eu) were investigated. EF was assessed with Trail Making Test B (TMT B). Global/lobar GM volumes were acquired with T1 MP-RAGE using a 3.0 Tesla Siemens scanner with a 32-channel headcoil. The brain imaging software package FreeSurfer was used to quantify GM volumes of the frontal, temporal, occipital and parietal brain lobes. Adjusting for key covariates including a brain atrophy index, multiple regression analysis was used to study associations of MRI markers and TMT B.

Results: All lobar/global GM volumes significantly predicted the TMT B score independently of brain atrophy (ß = −0.201 to −0.275, p = 0.001–0.012). Atrophy-corrected global GM volume was the most accurate predictor (ß = −0.275, p=0.001).

Conclusion: Our results indicate that atrophy-corrected GM volume as an archaeological estimate of maximal GM size in youth may serve as a future BR predictor for cognitive decline in the elderly.

Abstract (German)

Einleitung: Um im Alter einen normalen Tagesablauf gewährleisten zu können, ist vor allem der Erhalt exekutiver Funktionen (EF) grundlegend; diese scheinen zudem dementielle Entwicklungen vorhersagen zu können. Wir untersuchten die Assoziation zwischen atrophie-korrigierter grauer Substanz (GS), als Reserve für Gehirnkapazität, und dem Aufrechterhalten von EF im Alter.

Material und Methoden: Insgesamt wurden 206 präoperative Probanden ohne Anhalt für das Vorliegen neuropsychiatrischer Erkrankungen (72.50 ± 4.95 Jahre; durchschnittlicher MMSE Wert 28.50) im Rahmen der BioCog Kohortstudie (www.biocog.eu) untersucht. EF wurde primär beurteilt durch die Anwendung des Trail Making Test B (TMT B). Ein 3.0 Tesla Siemens Scanner mit einer 32-Kanal Kopfspule wurde zur Akquisition von T1 MP-RAGE Daten genutzt. Zur Bestimmung des globalen Volumens sowie der Volumina der GS der einzelnen Hirnlappen wurde die Software FreeSurfer angewendet. Mittels multipler linearer Regressionsanalysen, mit Korrektur für entscheidende Kovariaten, einschließlich eines Index für Hirnatrophie (Anteil von Hirnparenchym am intrakraniellen Volumen), wurden Volumina der GS mit dem TMT B assoziiert.

Ergebnisse: Alle Volumina der GS, insbesondere das Volumen der globalen GS, waren, unabhängig von der vorliegenden Hirnatrophie, signifikant mit dem TMT B assoziiert (ß = −0.201 bis −0.275, p = 0.001–0.012).

Schlussfolgerung: In künftigen Studien zur morphologischen Reservekapazität bei Älteren könnte das atrophie-korrigierte Volumen der GS, als eine Schätzung des maximalen Umfangs der GS in der Jugend, herangezogen werden und als Prädiktor für den Rückgang des kognitiven Vermögens dienen.

1. Introduction

Executive functions are referred to as higher-order thinking processes such as flexible problem-solving and response inhibition that enable and drive goal-oriented behavior (Rabinovici, Stephens, & Possin, 2015). The idea that a specific brain lobe might be associated with executive functioning (EF) was of special interest for the first time in the mid-19th century. More precisely, on September 13, 1848. On this day a tamping rod was driven by the explosion of a dynamite charge through the left side of 25-year-old Phineas P. Gage's (1823 – May 21, 1860) face and out the frontal portion of his cranium (Coolidge & Wynn, 2001).

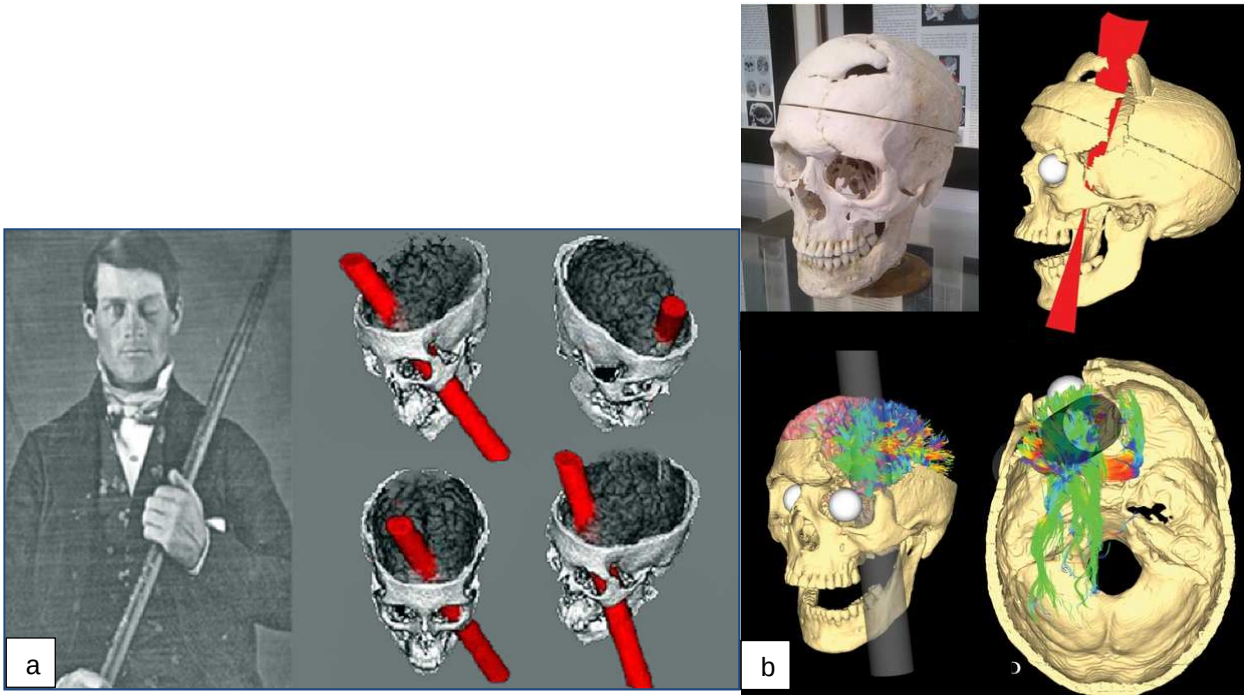

Fig. 1. a) "The strange yet instructive case of Mr Phineas Gage" (from www.onlinestorybank.com; March 22, 2014). b) Modelling the path of the tamping iron through the Phineas P. Gage skull and its effects on white matter structure (from van Horn, et al., 2012)

Besides the fact that his left eye was irreparably damaged and a ptosis of his left-eyelid remained (see Fig. 1 a), Gage's physical abilities were only slightly affected, although a significant change in behavior was recognized (Harlow, 1993). While his physical and cognitive abilities stayed the same, Gage lost his well-developed ability of "executing all of his plans of operation" - the first documented case of a potential link between the frontal lobe and executive function (Coolidge & Wynn, 2001). In the last few decades, the number of investigations examining associations of cognitive performance with specific brain lobes has increased and several case reports and smaller lesion studies (most

lesions are due to neurological diseases or vascular infarctions) found that patients with frontal lobe damage have significant impairments of psychological activities, particularly impairments in EF (Baddeley A. & Hitch G.J., 1974; Lurija, 1973; Stuss & Benson, 1986). Alexander Romanowitsch Lurija (1902 - 14.08.1977), a Russian neuropsychologist and a leading pioneer in the field of neuropsychology, was known for his extensive research concerning associations of the frontal lobes, especially the prefrontal cortices (PFC) (Coolidge & Wynn, 2001), with executive function (however, the term “executive function” comes from Lezak (1982)). In line with the findings of John Martyn Harlow (Gage's attending physician), Lurija noticed that patients with frontal lobe damage have significant impairments with respect to complex, purposive, and goal-directed actions and that his patients were unsuccessful in evaluating their failure of behavior, while, motor abilities and senses remained intact (Lurija, 1973).

