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Relationship between white matter alteration and encoding-related brain activation in connected brain regions: A DTI-fMRI-study

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Ich erkläre hiermit an Eides statt, dass die vorliegende Dissertation mit dem Titel „Relationship between white matter alteration and encoding-related brain activation in connected brain regions: A DTI-fMRI-study“ selbstständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.
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München, den 17.01.2023

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Hedwig Knaupp

Abstract:

Background: Aging is associated with alterations of white matter and brain activation. Functional MRI studies in elderly subjects showed changes in encoding related brain activation such as hyperactivation in frontal areas and hypoactivation in occipital gyrus in comparison to a younger control group. A contributing factor could be alterations of white matter integrity, resulting from age-related small vessel disease (SVD), a pathology that effects the small vessels of the brain or Wallerian Degeneration (WD) that explains axonal degeneration distal of an injury. These processes lead to changes such as white matter hyperintensities (WMH) detected by MRI or microstructural change assessed by the diffusion tensor imaging (DTI), marker mean diffusivity (MD) or peak width (PW). It was hypothesized that the directionality of the structure-function relationship of the brain is dependent on the investigated brain region. We aim to verify this assumption. Other studies focused on frontal brain regions. Instead we implemented a whole-brain analysis of the structure-function relationship. Therefore, the goal of this study was to investigate changes in white matter as a predictor of changed encoding-related brain activation in anatomically connected brain regions in cognitively normal performing older subjects. Furthermore, there are different theories that try to explain the changed brain activation in association with white matter change, such as compensatory mechanisms, dedifferentiation theory or inefficient neuronal processes. To gain a better understanding we examined the association between decreased brain activation respectively increased white matter changes in relation to cognitive performance of the subjects.

Methods: Cognitively healthy elderly subjects (N = 35) performed a face-name matching paradigm within the fMRI scanner with the encoding phase being relevant in the present study. The integrity of white matter was determined with measurement of WMH volume and DTI based markers such as MD and PW. We performed ANOVAs with DTI-markers as dependent and activation as the independent variable. Furthermore, we performed ANOVAs with white matter change or brain activation as dependent variable and cognitive performance as independent variable. Since we assumed that there are local differences of white matter change we created boxplots for the chosen MD, PW and WMH-ratio within the

chosen fiber tracts and global MD, PW and WMH-ratio. Additionally, we computed a correlation matrix between tract-specific MD or PW for a comparison of these two markers.

Results: We could demonstrate a significant positive association between PW in the inferior fronto-occipital fasciculus left (IFOF L) and the activation in the left frontal gyrus as well as PW in the inferior longitudinal fasciculus right (ILF R) and activation in the occipital gyrus. Furthermore, the data revealed no significant result for the relationship between white matter change and cognition or brain activation and cognition. The boxplot showed a significant difference between the white matter tracts when using MD and PW as marker. Because of its low burden we had to exclude WMH-ratio as a marker for white matter change. The correlation-matrix revealed that PW within the tracts correlated less with each other than MD.

Conclusion: These results suggest that microstructural changes lead to increased brain activation due to decreased white matter connectivity and reduced fidelity of data transmission. Additionally, the subjects' cognitive performance appears not to benefit from the increased brain activation. Thus, the negative structure-function relationship seems not to be based on a compensatory mechanism or dedifferentiation theory but most likely on an inefficient neuronal response.

White matter change can be considered as regionally variable as revealed by the boxplots and the correlation matrix. However, the structure-function relation seems not be dependent on brain region, because the whole brain analysis showed a consistent directionality of the structure-function relationship.

Zusammenfassung:

Hintergrund: Auch gesunde Alterungsprozesse gehen mit Veränderungen der weißen Substanz und der Hirnaktivierung einher. Funktionelle MRT-Studien an älteren Probanden zeigten im Vergleich zu einer jüngeren Kontrollgruppe Veränderungen in Hirnarealen, die mit Lernprozessen assoziierten sind, wie eine Überaktivierung in frontalen und einer Unteraktivierung im okzipitalen Bereich. Ein beitragender Faktor könnten Veränderungen der Integrität der weißen Substanz sein, die sich aus der altersbedingten Erkrankung „Small Vessel Disease“ (SVD) ergeben, einer Pathologie, die sich auf die kleinen Gefäße des Gehirns auswirkt, oder der Waller'schen Degeneration (WD), eine axonale Degeneration distal einer Verletzung. Diese Prozesse führen zu Veränderungen wie „White Matter Hyperintensities“ (WMH), nachweisbar mittels MRT, oder zu mikrostrukturellen Veränderungen, die durch Parameter der Diffusions-Tensor-Bildgebung (DTI) gemessen werden z.B. die mittlere Diffusivität (MD) oder die Peak-Breite (PW). Es wurde die Hypothese aufgestellt, dass die Direktionalität der Struktur-Funktions-Beziehung des Gehirns von der untersuchten Hirnregion abhängig ist. Diese Annahme wollen wir überprüfen. Außerdem konzentrierten sich weitere Studien auf frontale Hirnregionen. Stattdessen führten wir eine Analyse der Struktur-Funktions-Beziehung im gesamten Gehirn durch. Ziel dieser Studie war es daher, Veränderungen in der weißen Substanz als Prädiktor für eine veränderte lernbezogene Hirnaktivierung in anatomisch verbunden Arealen bei kognitiv normalen Probanden zu untersuchen. Darüber hinaus gibt es verschiedene Theorien, die versuchen, den Zusammenhang zwischen veränderter Hirnaktivierung und Veränderung der weißen Substanz zu erklären, wie z. B. kompensatorische Mechanismen, die Dedifferenzierungstheorie oder ineffiziente neuronale Prozesse. Um ein besseres Verständnis zu erlangen, untersuchten wir außerdem den Zusammenhang zwischen verringerter Hirnaktivierung oder erhöhter Veränderung der weißen Substanz in Bezug auf die kognitive Leistung der Probanden.

Methoden: Kognitiv gesunde ältere Probanden (N = 35) führten im fMRT-Scanner eine kognitive Aufgabe durch, in der Gesichter bestimmten Namen zugeordnet werden sollten. Für die vorliegende Studie war nur die Lernphase relevant. Die Integrität der weißen Substanz wurde durch Messung der WMH-Volumens und DTI-basierter Marker wie MD und PW bestimmt. Wir führten ANOVAs mit dem DTI-Marker als abhängige und der Aktivierung als unabhängige Variable durch. Außerdem führten wir ANOVAs mit der Veränderung der weißen

Substanz oder der Hirnaktivierung als abhängige Variable und der kognitiven Leistung als unabhängige Variable durch. Da wir davon ausgingen, dass es lokale Unterschiede in der Veränderung der weißen Substanz gibt, erstellten wir Boxplots für die ausgewählte MD, PW und WMH-Ratio innerhalb der ausgewählten Faserbahnen und die globale MD, PW und WMH-Ratio. Zusätzlich berechneten wir eine Korrelationsmatrix zwischen Trakt-spezifischer MD oder PW um beide Marker vergleichen zu können.

Ergebnisse: Wir konnten eine signifikante positive Assoziation zwischen PW im Fasciculus inferior fronto-occipitalis links (IFOF L) und der Aktivierung im linken Gyrus frontalis sowie PW im Fasciculus inferior longitudinales rechts (ILF R) und der Aktivierung im Gyrus occipitalis nachweisen. Darüber hinaus zeigen die Daten kein signifikantes Ergebnis für den Zusammenhang zwischen der Veränderung der weißen Substanz und kognitiver Leistung oder Gehirnaktivierung und Kognition. Der Boxplot zeigte einen signifikanten Unterschied zwischen den Trakten der weißen Substanz, wenn MD und PW als Marker verwendet wurden. Aufgrund der geringen Anzahl an WMH mussten wir die WMH-Ratio als Marker für Veränderungen der weißen Substanz ausschließen. Die Korrelationsmatrix zeigte, dass PW innerhalb der Trakte weniger miteinander korrelierte als MD.

Schlussfolgerung: Diese Ergebnisse deuten darauf hin, dass mikrostrukturelle Veränderungen zu einer erhöhten Hirnaktivierung führen, die auf eine verringerte Konnektivität der weißen Substanz und eine verminderte Qualität der Datenverarbeitung zurückzuführen ist. Außerdem scheint die kognitive Leistung der Probanden nicht von der erhöhten Hirnaktivierung zu profitieren. Die negative Struktur-Funktions-Beziehung scheint also nicht auf einem Kompensationsmechanismus oder der Dedifferenzierungstheorie zu beruhen, sondern höchstwahrscheinlich auf einer ineffizienten neuronalen Reaktion.

Wie aus den Boxplots und der Korrelationsmatrix hervorgeht, kann die Veränderung der weißen Substanz als regional variabel angesehen werden. Die Struktur-Funktions-Beziehung scheint jedoch nicht von der Hirnregion abhängig zu sein, denn die Analyse des gesamten Gehirns zeigte eine konsistente Direktionalität dieser Beziehung.

Table of contents

1. Introduction

During the last century medicine gained a lot of knowledge and made great progress. As a result industrialized nations are facing an aging society. In 2050, there will be 3.2 times as many sixty years or older people as there are four years old children or younger (Cohen, 2003). In addition, people not only live longer but also stay in better health. Nevertheless, even healthy aging is associated with changes. Focusing on the brain, even subjects without cognitive impairment show alterations in structure and function (Cabela et al., 2018, Madden et al., 2020). In this study we want to gain a better understanding of neurodegenerative processes that play a role in healthy brain aging.

1.1. White matter alteration

Healthy brain aging is accompanied by structural changes of white matter. An underlying pathophysiological mechanism of white matter alteration can be Wallerian degeneration (Pierpaoli et al., 2001, Le Bihan, 2003, Erten-Lyons et al., 2013). When neurons are impaired by trauma or degeneration, they fade away distal to the injury (Vargas & Barres, 2007, Wang et al., 2012). In vitro, different stages can be identified (Chen et al., 2017). Firstly, distal to the injury myelin sheds detach from the axons followed by axonal degeneration (Chen et al., 2017). Subsequently, myelin sheds degrade into smaller pieces (Chen et al., 2017). A chemical destruction of the proteins of the myelin sheaths and the successive degradation of lipids begins (Chen et al., 2017). All this results into degeneration, destruction of the blood brain barrier and immigration of glial cells to eliminate cell fragments (Waller, 1850, Vargas & Barres, 2007, Wang et al., 2012).

Small vessel disease (SVD) is another possible reason for white matter alterations (Pantoni, 2010, Croall et al., 2017, Wardlaw et al., 2019). The pathology affects especially small vessels such as arterioles, capillaries and venules (Pantoni, 2010, Gurol et al., 2020, Wardlaw et al., 2019). SVD is triggered by atherosclerosis, cerebral amyloid angiopathy, inflammatory and immunologically mediators and venous collagenosis (Pantoni, 2010, Wardlaw et al., 2019, Gurol et al., 2020). Post-mortem histological studies showed pathologies such as lacunar infarcts, microbleeds, enlarged perivascular spaces and white matter lesions (Pantoni, 2010, ter Telgte et al., 2018, Wardlaw et al., 2019, Gurol et al., 2020). They are considered to represent demyelination, gliosis and loss of oligodendrocytes and axons (ter Telgte et al.,

2018, Wardlaw et al., 2019). This leads to a diffuse breakdown of blood-brain-barrier and endothelial dysfunction (Wardlaw et al., 2019). SVD is detected in both cognitive normal people like our test group and cognitive impaired subjects (Pantoni, 2010). Thus, SVD is also related to reduced processing speed and executive function as well as depression, gait problems and an increased risk for stroke and dementia (ter Telgte et al., 2018, Wardlaw et al., 2019).

Both WD and SVD are examined in histopathological studies but can also be detected in vivo using neuroimaging (Chen et al., 2017, Reginold et al., 2018, ter Telgte et al., 2018, Wardlaw et al., 2019). Thus, a neuroimaging correlate for white matter lesions are white matter hyperintensities (WMH) (Pantoni, 2010, Croall et al., 2017). They are detected by FLAIR-MRI-sequencing (Reginold et al., 2018, ter Telgte et al., 2018, Wardlaw et al., 2019). This approach differentiates tissue into non-normal appearing white matter, the WMH, and normal appearing white matter (Maillard et al., 2011, de Groot et al., 2013, Maniega et al., 2015).

Other surrogate parameters for white matter alterations are diffusion tensor imaging (DTI) associated markers (Pierpaoli et al., 2001, Le Bihan, 2003, Bennett et al., 2010, Madden et al., 2012, Chen et al., 2017, Croall et al., 2017, Wardlaw et al., 2019). Here, tissue is examined at voxel level so that even diffuse change of white matter is detected (ter Telgte et al., 2018). Image contrast is given by the restriction of Brownian motion within a tissue by natural barriers like cell membranes, myelin sheds and axons, versus to free diffusion (Beaulieu, 2002, Le Bihan, 2003, Madden et al., 2012).

