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Neurobiological correlates of executive control in the healthy aging brain

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Zusammenfassung

Der Begriff exekutive Funktionen fasst verschiedene kognitive Fähigkeiten zusammen, welche die Handlungskontrolle im täglichen Leben ermöglichen. Ein bewährter Test zur Bewertung von Exekutivfunktionen ist der Trail-Making-Test B (TMT-B). Der Teil A dieses Testes bildet hingegen vor allem visuomotorische Fähigkeiten ab. Das Ziel der vorliegenden Arbeit ist es, an kognitiv nicht eingeschränkten älteren Teilnehmern zu untersuchen, welche neurobiologischen Korrelate mit einer guten Leistung in exekutiver Kontrolle zusammenhängen. Teilnehmer mit pathologischen MRT-Befunden wurden aus der Studie ausgeschlossen. Die interindividuelle Variabilität in der Testleistung ist die Basis für die statistischen Analysen bezüglich eines Zusammenhanges der Leistung mit strukturellen und funktionellen Aspekten des Gehirns. Mit dieser Zielsetzung wurde die Korrelation von der Testleistung im TMT-B mit dem Volumen der grauen Substanz sowie mit struktureller und funktioneller Konnektivität untersucht. Die Leistung im TMT-A wurde als Störgröße in der Analyse berücksichtigt.

Diese multimodale Analyse hat Daten von 397 Teilnehmern von 55 bis 80 Jahren untersucht. Als neurobiologische Korrelate wurden das Volumen der grauen Substanz mittels Voxel-basierter Morphologie (VBM), weiße Faserbahnen mittels Tract-based spatial statistics (TBSS) und die funktionelle Konnektivität mittels seed-based Resting-state funktionielle Magnetresonanztomographie (RS-fMRI) untersucht. Seed-based RS-fMRI wurde mit den signifikanten Clustern der VBM-Analyse durchgeführt.

Die Analysen basieren auf dem multiplen Regressionsmodell, d.h. der Anteil des Effekts, welcher schon durch die Störfaktoren Alter, Geschlecht, Depressivität (Beck-Depressions-Inventar BDI) und Händigkeit (Edinburgh Handedness Inventory EHI) erklärt wird, wurde herausgerechnet. Ebenso wurde die Leistung im TMT-A als Störfaktor in den TMT-B-Analysen herausgerechnet.

Als Ergebnis der Arbeit, konnten der Leistung im TMT-A sowie im TMT-B spezifische neurobiologische Korrelate zugeordnet werden.

Eine gute Leistung im TMT-A, welche gute visuomotorische Fähigkeiten darstellt, korrelierte mit dem Volumen der grauen Substanz in einem Cluster, welcher im linken Gyrus supramarginalis (SMG) lokalisiert ist. Die Leistung im TMT-B korrelierte mit dem Volumen der grauen Substanz in einem Cluster der linken inferioren frontalen Junktion (IFJ). Das Volumen dieses Clusters zeigte zudem einen positiven Zusammenhang mit der fraktionellen Anisotropie (FA) verschiedener weißer Faserbahnen: dem linken Fasciculus longitudinalis superior, der linken Capsula externa und zu einem geringeren Grad mit dem linken Fasciculus uncinatus. Hingegen zeigte der Cluster im linken SMG keinen signifikanten Zusammenhang mit der weißen Substanz. Weiterhin konnte gezeigt werden, dass der Cluster im linken IFJ, welcher mit einer guten Leistung im TMT-B korreliert, Teil eines frontoparietalen Netzwerkes ist.

Diese Arbeit weist auf eine Rolle des IFJ als Teil eines exekutiven Kontrollnetzwerkes hin und stützt die Rolle des SMG in visuomotorischen Fähigkeiten.

Summary

Executive function is a theoretical construct that summarizes a set of mental facilities that are essential for everyday life. A frequently applied test measuring executive function in research as well as clinical settings is the Trail-Making Test B (TMT-B). In contrast, TMT-A primarily reflects visuomotor abilities. The current study aims to explore different neurobiological correlates (grey matter volume, functional connectivity and structural connectivity) of performance in executive control in the healthy aging brain. Subjects were excluded if major pathological findings were detected in the MR data. Performance in TMT-A was regarded as a confounder in statistical analysis.

For this purpose, an interindividual variability approach was employed. It was investigated whether there are correlations between TMT performance scores and grey matter volume (GMV) as well as structural and functional connectivity. This multimodal approach is based on a population-based sample of 397 older adults between 55 and 80 years of age. For neurobiological analysis, GMV was examined by voxel-based morphometry analysis (VBM), structural white matter tracts by tract based spatial statistics (TBSS) and functional connectivity by seed-based Resting-State functional magnetic resonance imaging (RS-fMRI). Seed-based RS-fMRI was performed with significant seeds provided by previous VBM analysis. Notably, correlations were adjusted for the confounding effects of age, gender, depressiveness (Beck Depression Inventory BDI) and handedness (Edinburgh Handedness Inventory EHI). The same confounders were used in all statistical analysis.

VBM analysis revealed that performance in TMT-A positively correlates with GMV in a cluster of left the supramarginal gyrus (SMG) and performance in TMT-B with GMV in a cluster of the left inferior frontal junction (IFJ). In order to analyse whether local GMV is associated with the integrity of certain white matter tracts, the relationship between local volume and fractional anisotropy (FA) of white matter tracts was analysed. There was no significant correlation between GMV of the cluster in the left SMG and FA. In turn, a positive correlation between the local volume of the cluster in the left IFJ and FA of the left external capsule (EC), of the superior longitudinal fasciculus (SLF) as well as to a minor degree with FA of the uncinate fasciculus (UC) was observed. RS-fMRI revealed that the significant cluster in the IFJ, which correlates with good performance in TMT-B, is part of a fronto-parietal network.

Consequently, these results provide additional support for a role of the SMG in visuomotor abilities and a role of the IFJ in executive functioning. The study at hand reveals the integration of this latter in an executive control network and the correlation of GMV of this cluster with the integrity of important white matter tracts (i.e. the left external capsule (EC), the left superior longitudinal fasciculus (SLF) and the left uncinate fasciculus (UC)).

List of abbreviations

BDI Beck Depression Inventory
BOLD blood-oxygen-level dependent
CA Cornu ammonis
CSF cerebrospinal fluid
CT completion time
DWI diffusion weighted imaging
DTI diffusion tensor imaging
dl dorsolateral
EC external capsule
EHI Edinburgh Handedness Index
EPI Echo Planar Imaging
FA fractional anisotropy
FD Fascia dentata
FWE familywise error rate
fMRI Functional magnetic resonance imaging
GF gyrus fusiformis
GMV grey matter volume
HATA hippocampal-amygdaloid transitional area
IFJ inferior frontal junction
IPJ inferior parietal junction
MRI magnetic resonance imaging
MNI Montreal Neurological Institute
OP parietal operculum
PFC prefrontal cortex
RS-fMRI Resting-state functional magnetic resonance imaging
SCA Seed-based component analysis
SLF superior longitudinal fasciculus
SMG supramarginal gyrus
TBSS tract-based spatial statistics
TMT-A Trail-Making-Test-A
TMT-B Trail-Making-Test-B
UC uncinate fasciculus
VBM voxel-based morphometry
WM white matter
vl ventrolateral
vm ventromedial
WCST Wisconsin Card Sorting Test

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Neurobiological correlates of executive control in the healthy aging brain

1 Introduction

1.1 Executive function

1.1.1 Generalities

Executive control is a theoretical construct which implies distinct functions of the brain which are frequently associated with the prefrontal cortex (PFC) (Buchsbaum, Greer et al. 2005). It is a term commonly applied in psychology. However, up to now, there is no standard definition of executive functions. Several different cognitive abilities form this comprehensive theoretical construct.

The term subsumes cognitive processes such as working memory, cognitive flexibility, inhibition of irrelevant stimuli and temptations as well as interference control (Diamond 2013). Cognitive control is essential to manage various upcoming tasks and thoughts such as multitasking in everyday life and even self-regulation (Mischel, Ayduk et al. 2011). Patients with frontal lesions show reduced performance in daily-life functioning due to impaired executive functions (Godbout, Grenier et al. 2005).

Executive performance is influenced by specific genes (Barnes, Dean et al. 2011), but training (Dahlin, Neely et al. 2008, Diamond 2013), as well. To mention there is great interindividual variability in executive function capabilities in average population - especially when regarding aging people, even though they are healthy (Caspers, Moebus et al. 2014).

Furthermore, it is notable that executive function performance indeed predicts certain clinical and social differences (e.g. (Young, Friedman et al. 2009)). For instance, executive functions are of importance in neuropsychology of attention-deficit disorder (ADD)/ attention-deficit/hyperactivity disorder (ADHD)(Brown 2008), Parkinson`s disease (Dagher, Owen et al. 2001) and Alzheimer`s disease (Perry and Hodges 1999). Performance in executive control in patients affected by dementia may already be impaired in the preclinical phase (Rapp

and Reischies 2005). In any case, executive control skills actually contribute to quality of life (Brown and Landgraf 2010), achievements in school (Duncan, Dowsett et al. 2007) and work (Bailey 2007), health outcomes (Miller, Barnes et al. 2011), mental health (Diamond 2013) and social competences (Denson, Pedersen et al. 2011). Especially in the elderly, executive control can preserve autonomy and staying active (Poranen-Clark, von Bonsdorff et al. 2017).

There are plenty of studies on executive control. Some of them – especially the most preeminent studies that have been published up to now – are introduced in the next section.

1.1.2 Previous research on executive function

The most famous model was published by Miyake et al (2000) who propose that executive functions are mainly composed of shifting between tasks or mental sets, updating and monitoring of working memory and intended inhibition of prepotent, irrelevant responses (Miyake, Friedman et al. 2000). The authors suggest that although these subcomponents form a unity (the common executive function factor), they are also distinguishable as they are engaged separately, e.g. when performing the Wisconsin Card Sorting Test (WCST), the main executive function needed is shifting. This can be referred to as the unity and diversity model of executive functions. So different activities such as executive tasks retrieve these executive functions to different degrees.

The authors recently refined this theory by showing that inhibition, in contrast to updating and shifting, perfectly matches common executive functions as there are no inhibition specific factors contributing to general executive function (Miyake and Friedman 2012).

Even though, all components can be subdivided, e.g. inhibition has been divided into inhibition related functions (Friedman and Miyake 2004), which shows that the terms themselves are generalized and rather umbrella terms for elaborate cognitive functions.

In addition to Miyake, in scientific literature many different descriptions of executive control have been suggested which show differences but overlaps, as

well. Miyake introduced “updating, shifting and inhibition” as the fundamental three components of executive control, whereas Alvarez and Emory selected “working memory, attention and inhibition” as three elementary components (Alvarez and Emory 2006). Like in Miyake´s model, Allain includes inhibition and shifting of mental set in his definition, but adds abstract thinking (Allain, Nicoleau et al. 2005). These functions “act at the highest levels of cognition to optimize performance on complex laboratory or everyday tasks” (Allain, Nicoleau et al. 2005). Executive functions are needed to enable adaptation to complicated or novel situations, but even everyday tasks need control mechanisms to adjust to the given context (Collette, Hogge et al. 2006). So, executive control serves flexibility and accurate adaptation to the relevant context, i.e. updating and maintaining necessary information in working memory and integrating it into the current situation to achieve the most adequate action (Willcutt, Doyle et al. 2005).

It is obvious, that scientific literature offers lots of approaches to define executive control. Up to now, there is no unambiguous description of this theoretical construct.

Executive functions are usually related to the PFC. Importantly, performance is related to both grey matter volume (GMV) in specific regions (according to the function targeted) and structural connectivity/white matter (WM). Some authors have recently shown that in young subjects fractional anisotropy (FA) of selected white matter tracts is associated with grey matter morphometry. FA partially mediates the relationships of GMV with executive performance, e.g. research on structural correlates of executive control in healthy, young adults has brought to light that high performance in common execution functions as well as updating and shifting goes along with reduced GMV in the ventromedial (vm), ventrolateral (vl) and dorsolateral (dl) parts of PFC. Apart from shifting, good performance in these functions is accompanied by higher FA values in the superior longitudinal fasciculus (SLF) and inferior frontooccipital fasciculus (iFOF) (Smolker, Depue et al. 2014).

Variability in executive functions may also be attributed to resting state networks as performance could be shown to be correlated to certain patterns of resting-

state functional connectivity inside large-scale brain networks and between them (Reineberg, Andrews-Hanna et al. 2014). Two top-down control networks have been described: a cingulo-opercular network for stable set-maintenance and a fronto-parietal one for fast adaptive control (Dosenbach, Fair et al. 2008).

A common measure of executive control in clinical and experimental settings is the so called Trail Making Test (TMT) that is described in the next section.

1.1.3 Trail Making Test

Trail Making Test B (TMT-B) is a neuropsychological test that is commonly used as a measure of executive control. This easily applied test is even frequently used in clinical settings as a screening measure for executive dysfunction (Lezak 2004), e.g. TMT-B can even predict the progress from mild cognitive impairment to Alzheimer`s disease (Ewers, Walsh et al. 2012) and can frequently spot cognitive dysfunction in patients with minor stroke and transient ischemic attack (Soros, Harnadek et al. 2015).

TMT-B is the extended version of TMT-A which targets cognitive functions such as visuomotor speed, processing speed, attention, set-shifting and rule maintenance. Whereas TMT-B retrieves additional cognitive resources: working memory is essential for maintaining the current position in a sequence of letters and numbers and for updating it after switching. In addition, in TMT-B rule observance becomes more important since both automatically reproduced sequences need to be steadily interrupted because of switching. Consequently, attention has to be frequently shifted from letters to numbers and the other way round reflecting cognitive flexibility. Inhibition control is also required to focus on the relevant task. Thus, TMT-B may engage all functions of Miyake's model: shifting, updating and inhibition. Consequently it can be considered as a general measure of executive control, i.e. the common executive function factor.

Performance in TMT-B has found to be lower among people with different forms of brain damage and among older people (Spreen and Strauss 1998, Mitrushina, Boone et al. 1999, Salthouse, Toth et al. 2000, Lezak 2004). Neurocognitive aging is introduced in the next section (1.1.4)

In order to assess executive control performance three different scores are used to minimize the influence of visuomotor and processing speed on performance in TMT-B: B-A difference, B/A ratio (Corrigan and Hinkeldey 1987) and the B-A/A proportional score (Perianez, Rios-Lago et al. 2007).