It is hypothesized that the brain is capable of minimizing clinical manifestations in the face of age-related cerebral effects or the present neuropathology (Bartrés-Faz & Arenaza-Urquijo, 2011; Chen, et al., 2017). This concept is referred to as brain reserve (BR) and could be seen as analogous to cognitive reserve (CR), which states that patients with higher intelligence (IQ) or occupational attainment might have a functional advantage during late life (Stern, 2002) and thereby maintain the capability of performing cognitive tasks in the face of neurological disease with a subsequent loss of neuronal function (Stern, 2012). In recent decades, MRI (magnetic resonance imaging) acquisition has become increasingly available. Therefore using MRI as a biological measure of aging is very appealing. By applying structural and functional MRI analyses, several investigations confirmed the clinical observations of the association of the integrity of different brain lobes, and particularly the frontal lobe, with EF (Cardenas, et al., 2011; Dong, et al., 2015; Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Gunther, et al., 2012; Nee, Kastner, & Brown, 2011; Zhang, et al., 2011) as previously suggested by Harlow in the mid-19th century. Because age-related cognitive changes, and especially impaired EF, may lead to reduced activity and functioning in daily life, further research in this field is crucial (Drag & Bieliauskas, 2010; Salthouse, 2005; Salthouse, Atkinson, & Berish, 2003). Furthermore, since impaired EF is found to precede memory decline in the course of dementia development (Johnson, Lui, & Yaffe, 2007), brain morphology associated with EF might serve as an early marker of neurodegenerative disease (Chen, et al., 2017). In his "frontal-lobe hypothesis of aging“, West (1996) postulated that the development of age-related changes in cognitive performance and behavior are determined by

dysfunction of the prefrontal cortex, which, in his opinion, is particularly sensitive to the aging process. Several investigations confirmed this hypothesis and found that a preserved superior level of EF is associated with superior daily functioning and aging well in both neuropsychologically healthy patients and patients with mild cognitive impairment (MCI) (Darby, Brickhouse, Wolk, & Dickerson, 2017; Puente, Lindbergh, & Miller, 2015; Schmitter-Edgecombe, Parsey, & Cook, 2011). In line with this hypothesis, Phillips, Henry, Jacobs, & Anderson (2008) demonstrated that the neuropsychological test performance of older adults is highly dependent on EF, which in turn is associated with prefrontal brain function. More recently, however, Bettcher, et al. (2016) reported findings contrary to the hypothesis of a particular association of the frontal lobe with EF. In their study of 202 community-dwelling older adults, Bettcher, et al. (2016) found that the frontal GM lobe volume and the GM volume of additional individual brain lobes do not independently predict executive function performance when statistically corrected for the global GM brain volume. Notably, van Horn, et al. (2012) used computed tomography image data of Gage's skull in conjunction with modern anatomical MRI and diffusion imaging data to computationally simulate the passage of the iron through the skull. Aside from the reconstructed direct damage to the frontal cortex, the white matter connectivity of other brain areas was severely affected, which likely contributed significantly to the described behavioral changes (see Fig. 1 b). Bettcher, et al. (2016) and Cardenas, et al. (2011) observed that an atrophy of the anterior and superior regions of the corona radiata as well as the superior longitudinal fasciculus impair EF. Importantly, these studies predict EF by quantifying the different lobar GM volumes and the global GM volume in the elderly population without considering whether the maximal brain size in youth or GM atrophy during later life is more strongly associated with the cognitive domain of executive functions.

We aimed to estimate the global and specific lobar GM volumes during youth by correcting GM volume for a brain atrophy index (i.e., the brain parenchymal fraction). The applied brain atrophy index in turn is calculated by dividing the present brain parenchymal volume (includes GM and white matter [WM]) by the total intracranial volume (ICV). The brain atrophy index has been used to predict cognitive decline in dementia patients in prior studies (Callahan, Ramirez, Berezuk, Duchesne, & Black, 2015). However, applying atrophy-corrected lobar and global GM volume as the cortical BR marker to predict EF is, to our best knowledge, a novel strategy. Due to the correction of the individual GM volume for GM atrophy, this measure has the quality of a BR prediction marker even in the setting

of a cross-sectional study design with an imaging data collection in an advanced-age population. The neuropsychological assessment of EF was conducted by the Trail Making Test B (TMT B), which is commonly applied to assess the cognitive processes of flexibility and the ability to execute and modify a plan of action.

With respect to the conflicting results reported in literature and the attempt to apply a novel concept of a cortical BR marker, we tested the alternative hypotheses:

1) that the GM volumes of specific brain lobes, particularly the frontal lobe, and the global GM, when individually corrected for brain atrophy, are independently associated with executive function; and

2) that no such atrophy-corrected specific brain lobe association with EF exists when corrected for global GM volume.

2. Methodology

2.1 Participants

As part of an interim analysis, 206 neuropsychologically healthy adults aged between 65 and 87 years were selected from the umbrella Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study conducted at the study center in Berlin (www.biocog.eu). The BioCog study is a prospective multicenter cohort study aiming to establish valid clinical, neuroimaging and molecular biomarkers panels for risk and clinical outcome prediction of postoperative delirium and postoperative cognitive deficits in elderly elective surgical patients (Winterer, et al., 2018). The inclusion criteria comprise male and female patients aged ≥ 65 years and of European descent (Caucasian) who will undergo elective surgery with an operative time ≥ 60 minutes (general and spinal anaesthesia) with an expected hospital treatment period of at least seven days. 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 were excluded. All patients gave a written informed consent after receiving spoken and written information about the study. The study was approved by the local ethics committee and conducted according to the declaration of Helsinki. The baseline magnetic resonance imaging (218 MRI scans were available for this interim analysis from the patients from the clinical center of Berlin [N=291]) data acquisition together with clinical and neurocognitive assessments took place one day before surgery. Due to preterm finishing of the FreeSurfer processing pipeline in one case as well as 10 cases with gross anatomical aberrations seen while inspecting the post-processed images and the

withdrawal of consent by one patient after inclusion, 206 processed MRI scans were finally available for analysis. Out of 206 available MRI scans, EF data (TMT B score) were available for 174 subjects (for demographics see Table 1).