White matter alterations measured with DTI can be quantified by different parameters. Mean diffusivity (MD) indicates the average diffusivity of water molecules within one voxel. (Beaulieu, 2002, Le Bihan, 2003, Madden et al., 2012, Garcia-Lazaro et al., 2016). The higher the value of this parameter, the more pronounced the white matter change is (Beaulieu, 2002, Le Bihan, 2003, Bennett et al., 2010, Madden et al., 2012, Salami et al., 2012). Fractional anisotropy (FA) describes the anisotropy of a diffusion process (Beaulieu, 2002, Le Bihan, 2003, Madden et al., 2012), taking values between zero and one. If FA is zero, diffusion happens within every direction without limitation (isotropic diffusion) (Le Bihan, 2003, Madden et al., 2012). If FA is one, there is just one axis in which diffusion is possible (Le Bihan, 2003, Madden et al., 2012). Accordingly, alterations in the microstructure of the white matter can result in FA decreases (Damoiseaux et al., 2009, Bennett et al., 2010, Madden et al., 2012,

Salami et al., 2012, Garcia-Lazaro et al., 2016). A recently newly implemented marker to assess white matter integrity is peak width (PW). This is a histogram analysis and is defined as the width between the fifth and the ninety-fifth percentile of the distribution of MD values within white matter (Baykara et al., 2016, Deary et al., 2018, Wei et al., 2019, Low et al., 2020). When combined with skeletonization, it is called PSMD (Baykara et al., 2016, Deary et al., 2018, Wei et al., 2019, Low et al., 2020). Increased PSMD indicates decreased white matter integrity (Baykara et al., 2016, Deary et al., 2018, Wei et al., 2019, Low et al., 2020).

1.2. Alteration of brain activation

As aforementioned, white matter change is associated with altered brain function. Brain activation is measured by functional magnet resonance imaging (fMRI). The basis of functional MRI is the blood-oxygenation level-dependent (BOLD) contrast (Ogawa et al., 1990, Matthews & Jezzard, 2004, Huettel et al., 2009, Logothetis, 2008, Goense et al., 2016). When a certain area of the brain is activated, for example during memory encoding, it needs more oxygen (Ogawa et al., 1990). This leads to a dilation of arteries and a disproportionate overflow of oxygenated blood (Ogawa et al., 1990). Oxygenated and deoxygenated hemoglobin show differences in their magnetic properties (Ogawa et al., 1990, Matthews & Jezzard, 2004, Huettel et al., 2009, Logothetis, 2008, Goense et al., 2016). As a result, MRI signal intensity varies according to task demands (Ogawa et al., 1990, Matthews & Jezzard, 2004, Huettel et al., 2009, Logothetis, 2008, Goense et al., 2016).

One of the most important distinctions of fMRI paradigms is the differentiation between resting state fMRI (rsfMRI) and task-fMRI. During rsfMRI, subjects are instructed to lie still without thinking of anything specific (Chao-Gan & Yu-Feng, 2010, Barkhof et al., 2014, Damoiseaux, 2017). This technique can be used to determine functional connectivity (FC) by comparing the activation of brain regions (Barkhof et al., 2014, Damoiseaux, 2017). The rsfMRI allows the representation of time courses in which brain regions are synchronously activated and deactivated (Barkhof et al., 2014, Damoiseaux, 2017). Thereby, networks of rest can be identified such as the default mode network (DMN) (Barkhof et al., 2014, Damoiseaux, 2017). The task fMRI, in contrast to rsfMRI, is examining the working brain. Here, networks can also be identified but they are specific to particular cognitive processes, for example memory or recall (Sperling et al., 2002, Li et al., 2015).

Healthy elderly subjects without any decline in memory function show activation differences in brain regions that are involved in memory encoding processes compared to a young control group (Reuter-Lorenz & Park, 2010, Li et al., 2015). Previous papers corroborate frontal hyperactivation in addition with hypoactivation of occipital regions in elderly in comparison to young subjects (Cabeza & Dennis, 2014, Li et al., 2015). Furthermore, older people compared to younger subjects tend to recruit additional brain regions e.g. during working memory (Reuter-Lorenz & Park, 2010).

1.3. Relation between white matter change and altered brain activation

Current research has already described a relation between white matter alteration and changes in brain function (Bennett & Rypma, 2014, Taylor et al., 2017, Warbrick et al., 2017). Especially the relationship between structural white matter changes and functional alterations during rsfMRI is a well-studied issue (Honey et al., 2010, Taylor et al., 2017, Damoiseaux, 2017, Suarez et al., 2020). Taylor et al., (2017) demonstrated that increased burden of WMH within the inferior fronto-occipital fasciculus (IFOF) is related to decreased functional connectivity during rsfMRI in connected cortical areas in Alzheimer's diseased patients.

In contrast to rsfMRI there is a significantly smaller number of projects that investigated the relationship between white matter alteration and task fMRI (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Burzynska et al., 2013, Zhu et al., 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015, Webb et al., 2020a, Webb et al., 2020b). A review by Bennett & Rypma (2014) indicated the dependency between DTI-changes and task fMRI in healthy young and older subjects: In young subjects increased white matter integrity is mostly associated with increased brain activation. The inversed effect was revealed for the older age group (Bennett & Rypma, 2014). However, previous projects either correlated FA within all voxels of white matter with BOLD-signal in the voxel of gray matter (Burzynska et al, 2013) or focused their structure-function analysis to frontal brain regions (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Zhu et al., 2014, Daselaar et al., 2015, 2014, Hakun et al., 2015, Zhu et al., 2015, Webb et al., 2020b). The results showed a high variability. Some revealed a relationship between increased brain activation and decreased white matter integrity (Madden et al., 2007, Schulze et al., 2011, Zhu et al., 2014, Hakun et al., 2015, Zhu et

al., 2015). Others showed the inversed effect (De Chastelaine et al., 2011) or even no result in older subjects (Webb et al., 2020b).

Additionally, it is argued that the relationship between white matter change and altered brain activation is dependent of the investigated brain region (Bennett & Rypma, 2014, Warbrick et al., 2017). A review by Warbrick et al., (2017) analyzed the relation between structural degeneration measured in FA and task related brain activation in healthy elderly and patients (Warbrick et al., 2017). There, it was shown that the directionality of the relationship is dependent of the investigated cognitive task and the brain region (Warbrick et al., 2017). However, the review includes research that examined the structure-function relationship in young and old subjects but also in patient groups such as mental diseases, multiple sclerosis or epilepsy (Warbrick et al., 2017).

Moreover, there is evidence that anatomical connectivity between the investigated white and grey matter is important for this structure-function relationship (Bennett & Rypma, 2014, Damoiseaux, 2017, Warbrick et al., 2017, Rieck et al., 2020, Suarez et al., 2020). For example, an association between higher structural integrity and higher brain activation was revealed when neighboring brain regions of gray and white matter were investigated in young volunteers (Bennett & Rypma, 2014). This relationship reversed when the association between gray and white matter regions without proximity were examined (Bennett & Rypma, 2014). Furthermore, it was shown that fibers of the ILF that directly culminate into the fusiform face area are a predictor for specialized brain activation in this gyrus but not the entire part of the ILF (Rieck et al., 2020). It is also known that higher functional connectivity is strongly correlated with functional connectivity between examined brain areas (Damoiseaux, 2017, Suarez et al., 2020).

1.4. Relation between cognition and white matter change or altered brain activation

It has already been shown that even in healthy aging cognitive processes such as attention, memory encoding and working memory are compromised (Kennedy & Raz, 2009, Cabeza & Denniz, 2014, Daselaar et al., 2015, Cabeza et al., 2018). This cognitive decline is associated with both white matter change and altered brain activation (Cabeza & Denniz, 2014, Cabeza

et al., 2018). These findings brings us closer to understanding the underlying mechanism of the structure-function relationship.

The relationship between microstructural change and decreased cognitive performance indicates that individuals cannot meet the cognitive goal indicated by the failure to meet the task demands due to underlying structural changes (Cabeza & Denniz, 2014, Cabeza et al., 2018).

This raises the question of whether the altered brain activation compensates structural change to achieve a better cognitive performance (Grady, 2012, Cabeza & Dennis, 2014, Scheller et al., 2014). In this case, increased prefrontal activity is associated with a good cognitive performance in cognitive healthy subjects and thus considered to be compensational (Cabeza & Dennis, 2014, Scheller et al., 2014, Cabeza et al., 2018). Another approach is the dedifferentiation theory. It states that for a certain cognitional task less specialized brain regions are activated additionally in elderly (Goh, 2011, Koen et al., 2020, Rieck et al., 2020). For example, reduced selectivity in the ventral visual cortex is revealed during face processing (Rieck et al., 2020). Consequently, increased brain activation would be associated with poorer cognitive performance (Koen & Rugg, 2019). Others support the theory, that altered brain activity has no gain or purpose but only reflects an inefficient neuronal response (Zhu et al., 2015, Zhu et al., 2014, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al., 2020b). In that case, altered brain activation would be associated with poor cognitive performance (Bennett & Rypma, 2014, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al., 2020b).

1.5. Hypothesis

In conclusion, there was already shown a correlation between structural brain changes, detected by white matter alterations and brain function investigated by BOLD-signal. (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Burzynska et al., 2013, Zhu et al., 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015, Webb et al., 2020a, Webb et al., 2020b). Previous studies either correlated the FA within all voxels of white matter with BOLD-signal in the voxel of gray matter (Burzynska et al., 2013) or focused their analysis on the frontal brain region (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Bennett & Rypma, 2014, Zhu et al., 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015).

However, the directionality of this association is highly variable (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Zhu et al., 2014, Bennett & Rypma, 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015, Warbrick et al., 2017). There is evidence that the directionality of the structure-function relationship depends on different factors (Bennett & Rypma, 2014, Warbrick et al., 2017):

Firstly, it was shown that this relationship is influenced by the investigated brain region (Warbrick et al., 2017). However, this was only detected in a review based on a summary of different projects and not on an individual test person level (Warbrick et al., 2017). Others focused just on frontal brain regions (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Bennett & Rypma, 2014, Zhu et al., 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015). To further explore the structure-function relationship, a whole brain analysis was implemented on an individual test person level to investigate the structure-function relation of the brain during a cognitive task. Thus, it was able to test whether the encoding-related structure-function relationship is the same in all areas of the brain or whether it differs in dependency of brain region.

Secondly, the anatomical connection between white and gray matter has been shown to influence this structure-function relationship (Bennett & Rypma, 2014, Damoiseaux, 2017, Warbrick et al., 2017, Rieck et al., 2020, Suarez et al., 2020). Thus, the dependency of a close proximity between the investigated white matter tract and the activated brain area was assumed. Therefore, the analysis were just focused on white and grey matter regions that are anatomically connected.

In addition, it was decided to not only use the well-known parameters for white matter change such as WMH-ratio and MD but also the newly implemented parameter PW. This parameter is assumed to be the best marker to assess white matter alteration (Beaudet et al., 2020).

Furthermore, there is a controversy about the purpose of altered brain activation. There are supporter who advocate the compensation theory (Grady, 2012, Cabeza & Dennis, 2014, Scheller et al., 2014). Others argue for the dedifferentiation theory (Goh, 2011, Koen et al., 2020, Rieck et al., 2020). Still others speak of an undirected activation change (Zhu et al., 2015, Zhu et al., 2014, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al., 2020b). In order to further investigate this topic, data of the cognitive performance during the face-name

encoding task of the subjects were included to determine the underlying mechanism of the relationship between white matter alteration and changed brain activation.

Accordingly, the first hypothesis tests whether increased white matter change is related to decreased encoding-related brain activation in adjacent brain regions. White matter alterations are detected by increased WMH-ratio and DTI-parameters such as increased MD and PW within both, specific tracts and whole brain white matter. Brain activation is assessed by BOLD-signal during successful encoding.

The second hypothesis states that decreased cognitive performance is associated with decreased white matter integrity and decreased brain activation. This analysis is restricted to white and gray matter areas that had shown a significant result during the analysis of the first hypothesis.

2. Methods

This project was carried out at the Institute of Stroke and Dementia of the Ludwig-Maximilians-University (Prof. Dr. Michael Ewers).

2.1. Participants

46 healthy controls (HC) were included according to the following inclusion criteria: the subject had to be cognitively normal, as determined by the CERAD-Plus battery (performance within 1.5 standard deviations (SD) of the age-, gender- and education-adjusted norm levels in all subtests). Subjects had to agree to the disclosure of incidental findings, be covered by health insurance, their mother tongue had to be German and they had to be at least 60 years old. Exclusion criteria were: past neurological or psychological disorders, current or past substance abuse, drug-treated diabetes mellitus, a premorbid IQ under 85 and contraindications for MRI-scanning.

Eleven subjects were excluded for the following reasons (Fig 1): anatomical abnormalities (n = 2), problems in the acquired MRI scans (two showed signal drop-out-type artefacts and one showed ringing artefacts in the EPI sequences), inability to complete the memory task during fMRI (n = 2), excessive movement during resting state (n = 1) and failed pre-processing (n = 3) at normalization of FA- and MD maps (see below). The definitive number of subjects was 35.