Aiming at investigating whether TMT-B performance reflects executive control, a study tested the correlation with set-switching paradigms (Arbuthnott and Frank 2000). The authors found strong evidence that TMT-B represents executive control processes. Especially B/A ratio showed a positive correlation with alternating task performance. Consequently, they propose that the B/A ratio is the best indicator of executive control functions. The authors assume that in managing rapid alternation attentional control is necessary, which they particularly relate to the performance in dissolving inhibition of a previously-abandoned task, i.e. going back to a previous arrested task instead of focusing on attention switching.

Whereas another study proposes the B-A difference as the best indicator of executive control (Sanchez-Cubillo, Perianez et al. 2009). Therefore further investigation is necessary to prove which score optimally reflects executive control.

As introduced later, the current study has not used those scores. Instead a multiple regression model was applied, i.e. it has been analysed which effect is explained by performance in TMT-B, that is not already accounted for by performance in TMT-A (and other crucial regressors).

To emphasise, there are several tests reflecting executive control and at the time there is no test that is without having any doubt the best measure of executive control (Royall, Lauterbach et al. 2002).

1.1.4 Neurocognitive aging

In general, aging is associated with cognitive decline. Evidently, cognitive domains are affected to different degrees – cognitive control is one of the cognitive abilities that is affected most frequently (Hedden and Gabrieli 2004).

Studies performed on older adults reveal that high performance in executive control, measured by TMT and Backwards Digit Span, is positively correlated with GMV in vlPFC and dlPFC (Ruscheweyh, Deppe et al. 2013).

Correlation detected in this study potentially results from the general tendency that GMV (mainly in the PFC) and WM/structural connectivity are influenced by aging. These structural alterations in the aging brain are associated with lower performance in executive functions (e.g. (Burzynska, Nagel et al. 2012)). As brain performance decreases in general with increasing age some studies have shown that in addition to grey matter changes FA values as a measure of white matter decrease in the process of aging (e.g.,(Bennett and Madden 2013)), as well. Both structure, i.e. volume, thickness, folding and surface area decrease (Hogstrom, Westlye et al. 2013), and function change with increasing age. Network connectivity in Resting-State functional magnetic resonance imaging (RS-fMRI) analysis decreases with growing age (Allen, Erhardt et al. 2011). Moreover, in the context of aging increased recruitment of brain regions may represent a kind of compensation for degenerative aging processes (Buckner 2004).

These effects of aging on the human brain show that an aging population provides a lot of interindividual variability of cerebral structure and function. The study at hand has taken advantage of these interindividual variations in the aging brain by examining a huge cohort of older subjects aiming at investigating behavioural measures and brain structure as well as functioning. Therefore age has been included as a confounding factor in the multiple regression model that was applied for statistical analysis.

1.2 Aims of the study

The issue arises what range of interindividual variability is physiological, i.e. which extent of deviation cannot be ascribed to a pathological state such as Alzheimer´s disease. Up to now, no study has directly examined the relationships between GMV, FA, RS-fMRI and executive performance within a great sample of healthy older subjects. Therefore, further research is necessary to comprehensively elucidate structural and functional correlates of

executive control in a large sample of aging subjects. This comprehensive cohort study aims to elucidate which neurobiological correlates can be ascribed to good executive function capabilities – after controlling for general aging trends (Bennett and Madden 2013, Hogstrom, Westlye et al. 2013) and other relevant confounding variables. The objective is to disentangle higher-order cognitive processes (i.e. executive functioning) from more visuo-motor processes at the brain level. The study at hand will be introduced in the next section “Overview of the study”.

This study which just concentrates on neurobiological correlates of executive control performance may serve as a basis for future studies examining if there is some kind of cognitive reserve (Buckner 2004, Whalley, Deary et al. 2004, Stern 2012), which preserves performance, although structural or functional changes have occurred, i.e. which neurobiological changes occur during aging that correlate with a sustained executive control performance.

1.3 Overview of the study

Up to now, most studies have been performed on a small sample of people, whereas this study is an epidemiologic population-based comprehensive cohort study currently running at the research centre FZ Jülich. The large study size and the great scope of data acquisition provide an extensive opportunity to investigate the interindividual variability of structural and functional characteristics of the aging brain. A major advantage of the 1000 Brains study which is a German cohort study performed on older people, compared to pooled data is homogenous data collection. So acquisition variability is minimized and thus, interindividual variability is more reliable. Thanks to the large study size and homogenous data sets due to consistent data acquisition even small effects can be found.

As mentioned above, the main aim of this study is to investigate neurobiological correlates in terms of brain structure, function and connectivity of interindividual difference in executive functioning as measured by TMT-B within an aging population. As introduced in passage 1.1.4 which addresses the issue of neurocognitive aging, an aging population offers a lot of interindividual variability

in performance scores as well as in structural and functional brain aspects. The basis of this investigation is to calculate residual scores, i.e. to compute which neurobiological factors cannot be attributed to the general effects of aging or other possible confounders. Therefore the covariates Beck Depression Inventory (BDI) and Edinburgh Handedness Inventory (EHI) scores were included in statistical analysis as possible confounding influences on cognitive performance and hence on TMT performance. For the same reason it was also controlled for age and gender (e.g. Barnes et al (2010) showed that age and gender influence voxel based morphometry (VBM) results).

Additionally, the differentiation between TMT-A and TMT-B performance scores was made considering that executive functioning measured by TMT-B is a residual score, as well. The examination focused on what can be explained by TMT-B that is not already explained by TMT-A. TMT-A serves as a measure for general attention and rule maintenance as well as visuomotor abilities and processing speed. So the influence of these general abilities is subtracted from a TMT-B performance score which consequently represents executive control more purely.

In addition to the analysis of neural correlates of TMT-B, those of TMT-A were investigated, as well, to expose which neurobiological correlates reflect visuomotor abilities. The intention is to disentangle cognitive control processes from more visuomotor processes reflected by TMT-A performance.

Fundamentally, this study is a multimodal approach in order to get a comprehensive understanding of executive functions as grey matter and white matter are interdependent. There is the need to investigate both structural and functional characteristics to identify the whole cortical network engaged in executive performance.

In order to detect interindividual variability in the aging human brain, this study investigates the correlation of TMT performance with neuroimaging data acquired in the 1000 Brains study.

1. Voxel based morphometry (VBM) was used to examine regional volume of grey matter.

2. Seed-based Resting-state functional MRI (RS-fMRI) was applied to detect and evaluate functional networks. RS-fMRI is used to examine functional networks based on BOLD data sets (blood oxygenation level dependent). BOLD is an indirect measure of cerebral activity as increased cerebral blood flow is measured induced by increased cell metabolism due to neural activity (Logothetis and Wandell 2004). Using RS-fMRI it was analysed which cortical networks our clusters detected in VBM analysis are engaged in.
3. Further, diffusion imaging evaluated by tract based spatial statistics (TBSS) was performed to study white matter fibre tracks. At the time, Diffusion Tensor Imaging (DTI) is the only non-invasive method to track white matter tracts and to investigate connectivity in the brain (Le Bihan and Johansen-Berg 2012).

These methods facilitate comprehensive studies to investigate structure (VBM), functional connectivity (RS-fMRI) and structural connectivity (TBSS) of the human brain.

The expectation of the outcome of the current study is that there are cortical clusters which show enhanced grey matter density that can be ascribed to better performance in executive functions as measured by TMT-B as its performance scores capture variance in these clusters which cannot be explained by the aforementioned covariates. Furthermore, it is expected that a delineation of functional networks which the significant clusters are engaged in, as well as a delineation of corresponding white matter tracts is possible. Corresponding white matter tracts are fibre tracts whose FA shows a positive correlation with GMV of the significant clusters in the foregoing VBM analysis.

2 Methods

2.1 Participants

This work is based on data obtained through the 1000 Brains study that is currently running at FZ Jülich (Caspers, Moebus et al. 2014). This project aims at investigating structural and functional variability in the healthy aging human brain.

The Heinz Nixdorf Recall Study, which is an epidemiologic population-based German cohort study to investigate cardiovascular risk factors, provided participants who were followed up for ten years.

Exclusion criteria are coronary artery stents, cardiac pacemakers or surgical implants and implanted prostheses as well as claustrophobia, status post head surgery, tattoos or permanent make-up on the head. Dental implants and bridges are relative contraindications as they may produce artefacts in the MR images. Furthermore, subjects were excluded if major pathological findings were detected in the MR data. To note, neurological or psychiatric history is not an exclusion criterion.

The study protocol was approved by the local ethics committee of the University Duisburg-Essen (reference number: 11-4678). After a complete description of the procedure participants provided their written informed consent to take part in the study. In addition, the ethics committee of the Heinrich-Heine-University in Düsseldorf approved the evaluation of the data collected in the 1000 Brains Study to examine structure, function and connectivity of the human brain (study number: 5193).

From the original sample of the 1000 Brains study subjects who are between 55 and 80 years old were selected (Table 1). Further inclusion criteria were an assured right-handedness as reflected by scores greater than 20 at the Edinburgh handedness inventory (Oldfield 1971) and the absence of a clinical depression as reflected by scores below 14 at the Beck Depression Inventory (Beck, Ward et al. 1961, Hautzinger, Keller et al. 2006). Considering all these criteria a sample of 409 subjects was yielded. In the course of test implementation and analysis outliers were excluded for each TMT part when the

completion time (CT) exceeded 4 standard deviation (SD) from mean CT score (Table 1). Three subjects had to be excluded based on TMT-A CT scores and nine subjects had to be precluded based on TMT-B CT scores. Ultimately, the sample included 397 subjects (222 males and 175 females).

Table 1: Sample data – variable distribution

Variable	Mean	Standard deviation	Minimum	Maximum
Age	66.30	6.23	55	80
BDI	3.83	3.35	0	13.00
EHI	84.25	17.30	25.00	100.00
TMT-A	35.00	11.65	16.06	85.68
TMT-B	79.13	33.00	30.41	212.85

Age in years; Beck Depression Inventory (BDI) scores ranging from 0 to 63; Edinburgh handedness inventory (EHI) scores ranging from -100 (complete sinistrality) to 100 (complete dextrality); Trail-Making-Test-A (TMT-A) and Trail-Making-Test-B (TMT-B) scores in seconds

2.2 Neuropsychological assessment

In the 1000 Brains study extensive neuropsychological tests of attention, memory, executive functions and language as well as examinations of motor skills and ratings of personality, life quality, mood and daily activities were conducted and laboratory and genetic data were collected. TMT-A and TMT-B performance scores as well as BDI and EHI scores were chosen to be relevant for this study.

Participants performed both TMT-A and TMT-B. When undertaking TMT-A, the participants were instructed to link 25 ascending numbers spatially scattered on a sheet of paper as quickly as possible without lifting the pen. Given the well known ascending sequence of numbers in the normal population this task can be performed almost automatically. To consider, when an error occurs the

subject is immediately stopped and asked to correct his mistake. Consequently the error can be corrected but the time needed for the task increases.

TMT-B is an exacerbated version of TMT-A as the participant has to switch between linking the ascending sequence of numbers (1- 13) and linking letters (A-L) alphabetically which are again irregularly distributed on a sheet of paper. Once again, the time required for undertaking the test should be as short as possible. The pattern is 1A, 2B, 3C, 4D, 5E… Thus, TMT-B engages more cognitive resources than TMT-A and the above-mentioned partitions of executive control are added to the cognitive demands of TMT-A (visuomotor speed, processing speed, attention).

Total CT was selected as the performance score.

Impairment becomes obvious by a longer execution time. Maximum time for part A is set at three minutes and for part B at five minutes.

Outliers, whose scores varied more than four standard deviations, were removed from statistical analysis. Three subjects were excluded because they were considered as outliers for TMT-A and nine subjects were excluded as outliers for TMT-B.

In statistical analysis multiple regression was performed to obtain residual behavioural scores (for both TMT-A and TMT-B), i.e. the part of variance of behavioural performance was removed that was related to the confounding variables age, gender, BDI and EHI scores (and TMT-A scores for TMT-B analysis). Then in subsequent correlational analyses of the relationship between brain and performance scores, it was controlled again for the confounding effects of the confounders introduced above.

Consequently, it was detected which of the results can be explained by a good performance in TMT-A or TMT-B and is not already explained by the effects of aging, gender, depressiveness or handedness.

2.3 Magnetic resonance imaging acquisition

MRI was performed on a 3 Tesla MR scanner (Tim-TRIO, Siemens Medical Systems, Erlangen, Germany) in Research Centre Jülich. Namely, 3D-T1 scans (sequence parameters: 176 slices, TR = 2.25 s, TE = 3.03 ms, TI = 900 ms, FoV = 256 x 256 mm², flip angle = 9°, voxel resolution: 1 x 1 x 1 mm³) were acquired for structural analyses and myelin mapping. In addition, for TBSS diffusion tensor imaging (DTI) with high-angular resolution diffusion imaging (HARDI) subset (EPI (Echo Planar Imaging), TR = 6.3 s, TE = 81 ms, 7 b0-images (interleaved), 60 images with b = 1000 s/mm², voxel resolution = 2.4 x 2.4 x 2.4 mm³) were acquired for detailed fibre tracking and diffusion kurtosis imaging (DKI). T2-weighted resting-state scans (176 slices, TR = 3.2 s, TE = 417 ms, FoV = 256 x 256 mm², voxel resolution: 1 x 1 x 1 mm³) were acquired for functional analysis. Finally, fluid-attenuated inversion recovery (FLAIR) and MR angiography were acquired for clinical assessment of the subjects and white matter lesion mapping. In this study, imaging data analysis was restricted to 3D-T1-weighted scans, DTI and resting-state functional MRI as sufficient measures of structural, connectional and functional characteristics of the human brain.