Table 1. Cognitive and neuroimaging characteristics of participants

	N	Mean (SD)	Range
Demographics			
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

[a]Excluding primary motor cortex

[b]Excluding sensory cortex

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

2.2 Measures

2.2.1 Cognitive Assessments

For the assessment of EF, the Trail Making Test (TMT A and TMT B) was applied pre-operatively on the same day as the MRI investigation. During part A (visuoperceptual abilities), subjects were required to connect 25 randomly distributed numbers on a test sheet (see Fig. 2) in the correct order as quickly as possible.

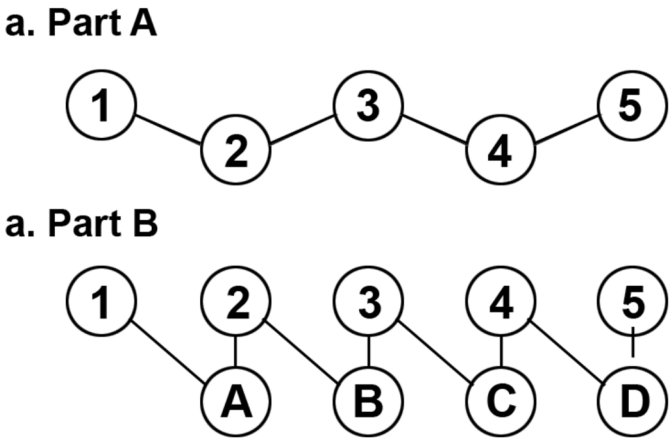

Fig. 2. Trail Making Test. (from Kim, et al., 2014)

Part B (inhibition and set-shifting) presented the encircled numbers from 1 to 13 and the encircled letters from A to L randomly distributed on the test sheet (see Fig. 2). The subjects were required to draw lines sequentially connecting them by alternating between numbers and letters (1, A, 2, B, 3, C, etc.). The required amount of time represented the score of the test, and the faster these paper-and-pencil tests were completed, the better the cognitive function of the participant (Reitan, 1958). The primary dependent variable in this study is the required time to finish the TMT B. Literature regarding standard cut-off for the TMT is sparse due to the dependence on intelligence, visuomotor coordination and age (Spreen & Strauss, 1998; Tombaugh, 2004). In addition, a multiple-choice vocabulary test ("Mehrfachwahl-Wortschatz-Intelligenztest" [MWT-A]) was applied to

measure premorbid crystallized cognitive ability. In this test, the principle of single choice was applied, and each row contained one existing word and four fictive new constructions of words. In each row, the participants were asked to mark the word they considered to exist. In total, there were 37 rows and thus 37 correct words with increasing levels of difficulty. The total number of correctly marked rows was compared to a representative sample of German adults aged between 20 and 64 (n=1952) (Siegfried Lehrl, 2005). The derived Intelligence Quotient (IQ) score correlated fairly well with global IQ in healthy adults (S. Lehrl, Triebig, & Fischer, 1995).

2.2.2 Education

The educational level of the subjects was classified into one of seven categories, namely (0) pre-primary 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, according to the International Standard Classification of Education (ISCED-1997).

2.2.3 Structural Neuroimaging

Identical neuroimaging protocols (using a 3.0 Tesla MRI with a 32-channel head coil, Siemens Magnetom Trio) applying standard operating procedures (SOP) were applied, including the implementation/validation of image-acquisition/processing techniques during the study set-up. These applied neuroimaging protocols were based on a set of parameters that were kept constant during the study. Structural imaging yielded whole-head, high-resolution anatomical magnetic resonance images using a 3D T1-weighted magnetization-prepared rapid gradient-echo sequence (MP-RAGE) for studying cortical, hippocampal and NMB (nucleus Basalis of Meynert) volume as well as standard DTI (45 directions) and T2-Flair. An axial-oblique 3D Fast Spoiled Gradient Recalled Echo (FSPGR) sequence for the T1-weighted sequence was applied (TR/TE = 2500/4.77 ms, $\alpha = 7°$) with a field of view of 256 x 256 mm (1 x 1 mm in-plane resolution and 1 mm slice thickness). After acquisition, all MRI images were checked on pathological intracranial processes by a board-certified neuroradiologist.

2.2.3.1 FreeSurfer

To process the T1 MP-RAGE structural MR images, the software FreeSurfer (version 5.30) was used. This software package was chosen due to its fully automated pipeline and its free availability (http://surfer.nmr.mgh.harvard.edu) as well as its high test-retest reliability (Han, et al., 2006; Jovicich, et al., 2006).

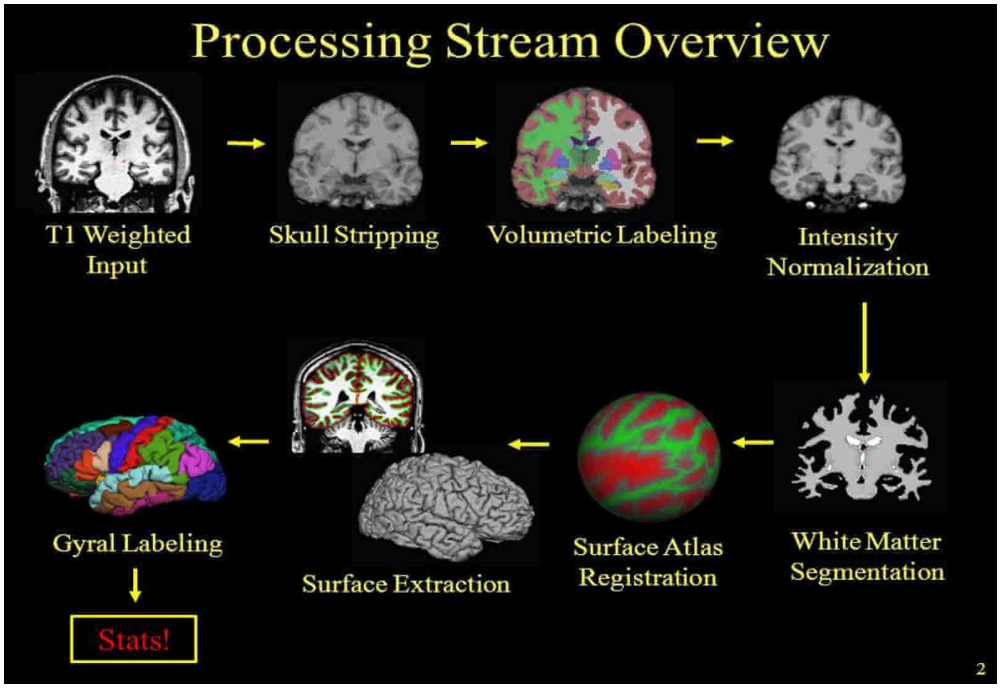

Fig. 3. Full processing stream of FreeSurfer for MRI data (from http://www.opensourceimaging.org/project/freesurfer/#; August 28, 2018)

See Fig. 3 for the complete processing stream overview of the software FreeSurfer. In detail, the executed steps were motion correction, removal of non-brain tissue and automated Talairach transformation (Segonne, Pacheco, & Fischl, 2007). In addition, segmentation of the subcortical white matter and deep grey matter into structural volumes (Bruce Fischl, et al., 2002; Bruce Fischl, et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the grey matter into structural volumes (Bruce Fischl, et al., 2002; Bruce Fischl, et al., 2004), automated topology correction (Bruce Fischl, et al., 2002) and surface deformation (Dale, Fischl, & Sereno, 1999; B. Fischl & Dale, 2000) were conducted when processing the FreeSurfer pipeline. Since the visual inspection for the accuracy of spatial registration and grey/white matter (e.g., removal of skull and dura matter and accurate delineation of grey/white matter and pial surfaces) of all surfaces of each individual image was performed by one researcher (Markus Laubach), potentially differing inter-observer interpretations of the accuracy of processed

images was avoided. On one hand, it was necessary to check the accuracy of the alignment of the grey and white matter boundaries. On the other hand, the automated segmentation was inspected to accurately follow the subcortical intensity boundaries. For details about the visual inspecting process, please see Fig. 4.