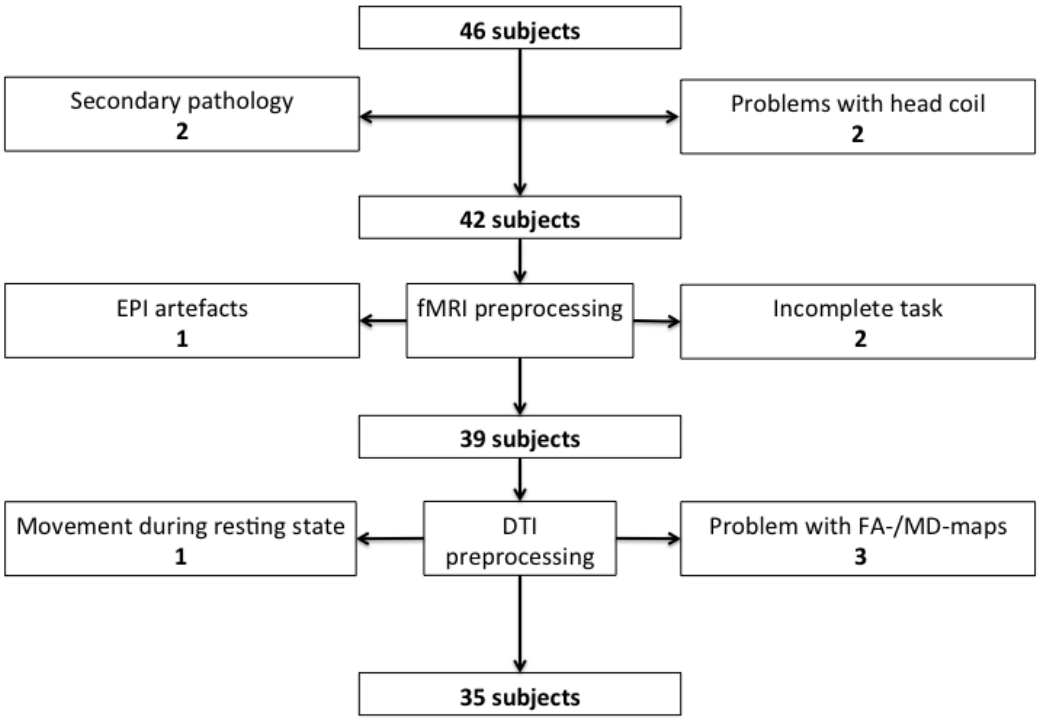

Figure 1: Flowchart for subject selection

From the initial 46 subjects eleven subjects had to be excluded for the reasons mentioned above.

2.2. Study design

Each subject underwent a clinical and neuropsychological examination on the first visit. The following tests were used to assess the cognitive status: "MWT-A Mehrfachwahl-Wortschatz-Intelligenztest" (German multiple vocabulary test) (Hessler et al., 2013) to test the premorbid intelligence level, the CERAD-Plus (The Consortium to Establish a Registry for Alzheimer's Disease, https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/), containing verbal and phonematic fluency, confrontational naming (15-item Boston Naming Test), mini-mental state examination (MMSE), word list memory, recall and recognition, constructional praxis performance and recall, trail making tests A and B, the GDS (Geriatric Depression Scale), the CDR (clinical dementia rating scale), symbol digit modalities test and a questionnaire about handedness.

On the day of the medical and neuropsychological examinations, the subjects participated in a structural-MRI session during which several sequences were recorded, including the 3D-T1-

weighted anatomical scan (MPRAGE; details in section Data collection), a T2-weighted FLAIR scan and a 30-direction diffusion-weighted DTI scan.

On the next day, the patients took part in the memory-task fMRI. Before the task, an additional anatomical MPRAGE T1 was obtained for alignment purposes. The task (Fig 2) was performed inside of the scanner. Simultaneously, a T2*-weighted EPI sequence was recorded (details in section "2.4: Data collection").

2.3. Face-name paradigm

The task consisted of a face-name matching paradigm. During the encoding phase subjects were presented with series of face-name pairs, which they had to memorize. During recall-phase they were shown one face along with two names from which the correct one (i.e. previously presented with the face during encoding) had to be chosen by pressing a button. The lure (wrong name) was in half of the trials a new name not previously presented and in the other half of the trials a name that had been previously shown (Fig 2). The accuracy in the memory task (ACC) was calculated in percentage, as number of correctly recognized names (summed for both conditions) divided by total number of face-name pairs.

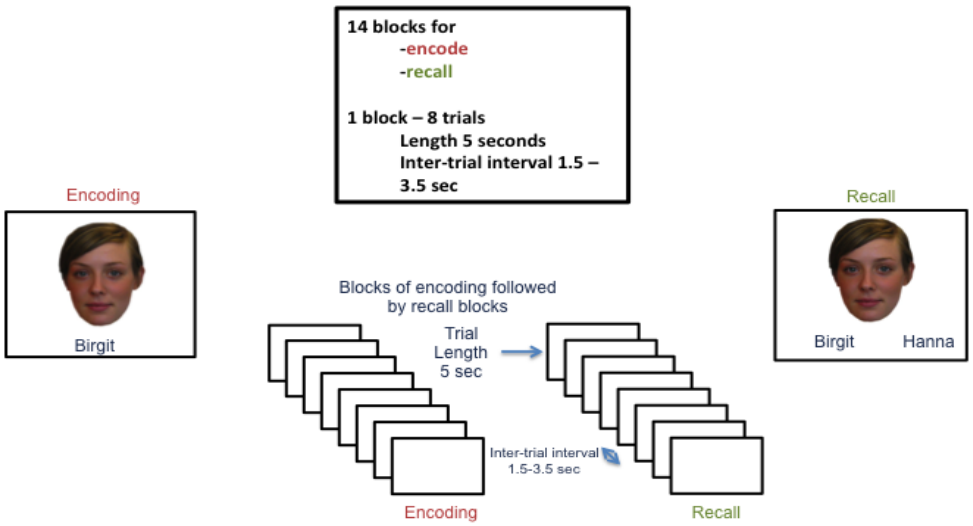

Figure 2: Face-name paradigm
Sequence and data of the encoding and recall blocks during fMRI.

The task consisted of 112 faces, chosen from the Glasgow Unfamiliar Face Database (GUFD - http://www.abdnfacelab.com/downloads) and selected based on European appearance,

straight gaze and without face jewelry or hairgrips. 168 names were chosen from a monolingual dictionary, the Leipzig Corpora Collection (http://corpora.informatik.uni-leipzig.de). This project by the University Leipzig provides dictionaries for many languages including German, in combination with statistical information such as word occurrence frequency (Goldhahn et al., 2012). The names were selected to be common based on a frequency distribution of names. However, this frequency distribution was not normally-distributed and therefore had to be log-transformed (Franzmeier et al., 2017, Franzmeier et al., 2018). An additional criterion was the number of letters (five or six). The stimuli were presented via eye-sight corrected goggles and the subjects were asked to select the correct name by pressing the right (index-finger) or left button (thumb) of a response paddle held in their right hand (the goggles and response paddles were manufactured by Nordic Neuro Lab (NNL), Oslo, Norway). There were 14 blocks for both encoding and recall. One block of encoding consisted of eight trials, meaning eight different face-name pairs. The corresponding block of recall (i.e. 8 faces with two names below each) immediately followed the encoding. Every trial lasted 5 seconds and the inter-trial interval lasted 1.5 to 3.5 seconds (Franzmeier et al., 2017, Franzmeier et al., 2018). The task was presented in three runs with breaks in between and had a total duration of 30 minutes.

2.4. MRI Data acquisition

All imaging data were collected in a Verio 3T Scanner (Siemens AG, Erlangen, Germany) based on standardized protocols developed by the German Center of Neurodegenerative Diseases (DZNE; with the exception of the T2*-weighted EPI for which the DZNE provides no standard). The following protocols were included:

- 3D T1-weighted magnetization-prepared gradient recalled echo sequence (MPRAGE), with echo time (TE)/inversion time (TI)/repetition time (TR) = 4.33/2500/1100 ms, flip angle = 7°, acquisition plane = sagittal, matrix size= 256 x 256, number of slices = 192, thickness = 1.00 mm and voxel size= 1.00 x 1.00 x 1.00 mm^3. 32 channel head-coil used for acquisition. No angulation.
- Fluid-attenuated Inversion Recovery (FLAIR) sequence, TE/TI/TR = 394/5000/1800 ms, flip angle = 120°, acquisition plane = sagittal, matrix size = 192 x 256 x 256 voxel,

number of slices = 192, slice thickness =1.0 mm and voxel size = 1.0 x 1.0 x 1.0 x mm^3. 32 channel head-coil used for acquisition. No angulation.

- A 2D diffusion weighted (DW) spin-echo EPI sequence, TE/TR = 88/12100 ms, matrix size = 128 x 128 mm, number of slices = 72, thickness = 2.0 mm, voxel size = 2.0 x 2.0 x 2.0 mm, b-value(1) = 0 s/mm^2, b-value(2) = 700 s/mm^2, b-value(3) = 1000 s/mm^2, number of gradient directions = 30, number of non-diffusion weighted images = 1. Angulated acquisition to the anterior commissure – posterior commissure line (AC-PC).
- T2*-weighted (EPI) sequence, head coil = 12-channel, TE/TR = 30/2000, flip angle = 90°, acquisition plane = axial, matrix size = 210 x 210, number of slices = 30, slice thickness = 3 mm, inter slice gap = 1 mm, voxel size= 3 x 3.3 x 3.3 mm^3 parallel acquisition (GRAPPA) with acceleration factor 2. 12 channel head-coil used for acquisition as the presentation goggles could not be fitted to the 32-channel coil. AC-PC angulation.

2.5. Pre-processing of the T1 scans

The T1 scans for both structural and functional sessions underwent the same (pre-) processing steps. The scans were angulated to the AC-PC line manually. Then the tissue was separated into white matter, grey matter and CSF probability maps with the algorithm "New Segment" (Ashburner & Friston, 2005) of SPM (http://www.fil.ion.ucl.ac.uk/spm/). Afterwards a sample-specific template was computed with the diffeomorphic image registration algorithm (DARTEL) (Ashburner, 2007), based on the subject's tissue probability map. Finally, the transformation parameters from native space to the DARTEL template (u-field map) were computed for each subject. They were compounded with the DARTEL-to-MNI affine transformation parameters so that definitive transformation parameters from native T1 space to MNI-space could be computed. All the T1 processing steps were performed with SPM version 12b (http://www.fil.ion.ucl.ac.uk/spm/).

2.6. Pre-processing of the DTI images

The DTI scans were eddy-current and motion corrected. A correction for susceptibility distortion was attempted, based on a nonlinear co-registration to the native T1 as implemented in the software ExploreDTI for Matlab (Leemans & Jones, 2009). The distortion correction did not improve the images significantly, so all analyses were performed with eddy-

current and motion-corrected images only. Additionally, diffusion-tensor fitting was executed and whole-brain maps of FA and MD were computed. These were registered to the native T1 images and normalized to MNI space with the parameters computed earlier for the native T1 images. The DTI processing pipeline was implemented in Explore DTI (Leemans & Jones, 2009), except for registration and normalization, which were done in SPM 12b.

To avoid partial-volume effects a binary white matter mask was created by thresholding the FA-images at FA > 0.25. The MD maps were masked with this mask for further analyses. In addition, the MD-maps were masked by a ventricle-excluding mask to avoid partial-volume effects from the ventricular CSF, which has very high MD values.

2.7. Pre-processing of the fMRI Data

The EPI images underwent standard fMRI processing steps: slice-time correction, field-map correction against susceptibility distortion artefacts (unwarping), realignment and registration to the native T1 images for normalization to MNI space, which was done using the normalized parameters computed before.

All of these steps were performed in SPM 12b.

2.8. Rating of WMH

The FLAIR images were registered to the T1 images, bias-corrected and segmented into three different tissue-classes. One of the tissue classes contained both CSF and WMH. To separate them the histogram segmentation method of Otsu (Admiraal-Behloul et al., 2005) was used, because CSF and WMH follow a bimodal intensity distribution in this class. This produced both clusters of true WMH and clusters misclassified as WMH. An in-house software tool was developed to manually rate the clusters as either WMH or artefacts (Taylor et al., 2017). As a criterion for a WMH cluster the size of more than five contiguous voxels labelled as WMH had to be present, and the voxels had to be located outside the cerebellum and brainstem. If it was located near the ventricles, it had to be more than two voxels apart (perpendicular to the ventricular surface) to minimize partial-volume effects. WMH were rated by two independent raters (Taylor et al., 2017), who showed a high degree of agreement (mean Dice Coefficient = 0.96, Intraclass Correlation = 0.98).

After rating, the WMH masks were co-registered to T1, then normalized to the MNI space applying the normalization parameters computed above.

2.9. Computation of markers of white matter changes

As marker for microstructural axonal changes three parameters were established: WMH volume ratio (WMH-ratio), mean MD (MD) and MD peak width (PW). Every parameter was computed globally (for all tracts of the JHU as a proxy for the global white matter), as well as locally (within every single tract of the JHU).

For computing the WMH-ratio the number of voxels classified as WMH in each subject was divided by the number of voxels of the white matter globally, to compute global WMH volume normalized by white matter volume, or locally within a specific tract, to compute tract-specific WMH burden.