2.4 Voxel based morphometry

To assess whole brain cerebral volume the voxel-based-morphometry toolbox implemented in SPM8 by Gaser (http://dbm.neuro.uni-jena.de/vbm/) was used to identify regional differences in brain volume that relate to a particular phenotype (here: performance in TMT). In order to achieve this, T1-weighted MR images were processed as firstly proposed by Ashburner (Ashburner and Friston 2000, Ashburner 2009): First, each image was aligned to a standard template in stereotactic space using linear/global and nonlinear/local normalization. Linear normalization means a proportional modification (e.g. sliding, enlarging, etc. of the whole brain), whereas nonlinear normalization means adjusting certain areas to the given template. In this context, modulation was considered (Good, Johnsrude et al. 2001) to take account for relative volume changes caused by nonlinear warping. Nonlinear warping means

adjusting particular brain regions to the template. This operation is encoded in by intensity values. For example, if a certain region shrinks to a quarter of its volume the intensity has to be quadrupled (i.e. has to be multiplied by its Jacobian determinant). Consequently, the volume of each location is sustained. Each voxel (1x1x1mm³) has a certain probability to belong to grey matter, white matter or cerebrospinal fluid (CSF) as a voxel may not be exclusively of one tissue class, but can consist of different tissues (partial volume effects , cf. (Van Leemput, Maes et al. 2003)). Consequently, high resolution (1 x 1 x 1 mm³) is preferable to minimize partial volume effects. Finally, smoothing by using an isotropic Gaussian kernel of 8 full width at half maximum was conducted to minimize the effects of noise and intersubject variability (Ashburner and Friston 2000). So each voxel`s value is a weighted average of a defined proximity. These steps resulted in one image per subject in standard space which contains for each voxel the local volume at the corresponding location of the individual brain. These were used for statistical analysis. For this purpose the performance in a given test or another aspect under study (here TMT performance) can be correlated with the volume of each voxel. Besides, the resulting values were adjusted for total brain sizes as only nonlinear modulated images were used.

2.5 Resting-state functional magnetic resonance imaging

RS-fMRI was used to examine functional networks based on BOLD (blood oxygenation level dependent) data sets. BOLD is an indirect measure of cerebral activity as increased cerebral blood flow is measured induced by increased cell metabolism due to neural activity (Logothetis and Wandell 2004). Slow (<0,1Hz) spontaneous fluctuations were registered.

FMRI time series were recorded while the subjects lay in a supine position in the scanner instructed to keep their eyes closed, letting their mind wander and not to fall asleep. Thus, spontaneous brain activity corresponding to an unconstraint flow of thought was measured. However, it should be considered that a subject is never really at rest, but is rather employed with various kinds of

thought processes with some evidence for a predominance of introspective mental operations.

Brain networks are revealed by resting-state analysis to show strong activity correlations which are similar to networks engaged in task-based fMRI studies (Smith, Fox et al. 2009). From this simultaneous activity one may infer that these cortical regions are interacting with each other being directly or indirectly structurally connected. It is not possible, though, to infer any causal connection as exact structural sequences underlying these mechanisms remain unknown.

Functional image processing was performed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and Matlab R2014a. Prior to further analyses, the first four scans were discarded and EPI images were corrected for head movements by affine registration. This was achieved by using a two-pass procedure in which the images were first aligned to the initial volumes and afterwards to the mean ones. The mean EPI image for each participant was then spatially normalized to the 2x2x2mm³ Montreal Neurological Institute (MNI) single-subject template employing the “unified segmentation” approach (Ashburner and Friston 2005). The subsequent deformation was then applied to the individual EPI volumes. Finally, images were smoothed by a 5-mm full-width at half-maximum (FWHM) Gaussian kernel in order to improve the signal-to-noise ratio and to compensate for residual anatomical variations.

The time-series data of each voxel were processed as follows. In order to reduce disturbing correlations variance that could be explained by the following nuisance variables was removed (cf. (Satterthwaite, Elliott et al. 2013) for an evaluation of this framework): the six motion parameters that originated from the image realignment; their first derivatives; mean white-matter, grey-matter and CSF signal per time-point as obtained by averaging across voxels attributed to the respective tissue class in the SPM8 segmentation. Finally, data was band-pass filtered with the cut-off frequencies of 0.01 and 0.08 Hz.

Seed-based component analysis (SCA) was performed and the significant clusters obtained in VBM analysis of TMT-A and TMT-B were selected as Seed

region A and Seed region B. The intention is to connect structural and functional analyses to examine in which cortical networks the clusters are integrated. First, clusters functionally coupled with our seed regions were analysed, i.e. voxelwise whole-brain correlations of time courses with our seeds were computed - the main effect of Seed A and Seed B. Afterwards a conjunction analysis was performed to reveal regions that are functionally related to both seeds. Finally, it was tested whether these correlations were modulated by performance in TMT A, TMT- B or age.

Finally, RS-fMRI is a complementary method to structural tools as RS-fMRI adds the dimension of time to brain analysis. This method enables the investigation how relevant regions detected by VBM are integrated into certain functional brain networks.

2.6 Tract based spatial statistics

In addition to structural analysis of grey matter and its functional connectivity the present study aims at investigating correlations between performance in TMT and the integrity of connecting tracts.

In the current study TBSS was employed which is a nonlinear registration algorithm that is used as an improved registration method for major white matter tracts in order to provide comparable data (Smith, Jenkinson et al. 2006, Smith, Johansen-Berg et al. 2007).

TBSS is a method to analyse properties of the brain's white matter, i.e. fibre tracts based on diffusion weighted imaging (DWI). DWI records the diffusion of water molecules which is a random motion of molecules dependant on thermal energy. It can either be isotropic or anisotropic. Isotropic water diffusion occurs when diffusion is unhindered in all directions (e.g. in liquids such as CSF). In contrast, anisotropic water diffusion appears when the grade of diffusion varies in diverse directions because of obstacles. Anisotropic diffusion is characteristic of white matter (Chenevert, Brunberg et al. 1990) in which the different axons and larger fibre bundles are arranged in parallel (Le Bihan, Turner et al. 1993).

Here motion is orthogonally restricted, e.g. by cell membranes and nearly unrestricted parallel to fibre tracts.

To note, when fibres spread while approaching the cortex or cross each other anisotropy declines.

The diffusion tensor (DT) is established out of three eigenvectors (Basser and Jones 2002). Each eigenvector is defined by its direction and eigenvalue. The eigenvector which presents the largest eigenvalue, reflects the major diffusion direction and is assumed to represent the major fibre orientation (Douek, Turner et al. 1991). FA is a commonly used parameter that quantifies the degree of anisotropy. FA is computed from the eigenvalues of the diffusion tensor and can take values between 0 and 1 reflecting the range from low to high anisotropy.

In this context, the study at hand aims at investigating correlations between performance in TMT and the intactness of connecting tracts. Some studies show that in general FA values decrease while aging (e.g. (Bennett and Madden 2013)). At present, DTI is the only non-invasive method to track white matter fibre tracts and to investigate connectivity in the human brain (Le Bihan and Johansen-Berg 2012).

The pre-processing of images included corrections for eddy currents and head motion. Afterwards, a diffusion tensor model was applied to the set of diffusion-weighted images. After that FA maps were calculated for each subject, which were visually inspected for data quality, artefacts and intensity range problems.

First, all subjects` FA images were aligned to a registration target, which is the most typical subject of the group, and then transformed into 1x1x1mm MNI152 space. Then the mean of all images was created and thinning was performed, i.e. non-maximum-suppression at right angle to the local tract structure and the voxel with the highest FA was declared the centre of the tract. A threshold of FA=0.2 was applied to restrict analysis to white matter and reduce the influence of low anisotropy, e.g. because of voxels composed of several tissue types (e.g. CSF is a quite isotropic medium and therefore its FA tends towards zero) and high intersubject discrepancies. This skeleton served as a template so that all FA images could be projected on. The maximum FA value perpendicular to the skeleton is the respective tract centre. This procedure makes major paths

comparable due to accounting for cross-sectional variability of equal pathways, e.g. because of enlarged ventricles (Smith, Johansen-Berg et al. 2007). Finally, voxelwise statistics was applied to evaluate the relationship between local FA and cognitive performance (in our case measured by TMT).

In the current study statistical analysis between our Seeds A and B, obtained by VBM analysis, and FA was performed to investigate whether there are any relationships between GMV in our region of interest and white matter integrity. The aim was to detect both negative and/or positive correlations between GMV of the seed regions A and B with the FA of white matter tracts on voxel level. Similar to VBM analysis, age gender, BDI and EHI were included as covariates in the design matrix.

2.7 Statistical analysis

Statistical analysis was performed using MATLAB. In all of the statistical analyses it was searched for both positive and negative correlations as the aim was to elucidate all relationships between performance in executive control and neurobiological correlates comprehensively, e.g. in VBM analysis, the objective is to identify cortical regions, whose GMV shows a negative or positive correlation with performance in TMT-A or TMT-B, i.e. good test performance correlates with either larger GMV or smaller GMV in certain cortical areas. In the same manner it was searched for both positive and negative correlations in all analyses conducted in this study, i.e. RS-fMRI and TBSS.

All of the analyses to be performed are voxel-based, i.e. each voxel in the brain was analysed individually. This raises the need to account for massive parallel testing. For that purpose permutation methods were conducted on structural results (i.e. for cognitive-morphological correlations and correlations between FA and cognitive performance/seeds). For VBM results 2646 permutations for TMT-B analysis/ 25000 permutations for TMT-A analysis and for TBSS results 10001 permutations were performed to build a null-distribution. The number of permutations performed has been determined by the available computation resources. Subsequently, only those voxels are declared to show a significant

effect, which show a greater effect than the maximum five percent achieved by permutation, i.e. under the null-distribution.

For VBM analysis the images in standard space resulting from the aforementioned pre-processing steps were used for statistical analysis. For this purpose TMT performance was correlated with the volume of each voxel. Correlations were controlled for age, gender, handedness and depressiveness. Performance in TMT-A, performance in TMT-B, Age, Gender, the BDI score and the EHI score were included as regressors in our design matrix in order to delineate which fraction of GMV is already accounted for by these regressors. So the resulting positive or negative correlation between test performance and GMV is adjusted for the effects of the mentioned confounders. Results are depicted in a statistical parametric map (SPM).

Significance of the correlations was assessed using Threshold-Free-Cluster-Enhancement (TFCE) (Smith and Nichols 2009). TFCE was preferred instead of cluster-based thresholding, which implies setting an arbitrary threshold of voxels, or voxelwise thresholding because the method shows greater sensitivity (Smith and Nichols 2009). TFCE output is better for subsequent analysis as it considers both cluster extent and signal height. In this study no threshold was set on cluster´s extent. The results were anatomically termed by reference to probabilistic cytoarchitectonic maps of the human brain using the SPM Anatomy Toolbox (Eickhoff, Stephan et al. 2005, Eickhoff, Paus et al. 2007).

The covariates mentioned above were applied for TBSS and RS-fMRI analysis, as well.

3 Results

3.1 Statistical analysis based on residual scores

The basis of the study at hand was that its approach is set on a multiple regression model, i.e. it is calculated which neurobiological factors cannot be attributed to relevant confounders. Age, gender, depressiveness and handedness were decided to be major confounding influences in terms of this study. Therefore they are included as regressors in addition to performance scores of TMT-A and TMT-B in each multiple regression model. Depressiveness is depicted by BDI scores and handedness by EHI scores.

To mention, CT-scores of TMT-A and TMT-B are included separately as regressors in the multiple regression model to delineate neurobiological correlates that are significant for TMT-A and TMT-B. The motivation is that TMT-A rather reflects visuomotor abilities as well as general attention and rule maintenance, whereas TMT-B is a frequently applied measure of executive control performance. Executive control is depicted more purely, when adjusting for TMT-A performance because the effect is adjusted for what is already accounted by TMT-A performance.

3.2 Voxel-based morphometry analysis

3.2.1 Correlations between grey matter volume (GMV) and Trail-Making-Test-A residuals

At first, it was examined, whether there are clusters of significance, when examining the correlation between time needed for performing TMT-A and GMV adjusted for the confounding effect of age, gender, BDI and EHI. The morphometric analysis revealed a cluster of significance consisting of 4 voxels (threshold $p< 0.05$ familywise error rate (FWE)) in the left supramarginal gyrus (SMG) located in the left inferior parietal junction (IPJ) (x=-54; y=-37.50; z=36.00) (Fig.2). This cluster reveals a negative correlation between local GMV and residuals standardized CT-scores of TMT-A (Fig.1). Consequently, better performance in TMT-A, i.e. lower CT-scores, is associated with higher grey matter density in this cluster.

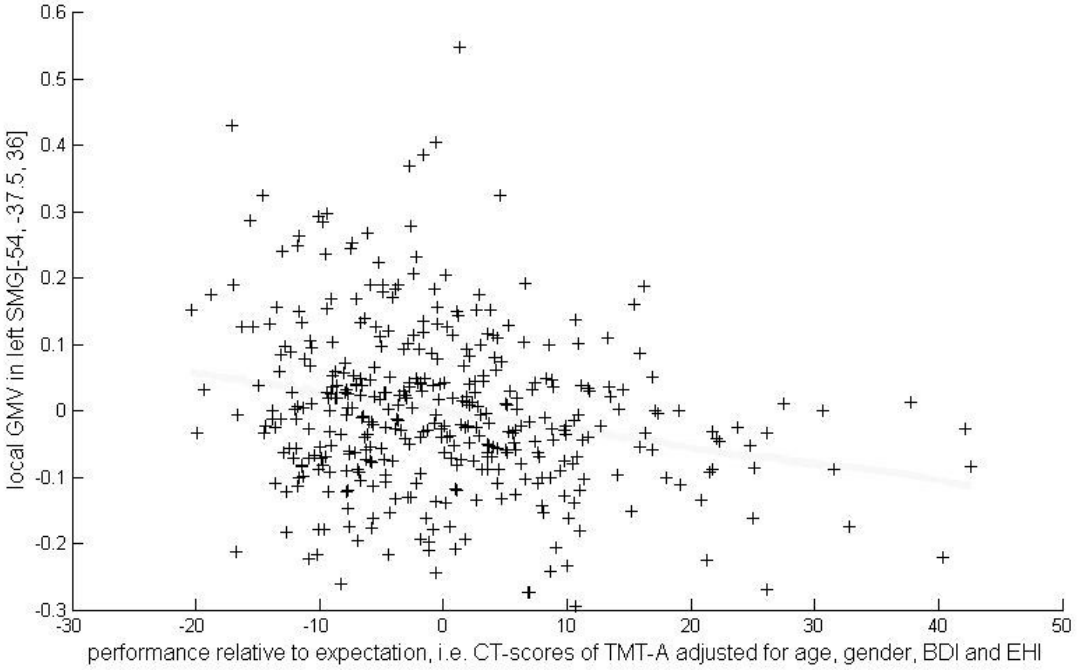

Fig. 1: Scatter plot representing the negative correlation between performance in Trail-Making-Test-A (TMT-A) and local grey matter volume (GMV) at the supramarginal gyrus (SMG) (x=-54; y=-37.50; z=36.00):

Performance in TMT-A is represented in residuals completion time scores (CT-scores), i.e. scores adjusted for effects of age, gender, Beck Depression Inventory (BDI) and Edinburgh Handedness Inventory (EHI).