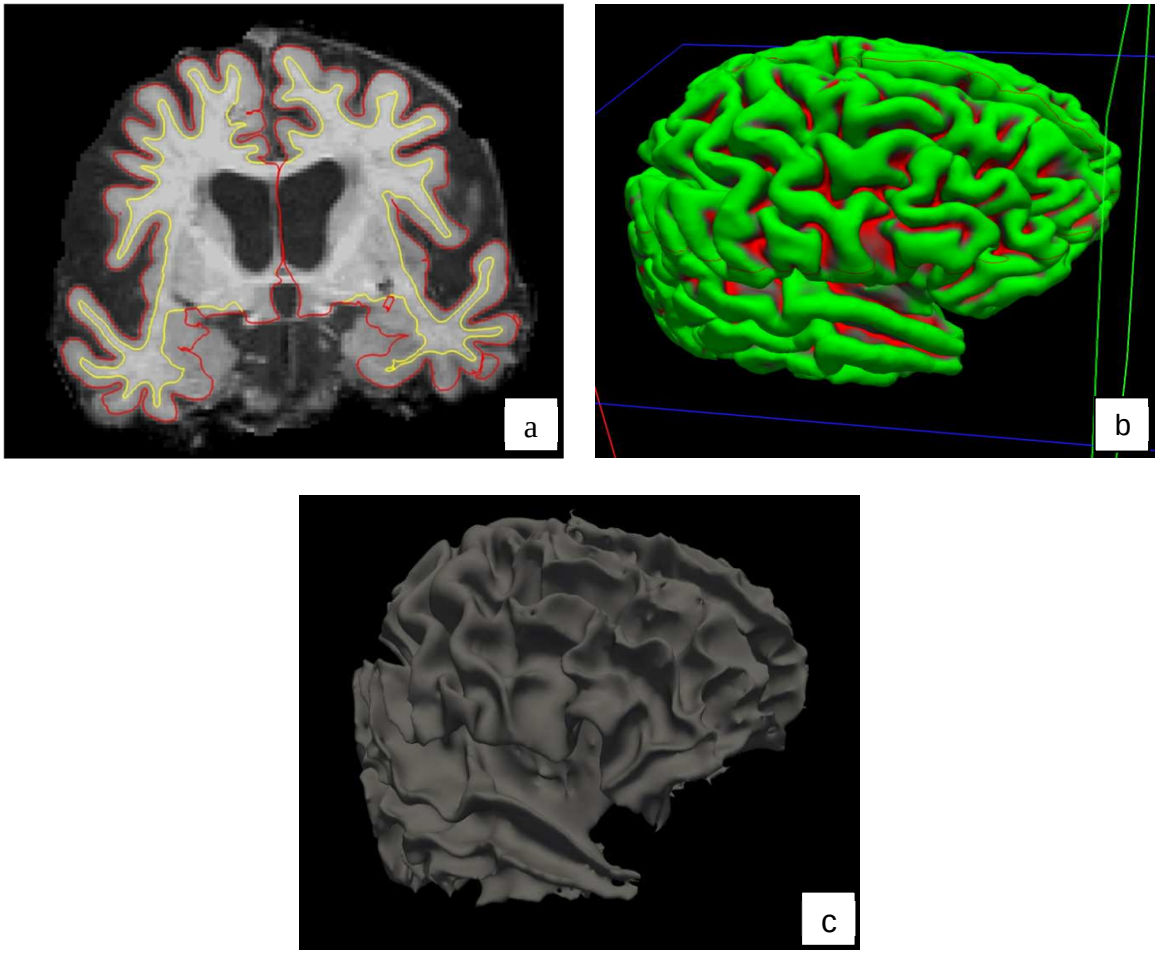

Fig. 4. Visual inspection of the post-processed images. a) White matter (yellow) and pial (red) surface on coronal view: To check the accuracy of the automated segmentation, the boundaries of the white matter, and the pial surface, all the coronal slices are controlled by scrolling in the coronal view from the most anterior part toward the most rostral part of the brain. b) Pial surface on a 3D-model: By visualizing the pial surface on a 3D-model, the accuracy of the latter is visually inspected. c) 3D-model of the smoothed white matter surface: The images showing the white matter boundaries are checked on irregularities which are indicated by hypointensities. Hypointensities appear in the form of white matter holes.

Gyral labeling (see Fig. 3) was the last step of the FreeSurfer processing stream and was performed by applying the Desikan-Killiany atlas (Desikan, et al., 2006). By applying the

Desikan-Killiany atlas, the pial surfaces were automatically given as inflated cortical representations (see Fig. 5).