MD describes the average of diffusion within all three axes of the diffusion ellipsoid (Madden et al., 2012). Both global MD, averaging MD within all the tracts of the atlas, as well as tract-specific MD were computed. Increased MD signifies reduced integrity of the white matter. Increased MD is associated with microstructural alteration of white matter (Damoiseaux et al., 2009, Madden et al., 2012, Salami et al., 2012).

PW is a recently developed marker to assess the integrity of the white matter (Baykara et al., 2016). It consists of a histogram analysis and is defined as the width between the fifth and the ninety-fifth percentile of the distribution of MD values within a particular region of the white matter. The step of skeletonization (PSMD) was omitted and PW was computed for the whole white matter (global) and tract-specific to keep the analysis consistent. Considering that an increased PSMD indicates decreased white matter integrity, an increased PW within tracts was expected to indicate decreased tract-specific white matter integrity (Baykara et al., 2016, Deary et al., 2018, Wei et al., 2019, Low et al., 2020).

2.10. Computation of brain activation related to correctly encoding

To create a model of the activation clusters for every subject, the fMRI data was separated into four regressors in a general linear model (GLM): Encode-Correct, Encode-Incorrect, Recall-Correct and Recall-Incorrect. Successful encoding is defined by the correct recognition of a face-name pair. Missed responses or responses after five seconds were labelled as

incorrect. For each regressor, temporal and dispersion derivatives were included to account for possible drifts in the BOLD modelling.

The six motion parameters derived from the motion-correction were included as regressors to remove spurious activation which can arise from involuntary movement. Each of the three EPI runs were modelled independently but activation contrasts were averaged across all three EPI runs.

The subject-level contrast was focused on regions that showed higher activation in correct encoding than in incorrect encoding. This contrast was called: encoding all-correct > encoding all-incorrect.

The group-level analysis was performed with a one-sample t-test against zero on the subject-level contrasts above. This analysis resulted in a global activation cluster covering most of the brain. A voxel-level significance threshold $p = 0.01$ (uncorrected) and a cluster extend threshold $k = 708$ (FWE corrected) was implemented. Using this global activation map masks were generated to extract activation values for each subject separately.

First, the activation map after significance-thresholding was binarized, resulting in a large, connected activation cluster. This cluster was divided into ten smaller, more specific clusters by SPM according to anatomical considerations. This allowed for an assignment of the activation to specific cortical regions.

The resulting clusters were located within both frontal gyri, the left medio-frontal gyrus, the left superior temporal gyrus, both nuclei caudati, right parietal lobule, the left and the right Hippocampi and one cluster within the occipital gyrus. Additionally, the activation of the cortical regions was restricted to regions connected by fiber tracts, which is described in the next section.

Since the hippocampal gyri play an important role during learning processes hippocampal activation was calculated separately to make sure these regions were included in the analysis. To guarantee this, an inclusive hippocampus mask taken from the Automated Anatomical Labeling Atlas (AAL) (Tzourio-Mazoyer et al., 2002) was used and overlaid on top of the activation map obtained above, with a significance threshold of $p = 0.01$ but no cluster-level threshold. For every subject the mean of activation (i.e. mean of the subject-level activation map) was calculated within the area covered by this hippocampal mask.

2.11. Combining neuroimaging data

In this step, the WM tracts that connected the activation clusters were identified. Therefore, the 20-tract ICBM probabilistic atlas of Johns Hopkins University (JHU) (Hua et al., 2008) was utilized. The clusters resulting from the previous steps were superimposed onto the fiber-tract-atlas in MNI space. A tract was selected for further analyses if it connected two different clusters. This was determined by visually assessing the proximity of the anatomically ends of the tracts (thresholded at probability >10%), the cluster locations and the anatomical knowledge regarding the courses of the tracts (Wakana et al., 2003, Wakana et al., 2007). Additionally, a task-related activation within hippocampal gyri was expected. Thus, fibers of the left and the right hippocampal part of the Cingulate bundle were chosen (Cing L/Cing R), which connect hippocampal activation clusters. Six tracts were identified (Fig 3).

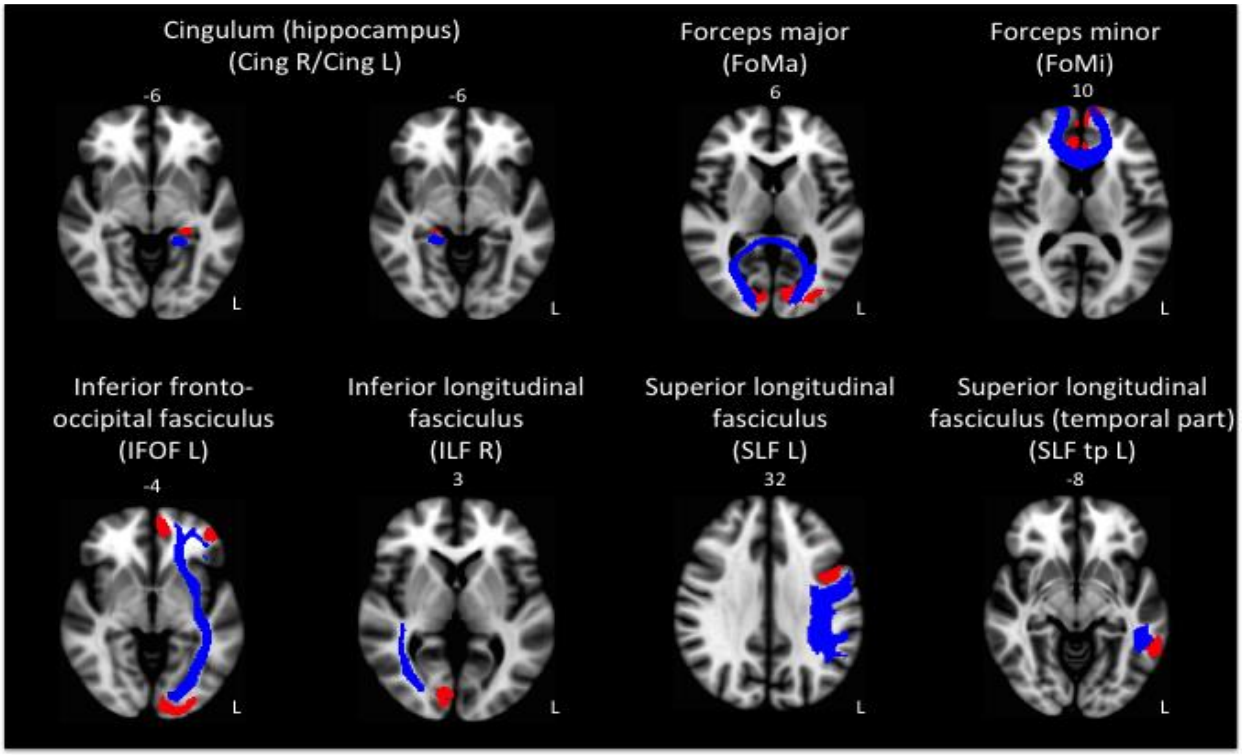

Figure 3: Selected tracts (blue) and related activation clusters (red):
Cingulum left (Cing L) or Cingulum right (Cing R) leading to hippocampus left or right/ Forceps major (FoMa) leading to primary visual cortices of both sides (BA 17)/ Forceps minor (FoMi) leading to orbitofrontal cortices of both sides (BA 10/11)/ Inferior fronto-occipital fasciculus (IFOF L) leading to left middle frontal (BA 46), prefrontal (BA 10) and the primary visual cortex (BA 17)/ Inferior longitudinal fasciculus (ILF R) leading to right fusiform (BA 37) and primary visual cortex (BA 17) / Superior longitudinal fasciculus left (SLF L) leading to left medial frontal (BA 8/9) and lateral occipital gyrus (BA18/19)/ Superior longitudinal fasciculus temporal part (SLF tp L) left leading to the left superior temporal gyrus (BA 22).

In order to obtain the mean activation within the cortical projection areas in the proximity to the fiber bundle ending, the overlap between the activation maps and the fiber projection endzones had to be established. Only the portions of the activation cluster that were connected by a particular white matter tract were of interest. Therefore, the following procedure was applied: each of the chosen tracts was dilated by six millimeters, masked with a grey matter mask and superimposed onto the activation clusters, thereby determining the overlap between the end of the tract and the corresponding activation clusters (Taylor et al., 2017). The resulting overlap of the dilated tract the grey matter mask and the cluster was extended once more by six millimeters to obtain sufficiently large cortical regions of activation, i.e. to include all the cortical column up to the surface of the cortex corresponding to the activation region. This two-step dilation with a masking in between was chosen instead of a full 12 mm dilation to minimize the possibility of expanding the main body of the tract into lateral regions that do not correspond to the terminal ends of the tract.

In some cases, different tracts led into the same cluster of activation and formed overlapping activation regions. Here the intersection of these two masks was determined by multiplication resulting in only the overlapping parts of the activation clusters remaining. Activation clusters belonging to the same tract were treated as one large cluster (Fig 4), i.e. without differentiation of anterior/posterior or left/right activation regions.

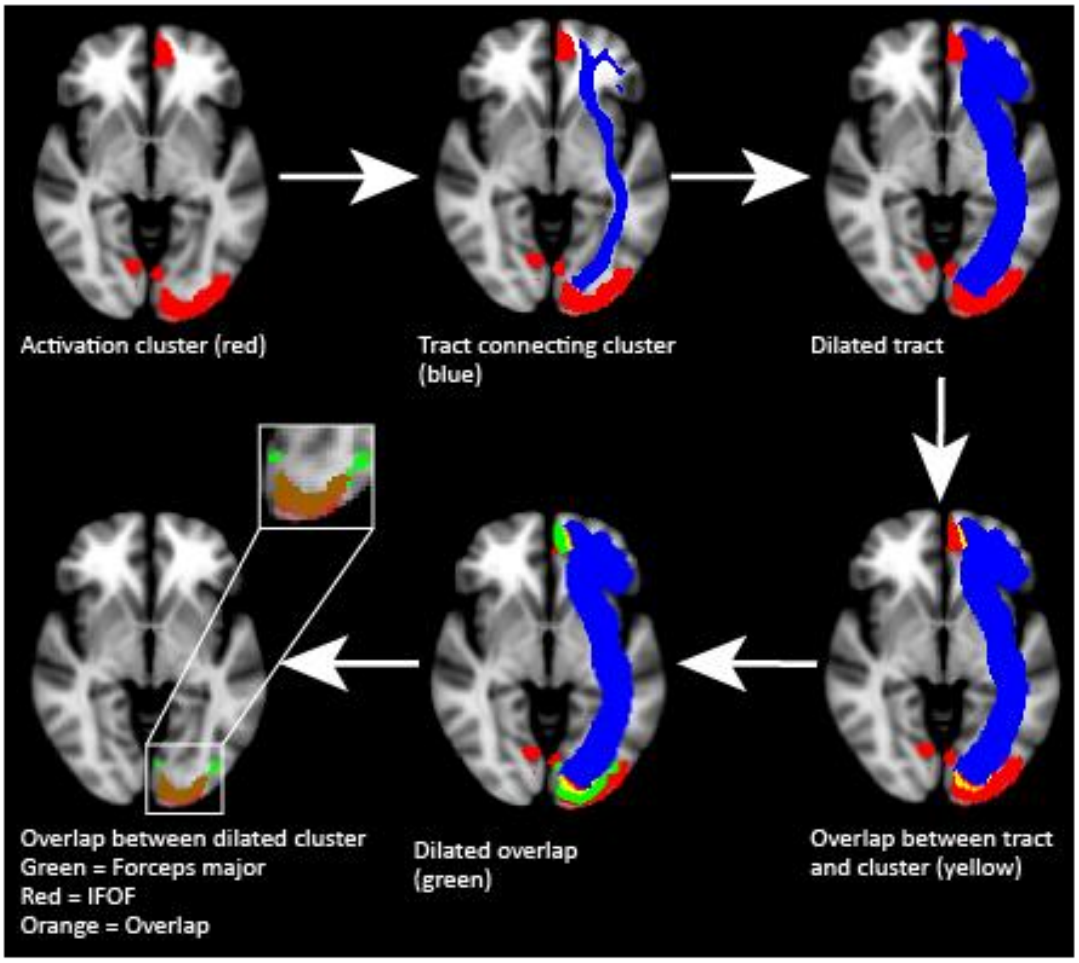

Figure 4: Producing the part of the activation cluster for analysis
Selection of tracts and dilation of the tracts within adjacent brain region leads to an overlap between tract and gyrus. This overlap within the gyrus is the relevant part of activation cluster that is analyzed in statistics.