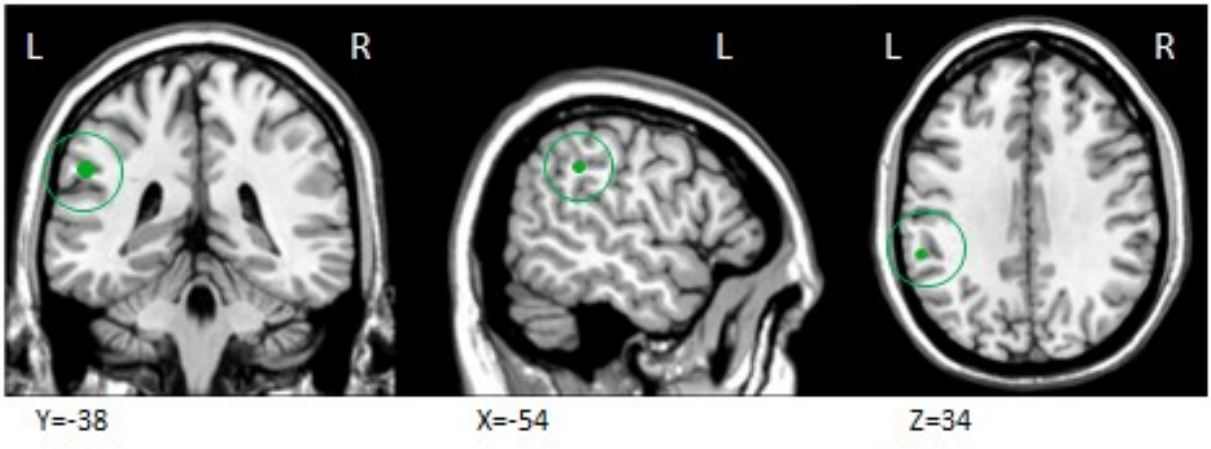

Fig. 2: Cerebral location of the cluster in the left supramarginal gyrus (SMG):

In Voxel-based morphometry (VBM) analysis, a significant negative correlation between completion time (CT) of Trail-Making-Test-A (TMT-A) and grey matter volume (GMV) of a cluster in the left supramarginal gyrus (SMG) (x=-54; y=-37.5; z=36) was observed. Cluster size is 4 voxels. The cluster is displayed and accentuated using a threshold at $p<0.05$. X, Y and Z represent the coordinates of the slices in Montreal Neurological Institute (MNI) space. L=left; R=right

3.2.2 Correlations between grey matter volume (GMV) and Trail-Making-Test-B residuals

Secondly, it was analysed if there is a correlation between performance in TMT-B and GMV, i.e. whether there is a cluster of voxels, in which a shorter completion time for TMT-B (i.e. a better performance in this test) correlates with increased GMV when adjusting for the confounding effects of age, gender, BDI, EHI and performance in TMT-A. One significant cluster consisting of 10 voxels was detected, which showed such a negative correlation with residuals TMT-B performance (threshold $p< 0.05$ (FWE) and extent threshold k= 0 voxels) (Fig.3). Its location is in the left inferior frontal junction (IFJ) (Fig.4) (x=-35; y=11; z=36).

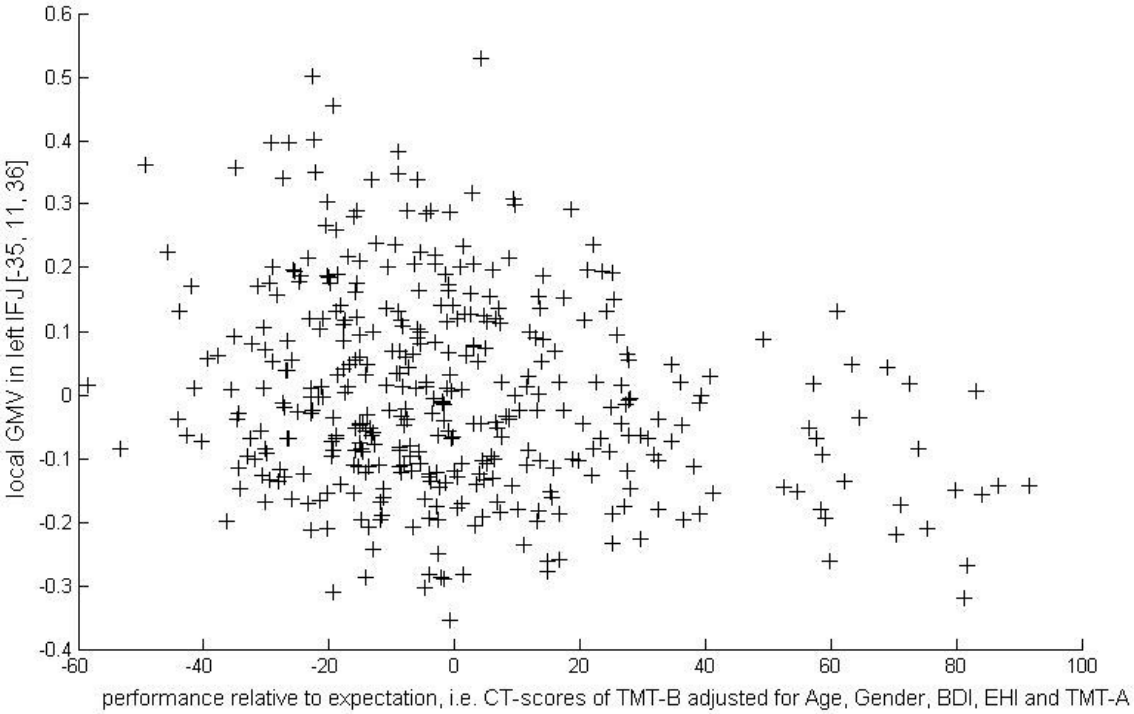

Fig. 3: Scatter plot representing the negative correlation between performance in Trail-Making-Test-B (TMT-B) and local grey matter volume (GMV) at the cluster located in the left inferior frontal junction (lFJ) (x=-35; y=11; z=36):

Performance in TMT-B is represented in residuals completion time scores (CT-scores), i.e scores adjusted for effects of age, gender, Becks Depression Inventory (BDI), Edinburgh Handedness Inventory (EHI) and Trail-Making-Test-A (TMT-A).

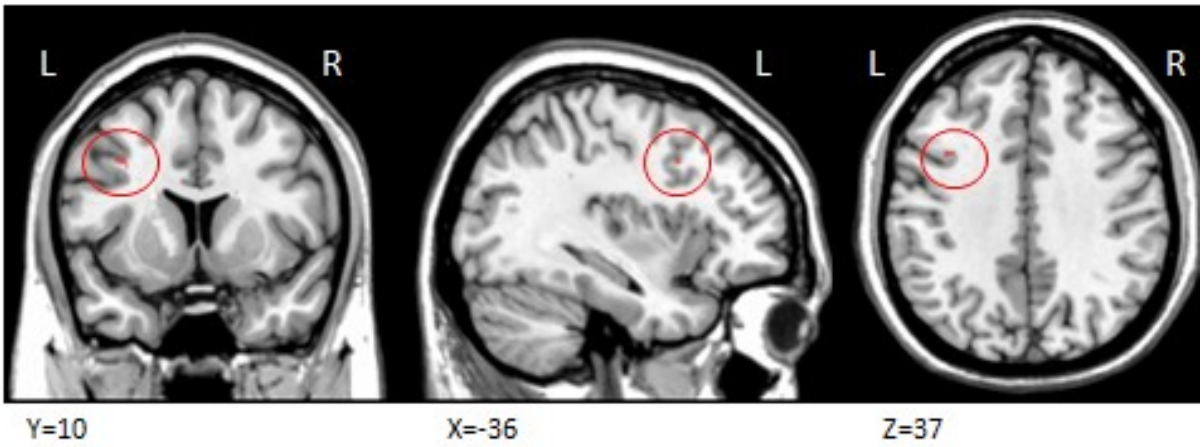

Fig. 4: Cerebral location of the cluster in the left inferior frontal junction (IFJ)

In voxel-based morphometry (VBM) analysis, a significant negative correlation between completion time (CT) of Trail-Making-Test-B (TMT-B) and grey matter volume (GMV) in the left inferior frontal junction (IFJ) (x=-35; y=11; z=36) was observed. Cluster size is 10 voxels. The cluster is displayed using a threshold at p<0.05. X, Y and Z represent the coordinates of the slices in Montreal Neurological Institute (MNI) space. L=left; R=right

3.3 Resting-State functional magnetic resonance imaging

Following VBM analysis, seed-based RS-fMRI analysis was started to integrate the structural findings into a functional context. For this purpose, the clusters identified by our VBM analysis were chosen as seed regions and different statistical tests were conducted in order to detect cortical regions that are functionally coupled with a seed region. Family-wise error (FWE) – correction with p<0.05 was performed.

3.3.1 Seed A (inferior parietal junction)

VBM analysis indicated that GMV in a cluster in the left SMG of the IPJ (x=-54; y=-37.50; z=36.00) is negatively correlated with time needed for performing

TMT-A. Subsequently, it was searched for clusters that are functionally coupled with this seed region during resting state (threshold p< 0.05 (FWE)).

The main effect of Seed A was analysed at first, i.e. which regions are functionally coupled with Seed A. As can be seen in figure 5, these clusters form functional networks, which the seed region is engaged in. Part of this or these networks (as our seed region may be engaged in more than one functional network) are left and right Area 44 (it belongs to Broca`s Area located in the inferior frontal gyrus), the left Area OP1 (belongs to parietal operculum) (Eickhoff, Schleicher et al. 2006) (Eickhoff, Amunts et al. 2006), left middle frontal gyrus, right IFJ, right SMG, right insula lobe, right middle cingulated cortex, left GF1 (area of gyrus fusiformis) (Caspers, Zilles et al. 2013), left inferior temporal gyrus, left nucleus dentatus (cerebellum), right nucleus accumbens and nuclei pontes striate caudate, left Area Fo3 and Fo4 as well as right area Fo3 and Fo1 (areas of the inferior frontal gyrus) (Table 2).

Table 2: Main effect of Seed A

The table lists significant clusters, which are the result of Resting-State functional magnetic resonance imaging (RS-fMRI) analysis of Seed region A in the left supramarginal gyrus (SMG) of the inferior parietal junction (IPJ) (x=-54; y=-37.50; z=36.00). Coordinates are reported in Montreal Neurological Institute (MNI) space.

	Location		
Anatomical region	X	Y	Z
Left Area 44/ Left Area OP 1	- 34	- 19	+ 33
Left inferior temporal gyrus	- 56	- 60	- 4
Left GF 1	- 52	- 58	- 4
Left nucleus dentatus	- 33	- 58	- 30
Left middle frontal gyrus	- 38	+ 42	- 28
Left Area Fo3/Fo4	- 24	+ 37	- 16
Right Area Fo1/Fo3	+ 20	+ 31	- 19

Right SMG	+ 62	- 36	+36
Right insula lobe	+ 34	+ 18	+ 8
Right middle cingulate cortex	+ 6	+ 6	+ 42
Right nucleus accumbens and nuclei pontes striate caudate	+ 12	- 12	+ 7
Right Area 44/ Area IFJ2	+ 35	- 14	+ 34

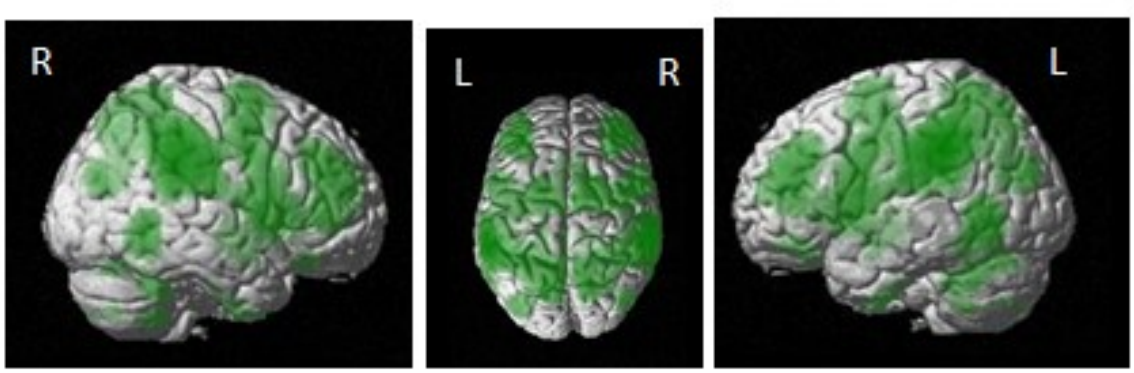

Fig. 5: Resting-State functional magnetic resonance imaging (RS-fMRI), main effect of Seed A:

These images display significant brain regions that are functionally coupled with Seed A. $p<0.05$. The results are superimposed on a 3D-standardized T1 brain template. L=left; R=right

3.3.2 Seed B (inferior frontal junction)

Whereas the VBM analysis of TMT-B yielded a cluster in the left IFJ (x=-35; y=11; z=36), which shows a negative correlation with time needed for performance of TMT-B suggesting that it plays a role in a functional network retrieving resources for executive control. This cluster is named Seed B for RS-fMRI analysis. In RS-fMRI analysis, Seed B is functionally coupled with clusters in the right IFJ, left Fp1 (frontal pole), left Area Fo5 (inferior frontal gyrus) and left Area Pfm (part of the inferior parietal lobe)(Caspers, Geyer et al. 2006), left superior parietal lobule, bilateral inferior temporal gyrus, the right Nucleus

dentatus, left pontes striate caudate, bilateral amygdala, right area Fo3-5 (areas of the inferior frontal gyrus), right middle frontal gyrus, right OP2 and OP3 (parietal operculum)(Eickhoff, Amunts et al. 2006, Eickhoff, Schleicher et al. 2006), left entorhinal cortex, left hippocampal-amygdaloid transitional area (HATA)(Amunts, Kedo et al. 2005) and left CA2, CA3 (Cornu ammonis) and FD (Fascia dentata) of Hippocampus (Fig.6).

These areas form a fronto-parietal network.

Table 3: Main effect of Seed B

The table lists significant clusters, which are the result of Resting-State functional magnetic resonance imaging (RS-fMRI) analysis of Seed region B in the left inferior frontal junction (IFJ) (x=-35; y=11; z=36). Coordinates are reported in Montreal Neurological Institute (MNI) space.