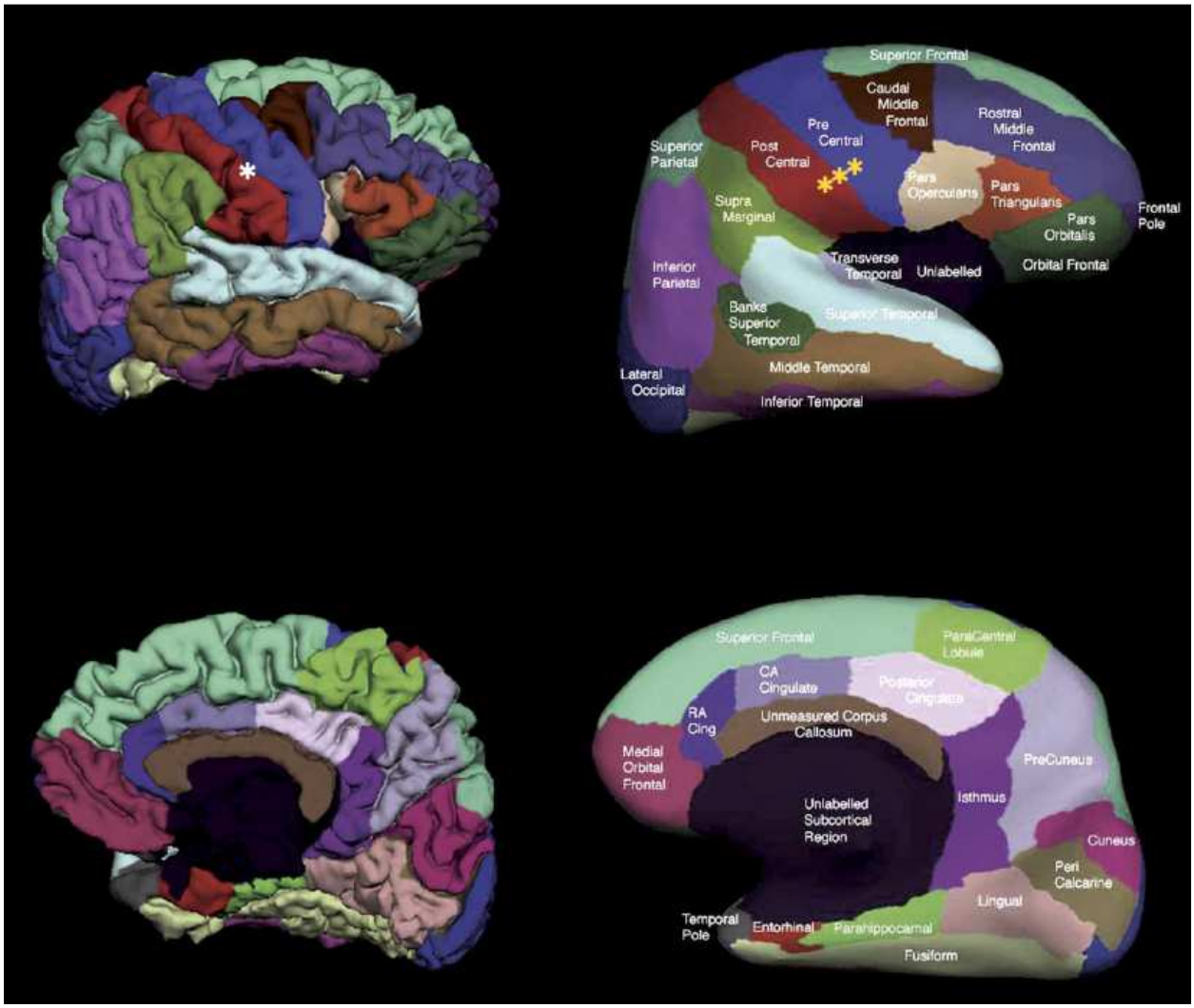

Fig. 5. Division of the cerebral hemispheres into 34 regions based on the Desikan-Killiany atlas (from Desikan et al., 2006). On the left side the pial and on the right side the inflated cortical representations are shown. The lateral view of the hemisphere is shown at the top, and the medial view of the hemisphere is depicted in the bottom row.

These inflated cortical representations consisted of specific GM volumes that were automatically subdivided into 34 parcellations for each cerebral hemisphere. Then, the different GM volumes belonging to the 34 parcellations were extracted from FreeSurfer. Subsequently the different volumes of the parcellations were manually summed up with SPSS to estimate the frontal, temporal, occipital and parietal lobe GM volumes as well as the global GM volume. The occipital lobe consisted of the lingual, pericalcarine, cuneus, and lateral occipital grey matter volumes. The parietal lobe was calculated by summing up the posterior cingulate, inferior parietal, precuneus, superior parietal and supramarginal GM volumes. The frontal lobe was defined by the rostral middle frontal,

caudal middle frontal, inferior frontal (pars opercularis, pars triangularis, pars orbitalis), anterior cingulate (rostral anterior cingulate and caudal anterior cingulate), orbitofrontal (lateral orbitofrontal and medial orbitofrontal) and superior frontal GM volumes as well as the GM volume of the frontal pole. The cortical volumes involved with controlling motor action and receiving input from peripheral mechanoreceptors (the primary motor and the sensory cortex) were excluded due to the dexterity and somatosensory inaccuracy in respect to the conducted neuropsychological tests.

2.2.3.2 Brain Parenchymal Fraction

To correct for global cerebral atrophy, the estimated total intracranial volume (eTIV, aka ICV) and the total brain parenchymal volume (global GM volume plus total WM volume excluding ventricles) were calculated. Then, the cerebral atrophy index (i.e., the brain parenchymal fraction [BPF]) was derived by dividing the total brain parenchymal volume (BPV) by the total intracranial volume (ICV) (Callahan, et al., 2015; Rudick, Fisher, Lee, Simon, & Jacobs, 1999):

$$Brain\ Parenchymal\ Fraction\ (BPF) = \frac{Brain\ Parenchymal\ Volume\ (BPV)}{Intracranial\ Volume\ (ICV)}$$

During the statistical analyses, the BPF was applied as an independent variable to correct the different GM lobe volumes and the global GM volume for brain atrophy.

2.3 Statistical analysis

For statistical analyses, IBM SPSS Statistics (version 25) was used. Multiple linear regression analyses were mainly used in this study and aimed to evaluate medical data in respect to correlations between different variables. In general, the model of multiple linear regression analysis consists of a so-called dependent variable – EF in this study - and two or more independent variables that aim to explain the dependent variable. In total, two main sets of multiple linear regression analyses were executed: 1) Separate multiple linear regression analyses for each of the four brain lobes (GM volume) and the global GM volume as well as age, the BPF and sex as the independent variables and the TMT B score as the dependent variable. As a minor side analysis a multiple regression analysis including the global GM volume, age, BPF and sex as the independent variables was repeated analogously with the TMT_{Diff} score (TMT B - TMT A) instead of the TMT B score as the dependent variable; 2) To adjust for global GM volume, the GM volume of each of the four lobes was divided by the global GM volume and the regression analyses,

with the TMT B scores as dependent variables repeated analogously. The critical value for significance was set to $p<0.05$.

3. Results

The included 206 non-demented elderly patients 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 different brain lobes and the global GM volume were negatively associated with the TMT B scores (see Table 2).

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

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

The model consists of the different grey matter volumes, age, 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

The negative estimate reported by a beta range of - 0.201 to - 0.275 indicates that an inferior performance of the TMT B tests is correlated with a smaller individual lobar as well as smaller global GM volume. An increase of one SD of the individual lobar or the global GM volume decreases the TMT B score by the amount of the standardized regression coefficient. The standardized coefficient (ß) of the global GM cortical volume of -0.275 (p=0.001) is shown to be most negatively related to the value of the TMT B test results in the prior described model and is thus, in the latter model, the most accurate predictor of EF. In other words, predicting EF in the elderly was in this study most accurately correlated with atrophy-corrected GM volume. Age as one of the additional independent variables also has significant explanatory power to predict TMT B performance. Increased age is associated with a higher TMT B score (ß=0.792-0.804, p=0.007-0.015). No sex-specific tendencies were observed (ß=-0.085 to -0.139, p=0.096-0.326). 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). In all of the conducted analyses, except for the regression analysis including the parietal lobe (p=0.045), the BPF itself did not significantly contribute to the prediction of EF measured by the TMT B (p=0.056-0.121). Overall, non-significant trends were observed. No statistically significant associations between the different brain lobes and EF were revealed by regressing EF on the adjusted GM volume (individual brain lobe volume divided by the global GM volume) (p=0.388-0.789). Thus, no significant associations between EF and the volume of a certain lobe independent of the total GM volume could be shown.