3. Statistical analysis

3.1. Hypothesis 1 – Structure-Function Analysis

The first hypothesis stated that fiber tract changes within specific white matter tracts and whole brain white matter are associated with brain activation during encoding within regions that are connected by the investigated white matter tracts. For white matter alteration the DTI-marker MD and PW were established. WMH-ration as a marker for white matter change had to be excluded because of its low burden (see 4.5). To analyze brain function BOLD-signal during successfully encoding was chosen. Table 1 gives an overview about the computed models. The statistical analysis to test this hypothesis is presented in the following section.

	fMRI cluster – DTI tract
Model 1 **Orbitofrontal** **BA 10/ 11**	Orbitofrontal – FoMi
Model 2 **Medial frontal** **BA 8/9**	Medial frontal gyrus left – SLF L+ SLF tp L
Model 3 **Middle frontal** **BA 46**	Frontal gyrus left – IFOF L
Model 4 **Prefrontal** **BA 10**	Prefrontal gyrus left – FoMi + IFOF L
Model 5 **Superior Temporal** **BA 22**	Superior temporal gyrus left – SLF L + SLF tp L
Model 6 **Primary visual cortex left** **BA 17**	Occipital gyrus left – FoMa + IFOF L
Model 7: **Primary visual cortex right** **BA 17**	Occipital gyrus right– FoMa + ILF R
Model 8 **Lateral occipital** **BA 18/19**	Occiptial gyrus left – SLF L
Model 9: **Fusiform** **BA 37**	Temporal gyrus right – ILF R
Model 10: **Hippocampus – Cing L**	Hippocampus left – Cing L
Model 11: **Hippocampus – Cing R**	Hippocampus right – Cing R
Model 12: **Whole – whole**	Whole cluster – whole tracts

Table 1: List of the computed models

White matter tracts were selected that reach into areas of encoding-related brain activation. In model 2, 4, 5, 6 and 7 two tracts led to the same brain area.

Tracts and their abbreviations: Forceps minor (FoMi)/ Forceps major (FoMa)/ Left inferior frontal-occipital fasciculus (IFOF L)/ inferior longitudinal fasciculus (ILF R)/ Left superior longitudinal fasciculus (SLF L)/ temporal part of the left superior longitudinal fasciculus (SLF tp L), left Cingulum (Cing L), right Cingulum (Cing R).

3.2. Collinearity assessment

While testing the main hypothesis, that higher MD, or PW in fiber tracts, is associated with lower regional brain activation in the connected regions, the following problem occurred: Sometimes two tracts led to the same activation cluster and built an overlapping part. To assess if correlation existed between these two tracts, a collinearity analysis was executed.

If values of MD or PW of two tracts leading to the same overlapping part showed a high correlation, the association between the ROI activation and tract changes were analyzed for each tract in separate analyses in order to avoid collinearity effects between these two tracts. If the correlation between the DTI markers measured in multiple tracts connecting the same ROI was low, all predictors were included in the same robust regression model to test the prediction of ROI activation (Fig 5).

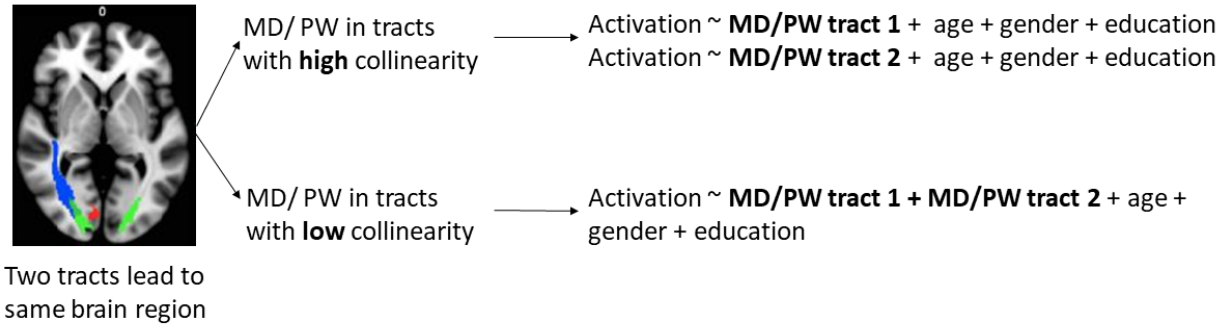

Figure 5: Forming models

When two tracts with a high collinearity lead to the same brain regions two separate models are computed.

Green = tract 1/ blue = tract 2/ red = activation cluster.

This analysis strategy allows to conclude that in case of a significant association between DTI changes and brain activation only one tract independently from the other one can accounted for the significance. The alternative model of including highly correlated predictors in the same model could result in misleading parameter estimates for each predictor. Thus, the former approach was preferred for this study.

3.2.1. ANCOVAs

For all the models listed in table one, a robust regression model was formulated since MD, PW and activation were not always normally distributed.

Tract-specific WMH-ratio as a marker for microstructural damage had to be excluded because of its low burden (see 4.5).

An ANCOVA was performed with respectively tract-specific or global MD or PW as independent variables, region-specific or global activation as the dependent variable and age, gender, education as covariates. The p-value was calculated with a two-tailed t-test with a significance level ≤ 0.05. In order to test whether the tract-based analyses showed region-specific effects, an additional control variable for global MD or respectively global PW was included. The ANCOVAs were also corrected for ventricle volume to rule out the influence of the incomplete correction of the partial volume effects on the results. To assess model quality, the residuals of each significant model were tested for normality (Shapiro Wilk test).

3.2.2. Sensitivity analysis to the influence of potential outliers

During the neuropsychological testing 33 subjects showed a CDR (= clinical dementia rate) of 0 and two subjects a CDR of 0.5. In order to determine, whether those two subjects influenced the results, all analyses with those two subjects being excluded were repeated.

3.3. Hypothesis 2 – Structural or functional change in association with cognition

The second hypothesis stated the following: on the one hand increased white matter changes within the ILFr and IFOFl, that revealed a significant result in the first hypothesis are associated with worse cognitive performance during the face-name paradigm. On the other hand encoding-related decreased brain activation within left frontal and right occipital brain regions, that revealed a significant result in the first hypothesis, are negatively related to the accuracy during the encoding task.

3.3.1. ANCOVAs

An ANCOVA was performed with PW in the IFOF or the ILF as independent variable and accuracy within the scanner as dependent variable. An ANCOVA was also performed with brain activation within left frontal or right occipital brain activation as independent and accuracy within the scanner as dependent variable. All the ANCOVAS were corrected for age and gender. An outlier in cognitive performance (accuracy <0.4) had to be excluded for all

these analysis.

3.4. Analysis of markers of white matter change

The distribution of the markers indicating white matter alteration was also investigated. Therefore, a pairwise t-test was calculated to identify differences between the markers.

To determine whether WMH were homogenously contributed within the white matter a WMH probability map was created by computing the ratio of subjects with WMH to the total number of subjects voxel-by-voxel.

Additionally, MD and PW were compared to test the specificity of these two predictors. Therefore, a correlation matrix between global and tract-specific MD or PW was computed. Ventricle volume as additional regressor was included in the correlation matrices to control for potential partial-volume effects.

4. Results

4.1. Demographics

35 healthy elderly subjects (see Table 2) were tested. The average age was 69.4 (SD = 5.2), 23 were female, 12 male and the mean years of education were 13.6 (2.95). During neuropsychological testing they performed almost at the highest level with an average MMSE of 29.4 (0.7). After excluding two subjects because of their divergent CDR all the computations were rerun but the results remained the same.

N	35
Gender f/m	23/12
Age	69.4 (5.2 [a])
Years of education	13.6 (2.95 [a])
CDR 0/0.5/1	33/2/0
MMSE	29.4 (0.7 [a])

Table 2: Demographics

Abbreviations: HC = healthy control, MMSE = Mini-Mental State Examination, [a]Values are mean (SD).

4.2. Activation Cluster

The activation cluster was formed out of brain regions that showed higher activation when subjects remembered correctly to a face-name pair than incorrectly (Fig 6). Thus, all brain areas were examined that are activated during successful encoding (Suppl 2). For this study the most important activated brain regions out of this cluster were: the orbitofrontal gyrus of both sides (Brodmann area (BA) 10/ 11), left medial frontal gyurs (BA 8/9), left middle frontal gyrus (BA 46), superior temporal gyrus of both sides (BA 22) and left fusiform (BA 37) gyrus, caudates of both sides, primary visual cortex (BA 17) of both sides, lateral occipital cortex left (BA 18/19) and both Hippocampi.

The prevalence within the literature of reported brain activation during encoding-related BOLD activation in fMRI were investigated and revealed a high consistency with the activation cluster of the present project (Sperling et al., 2002, Li et al., 2015).

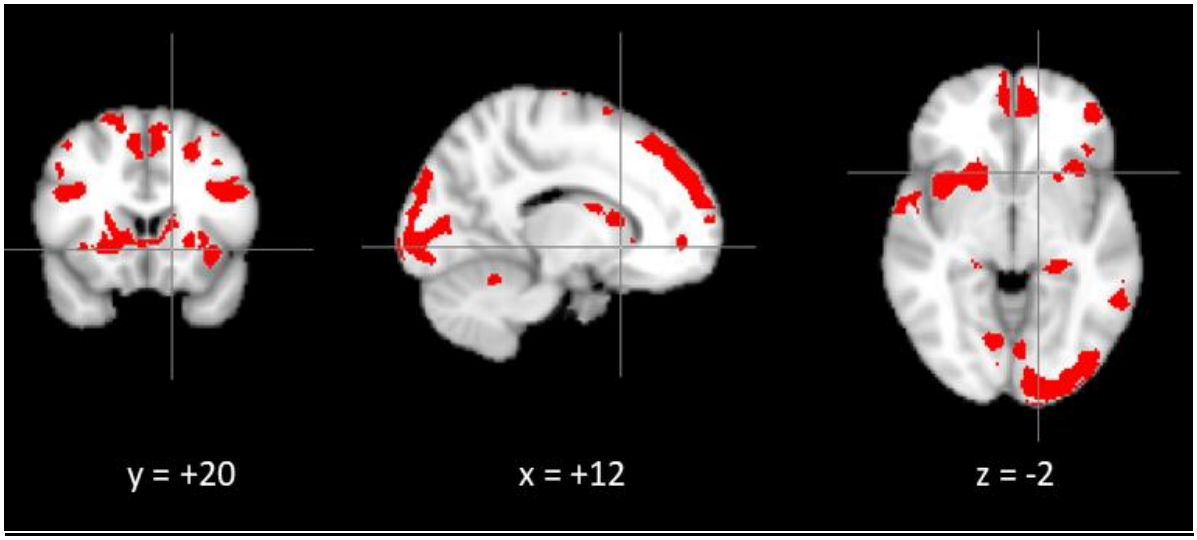

Figure 6: Activation Cluster
Brain regions that showed a higher BOLD-signal when subjects remembered correctly to a face-name pair than incorrectly.

4.3. Hypothesis 1 – Structure-Function Analysis

In the first hypothesis the association between white matter alteration and encoding-related brain activation was investigated.

4.3.1. Collinearity assessment

As described above a fiber tract specific and global MD or PW collinearity analysis was computed. When MD or PW of the two tracts leading to the same activation cluster showed a high correlation between each other, two separate robust regression models were computed. Otherwise, both tracts were used as independent variables within the same model. For MD all the models with two tracts leading to one activation cluster showed a high correlation. These clusters included the medial frontal model (model 2), the prefrontal model (model 4), the superior temporal model (model 5) and the primary visual cortex left model (model 6). For these models two separate ANCOVAs for each tract per cluster were computed. (Table 3)

For PW just the primary visual cortex left (model 6) and right (model 7) showed no significant correlation between the values within the corresponding tracts. Only in this case a robust regression could be computed with both tracts as independent variables.

	MD: cluster – tract	Correlation between the tracts	Robust regression models	
			Separate	One
Model 2: Medial frontal	**a)** Frontal gyrus left – SLF L **b)** Frontal gyrus left - SLF tp L	SLF L and SLF tp L, r = 0.98, (t(33) = 29.08, **p <0.001**)	**X**	
Model 4: Prefrontal	**a)** Medio frontal gyrus left – FoMi **b)** Medio frontal gyrus left – IFOF L	FoMi and the IFOF L, r = 0.83, L (t(33) = 8.56, **p <0.001**)	**X**	
Model 5: Superior Temporal	**a)** Superior temporal gyrus left – SLF L **b)** Superior temporal gyrus left – SLF tp L	SLF L and SLF tp L, r = 0.98, (t(33) = 29.08, **p <0.001**)	**X**	
Model 6: Primary visual c. l	**a)** Occipital gyrus left – FoMa **b)** Occipital gyrus right – IFOF L	FoMa and the IFOF L, r = 0.78, (t(33) = 7.20, **p <0.001**)	**X**	
Model 7: Primary visual c.r.	**a)** Occipital gyrus – FoMa **b)** Occipital gyrus – ILF R	FoMa and ILF R, r = 0.67, (t(33) = 5.12, p <0.001)	**X**	

Table 3: MD – Collinearity between the tracts and resulting robust regression models
For MD all the relevant tracts showed a high collinearity between each other, so separate robust regression were computed.

	PW: cluster – tract	Correlation between the tracts	Robust regression models	
			Separate	One
Model 2 Medial frontal	**a)** Frontal gyrus left – SLF L	SLF L and SLF tp L, r = 0.83; (t(33) = 8.67, **p <0.001**)	**X**	
	b) Frontal gyrus left – SLF tp L			
Model 4 Prefrontal	**a)** Medio frontal gyrus left – FoMi	FoMi and the IFOF L, r = 0.39, (t(33) = 2.44, p = 0.02)	**X**	
	b) Medio frontal gyrus left – IFOF L			
Model 5 Superior Temporal	**a)** Superior temporal gyrus left – SLF L	SLF L and SLF tp L, r = 0.83; (t(33) = 8.67, **p <0.001**)	**X**	
	b) Superior temporal gyrus left – SLF tp L			
Model 6 Primary visual c. l.	Occipital gyrus left– FoMa/ IFOF L	FoMa and the IFOF L, r = 0.22, L (t(33) = 1.32, p = 0.20)		**X**
Model 7 Primary visual c. r.	Occipital gyrus right – FoMa/ILF R	FoMa and ILF R, r = 0.23, (t(33) = 1.35, p = 0.19)		**X**

Table 4: PW – Collinearity between the tracts and resulting robust regression models

For PW the models 6 and 7 showed no correlation. Here, one robust regression was calculate with FoMa and IFOF L as two covariables for model 6 and FoMa and ILF R as two covariables for model 7.