	Location		
Anatomical region	X	Y	Z
Left Area Pfm	- 48	- 52	+ 42
Left CA2, CA3	- 32	- 31	- 5
Left entorhinal cortex, left HATA	- 11	- 12	- 17
Left Area Fo5	- 36	+ 10	+ 38
Left area Fp1	- 14	+ 60	- 13
Left inferior temporal gyrus	- 54	- 12	- 32
Left pontes striate caudate	- 16	+ 2	+ 14
Left superior parietal lobule	- 23	- 73	+ 49
Left amygdala	- 25	- 8	- 10
Right amygdala	+ 25	- 6	- 10
Right inferior temporal gyrus	+ 65	- 35	- 12
Right Area OP2/OP3	+ 34	- 22	+ 24

Right area Fo3-5	+ 40	+ 46	- 8
Right nucleus dentatus	+ 30	- 74	- 35
Right middle frontal gyrus	+ 44	+ 50	+ 20
Right IFJ	+ 36	+ 14	+ 36

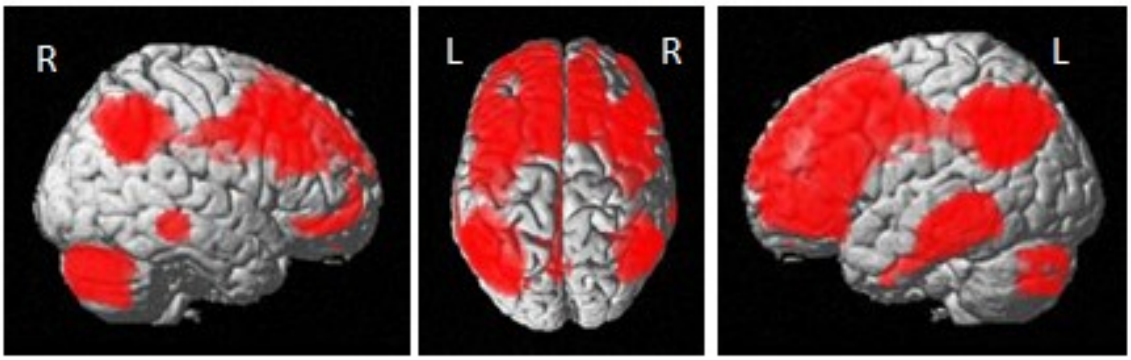

Fig. 6: Resting-State functional magnetic resonance imaging (RS-fMRI), main effect of Seed B:

These images display significant brain regions that are functionally coupled with Seed B. $p<0.05$. The results are superimposed on a 3D-standardized T1 brain template. L=left; R=right

3.3.3 Functional network common to Seed A (inferior parietal junction) and Seed B (inferior frontal junction)

In the following, a conjunction analysis of the main effect of Seed A and the main effect of Seed B was performed to examine which cortical areas are functionally coupled with both seed regions (Fig.7). Left Area 44 and bilateral 45 (Broca`s Area, part of inferior frontal gyrus), bilateral IFJ, bilateral Pfm (part of inferior parietal lobe)(Caspers, Geyer et al. 2006), right intraparietal sulcus (hIP1)(Choi, Zilles et al. 2006), left Area 33 (anterior cingulate cortex), left Area p24a and p24b (posterior midcingulate cortex), left inferior temporal gyrus, bilateral amygdala, bilateral basal forebrain, right pontes striate caudate, right area OP2, OP3 and OP5 (parietal operculum)(Eickhoff, Amunts et al. 2006, Eickhoff, Schleicher et al. 2006) and left Area Fo4 (inferior frontal gyrus) were

cortical regions that showed coactivations with both seeds in RS-fMRI analysis (threshold p< 0.05 (FWE)).

Table 4: Conjunction analysis of main effect of Seed A and main effect of Seed B

The table lists significant clusters, which are the result of Resting-State functional magnetic resonance imaging (RS-fMRI) conjunction analysis of Seed region A in the left supramarginal gyrus (SMG) of the inferior parietal junction (IPJ) (x=-54; y=-37.50; z=36.00) and Seed region B in the left inferior frontal junction (IFJ) (x=-35; y=11; z=36). Coordinates are reported in Montreal Neurological Institute (MNI) space.

	Location		
Anatomical region	X	Y	Z
Left Pfm/ Area 44/ IFJ	-39	-23	+38
Left Area 45	-40	+36	+21
left Area 33 (anterior cingulate cortex)	-8	-16	+33
left Area p24a and p24b (posterior midcingulate cortex)	-8	-16	+33
Left inferior temporal gyrus	-60	-52	-8
Left amygdala/ basal forebrain	-25	-8	-10
Left area Fo4	-31	+40	-12
Right Pfm/IFJ/ hlP1	+37	-13	+39
Right pontes striate caudate	+17	-8	+13
right area OP3/OP5	+40	-13	+24
Right area OP2/OP3	+34	-22	+24
Right amygdala/basal forebrain	+25	-5	-10
Right Area 45	+48	+20	+15

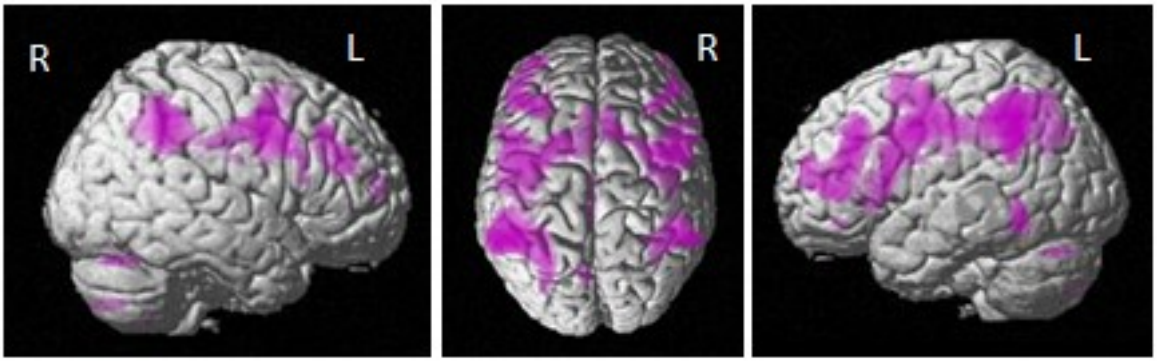

Fig. 7: Resting-State functional magnetic resonance imaging (RS-fMRI), conjunction analysis resulting in a functional network common to Seed A (inferior parietal junction, IPJ) and Seed B (inferior frontal junction, IFJ):

These images show significant brain regions that are functionally coupled with both Seed A and Seed B. $p<0.05$. The results are superimposed on a 3D-standardized T1 brain template. L=left; R=right

3.3.4 Correlations with age

Significant correlations particularly regarding age were detected. The aim by performing this analysis is to examine whether there are specific cortical areas (both for performance of TMT-A and TMT-B), which are functionally connected to the seed regions in relation with age, i.e. whether there are positive or negative correlations of functional connectivity between the seed region and other cortical regions and age.

The motivation is that on the one hand there may be an increased recruitment of brain regions with increasing age that could represent a kind of compensation for degenerative processes in the healthy aging brain (Buckner 2004) and on the other hand that there may be a decreased recruitment of brain regions due to aging processes.

3.3.4.1 Correlation between age and Seed A

Seed A (x=-54, y=-37.50, z=36.00) in the left inferior parietal junction showed a stronger functional connectivity with a cluster in the left SMG (x=-46, y=-30, z=30) in correlation with age. Indeed, this cluster is located in the same cortical region as Seed A itself.

No significant cluster was found showing a negative correlation between age and the functional connectivity of Seed A at the selected threshold (threshold p< 0.05 (FWE) and extent threshold k= 0 voxels).

3.3.4.2 Correlation between age and Seed B

Seed B located in the left IFJ showed stronger functional connectivity with clusters in the bilateral anterior midcingulate cortex (left cluster: x=-12, y=12, z= 39; right cluster: x=4, y=23, z=31) in correlation with increasing age. But a negative correlation was found, as well, i.e. a weaker connectivity of the seed region and other regions with growing age. Seed B showed a weaker connectivity with clusters in the right fusiform gyrus (x=41, y=-44, z=-9), in the left insula lobe (x=-30, y=10, z=-6), in the left Subiculum (75%)/Presubiculum (25%) (x=-22, y=-34, z=-12) and in the left medial temporal lobe (x=-30, y=6, z=-38).

3.3.5 Correlations with performance

No significant clusters functionally coupled with neither seed A nor seed B in correlations with performance scores of TMT-A or TMT-B were found at the selected threshold (threshold p< 0.05 (FWE)).

3.4 Tract-based spatial statistics analysis

In order to examine whether there are any relationships between GMV and white matter integrity, TBSS analysis was performed and TFCE was employed for statistical analysis.

The objective was to have a look at the correlation between FA and performance in TMT-A and TMT-B. At the selected threshold ($p<0.05$), no significant correlation was examined.

Subsequently, it was looked for any positive or negative correlation between GMV of the seed regions A and B with the FA of white matter tracts on voxel level. For this purpose, age, gender, BDI and EHI were included as covariates.

3.4.1 Correlation with Seed A

No significant correlations between GMV of Seed A and FA were found at the selected threshold.

3.4.2 Correlation with Seed B

A positive correlation between GMV of Seed B and FA of the left external capsule (EC) and left superior longitudinal fasciculus (SLF) as well as minor results between Seed B and FA of the left uncinate fasciculus (UC) (Fig.8; Fig.9) was found. That means the bigger GMV in the left IJF, the higher FA, i.e. structural integrity of these white matter tracts.

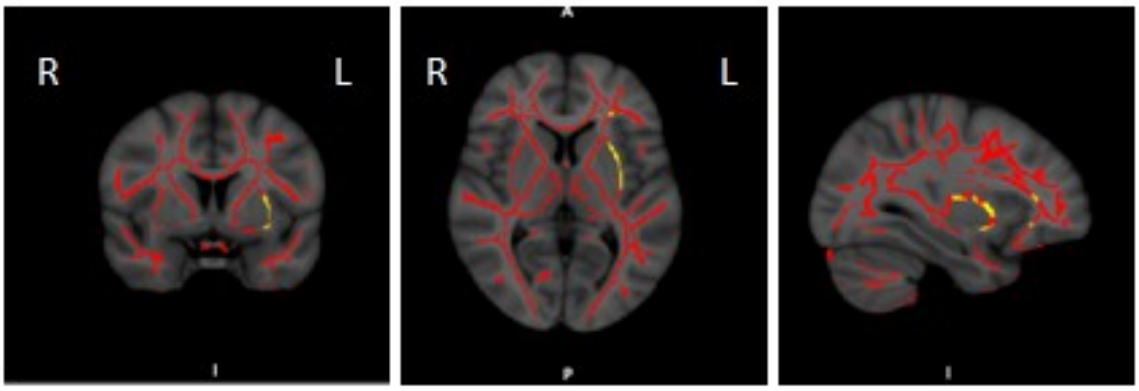

Fig. 8: Location of white matter tracts positively correlating with grey matter volume (GMV) of Seed B:

Fractional anisotropy (FA) skeleton regions, where GMV of Seed B showed a significant positive correlation with FA (marked in yellow). These regions are located in the left external

capsule (EC), superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF). The FA skeleton is marked in red, using the standard Montreal Neurological Institute (MNI) 152 1x1x1mm brain template.

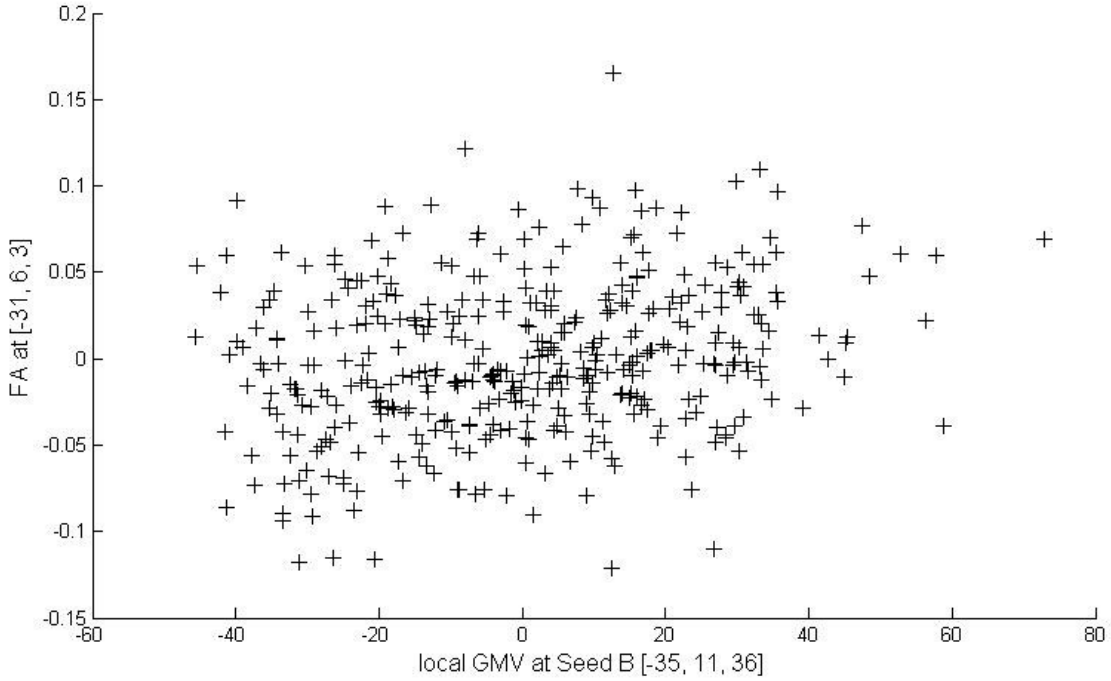

Fig. 9: Positive correlation of grey matter volume (GMV) at Seed B and fractional anisotropy (FA):

FA (x=-31, y=6, z=3) is chosen from a voxel in the centre of the superior longitudinal fasciculus (SLF) and demonstrates the positive correlation with Seed B.

4 Discussion

4.1 Introduction

The main objective of the current study was to examine interindividual variability in executive functions in an aging population and to disentangle these higher-order cognitive processes from more visuo-motor processes using a multimodal approach. The large sample compared to other studies offered the possibility to ascribe certain neurobiological correlates to a good performance in TMT-A (representing processing speed) and TMT-B (representing executive control). VBM analysis resulted in attributing bigger GMV in left SMG to better performance in TMT-A and larger GMV in the left IFJ to enhanced performance in TMT-B.

Subsequently, it was possible to outline the involvement of these in functional cortical networks. Moreover, a correlation between grey matter density in the left IFJ and FA of the left EC and SLF was found.

How do these findings join into previous literature?