4. Discussion

In this study, the structural associations of the frontal lobe, the parietal lobe, the temporal lobe, the occipital lobe and the global GM volume with EF measured by the neuropsychological Trail Making Tests A and B were investigated in a subgroup of participants of the BioCog study. We found that each individual brain lobe volume as well as the global GM volume is significantly associated with EF (i.e., a larger GM volume demonstrated superior TMT B performance). The total cortical GM volume was observed to be the major predictor for EF. These associations of different volumes of the brain lobes with EF are in line with several prior investigations (Cardenas, et al., 2011; Elderkin-Thompson, et al., 2008; Zhang, et al., 2011). The GM volume was corrected for brain atrophy as part of the multiple regression analyses. The derived “corrected GM volume” can be considered an “archaeological” estimate of the maximal brain size in youth (Royle, et al., 2013). Accordingly, despite we adopted a cross-sectional study design, atrophy-corrected global GM volume can be used as a predictor of EF in advanced aged subjects. The observed morphological advantage is in line with previous studies that show, for example, a larger ICV being able to protect against dementia development (Groot, et al., 2017; Guo, Alexopoulos, Wagenpfeil, Kurz, & Perneczky, 2013; Negash, et al., 2013). The investigations of Cardenas, et al. (2011), Elderkin-Thompson, et al. (2008) and Zhang, et al. (2011) are limited due to an image processing approach accompanied by a compelling inter-interpreter variance and the lacking use of a software with high test-retest reliability with respect to quantify brain volumes accurately. By applying the software package FreeSurfer (version 5.10) as an image analysis suite Dong, et al. (2015) could overcome these limitations and show in a comparably large sample size of 813 participants associations between grey matter volumes and cognitive performance. Superior performances in tests of EF were associated with greater GM frontal lobe volume (Dong, et al., 2015). However, due to the inclusion of patients younger than 70 years of age and because of not excluding subjects with neurocognitive disorders (Dong, et al., 2015), the possibility of associating cortical volume with EF and comparing with our findings, is limited. Bettcher, et al. (2016) were the first to apply an image analyzing software accompanied with low inter-interpreter variance (FreeSurfer) and did not include participants with neurocognitive disorders in their study, which consisted of a large sample size investigating the associations of cortical volume with EF. In line with our findings, Bettcher, et al. (2016) revealed that in neuropsychologically healthy older adults, greater GM cortical volume of the four brain lobes as well as the total cortical brain volume

were associated with superior performances on tests for measuring EF. When statistically isolating the different lobar volumes from global cortical GM volume, in line with Bettcher, et al. (2016), we could not show an independent prediction of EF; thus, an isolated view on particular cortical brain lobe volumes might not be sufficient to show certain associations with EF. The significant impact of age on EF is in line with several prior investigations (Buckner, 2004; Cardenas, et al., 2011; Kennedy, et al., 2009; Raz, et al., 2005; Walhovd, et al., 2005). This reflects the substantive effect of age on the observed relationship between the capacity of executive functions and specific lobar as well as global cortical volume. Considering the sample composition of a neuropsychologically healthy elderly population, the strong association of age with executive function is somewhat surprising.

Because we found that the frontal lobe independent of global GM volume is not significantly associated with EF, future research should focus on in-depth investigations of the complementary brain structures. Lurija (1973) and Damasio (1994) found that the frontal lobes have abundant and reciprocal connections to the thalamus, basal ganglia and limbic system as well as the posterior portions of the cortex. This means that the frontal cortex might have greater access to other domains and functions of the brain than any other domain (Coolidge & Wynn, 2001). Furthermore, the presence of abundant white matter projections of the frontal lobe that are pivotal to the connectivity and cognitive function of the human brain, as shown by Spence (2005), should be further explored. Supplementary to focusing on only one metric (structural neuroimaging as in the present study), further investigations on cortico-cortical connectivity to assess the integrity of specific cognitive domains, the efficiency of network connections and synaptic complexities are needed (Alvarez & Emory, 2006; Carmichael, et al., 2012; Dong, et al., 2015; Zelazo, Carter, Reznick, & Frye, 1997). For instance, Gupta, et al. (2015) observed that only 33% of variance in cognition can be attributed to brain volumetrics. In line with Gupta, et al. (2015), the adjusted R-squared values in our investigation, ranging from 0.157 (occipital lobe) to 0.181 (parietal lobe and global GM volume), indicate that an essential part of residual variation between individuals in EF cannot be attributed to cortical GM volume (corrected for key predictors). In addition to the complex neuroimaging analyses, molecular and genetic markers derived from blood might provide microscopic measures of neuropathological activity and could serve as a complement to the macroscopic view provided by MRI (Carmichael, et al., 2012).

There are a few limitations regarding this investigation that are important to mention at this point. Across different brain tissues, the brain atrophy trajectories might be non-linear; for example, in people of advanced age, WM volume decline is more pronounced than GM volume decline (Royle, et al., 2013). Since there currently are no long-term data on changes in the grey/white matter ratio, this might impede the strategy of applying BPF for brain atrophy correction. Thus, BPF varies throughout an individual's life-time (Vågberg, Granåsen, & Svenningsson, 2017) and no normative age-related values have been established so far. Furthermore, across the different brain regions, a non-uniform longitudinal loss of cortical GM volume was observed, which should be considered when applying a cross-sectional study design. The calculations of the different brain lobe volumes are dependent on the chosen post-processing method for brain volume quantification; thus, direct comparability of data between different studies in general and BPF in particular are impaired (Vågberg, et al., 2017). In addition, as the TMT was the only test applied to quantify EF, a detailed characterization of executive functions could not be achieved. Future investigations that aim to associate morphological markers with EF might want to use neuropsychological tests covering various EF domains, thereby reducing bias and more adequately validating the role of atrophy-corrected GM volume as a potential reserve marker for EF in late life.

Nonetheless, by predicting EF in the elderly, we suggest for the first time that atrophy-corrected global GM volume is a promising quantitative brain reserve marker. Because brain atrophy may serve as an early risk indicator, brain imaging might be beneficial for delivering diagnostic and prognostic information to patients in the process of individual, personalized medicine.

5. Index

5.1 Bibliography

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5.2 Figure index

5.3 Table index

Affidavit

I, Markus Laubach, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic „Associations between executive functioning and cortical grey matter volume in the elderly“. I wrote this thesis independently and without assistance from third parties, and I used no aids other than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, indicated in proper citations (see “uniform requirements for manuscripts (URM)”, ICMJE www.icmje.org). The sections on methodology (in particular cognitive assessments, practical work, laboratory requirements, statistical processing) and results (in particular, tables and figures) correspond to the URM. My contributions in the selected publication for this dissertation correspond to those specified in the following joint declaration with the responsible person and supervisor. The publication resulting from this thesis and of which I am the author corresponds to the URM (see above), and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156, 161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Berlin, 05.11.2018

_____ _____

Location, date Signature

Declaration of the publication

Markus Laubach had the share as stated below in the following publication:

Laubach, M., Lammers, F., Zacharias, N., Feinkohl, I., Pischon, T., Borchers, F., Slooter, A. J. C., Kuhn, S., Spies, C., & Winterer, G. (2018). Size matters: Grey matter brain reserve predicts executive functioning in the elderly. Neuropsychologia, 119, 172-181. DOI: 10.1016/j.neuropsychologia.2018.08.008.