4.3.2. ANCOVAs

As mentioned above an ANCOA with tract-specific MD or PW as independent variables was computed, brain activation as the dependent variable and age, gender, education as covariates. In significant models additionally for ventricle volume and global MD or PW was corrected.

4.3.2.1. Association between brain activation and MD

For each cluster of brain activation, the values of MD in a particular tract and globally (Table 1) was tested. Only the prefrontal model (Model 4b) revealed an association between increased tract-specific MD within the IFOF L and increased activation within the left frontal

gyrus. However, this model showed just a trend-level result (t (30) = 2.01, p = 0.05), controlling for age, gender, education, ventricle volume and global MD.

4.3.2.2. Association between brain activation and PW

For PW the same models as listed in Table 1 were computed. Similar to MD a significant association in the prefrontal model (model 4b) between higher PW within the IFOF L and the higher fMRI activation within the left frontal gyrus (t (30) = 2.60, p = 0.01) (Fig 7) was found, controlling for age, gender, and education. This effect did not stay significant after correcting for global PW and ventricle volume (t (30) = 0.82, p = 0.42). This effect can be primarily assigned to global PW.

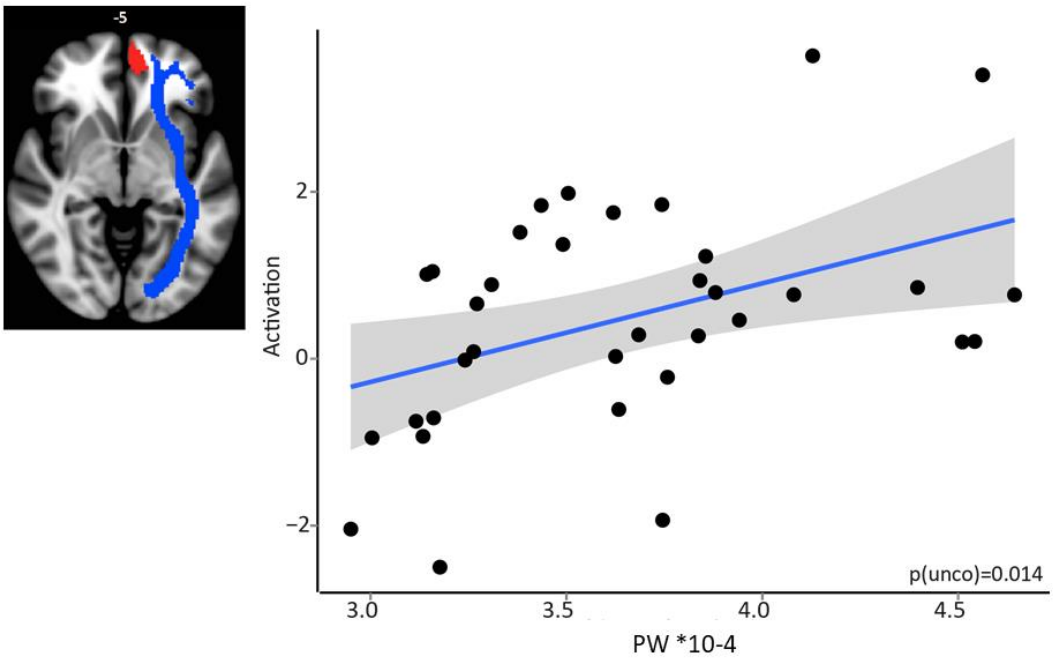

Figure 7: Positive relation between white matter change in IFOF L and prefrontal activation left

Model of prefrontal cortex left (model 4b) – Higher PW within the IFOF L predicts brain activation within frontal gyrus.
Blue = IFOF L, red = prefrontal activation.

In the model of the primary visual cortex right (model 7), both FoMa and ILF R reached in the right occipital activation cluster. PW within these both tracts showed no collinearity. Thus, both tracts were chosen as independent variables. In contrast to FoMa, in the ILF R the correlation between PW and activation of the occipital gyrus was significant (t (30) = 2.71, p =

0.01) (Fig 8). Even after correcting for age, gender, education, global PW and ventricle volume a significance was revealed (t (30) = 2.92, p = 0.007).

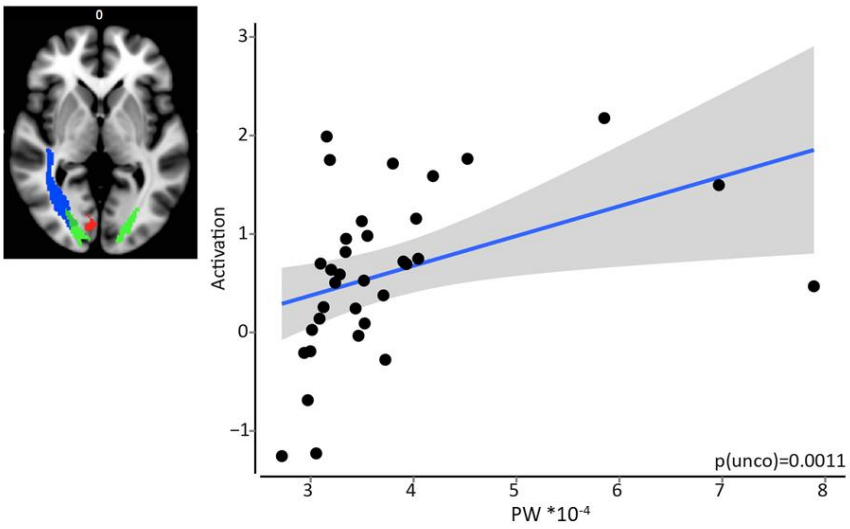

Figure 7: Positive relation between white matter change in ILF R in and right occipital activation

Model of the primary visual cortex right (model 7) – higher PW within the ILF R is associated with higher brain activation within occipital gyrus.
Green = FoMa; blue = ILF R, red = occipital activation.

In conclusion, the results showed a positive association between PW in the IFOF L or ILF R and the prefrontal cortex or occipital region. Increased PW indicates decreased white matter integrity or increased white matter alteration. Accordingly, a negative association between white matter integrity and brain activation is revealed or a positive relationship between white matter alteration and brain activation.

4.4. Hypothesis 2 – Structural or functional change in association with cognition

In the second hypothesis the relationship between white matter change or encoding-related brain activation and cognitive performance during the memory task within the scanner was investigated.

4.4.1. ANCOVAs

As mentioned above, an ANCOVA with PW of the IFOF left and ILF right as independent and accuracy within the scanner as dependent variable was computed, correcting for age and gender. The same ANCOVA was conducted with brain activation within left frontal or right occipital activation as independent variable.

However, in all the computed ANCOVAS no significant results were revealed.

4.5. Analysis of markers of white matter changes

To analyze the distribution of the markers of white matter alterations, further statistics were performed. They also allowed the comparison between MD, PW and WMH-ratio.

For all further calculations in which WMH-ratio was involved the outliers with global WMH-ratio > 0.015 (three standard deviations away from the mean) were excluded.

Global WMH-ratio was neither associated with global MD ($t(29) = 0.37$, $p = 0.71$) nor with global PW ($t(29) = 1.48$, $p = 0.15$).

For each of the three white matter markers, a pairwise t-test compared the white matter alterations within the tracts to determine if all markers showed different burden of white matter change. This would indicate that the white matter alteration can be considered as regionally variable and thus also as tract-specific (Fig 9, Fig 10**,** Suppl 1). Systematic differences between the tracts were revealed when using the marker MD and PW (Fig 10). In contrast to these two markers, the MWH-ratio showed no difference between the tracts (Fig 9). All these results already indicate the low WMH load, which will be elaborated below.

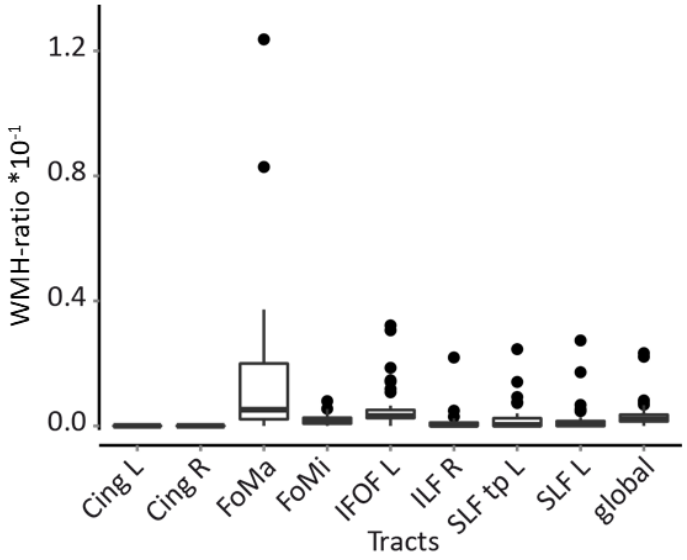

Figure 9: Tract-specific WMH-ratio

The box-whisker plot of WMH-ratio within each selected fiber tract and whole brain WMH-ratio (=global).

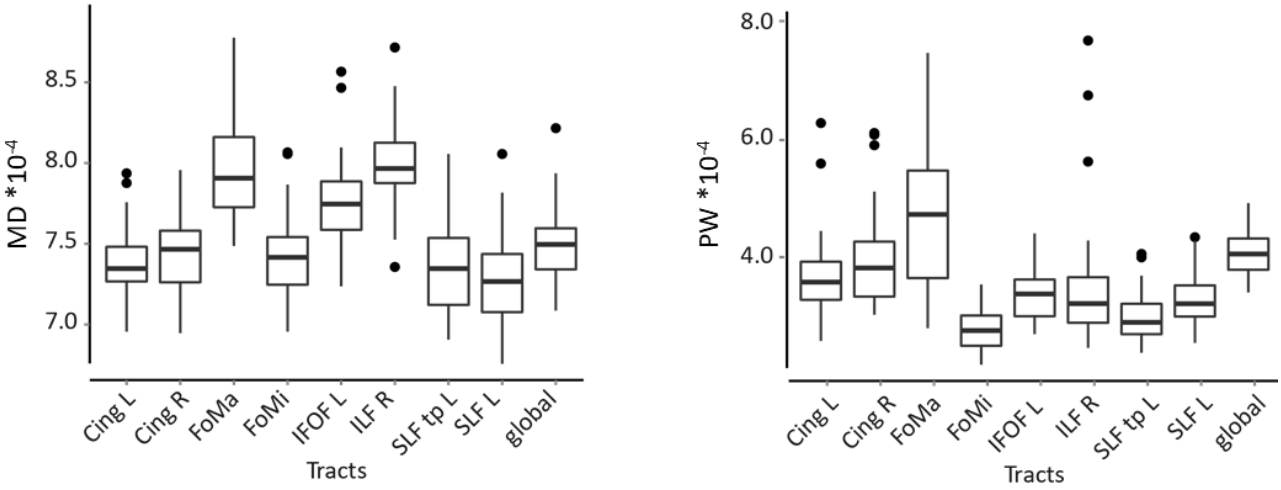

Figure 10: Tract-specific MD and PW

The box-whisker plot of a) MD and b) PW within each selected fiber tract and whole brain MD/ PW (=global).

As aforementioned a WMH-probability map was computed (Fig 11). This map showed that the values of the white matter probability map are below 0.4. Only in periventricular areas a burden around 0.4 was detected. The many zero values of WMH-ratio render the distribution highly skewed and severely compromises the statistical power to test an association between WMH-ratio and brain activation. Additionally, a table with the number of subjects that did not

show any WMH in its white matter tracts was computed to illustrate this effect (Table 3). This ranged from 100% in the left Cingulum (Cing L) to 3% in the left inferior frontal-occipital fasciculus (IFOF L). If WMH-ratio would have been taken as a tract specific marker, in some models a high number of subjects would have values of zero (Table 5). As a result, WMH-ratio as a marker of white matter change had to be excluded in the hypotheses.