4.2 Trail-Making-Test-A – the role of the left supramarginal gyrus

4.2.1 Generalities

TMT-A mainly engages visuoperceptual abilities (Sanchez-Cubillo, Perianez et al. 2009) as well as motor speed (Crowe 1998) as the task requires lining numbers in an ascending sequence as quickly as possible. The lining in great velocity retrieves motor abilities and the scanning of numbers scattered on a sheet of paper retrieves visuoperceptual abilities. These skills are essential for performing TMT-B, as well. Although switching between numbers and letters adds a further dimension to this task. Consequently, capabilities needed for performing TMT-A form an elementary basis for a good performance in TMT-B.

The left SMG whose GM volume (x=-55, y=-37, z=36) which was found to have a significant positive correlation with performance in TMT-A (i.e. a negative

correlation with time needed for fulfilment of TMT-A), has already been detected to play a significant role in the integration of perceptual spatiotemporal information (x=-60, y=-36, Z=34) (Assmus, Marshall et al. 2003).

The SMG (BA 40) forms the anterior part of the inferior parietal lobe which is divided by the intraparietal sulcus from the superior parietal lobe.

An event-related fMRI study demonstrated that the left SMG is activated during tasks retrieving motor attention and planning irrespective of the movement itself (Hesse, Thiel et al. 2006). For this purpose, they evaluated differential BOLD signal changes by comparing motor task and neutral task BOLD signals as well as motor and spatial task BOLD signals with the aforementioned result. Motor cues announced to respond either with the left or with the right hand to the cue. Neutral cues just attracted attention and spatial cues displayed the side the target would emerge. All cues were followed by the same targets and reactions. To note, as in the study at hand, the results of Hesse et al. showed a left lateralized role of the SMG in motor attention which has also been demonstrated in other studies, e.g. the results of a PET study (Rushworth, Krams et al. 2001). This PET study supported a role of the left SMG in motor attention.

In contrast to these studies, other cognitive abilities show a lateralization to the right hemisphere. An fMRI study on the tactile location and form processing (Van Boven, Ingeholm et al. 2005) found out that clusters in the right hemisphere similar to cluster of this study in the left SMG are rather activated in location processing than orientation processing. Vingerhoets (2014) examined amongst others the role of the left SMG in the use of tools. Regarding the study at hand, performing TMT requires that the subject uses a pen as a tool to connect numbers and letter. In this context the SMG is subdivided in the inferior anterior (x=-56, y=-31, z=34) and superior posterior (x=-43, y=-43, z=54) SMG and their different functions are examined. The inferior anterior SMG serves the goal specific planning of movements, whereas the superior posterior SMG is involved in retrieving functional motor schemata for familiar tools (Vingerhoets 2014). The coordinates of the significant cluster of our VBM analysis of performance in TMT-A (x=-55, y=-37, z=35) resemble the coordinates of the

inferior anterior SMG of Vingerhoets study. This is in line with Vingerhoet`s definition as performance of TMT-A retrieves goal specific planning of movements, i.e. connecting numbers in ascending order and switching between numbers and letters in ascending order when performing TMT-B.

Transcranial magnetic stimulation (TMS) inducing temporary interference has been used to demonstrate the role of the anterior SMG together with the anterior intraparietal sulcus in integrating sensory information for online control of reaching (Reichenbach, Bresciani et al. 2011), showing that not only motor ability but also sensory feedback is necessary to choose the adequate motor hand movement.

A kind of visual processing can be attributed to a cluster (x = -50, y = -38, z = 34) near the cluster in the SMG of this study because a study on fear conditioning (Armony and Dolan 2001) found out that this cluster is active when an auditory stimuli occurs in a threatening visual environment in contrast to a non aversive context.

To sum up, the cluster in the left SMG (x=-55, y=-37, z=36) which was found to show a positive correlation with performance in TMT-A, has been reported in previous studies to play an important role in the integration of perceptual spatiotemporal information (Assmus, Marshall et al. 2003), motor attention (Rushworth, Krams et al. 2001, Hesse, Thiel et al. 2006), planning and performing goal-directed movements (Vingerhoets 2014) as well as visual processing (Armony and Dolan 2001). So our findings strengthen the prevailing level of knowledge about the function of the SMG.

4.2.2 Clinical context and further roles of the supramarginal gyrus

Clinical studies could show a relationship between certain disease patterns, e.g. stroke patients (Haaland, Harrington et al. 2000), monocular amblyopia (Li, Jiang et al. 2013) as a disease affecting visual processing and Alzheimer´s disease (Schroeter and Neumann 2011) and the SMG.

A study on stroke patients showed that the left inferior and superior parietal cortex as well as the left middle frontal gyrus were cumulatively affected by

damage in patients with ideomotor limb apraxia (Haaland, Harrington et al. 2000), which underlines the role of the inferior parietal cortex in performing goal-directed movements. Furthermore, the more severe the damage of the SMG, the lower the performance of stroke patients is in adaptation to new incoming visuo-motor mappings (Palluel-Germain, Jax et al. 2011).

Another disease study performed on children hit by monocular amblyopia discovered GMV reduction in cortical regions activated in visuospatial processing (Li, Jiang et al. 2013). One of the GMV reduction discovered in this study is located in the SMG (x=-46.5, y=-22.5; z=34.5). This correlation supports the role of the SMG in visuospatial processing.

Consequently, neurobiological measures of the SMG may be a helpful clinical tool for the investigation of certain diseases affecting visuomotor abilities in the future.

Admittedly, the SMG is not uniquely engaged in visuomotor capabilities needed for TMT-A but also for other cognitive competences, e.g. the SMG is activated in random episodic memory (Andreasen, O'Leary et al. 1995). Random episodic memory means that it was investigated during a condition of free association. Moreover, a cluster (x=-56, y=-38, z=36) is activated when experiencing virtual violence (Mathiak and Weber 2006) which demands attention and coordination. Another related cluster (x=-52, y=-36, z=38) showed activation during voluntary risk taking (Rao, Korczykowski et al. 2008). Additionally, innocuous heat stimuli in contrast to nocuous ones activate a cluster (x=-52, y=-40, z=40) in the inferior parietal lobule (Tseng, Tseng et al. 2010) and object naming of action images activates a nearby cluster (x=-50, y=-38, z=38) (Liljestrom, Tarkiainen et al. 2008), as well.

To conclude, it is obvious that the SMG is not solely activated during visuomotor activities. It is rather part of diverse cortical networks as lots of tasks need visuomotor feedback. Further research is necessary to substantiate if there are even more concrete cognitive abilities correlating with characteristics of the left SMG.

4.2.3 The supramarginal gyrus in the aging brain

Recently it could be shown that the SMG shows significant volume reduction with growing age (Chen and Herskovits 2014) but contrary to hippocampal volume, SMG volume could not be ascribed to dementia.

In a spatial memory task old people showed weaker activation of the SMG than the younger control group (Meulenbroek, Petersson et al. 2004). These findings support that the SMG is functionally and structurally altered in aging.

Besides, research on the lateralization of resting state networks has shown that left lateralization of the SMG decreases while aging (Agcaoglu, Miller et al. 2014), although one has to note that the subgroup aged from 12 to 29 years does not overlap with the age range of the sample provided by the study at hand. So the study depicts changes with growing age, but does not examine the brain of the elderly. A decline of lateralization would fit the HAROLD (hemispheric asymmetry reduction in older adults) model (Cabeza 2002).

Older people showed lower performance in TMT-A (Mitrushina, Boone et al. 1999, Lezak 2004). So the SMG may play a role in decreased visuo-spatio-motor integration processes of physiological aging.

To note, patients with Alzheimer`s disease showed poor performance in visuomotor coordination compared to healthy controls (Verheij, Muilwijk et al. 2012). Additionally, patients with Alzheimer´s disease revealed hypoperfusion and hypometabolism in the SMG (Schroeter and Neumann 2011). SMG volume can help to differentiate between mild cognitive impairment and healthy controls (Hanggi, Streffer et al. 2011). So the SMG plays a role in pathological aging, as well. Consequently, further studies are necessary to precisely distinguish between physiological and pathological aging in order to incorporate these neurocognitive examinations in everyday clinical settings.

According to the study at hand, these effects of aging depicted in lots of other neurocognitive studies show that age was necessarily considered to be one relevant confounder in statistical analyses.

4.3 Trail-Making-Test-B - The role of the left inferior frontal junction

4.3.1 Generalities

After controlling for the covariates performance in TMT-A, age, gender, BDI and EHI scores, a cluster in the left IFJ (x=-35; y=11; z=36) was detected in VBM analysis. Its GMV showed a negative correlation with CT of performing TMT-B. Does this finding coincide with current knowledge?

Firstly, one needs to consider a common definition of the location of the IFJ. It has been defined as being located near the junction of the inferior frontal sulcus and the inferior precentral sulcus (Derrfuss, Brass et al. 2004, Derrfuss, Brass et al. 2005) and between the prefrontal and premotor cortex (Brass, Derrfuss et al. 2005).

A metaanalysis evaluating coactivations patterns demarcated the IFJ (x=-37; y=5; z=31) from neighbouring clusters because of its specific cortical coactivations (Muhle-Karbe, Derrfuss et al. 2016).

Due to the purpose of this study one needs to investigate and compare the role of the IFJ in current literature. The aim is to interpret its role in executive control, which is the main focus of this study, in the light of existent neurobiological knowledge.

4.3.2 Current literature about the role of the inferior frontal junction

In current literature there are some studies that conform to the findings of the study at hand, but studies that elucidate other characteristics of the IFJ, as well.

One meta-analysis (Derrfuss, Brass et al. 2005) of event-related fMRI and blocked fMRI studies spotted highly significant activation in the IFJ in task-switching, set-shifting and stimulus-response studies, as well as in colour-word Stroop studies. All these functions can be attributed to executive control. They summarized the significant coordinates as follows: x=47 or lower, y=between 1-10 and z=between 27 and 40. The coordinates of the significant clustering in our VBM analysis of TMT-B conform to these general coordinates. In the same

context a cluster in the IFJ(x=-42.5, y=9.5, z=29.7) was found to be activated, when switching from a difficult to an easy task (Jimura, Cazalis et al. 2014).

Once more the significance of a clustering in the IFJ (x=41; y=12; z= 25) in matters of switching could be shown in a study which compared ventrolateral frontal cortex with similar areas of macaques (Neubert, Mars et al. 2014). Their RS-fMRI study showed that the IFJ is functionally coactivated with areas in the occipitotemporal cortex (i.e. visual association areas) and dorsolateral PFC. So the IFJ may serve as a central executive in handling different upcoming stimuli by getting processed visual as well as intentional information. The neighbouring region area 44v is complementarily engaged in typical inhibition tasks which implies that executive functions need to be subdivided as proposed by Miyake. However, the current study did not differentiate between the different subcomponents of executive control defined by Miyake as performance in TMT-B representing executive functions was regarded in general. Area 44v and the IFJ are stronger coupled in the human brain than in the macaque´s matching the less instinctive and more sophisticated human behaviour. Furthermore, other neighbouring regions such as area 45 are not engaged in cognitive control at all, but rather needed for social and language competences. To note, in the study of Neubert et al. they focused on the right ventrolateral frontal cortex as they decided results of both hemispheres to be alike enough, which is not consistent with the study at hand and the lateralization of brain functions (Aboitiz 1989).

In this context an fMRI study based on the WCST could prove the hemispheric asymmetry in the lateral frontal cortex (Konishi, Hayashi et al. 2002). In the study of Konishi et al. negative feedback of the WCST could be attributed to the right lateral frontal cortex, whereas the process of updating correlates with activity in the left lateral frontal cortex. In modern-day research both hemispheres have to be examined separately and there is evidence that the inferior frontal cortex of both hemispheres account for executive control processes. An fMRI study could show that the right IFJ is part of attentional networks (Sebastian, Jung et al. 2016). Although, in the study at hand there was no correlation between TMT-B performance and GMV of the right IFJ, it

could be shown that the right IFJ is part of the resting state functional network of Seed B.

Another meta-analysis to examine neurobiological correlates of task switching detected the IFJ and the posterior parietal cortex as primarily activated regions defining this function (Kim, Cilles et al. 2012).

An fMRI study on executive functions (Sylvester, Wager et al. 2003) detected a cluster (x=-34; y=5; z=37) of similar location as the cluster in the IFJ that showed a significant correlation with TMT-B performance in this study. This cluster showed activation in a counter switching task as well as a stimulus-response inhibition task but was specific neither of switching nor of inhibition tasks. So this cortical area in the IFJ may be the essential executive control "office".

To note, a fMRI study exploring repetition priming found out that a region in the left inferior frontal gyrus - similar to the cluster in the IFJ detected in this study - shows a reduced blood oxygenation level-dependent-contrast fMRI signal in correlation with faster response times (Buckner, Koutstaal et al. 2000). The effect of priming was the reduction of neural activity within cortical regions that were already engaged in the task. Hence, previous stimuli facilitate cognitive processes in corresponding cortical areas resulting in more rapid completion times. Regarding the study at hand, frequently repeating the TMT may influence performance and should be considered in statistical analyses, but could be neglected as the subjects of this study did not reiterate the TMT.

There are studies which investigate executive control in tasks of everyday life. An fMRI study focusing on which cortical areas maintain driving performance during a concurrent conversation task detected amongst others a cluster in the left inferior frontal gyrus (x=-32; y=9; z=27) (Hsieh, Young et al. 2009). So a role in attention modulation as a component of executive control enabling multitasking can be ascribed to this cluster.

A working memory fMRI study illustrated that the IFJ together with the Supplementary Motor Area and the Middle Frontal Gyrus is engaged in updating working memory whatever information has to be updated (Roth and Courtney 2007). Working memory is one subcomponent of the theoretical

construct of executive functions in Miyake`s model. So this finding is in line with the study at hand.

To summarize, the findings of this study are in line with current literature. Cortical areas near the significant cluster in the IFJ (x=-35; y=11; z=36) could be attributed to components of executive control.

4.3.3 Modality and task complexity factor dependence of the inferior frontal junction

Admittedly, executive control is a definitely global cognitive domain. Executive functions as a central executive are needed to manage various operations in everyday life. Is the role of the IFJ respective executive control restricted to certain modalities or is it engaged modality-independent? Besides, is IFJ activation dependent on task difficulty?

One fMRI study, examining task preparation, attributed an updating function to the IFJ, i.e. the updating of context related task representations (Brass and von Cramon 2004). In this context one needs to examine whether updating is dependent on modalities. An event related fMRI study of auditory and visual oddball tasks (Stevens, Skudlarski et al. 2000) delineated that there is an updating function that is modality independent. Alongside other parietal, e.g. bilateral SMG and frontal areas, the conjunction analysis of visual and auditory conditions revealed bilateral activation at the junction of the inferior frontal and precentral gyri.