Journal Impact-Factor (year 2017): 2.888

Contribution in detail:

As of February 2016 Markus Laubach is participating as a researcher in the European research consortium BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly) funded by the European Union. As a member of the neuroimaging research group he is mainly responsible for MRI acquisition and statistical data analysis of the acquired imaging data. In the very beginning of his contribution, he drafted a proposal with in depth elaboration of the applied methods and materials as well as the hypotheses for the projected publication „Size matters: Grey matter brain reserve predicts executive functioning in the elderly“. The proposal was accepted by the steering committee of the BioCog consortium. As a member of the neuroimaging group within the BioCog project, Markus Laubach was responsible for equipment (e.g. applying an EEG cap) and supervision of the patients during the acquisition of the MRI. Next to his contribution during the acquisition of the MRI Markus Laubach was further responsible for data collection as well as processing of the data with the software package FreeSurfer. He used the software FreeSurfer to perform all morphological reconstructions necessary to quantify brain volumetrics. Therefore, he autonomously acquired the required skills to operate properly with the software FreeSurfer. In order to get in depth knowledge for applying the software FreeSurfer, Markus Laubach took part at a professional FreeSurfer training in Tours (France). After processing the imaging data with FreeSurfer, he conducted the visual inspection of all post-processed imaging data that were used for the publication. In addition to the used imaging data for the publication, he provided other researchers within the BioCog consortium with post-processed and visually inspected imaging data. According to his hypotheses, he conducted the statistical analysis of the

data with SPSS. In a next step he wrote the manuscript and created the graphics as well as the tables required for the publication. Markus Laubach submitted the manuscript to the journal *Neuropsychologia* and was responsible for the correspondence with the editor/reviewer.

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Prof. Georg Winterer, MD
BioCog Project Coordinator
Neuroimaging Research Group Leader

_____

Markus Laubach

EXTRACT JOURNAL SUMMARY LIST

(ISI WEB OF KNOWLEDGE[SM])

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: "**BEHAVIORAL SCIENCES**" Selected Category Scheme: WoS

Gesamtanzahl: 51 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	TRENDS IN COGNITIVE SCIENCES	25,391	15.557	0.040790
2	BEHAVIORAL AND BRAIN SCIENCES	8,900	15.071	0.010130
3	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	24,279	8.037	0.048460
4	Advances in the Study of Behavior	1,219	5.200	0.001020
5	CORTEX	9,506	4.907	0.023240
6	HORMONES AND BEHAVIOR	11,304	4.418	0.015540
7	Autism Research	2,439	3.768	0.006980
8	EVOLUTION AND HUMAN BEHAVIOR	4,043	3.623	0.006730
9	GENES BRAIN AND BEHAVIOR	3,477	3.496	0.005830
10	BEHAVIORAL ECOLOGY	10,126	3.347	0.014940
11	NEUROBIOLOGY OF LEARNING AND MEMORY	6,610	3.244	0.012470
12	CHEMICAL SENSES	4,756	3.235	0.004650
13	APPETITE	14,776	3.174	0.024390
14	BEHAVIOURAL BRAIN RESEARCH	25,309	3.173	0.036610
15	Frontiers in Behavioral Neuroscience	5,665	3.138	0.020690
16	ANIMAL BEHAVIOUR	27,186	3.067	0.024080
17	STRESS-THE INTERNATIONAL JOURNAL ON THE BIOLOGY OF STRESS	2,421	3.047	0.004310
18	BIOLOGICAL PSYCHOLOGY	9,081	2.891	0.013510
19	NEUROPSYCHOLOGIA	24,704	2.888	0.028190
20	ANIMAL COGNITION	3,313	2.805	0.006420
21	EPILEPSY & BEHAVIOR	9,684	2.600	0.016330
22	COGNITIVE AFFECTIVE & BEHAVIORAL NEUROSCIENCE	3,566	2.565	0.006880
23	PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR	12,203	2.538	0.010510
24	PHYSIOLOGY & BEHAVIOR	20,530	2.517	0.021730
25	BEHAVIORAL NEUROSCIENCE	7,111	2.507	0.004730

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
25	BEHAVIORAL NEUROSCIENCE	7,111	2.507	0.004730
26	BEHAVIORAL ECOLOGY AND SOCIOBIOLOGY	12,110	2.473	0.011230
27	Behavioral and Brain Functions	1,573	2.449	0.002360
28	BEHAVIORAL MEDICINE	752	2.442	0.001100
29	HUMAN FACTORS	5,362	2.371	0.004430
30	Brain and Behavior	1,351	2.219	0.005440
31	AGGRESSIVE BEHAVIOR	3,222	2.216	0.003350
32	JOURNAL OF DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS	3,818	2.199	0.004930
33	Language Cognition and Neuroscience	566	2.086	0.002580
34	BEHAVIOR GENETICS	3,236	2.036	0.004610
35	JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR	3,035	2.010	0.001790
36	JOURNAL OF COMPARATIVE PHYSIOLOGY A-NEUROETHOLOGY SENSORY NEURAL AND BEHAVIORAL PHYSIOLOGY	5,159	1.970	0.004510
37	JOURNAL OF ECT	1,556	1.896	0.002100
38	JOURNAL OF EXPERIMENTAL PSYCHOLOGY-ANIMAL LEARNING AND COGNITION	2,061	1.861	0.001380
39	BEHAVIOURAL PHARMACOLOGY	2,653	1.854	0.003220
40	JOURNAL OF COMPARATIVE PSYCHOLOGY	2,782	1.771	0.002040
41	ETHOLOGY	4,487	1.697	0.004950
42	BRAIN BEHAVIOR AND EVOLUTION	2,427	1.650	0.001840
43	ACTA ETHOLOGICA	446	1.625	0.000930
44	BEHAVIOURAL PROCESSES	4,337	1.555	0.006980
45	Journal of Veterinary Behavior-Clinical Applications and Research	1,124	1.554	0.002340
46	APPLIED ANIMAL BEHAVIOUR SCIENCE	8,022	1.548	0.005780
47	BEHAVIOUR	5,274	1.484	0.003260

Selected JCR Year: 2018; Selected Categories: "BEHAVIORAL SCIENCES"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
48	Cognitive and Behavioral Neurology	766	1.444	0.000770
49	LEARNING & BEHAVIOR	814	1.434	0.001220
50	ETHOLOGY ECOLOGY & EVOLUTION	872	1.270	0.000990
51	JOURNAL OF ETHOLOGY	854	1.127	0.001220

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

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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-

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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