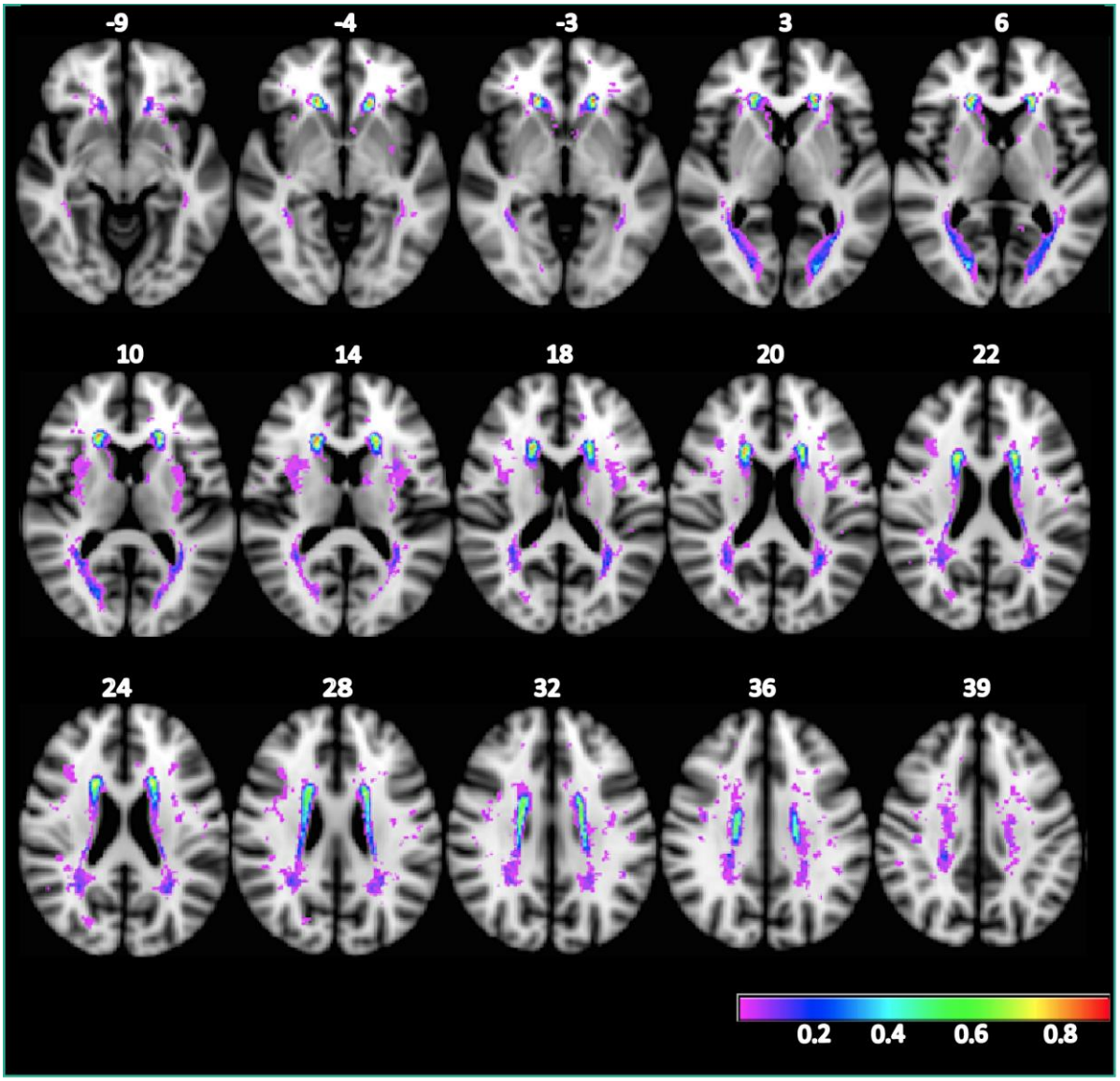

Figure 11: WMH probability map
WMH probability maps reveals low burden of WMH-ratio.

	Subjects that showed no WMH in this tract	
	Number	**Percentage**
Cing R	31	(88.6%)
Cing L	35	(100%)
FoMa	5	(14.3%)
FoMi	4	(11.4%)
IFOF L	1	(2.9%)
ILF R	17	(48.6%)
SLF L	14	(40 %)
SLF tpL	17	(48.6%)

Table 5: Numbers of subjects without any WMH in a tract

To compare the two DTI-associated markers of white matter impairment MD and PW, a correlation matrix (Fig 12) was computed. It was revealed that the tract-specific MD-values correlated more with each other than tract-specific PW. Therefore, PW seems to be a more sensitive marker for white matter alteration than MD. In the correlation matrix ventricle volume as additional regressor was added to demonstrate that both MD and PW are not strongly affected by partial volume effects.

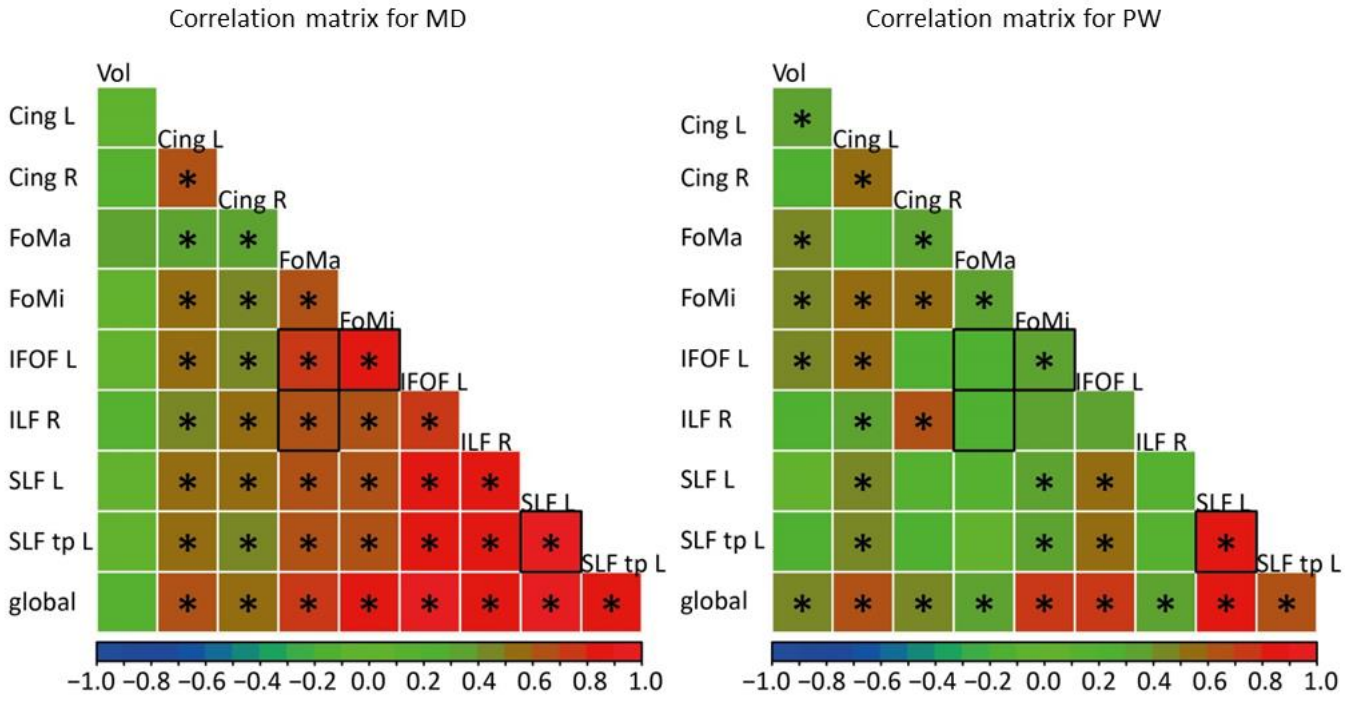

Figure 12: Correlation matrix with ventricle volume as additional regressor

a) MD and b) PW and ventricle volume (Vol); * = p ≤ 0.05/ for model 2, 4, 5, 6, 7 relevant correlations are highlighted with black background.

5. Discussion

This work examined the relationship between microstructural change of the white matter and encoding-related brain function in anatomically connected white and grey matter in cognitive healthy older people. In addition, the relationship between brain activation or white matter integrity and cognitive performance during the memory task in the MRI scanner was investigated. The results demonstrate that decreased white matter integrity indicated by increased PW is associated with increased brain activation in two brain regions: in the white matter tract IFOF left and activation in the left prefrontal cortex as well as in the white matter tract ILF right and activation in the right occipital cortex. Furthermore, the investigations between cognitive performance and frontal or occipital brain activation obtained no significant result. This was also found to be true for the relationship between cognitive performance and white matter integrity in the IFOF left or the ILF right.
Additionally, the currently developed DTI-marker PW proved to be a region-specific marker of microstructural white matter change.

The results of the present work confirm current research which demonstrates that negative structure-function relationship in older adults, meaning increased white matter change is associated with increased brain activation, was predominant. Thus, several studies reported an inverse association between white matter integrity and frontal brain activation during different tasks such as sensory processes (Madden et al., 2007), task switching (Zhu et al., 2014, Hakun et al., 2015, Zhu et al., 2015), working memory (Schulze et al., 2011, Burzynska et al., 2013) and episodic memory (Persson et al., 2005, Daselaar et al., 2015). In contrast, one project revealed an opposing effect: A relation between increased white matter integrity of the anterior callosum and increased encoding related right frontal brain activation in older subjects is demonstrated (De Chastelaine et al., 2011). Others found in middle aged but not older (age > 60 years) adults an association between increased whole-brain MD and a reduced dynamic range of brain activation in the striatum (Webb et al., 2020b). Additionally, Bennett & Rypma, (2014) and Warbrick et al., (2017) claimed that the structure-function relationship is dependent of age (Bennett & Rypma, 2014) and brain region (Warbrick et al., 2017). However, the comparison of the results between studies is compromised by the large variability in the methodological approaches used: White matter changes were assessed by

either correlating FA and brain activation of the whole brain (Burzynska et al., 2013) or by focusing on the frontal brain region (Persson et al., 2005, Madden et al., 2007, Schulze et al., 2011, Bennett & Rypma, 2014, Zhu et al., 2014, Daselaar et al., 2015, Hakun et al., 2015, Zhu et al., 2015). The regional assessment of DTI measures of the white matter differed between previous studies: Some used the JHU-atlas to define ROIS (Zhu et al., 2014, Zhu et al., 2015) or established ROIS manually on the anatomical basis of white matter tracts (Persson et al., 2005, Madden et al., 2007) or lobes (Daselaar et al., 2015, Schulze et al., 2011). Others defined the white matter to be analyzed by white matter tractography (Hakun et al., 2015, Webb et al., 2020b).

Thus, the heterogeneity of these results could be attributed to the wide variance of the chosen approaches. Different methods were used for the investigation of the white matter. The selection of the examined brain region differed from each other and even within the frontal cortex different parts of this gyrus were analyzed. As well, several cognitive processes were investigated. However, the present project established a whole-brain analysis and focused on the relationship between changed white matter and brain activation in connected brain regions. Thus, the structure-function association could be investigated assuming that due to the anatomical connectivity also a functional relationship exists. (Bennett & Rypma, 2014, Damoiseaux, 2017, Rieck et al., 2020, Suarez et al., 2020).

We found age-related decrease in white matter integrity: Higher DTI-based marker PW is found to be an indicator for decreased white matter integrity (Baykara et al., 2016). This project revealed that lower white matter integrity was associated with higher brain activity. Consistent with those results, a correlation between lower cortical fractal dimensionality (FD) – a DTI-associated research approach – and higher encoding-related brain activation in the lateral parietal cortex revealed the same directionality of the structure-function association (McDonough & Madan, 2021). Furthermore, decreased FA of the ILF was associated with increased N400m latency and amplitude in MEG during a visual semantic processing task (Shin et al., 2019), suggesting that increased brain activity is associated with lower fiber tract integrity (Shin et al., 2019). Thus, different methods lead to the same result: an association between increased structural changes and hyperactivation (Shin et al., 2019; McDonough & Madan, 2021). Therefore, explanations on the common denominator, the cellular level, can

be sought for example by electrophysiological methods (Burke & Barnes, 2010, Daselaar et al., 2015) or neurochemical changes (Morcom & Henson, 2018).

The present finding of higher brain activation in association with decreased PW in connecting fibers is consistent with the result of an electrophysiological study in animals. By comparing young and old adult rodents it was shown that in a circuit of neurons the decreased number of afferent fibers lead to an increased electrical activation of neurons (Burke & Barnes, 2010, Daselaar et al., 2015). Thus, increased synaptic response is evoked because of reduced local connectivity due to reduced number of white matter fibers. (Burke & Barnes, 2010, Daselaar et al., 2015). Therefore, reduced local connectivity may lead to altered signal transmission and to an increased brain activation. Another possible mechanism for increased brain activation due to white matter change can be measured when combining imaging techniques such as fMRI and PET. Changed dopaminergic neuromodulation in older adults for example in the frontal-hippocampal-striatal circuitry leads to reduced processing fidelity and increased frontal activation (Li & Rieckmann, 2014, Koen et al., 2019). Thus, an explanation for the relationship between white matter change and hyperactivation can be found at a basic level. This is confirmed by other neuroimaging studies which confirms that increased brain activity is revealed due to changed local data transmission of altered grey matter (Bennett & Rypma, 2014, Zhu et al., 2015, Warbrick et al., 2017, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al., 2020b).