In addition, it has been shown that olfactory working memory retrieves similar cortical regions (amongst others a cluster (x=-40, y=11, z=36) near the cluster of this study in the IFJ) like working memory of other modalities (Dade, Zatorre et al. 2001).

The modality-independent role of the IJF is crucial to support its role as a central executive because there are lots of studies which ascribe the IFJ a solely modality-dependent role. For instance, PET activation studies focusing on verb and noun retrieval (Warburton, Wise et al. 1996) point at a role of a region of the inferior frontal gyrus (x=-38; y=10; z= 32) near our significant

cluster in verbal working memory. There are studies demonstrating a role of the cortical region in visual working memory (Stern, Owen et al. 2000). Moreover, a fMRI study examining different activations in word and number problem solving identified a cluster in the precentral sulcus (x=-36; y=10; z=32) that showed increased activation in word problem solving (Newman, Willoughby et al. 2011). Further research is necessary to confirm modality-independence.

To note, it has to be considered that activation may be dependent on task complexity. A fMRI study on episodic retrieval demonstrated that a cluster in the left dorsal PFC (x=-37; y=6; z=34), which coordinates resemble the location of the cluster significant in the study at hand, shows increased activation when requesting high retrieval effort (Buckner, Koutstaal et al. 1998). In contrast, low retrieval effort is characterized by activation of other cortical regions. To take account of this confounder, one could repeat this study with different levels of difficulty of the TMT or other cognitive tests reflecting executive control to imply different task complexities.

All in all, to precisely analyse the role of the IFJ one has to regard both various modalities and different task complexities. With regard to current literature, the IFJ seems to have a modality-independent function but may be activated rather during higher task complexity.

4.3.4 Confounding effects

The previous passage introduced two factors that need to be regarded, when analysing the role of the IFJ. Are there other confounding effects that could influence results?

In line with the study at hand, a meta-analysis from Yuan and Raz showed that larger PFC volume, particularly in the lateral parts, is associated with better performance in executive functions (Yuan and Raz 2014). This meta-analysis displayed certain moderators. Firstly, age variability rather than the mean age of a study sample is responsible for the effect size, presumably because both GMV (Good, Johnsrude et al. 2001) and performance in executive control (Tombaugh 2004) decrease with higher age. In matters of the study at hand,

which included participants from 55 to 80 years, the large age range was deliberately employed to yield a considerable effect size as the age range provides interindividual differences. However, age was considered as a confounder in the design matrix. Furthermore, Yuan and Raz detected that the strength of this correlation depends on the test used as a measure for executive control, e.g. the WCST showed a stronger correlation than the TMT. So the question arises whether we have chosen the test which represents executive control best. However, it could be shown that TMT is more sensitive than WCST in evaluating executive functions of patients suffering from dementia-like diseases (Hammers, Ramirez et al. 2015). Besides, some authors even proposed that multitask tests may be suited best for a comprehensive assessment of executive control (Bombin-Gonzalez, Cifuentes-Rodriguez et al. 2014). One could repeat our study using another test/test battery displaying executive control and compare the results.

A further confounder to take into account is depressiveness. The importance becomes obvious as an fMRI study could show that negative emotional judgment correlates with hypoactivity in a cluster in the left dorsolateral PFC (x=-40; y=10; z=34) (Grimm, Beck et al. 2008). In contrast, right dorsolateral PFC rather showed hyperactivity in depressive people. Therefore BDI scores were included as confounders in the design matrix.

Consequently, age and BDI scores were included in statistical analyses as well as EHI scores because it is established that handedness influences lateralization of the hemispheres (Levy 1977).

4.3.5 The inferior frontal junction in the aging brain

Due to the fact that the 1000 Brains Study included an aging population it is relevant whether and how aging affects structure and function of the IFJ.

A meta-analysis (Di, Rypma et al. 2014), which investigated fMRI and VBM studies of the aging brain, detected an enhanced activation in different regions of the left inferior frontal gyrus in the older group compared to the younger group. Moreover, they found grey matter reduction in the left inferior frontal

gyrus (x=-48, y=12, z=32). So hyperactivation (i.e. increases in neural metabolic or BOLD activity) and grey matter reduction overlapped in the inferior frontal gyrus. It is questionable whether this hyperactivation represents deterioration (i.e. dedifferentiation) or a kind of compensation for the reduced GMV. The regions in the inferior frontal gyrus of their study are spatially close to the region, which is significant in this TMT-B VBM study (x=-35, y=11, z=36). In this region located in the left IFJ, better performance (i.e. shorter time needed to perform TMT-B) and GMV are correlated positively. Although the study at hand did not primarily concentrate on the comparison of performance in executive function in different age groups, the age range provided interindividual variability to correlate differences in performance with structural and functional differences.

As the study at hand did not compare different age cohorts, effects of hyperactivation in an aging group compared to a younger group could not be detected in this study.

4.3.6 Clinical context

Finally the fact that the IFJ is an important region for executive control is of interest for clinical purposes. Both patients with Alzheimer´s disease and schizophrenia show neurobiological changes in inferior frontal regions which suits the disease pattern as both illnesses go along with reduced performance in executive control.

A PET study performed on people with early dementia, primarily Alzheimer´s disease and frontotemporal lobar degeneration as well as prodromal stages, illustrated hypometabolism in the left IFJ in subjects with Alzheimer´s disease and frontotemporal lobar degeneration in various neuropsychological tests (Schroeter, Vogt et al. 2012). The results of this study based on the TMT-B affirm the correlation between performance in executive control and the IFJ. So the TMT-B seems adequate to evaluate performance in executive control for clinical purposes.

Looking at schizophrenia, a PET study showed that patients in contrast to healthy controls did not show increased regional cerebral blood flow in the inferior frontal region while performing the WCST, which is another frequently applied test measuring executive control (Ragland, Gur et al. 1998). In this context one could examine, e.g. with VBM and RS-fMRI, whether there is a correlation between the IFJ and the TMT-B, as well.

So structure and function of the IFJ are altered in patients who suffer from diseases that go along with reduced performance in executive control even in prodromal stages of Alzheimer´s disease. Consequently MRT investigations may be utilized and applied for research on these neurocognitive illnesses and in the future maybe for diagnostic purposes, as well.

4.3.7 Comparison with Miyake´s model and future objectives

To conclude, in reference with Miyake´s model of executive functions, in scientific literature the IFJ has been attributed to both shifting between tasks or mental sets and updating and monitoring of working memory. The results of this study present that better performance in TMT-B positively correlates with increased GMV in a cluster located in the left IFJ which is in line with current knowledge. The IFJ is a separable area integrating modality-independent information to enable goal-specific action. Nevertheless, further research is necessary to elucidate the role of the different subcomponents of executive control (Kim, Wittenberg et al. 2017). It is e.g. questionable whether inhibition can be attributed to the IFJ, as well, or rather is attributed to the neighbouring area 44v as proposed by Neubert et al, 2014. A coactivation pattern metaanalysis assigned shifting and inhibition to a cluster in the anterior inferior frontal sulcus (Muhle-Karbe, Derrfuss et al. 2016). Furthermore, lateralization of the subcomponents should be examined precisely as the right IFJ is activated during executive control tasks, as well (Konishi, Hayashi et al. 2002, Sebastian, Jung et al. 2016). Moreover, there is the need to exactly define the extent of task dependence of the IFJ.

Supplementarily one could perform the same analysis with another established test for executive control, e.g. the WCST, and compare and possibly reassure results.

4.4 Cognitive Control Network

Most studies detect, in addition to a cluster in the IFJ, further cortical regions correlating with performance in executive control. Therefore RS-fMRI was performed to delineate the cortical network which the cluster in the IFJ is integrated in.

A coactivation pattern metaanalysis showed that a cluster in the IFJ (x=-31; y=5; z=31) is functionally connected to the right IFJ, the pre-supplementary motor area, the left intraparietal sulcus and the right anterior insula (Muhle-Karbe, Derrfuss et al. 2016). This coactivation pattern overlaps with the frontal-parietal network that was delineated in the study at hand using Seed B. Muhle-Karbe et al delineated that their cluster in the IFJ has linguistic and executive functions – especially sticking to task requirements.

An event-related fMRI study (Dove, Pollmann et al. 2000) detected a region similar to our finding (x=-44; y=5; z=37) which is activated under task switching conditions as a measure for executive control. In this study bilateral premotor cortex, the anterior insula bilaterally and the left intraparietal sulcus were activated, as well. So one cannot attribute performance in executive control exclusively to one cortical area but instead has to consider the whole cortical network. Therefore this study is not solely a VBM study but instead a RS-fMRI study, as well. The seed-based RS-fMRI analysis of Seed B delineated a fronto-parietal network the IJF is integrated in. A fronto-parietal network responsible for working memory and cognitive control has been registered in an fMRI study (Harding, Yucel et al. 2015). They delineated task-related dynamics within this network. So the different subcomponents of Miyake`s model may activate different components of the cognitive control network.

Likewise, functional connectivity studies have revealed that the IFJ is part of a cognitive control network (Cole and Schneider 2007, Sundermann and

Pfleiderer 2012). Sundermann and Pfleiderer found out by meta-analysis and a comparative RS-fMRI study that the IFJ shows functional connectivity with regions in the ventro- and dorsolateral PFC, in the anterior insula, the medial frontal gyrus/ pre-SMA, the posterior parietal cortex, the occipitotemporal junction/ cerebellum, as well as in the putamen, the thalamus and language and motor areas.

Similar to the cognitive control network, a conjunction analysis delineated a multiple-demand network (Muller, Langner et al. 2014), i.e. a network of cerebral areas permanently activated during attention, inhibitory control and working memory exercises. These three cognitive abilities are basic components of executive control. The multiple-demand network consists of clusters in the midcingulate cortex extending into pre- and supplementary motor area, bilateral anterior insula, bilateral inferior frontal junction/gyrus, right middle frontal gyrus as well as right intraparietal sulcus.

As referred to in the introduction, two top-down control networks have been described: a cingulo-opercular network for stable set-maintenance and a fronto-parietal one for fast adaptive control (Dosenbach, Fair et al. 2008).

Regarding clinical future objectives, it has been shown that mindfulness meditation training enhances resting state functional connectivity between dorsal and ventral components of the cognitive control network (Taren, Gianaros et al. 2017).

In the study at hand the main effect of Seed B, i.e. the cluster in the IFJ, showed that it is part of a fronto-parietal network, as well. This is in line with the study of Dosenbach et al (2008) as adaptive control is a subcomponent of executive control. Seed B displayed similar functional couplings as described in the cognitive control network by Sundermann and Pfleiderer, in the multiple-demand by Müller at al and in the coactivations pattern by Muhle-Karbe et al. Likewise, this study can substantiate that the IFJ is part of a cognitive control network.

4.5 Trail-Making-Test studies

This study is a multimodal approach based on structural, functional and diffusion MRI images. What kind of other studies have been performed to investigate performance in the TMT? Are their results in line with our approach?

The current study shows that executive functions are characterized by left hemisphere dominancy. In line with our findings, this is supported by a near-infrared study (Zakzanis, Mraz et al. 2005) which demonstrated left-sided medial and dorsolateral activity when comparing TMT-B with TMT-A. A lack of lateralization could be an indicator for compensation for cerebral dysfunction, as it was demonstrated on schizophrenic patients who showed a reduced lateralization for B-A activation (Fujiki, Morita et al. 2013).

A study based on cortical thickness and voxel-based lesion-symptom mapping showed that structural changes in the left dorsomedial prefrontal lobe are linked to reduced performance in TMT-B (Miskin, Thesen et al. 2015).

Additionally, another near-infrared spectroscopy study (Hagen, Ehlis et al. 2014) showed frontal activation in the dorsolateral PFC during TMT performance, but in Broca´s area and frontopolar area, as well. They examined the discrepancy in activation between healthy younger and older people and found out that older people´s activation during performing the TMT is less focused. This reduction of hemispheric asymmetry has been reported by other studies, as well (Muller, Guhn et al. 2014). Older people particularly showed more bilateral dlPFC activation. As mentioned above, there are two hypotheses: the dedifferentiation and the compensation hypothesis. A PET study (Cabeza, Anderson et al. 2002) illustrated that high performing older people in various neurological tests activating the PFC showed activation in bilateral PFC, whereas low performing aged adults engaged similar regions as young adults. The bilateral activation in older people is called the HAROLD (Hemispheric asymmetry reduction in old adults) model (Cabeza 2002). Consequently, bilateral activation may be interpreted as a kind of cognitive reserve.

Furthermore**,** an evaluation of the Women's Healthy Ageing Project could show that an adequate vitamin D level correlates with a better performance in TMT-B (Goodwill, Campbell et al. 2018). Consequently, one has to regard that there

are external neuroprotective factors such as the vitamin D level contributing to preserved executive function.

In the study at hand, TMT-A was used as a regressor to substract the influence of processing speed on TMT-B results. A study by MacPherson et al (2017) controlled for processing speed using a “common variance across five speed of processing tasks” instead of TMT-A results. When they controlled for processing speed most of the correlations between TMT-B results and measures of grey and white matter were mitigated (MacPherson, Cox et al. 2017).

In the context of the study at hand, the cluster in the IFJ showed stronger functional connectivity with clusters in the bilateral anterior midcingulate cortex (left cluster: x=-12, y=12, z= 39; right cluster: x=4, y=23, z=31) in correlation with increasing age. But a negative correlation was found, as well, i.e. a weaker connectivity of the seed region and other regions with growing age. Seed B showed a weaker connectivity with clusters in the right fusiform gyrus (x=41, y=-44, z=-9), in the left insula lobe (x=-30, y=10, z=-6), in the left Subiculum (75%)/Presubiculum (25%) (x=-22, y=-34, z=-12) and in the left medial temporal lobe (x=-30, y=6, z=-38). Hence there may be a compensation or dedifferentiation due to the increased recruitment of bilateral anterior midcingulate cortex. Further research is necessary to find out whether compensation or dedifferentiation is the reason for increased recruitment. Furthermore, decreased connectivity with several clusters may be a general aging process. There is the need to examine the correlation of increased or decreased recruitment in correlation with performance.

4.6 White matter analysis

4.6.1 Generalities

In TBSS analysis a positive correlation between GMV of Seed B and FA of the left EC and SLF was found as well as minor results between Seed B and FA of the left UC.