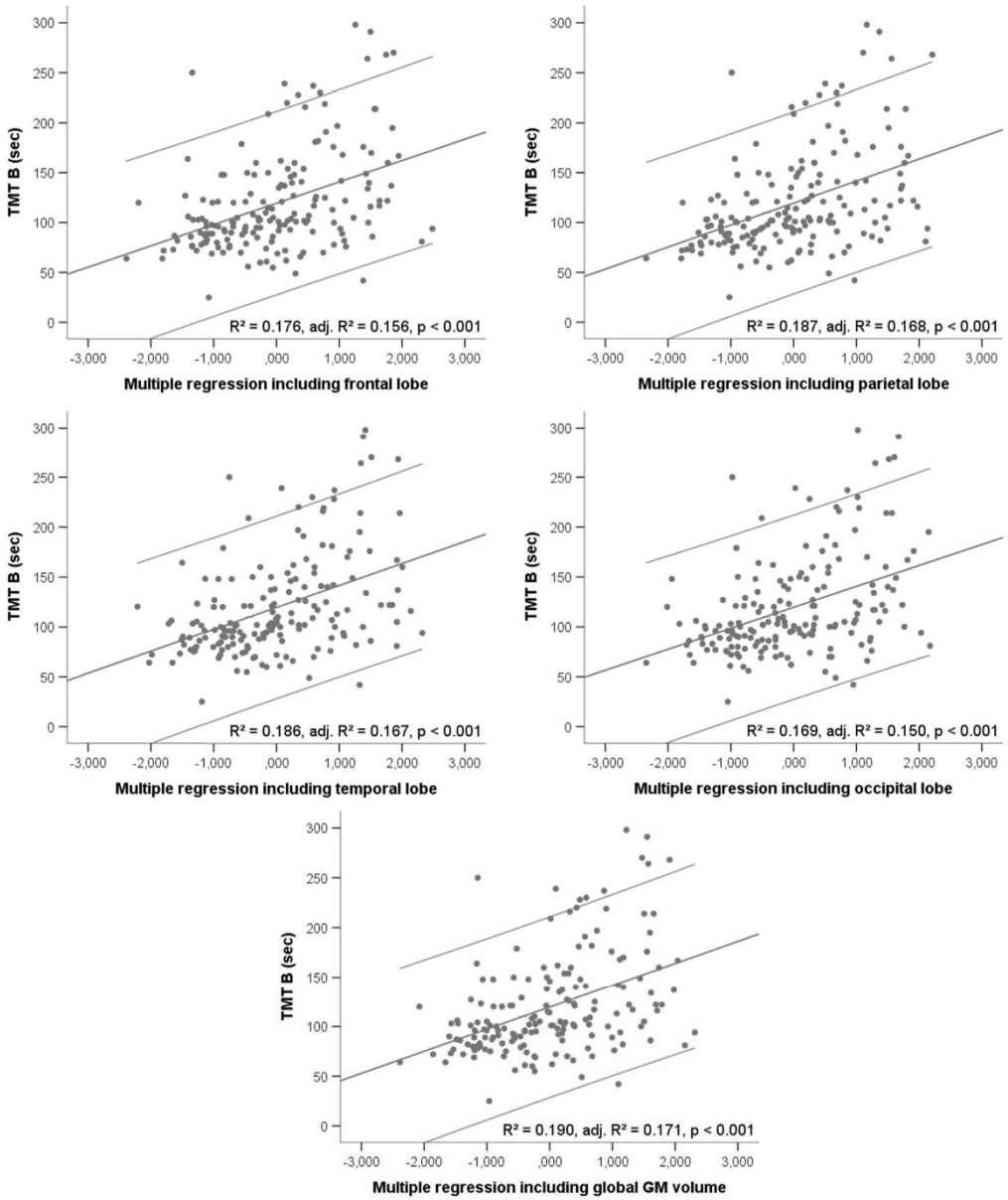

Fig. 1. Each scatterplot consists of the graph of the standardized predicted values derived from the regression equation composed of the individual GM volumes (excluding primary motor and sensory cortex) as well as the covariates age, BPF and sex (95% CI). Key: BPF, Brain Parenchymal Fraction; CI, Confidence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

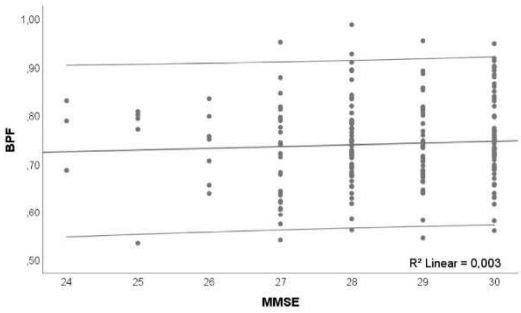

Fig. 2. The scatter plot consists of the brain parenchymal fraction (BPF) shown on the y-axis which is derived by dividing the total brain parenchymal volume (BPV) by the total intracranial volume (ICV). The MMSE score is shown on the x-axis (95% CI). **Key: CI, Confidence Interval; MMSE, Mini-Mental-State-Examination.**

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

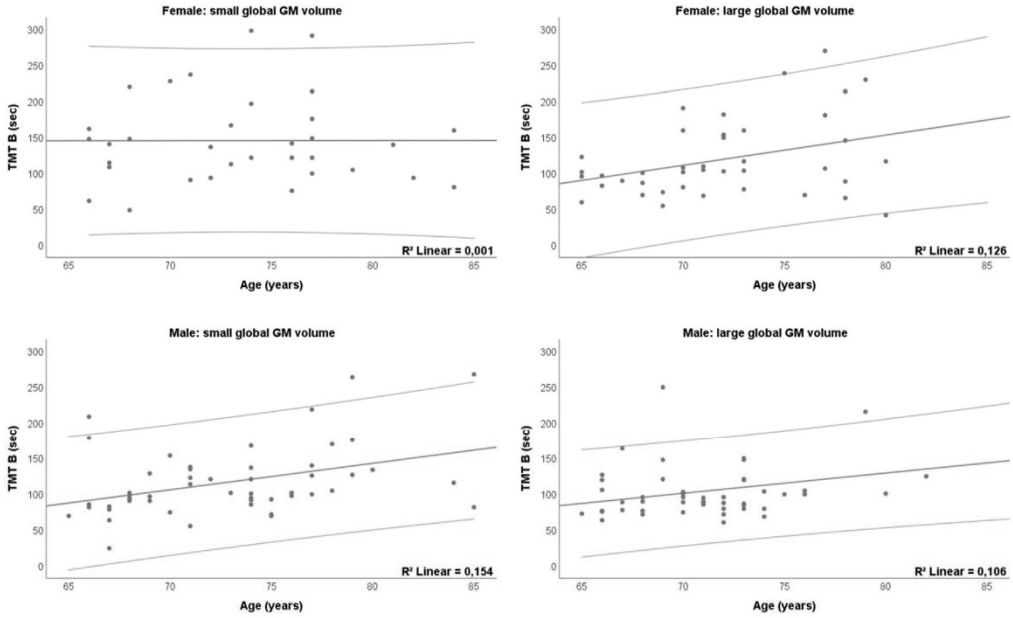

Fig. 3. To assess the effects of GM volume on the TMT B score, we assigned the subjects into four groups. This was done by a median split of the global GM volume (primary motor and sensory cortex are excluded) for the female and the male subjects separately. On the top of this figure, displayed for female 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.

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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.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publication list

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