In the current study higher brain activation in association with increased white matter change was observed specifically in two brain regions: the prefrontal cortex and the occipital cortex. The frontal cortex is assigned to complex cognitive abilities such as creation and adjustment of feelings (Dixon et al., 2017), working memory (Lara & Wallis, 2015) and episodic memory (Fletcher et al., 1998, Rajah & D'Esposito, 2005, Eichenbaum, 2017). Especially frontal brain activation is addressed to compensational purpose (Cabeza et al., 2018). To achieve the required task demands, additional reserve of neural resources is applied that results in increased activation (Cabeza & Dennis, 2014, Cabeza et al., 2018). Increased frontal activity in older compared to young subjects is often associated with a better cognitive performance and is considered to be compensatory (Cabeza & Dennis, 2014, Daselaar et al., 2015, Cabeza et al., 2018). For example, one study showed that low performing older subjects achieve increased

success-associated activation in the prefrontal area during a source memory task (Daselaar et al., 2015). Accordingly, the finding of the present study of left frontal brain activation revealed during an encoding task can possibly be considered to have compensational purpose due to its localization.

However, this study also assessed the right occipital brain region. Other studies also showed encoding-related activation in these areas (Li et al., 2015). Here, in contrast to the frontal region, a lower activation is shown in comparison to young subjects (Davis et al., 2008, Scheller et al., 2014, Li et al., 2015). The occipital gyrus is responsible for the perception of visual information such as color, object selection, motion and depth perception, especially for sensory processes (Grill-Spector & Malach, 2004, Li et al., 2015). Thus, decreased activation is explained by the reduced attenuated sensual processing of older subjects (Li et al., 2015, Madden et al., 2017). The results of the present study seem to contradict these findings. However, it must be noted that this study only shows a correlation between lower white matter integrity and higher occipital brain activation without comparing brain activity with a young control group. Thus, the extent of altered activation cannot be assessed.

Additionally, in the current project no significant relationship was revealed between both frontal and occipital brain activation and memory performance during the encoding task. Thus, despite increased brain activation no improved cognitive performance was achieved. Therefore, the present results contradict the compensation theory.

Another approach is the dedifferentiation thesis (Park et al., 2004, Voss et al., 2008, Goh, 2011, Koen et al., 2020). Due to microstructural change higher regional brain activation may indicate recruitment of additional brain regions during a cognitive process that are not involved in a young control (Park et al., 2004, Voss et al., 2008, Goh, 2011, Koen et al., 2020). Especially occipital activation is often mentioned in connection with the dedifferentiation thesis (Koen & Rugg, 2019). An age-related recruitment of additional brain regions, for example in the ventral occipital-temporal cortex during analysis of scenes or faces, is an often-replicated finding (Koen & Rugg, 2019, Koen et al., 2020). A voxel-based analysis revealed that in ventral visual cortex (VVC) the specificity of the activation pattern was reduced during visual stimulation via items, pseudo-words and faces. However, this reduced specificity was not limited to the VVC but was shown also for the early visual cortex, prefrontal cortex and the inferior parietal cortex (Carp et al., 2012). When cognitive data is added to these findings,

higher specificity of brain activation is associated with better brain performance, independent of age. Thus, higher brain activation is associated with poorer cognition (Koen & Rugg, 2019). Therefore, the finding of the present study indicating that brain activation is not related to cognitive performance does not contradict dedifferentiation theory. On the other hand, the pattern of brain activation that was revealed during the used face-name paradigm in both frontal and occipital brain regions showed consistency with other studies that investigated encoding-related brain activation (Sperling et al., 2002, Li et al., 2015). Thus, an activation of additional brain regions or in other words a decrease in specificity of brain activation could not be demonstrated. Consequently, dedifferentiation theory seems unlikely to explain the changed brain activation revealed in this present study.

Others attribute the increased frontal brain activation to a local inefficiency during the communication between anatomically connected white and grey matter areas (Rypma & Prabhakaran, 2004, Salat et al., 2011, Zhu et al., 2015, Zhu et al., 2014, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al., 2020b). Global impaired brain function is evoked due to changed signal transmission or neuromodulation within white matter without gain or purpose (Bennett & Rypma, 2014, Cabeza et al., 2018, Quin & Basak., 2020, Rieck et al., 2020, Webb et al., 2020a, Webb et al., 2020b). Consistent with these findings are the previously mentioned results that at a cellular level increased synaptic activity can be detected resulting from a reduced number of white matter fibers and thus decreased connectivity (Burke & Barnes, 2010, Daselaar et al., 2015). This is supported by neuroimaging studies. For example, one study used multivariate analysis to investigate whether increased frontal activity was evoked due to additional information indicating compensation (Morcom & Henson, 2018). However, frontal activity did not show an expanded distribution of weights within voxels (Morcom & Henson, 2018). This argues against additional information but rather for a neuronal inefficiency (Morcom & Henson, 2018). Another project demonstrates that increased frontal task-switching paradigm-associated brain activation in older subjects is related to lower integrity of connecting white matter tracts (Zhu et al., 2015). Additionally, increased BOLD-signal is associated with a higher error rate and reaction time indicating reduced efficiency of neuronal response (Zhu et al., 2015). Other projects also show a negative relationship between activation and cognitive performance in connection with inefficiency theory (Bennett & Rypma, 2014, Morcom & Henson, 2018, Webb et al., 2020a, Webb et al.,

2020b). As mentioned above, the present project did not reveal a relationship between brain activation and cognitive performance. That rather supports the assumption that impaired brain activation has no gain for the cognitive performance of older aged subjects. Thus, the result does not contradict but rather corresponds with the theory of altered data transmission in the white matter resulting in inefficient brain activation.

In this context, no significant difference in brain activation was shown when comparing occipital and frontal task-related brain activation (Morcom & Henson, 2018). In line with this result, this present study revealed the same directionality of the structure-function relationship in both the occipital and frontal brain region. In both brain regions white matter change was associated with increased brain activation. This argues against the assumption that the structure-function relationship depends on the investigated brain region, as Warbrick et al., (2017) stated in his review.

The results also revealed no significant relationship between performance during the face-name paradigm and white matter integrity. White matter change was detected with the DTI-associated parameter PW. That the well-known DTI-associated parameters MD indicates white matter alteration and is associated with decreased cognitive performance in healthy elderly is well-known (Daselaar et al., 2015). However, different results were shown for the DTI-parameter PW: A correlation between increased PW and decreased cognitive performance in patients with WMH (Wei et al., 2019, Low et al., 2020) but not in the healthy control group was revealed (Wei et al., 2019).

Additionally, a previous paper investigated the time course of DTI-imaging marker such as MD and PW, which differed significantly from each other. MD shows a U-shaped progression throughout the life span, whereas PW increases continuously (Beaudet et al., 2020). Thus, it is proposed that PW is an early marker of aging (Beaudet et al., 2020). Therefore, if PW is a sensitive marker of early aging, it may also indicate lower levels of WM alteration.

The sample of the present study showed little white matter change. Therefore, two indicators are important: Firstly, MD as a marker for white matter change showed no results in the present analysis. This possibly indicates that in contrast to MD, PW shows even diffuse change of white matter within the subjects. Secondly, WMH showed such a low burden that they had

to be excluded as a marker for white matter alterations. This also may point out that the existing white matter changes within the present sample are diffuse at a beginning level.
Thus, the insignificant association between structural change and cognition suggest that white matter alterations are not substantial enough to influence the cognitive performance.

In addition to the main findings of this study, the results also provide support for the recently developed DTI-marker PW. This parameter seems to be a region-specific marker for microstructural white matter alteration as revealed by the correlation matrix. Beaudet et al., (2020) highlights the lack of local analysis of PW in order to obtain more detailed knowledge in this issue. The present study established both whole brain and tract-specific PW and compared them by using a correlation matrix. However, it should be noted that the correction for whole PW in one of the two significant analyses of structure-function relation led to an insignificant result. This would contradict the local specificity of the marker. Nevertheless, the correlation matrix showed that the tracts primarily did not correlate significantly with each other in contrast to MD. This suggests that the DTI-marker PW is a specific marker for local white matter change.

Several limitations have to be addressed when discussing the results of this study. In this project only cortical brain regions were investigated that were connected by a white matter tract to gain knowledge about the relationship between structural and functional changes. However, it should be kept in mind that the activation in these cortical brain regions is also influenced by subcortical regions. Nevertheless, the chosen approach allows to approximate to the reality without being too complex.
Additionally, the study was primarily based on the institute for stroke and dementia research. Voluntary tests were offered in the outpatient clinic to rule out memory impairment. It is reasonable to assume that especially intellectuals were attracted by this offer. This could have resulted in a selection bias that could have influenced cognitive performance.
Furthermore, this study has a small number of participants. Therefore, the present results should be verified using a larger sample.

Conclusion: This study revealed a relation between white matter tract changes and increased brain activation in frontal and occipital brain areas. This relation was independent of the investigated brain region. Additionally, there was no significant relation between white matter change respectively brain activation and cognitive performance. This suggests that microstructural alteration of white matter results in a decreased white matter connectivity. This leads to a reduced fidelity of data transmission. Consequently, increased brain activity is an indication of inefficient neuronal response.

6. List of abbreviations

AAL	Anatomical Labeling Atlas
AC-PC	anterior commissure – posterior commissure
ACC	accuracy in memory task
ANOVA	analysis of variance
BOLD	Blood oxygen level dependent
BA	Brodmann Area
CDR	Clinical Dementia ration scale
Cing L	Cingulum left
Cing R	Cingulum right
CSF	cerebrospinal fluid
DARTEL	Diffeomorphic Anatomical Registration Using Exponentiated Lie Algebra
DMN	Default mode Network
DTI	Diffusion tensor imaging
DW	diffusion weighting
DZNE	German Center of Neurodegenerative Disease
EPI	Echo-planar imaging
ERP	event related potential
FA	functional anisotropy
FC	functional connectivity
FDR	false discovery rate
FWE	family wise error
FLAIR	Fluid-attenuated inversion recovery
fMRI	functions magnetic resonance imaging
FoMa	Forceps Major
FoMi	Forceps Minor
GDS	Geriatric Depression Scale
GLM	general linear model
HC	healthy controls
ICBM	International Consortium for Brain Mapping

IFOF L	Inferior fronto-occipital fasciculus left
ILF R	Inferior longitudinal fasciculus right
JHU	Johns Hopkins University
MD	mean diffusivity
MWT-A	Mehrfachwahl-Wortschatz-Intelligenztest
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared - Rapid Gradient Echo
NNL	Nordic Neuro Lab
PET	positron emission tomography
PSMD	peak width of skeletonized mean diffusivity
PW	peak width
rsfMRI	resting state functions magnetic resonance imaging
SC	structural connectivity
SD	Standard deviation
SLF L	Superior left fasciculus left
SLF tp L	Superior left fasciculus temporal part left
SPM	statistical parametric mapping
SVD	Small vessel disease
TE	echo time
TI	inversion time
TR	repetition time
VASCAMY	Vascular and amyloid predictors of neurodegeneration and cognitive decline
WD	Wallerian degeneration
WMH-ratio	White matter hyperintensities volume-ratio

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8. Supplementary

Supplementary 1

Pairwise t-test for MD within tracts

	Cing L	**Cing R**	**FoMa**	**FoMi**		**SLF tp L**		
Cing R	1.00000							
FoMa	< 2e-16	2.7e-16						
FoMi	1.00000	1.00000	< 2e-16					
IFOF L	1.0e-09	4.7e-07	5.2e-05	1.3e-11				
ILF R	< 2e-16	< 2e-16	1.00000	< 2e-16	3.6e-07			
SLF tp L	1.00000	1.00000	< 2e-16	1.00000	2.8e-16	< 2e-16		
SLF L	1.00000	0.19154	< 2e-16	0.05899	< 2e-16	< 2e-16	1.00000	
whole	0.68489	1.00000	2.1e-12	1.00000	0.00025	9.9e-15	0.19154	0.00318

Pairwise t-test for PW within tracts and global

	Cing L	**Cing R**	**FoMa**	**FoMi**	**IFOF L**	**ILF R**	**SLF tp**	**SLFl**
Cing R	0.86958							
FoMa	8.2e-07	0.00144						
FoMi	8.3e-06	1.2e-09	< 2e-16					
IFOF L	0.86958	0.01850	6.4e-11	0.00755				
ILF R	1.00000	0.09452	2.1e-09	0.00099	1.00000			
SLF tp L	0.00144	8.2e-07	< 2e-16	1.00000	0.19686	0.04508		
SLF L	0.19686	0.00150	5.1e-13	0.06841	1.00000	1.00000	0.86958	
whole	0.23402	1.00000	0.01324	2.2e-11	0.00215	0.01567	2.4e-08	0.00011

Supplementary 2

Brain regions of present study that were important	**Sperling et al., 2002**	**Neurosynth**
Left frontal gyrus		x-8/ y 54/ z34
Medio frontal gyrus left		x-42/ y26/ z24

	Fusiform and dorsolateral prefrontal cortices	
Superior temporal gyrus let		x-32/ y-18/ z-16
Occipital gyrus left		x-26/ y-76/ z-6
Temporal gyrus right		X 28/ y-12/ z -16
Hippocampus left	Hippocampus	X28/ y-36/ z-16
Hippocampus right	Hippocampus	x-28/ y-34/ -
	Pulvinar nucleus of thalamus	

http://www.neurosynth.org/analyses/terms/memory%20encoding/

http://neurosynth.org/faq/#q18F