The SLF is a major white matter tract connecting the ipsilateral frontal, parietal, occipital as well as the temporal lobe. Its long association fibres run bidirectionally. The SLF consists of four subcomponents: SLF1, SLF2, SLF 3 and the arcuate fascicle (AF) (Makris, Kennedy et al. 2005) – especially the SLF 2, which displays the lateral part of the SLF, is ascribed to attentional maintenance (Schmahmann, Smith et al. 2008) that is part of our construct of executive control.

The EC is an association fibre tract connecting the cerebral cortex with the basal forebrain. Anatomically it is located between the claustrum and the nucleus lentiformis.

The UC connects the rostral temporal lobe with the PFC, particularly medial, rostral and orbital portions (Schmahmann, Pandya et al. 2007).

4.6.2 Current literature

As it was already referred to in the introduction a study showed that in healthy, young adults increased FA in the right SLF and bilateral inferior frontooccipital fasciculus (IFOF) showed a positive correlation with common executive functions (Smolker, Depue et al. 2014). In contrast to this study Smolker detected the significant correlation in the right hemisphere. Further research is necessary to prove if there is an effect of lateralization.

A study examining the decrease in brain glucose metabolism in the aging brain and its correlation with white matter structural integrity and functional connectivity identified a peak in the left IFJ (x=-56, y=12, z=28) as the region in the brain showing the highest metabolism decrease with growing age (Chetelat, Landeau et al. 2013). So there can be found a high interindividual variability in this cortical area in an aging sample, which was utilised in the approach of the study at hand.

Respective this study, Chetelat et al. found a positive correlation of glucose metabolism in the IFJ with performance in TMT-B but the correlation was lower as with forward and backwards digit span which are tests for performance in working memory. The glucose metabolism of the IFJ showed a significant

positive correlation with the WM volume of the inferior longitudinal fasciculus (ILF) and the anterior part of the body of the corpus callosum. Similarly, on a more microstructural level there is a positive correlation with the FA in the ILF, in the UC, the SLF, the rostral part of the cingulum and the frontal portion of the corpus callosum. When brain glucose metabolism decreases in the IFJ it goes along with reduced WM structural integrity - this correlates with aging. Although one has to take account of the myelin reduction in WM fibres in the aging brain in general (Peters 2002). Mostly long association fibres are affected.

In general, microstructural changes (detected by DTI) are better identified than macrostructural changes (detected by WM volume measures) (Fjell, Westlye et al. 2008) either because of better measures or because of the eventuality that microstructural changes occur earlier.

To note, when analysing white matter characteristics creating causal relationships is not possible, so one cannot determine whether reduced metabolism results in myelin degeneration or myelin degeneration results in reduced metabolism.

Comparing the findings of Chetelat et al (2013) with our study we found a positive correlation between GMV in the left IFJ and FA of the left SLF and EC such as minor results in the UC. The study of Chetelat et al. (2013) was able to find a positive correlation of FA in the UC and the SLF with metabolism in the IFJ. So results overlap to some extent. Further studies and meta-analyses are necessary to precisely define which white matter tracts are part of an executive function network.

However, the study of Chetelat et al. could not detect a correlation of brain metabolism of IFJ with functional connectivity, whereas, the study at hand was able to delineate a cortical network the cluster in the IFJ is engaged in.

In line with other studies their study suggests that the main effects of aging take place in the frontal brain.

Regarding the UC a DTI study on patients with left temporal lobe epilepsy (Diao, Yu et al. 2015) could show that worse performance in tests examining

executive control (including TMT) goes along with abnormal FA values in the left UC.

A study by Gold et al. explored the correlation of switching time and FA of the SLF. The SLF connects the IFJ and the posterior parietal cortex (Makris, Kennedy et al. 2005). Switching time and FA of the SLF showed a negative correlation. This means that a higher FA in left frontoparietal white matter which serves as a measure of the degree of white matter direction, goes along with a shorter switching time in young and old people (Gold, Powell et al. 2010).

One study examined the correlation of performance in TMT (B-A score) with DTI parameters and found out that the B-A score correlated with mean diffusivity of anterior white matter regions (O'Sullivan, Jones et al. 2001), i.e. higher mean diffusivity negatively correlates with performance in this test of executive control.

It has even been proposed that executive functions could be the cognitive ability most susceptible to white matter degeneration in the course of aging (Shenkin, Bastin et al. 2005) as this study found a correlation of MD and cognitive ability, particularly verbal fluency.

There are some studies with overlapping results in comparison with the study at hand: a study analysing the correlation of DTI measures and Digit Symbol performance (a test, that represents attentional, executive and memory capabilities) found a correlation of performance (the score was the amount of correctly filled boxes in 90 seconds) with internal and external capsules, SLF, frontal forceps and fornix (Sullivan, Rohlfing et al. 2010). DTI parameters of the SLF and of frontal white matter correlated with performance in executive functions (Sasson, Doniger et al. 2012).

Grieve et al. (2007) examined the relation between attention-switching performance (measured by a computerized form of the TMT-B) and FA which are positively correlated. Although they did not assign it to a defined anatomic region (Grieve, Williams et al. 2007), which was possible in this study.

A TMT-based study performed on poststroke patients could show that damage of the SLF accounts for shortcomings in executive functioning (Muir, Lam et al. 2015).

However, a study examining the correlation between white matter microstructure and performance in executive function based on Miyake´s model showed that especially the FA of corpus callosum and cingulum is linked to executive control performance (Bettcher, Mungas et al. 2016). The study at hand, which hat a larger study size, did not yield results at the selected threshold, when correlating TMT test results with FA values.

Finally, the study at hand could affirm the role of SLF integrity in executive control which has already been shown by some other studies (Makris, Kennedy et al. 2005, Sullivan, Rohlfing et al. 2010, Sasson, Doniger et al. 2012). The role of the EC (Sullivan, Rohlfing et al. 2010) and the UC (Diao, Yu et al. 2015) in executive control has been demonstrated before, as well.

Chetelat et al. (2013) demonstrated a positive correlation of metabolism in the left IFJ and FA in the UC. In this study just minor results between GMV of Seed B and FA of the UC were found. So further research is necessary to elucidate the role of the UC in executive control and to distinguish whether there are more white matter tracts predicting executive control performance.

4.6.3 White matter changes in the healthy aging brain

Due to the fact that this study examined an aging population one has to differentiate between general changes during aging and correlations between TMT performance and white matter changes. This study analysed the correlation of the clusters in the SMG and the IFJ and FA of white matter tracts. Due to the general aging trends discussed in the subsequent passage age was taken as a confounder in statistical analysis.

DTI studies in healthy aging have shown FA reduction (Pfefferbaum, Sullivan et al. 2000, Grieve, Williams et al. 2007, Kochunov, Thompson et al. 2007) and mean diffusivity (MD) increase (O'Sullivan, Jones et al. 2001, Charlton, Barrick et al. 2006, Yoon, Shim et al. 2008); especially in the frontal brain (O'Sullivan,

Jones et al. 2001, Abe, Aoki et al. 2002, Bennett, Madden et al. 2010). Abe et al. (2002) detected a significant increase of mean diffusivity in frontal white matter (and lentiform nucleus) and a significant FA decline in the genu of the corpus callosum with increasing age. One DTI study even detected a temporal aspect of degeneration as it occurred earlier in frontal regions (Yoon, Shim et al. 2008). Nevertheless, the mainly frontal degeneration is controversial as Barrick at al. (2010) could not find an accelerated decline during a period of two years in their longitudinal design and e.g. (Charlton, Barrick et al. 2006) did not find this frontalisation, as well. The longitudinal design of the aforementioned study detected significant white matter integrity changes during a period of two years.

Similar to the anterior-posterior gradient, a superior-inferior gradient is described, as well (Sullivan, Rohlfing et al. 2010). In this study they found a decreased FA especially in superior fibre tracts such as the longitudinal fascicule and cingulated bundles. As the study at hand found a FA reduction in the SLF positively correlating with GMV of Seed B this superior-inferior gradient may make a contribution to the findings of this study.

Nonetheless, instead of the anterior-posterior or superior-inferior gradient it may be better to examine defined white matter tracts as there is a regional vulnerability for white matter degeneration while aging (Yoon, Shim et al. 2008).

FA reduction with increasing age is found nearly in the entire brain. However, the internal and external capsule are an exception in a TBSS study (Barrick, Charlton et al. 2010), whereas, another study found contrary results. In line with general FA reduction, they found FA reduction in the EC with growing age (Burzynska, Preuschhof et al. 2010).

The current study could show that GMV in the IFJ (alluding to playing a central role in executive control) is positively correlated with FA in the EC. However, further research is necessary to elucidate the development of FA of the EC in the aging brain as this study only examined in which WM tract FA correlates with GMV and not in which WM tract FA correlates with age.

To note, this study decided to use FA as a measure of white matter integrity. Some studies differentiate between axial and radial diffusion (AD and RD). Studies of the aging brain detected that especially radial diffusion increases with

age (Bennett, Madden et al. 2010, Sullivan, Rohlfing et al. 2010). An increase in radial diffusion is attributed to demyelinisation processes, whereas an increase in axial diffusion is ascribed to axonal damage (Sun, Liang et al. 2006). One could differentiate between radial and axial diffusion in order to detect whether demyelinisation or rather axonal damage is responsible for FA reduction. Both axial and radial diffusion are related to worse cognitive performance (Vernooij, Ikram et al. 2009). Besides, FA reduction with growing age can be attributed to white matter atrophy and white matter lesions (Vernooij, de Groot et al. 2008).

Especially smaller fibre bundles – particularly associative fibre tracts – are affected by microstructural degeneration processes, e.g. by damage of the myelin sheath or even loss of myelination (Peters 2002). Thickly myelinated WM tracts such as sensory and motor tracts degenerate later. For example, smaller fibre bundles in the genu of the corpus callosum are hit by microstructural degeneration processes before thickly myelinated parts of the corpus callosum (Pfefferbaum, Sullivan et al. 2000).

Loss of white matter integrity may result in age-related reduced performance in cognitive functions (Madden, Spaniol et al. 2009) due to decreased connectivity based on tract disruption called “disconnection” hypothesis (O'Sullivan, Jones et al. 2001). One cognitive function especially hit by white matter degeneration is working memory (Charlton, Barrick et al. 2006, Charlton, Barrick et al. 2010). They could show that connectivity between different brain regions needed for this function is reduced.

All in all, white matter is hit by aging processes. This has to be taken into account, when analysing white matter in an aging population and it may also be suitable for clinical purposes.

4.7 Limitations of the current study

Despite this study respected important confounders, there may be some further factors which need to be addressed as they could possibly influence results and leave open-ended questions.

When designing the structure of this study relevant available confounders (age, gender, BDI and EHI scores) were included in the multiple regression model. However, one has to regard that there are more possible confounding effects such as stress, being short of sleep or a deficit of physical exercise which influence the capabilities in executive control (Diamond 2013). Furthermore, an adequate vitamin D level seems to be neuroprotective and may contribute to preserved executive function (Goodwill, Campbell et al. 2018).

Additionally, it is questionable whether the TMT-B is the neurocognitive test displaying executive control best. Does TMT-B represent executive control purely, when discounting the effects, which are already explained by TMT-A? One has to regard that TMT-B trail is longer than TMT-A trail resulting in more time needed to perform TMT-B (Gaudino, Geisler et al. 1995, Vickers, Vincent et al. 1996). In addition, there are more circles distracting during the visual search for the right letter or number, so the distance between the circles is larger (Gaudino, Geisler et al. 1995). Other test restrictions may be that A is always registered before B, the distribution of letters and numbers differs in diverse tests, letters occur only in part B and in part B and it is always the sequence numbers before letters (Fossum, Holmberg et al. 1992, Arnett and Labovitz 1995). Consequently, those possible confounding influences should be taken into account when investigating performance in TMT-A and TMT-B.

Furthermore, there may be neurocognitive tests more appropriate to represent executive functions. Alternative tests measuring executive control are the WCST or the Stroop Colour Word Interference Test. Some authors even propose that a multitask test may display executive functions more comprehensively than a single test, which rather represents certain subcomponents of executive control (Bombin-Gonzalez, Cifuentes-Rodriguez et al. 2014). Equally, it is questionable whether performance in TMT-A is the most accurate variable representing processing speed or whether processing speed should rather be displayed by a composition of tests (MacPherson, Cox et al. 2017).

As mentioned before, test complexity (Buckner, Koutstaal et al. 1998) and task modalities can influence study results.

Regarding RS fMRI, there is proof that in comparison with younger people older people´s network structure varies more between task and resting state conditions (Gallen, Turner et al. 2016). To evaluate executive control networks comprehensively, one should compare task-based and resting state fMRI of the participants. This was not performed in this study.

Besides, there may be other neuroimaging techniques that could map the structural and functional characteristics of the brain more realistically. For instance BOLD data sets represent brain activation with a few seconds delay due to increased blood flow because of raised metabolism. So, future developments may offer new potential to depict structure and function of the human brain.

To strengthen the results of the present study one could repeat all analyses with other tests that measure performance in executive control and consequently compare these results.

Finally, metaanalyses offer a great potential for future research as they bring multiple studies together, which results in a higher statistical power. Huge data sets of metaanalyses offer more precision in delineating structural and functional characteristics of the human brain.

5 Conclusion

The constitutional aim of the study at hand is to examine neurobiological correlates of cognitive control within a great sample of healthy older subjects. Particularly, higher-order cognitive processes (i.e. executive functioning) were disentangled from more visuomotor processes. The TMT served this purpose as Part A rather reflects visuomotor processes and Part B provides an approved measure of cognitive control.

Fundamentally, neurobiological correlates were examined comprehensively, i.e. that both structural (grey and white matter) and functional characteristics were incorporated.

The main conclusion of the present study is that bigger GMV in the left SMG correlates with a better performance in TMT-A (visuomotor processing), and GMV in a cluster of the left IFJ positively correlates with performance in TMT-B.

Subsequently, it was possible to outline the involvement of both clusters in functional cortical networks. The convergence of the findings of many studies performed on executive functions show that a fronto-parietal network is engaged during activities that need executive control abilities. The study at hand can affirm that the IFJ is part of a fronto-parietal network.

Finally, a correlation between GMV in the left IFJ and FA of the left EC and SLF as well as minor results between GMV in the left IFJ and FA of the left UC were found. Consequently, neurobiological correlates of good performance in executive control need to be examined comprehensively as both structural (grey and white matter features) and their functional interaction establish performance abilities.

In the introduction the “cognitive reserve” theory (Buckner 2004, Whalley, Deary et al. 2004, Stern 2012) was presented. The current study examined a large sample of healthy aging subjects. So the results of this study show which neurocognitive characteristics may sustain good performance in cognitive control in the aging brain.

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