Aus der
Radiologischen Universitätsklinik Tübingen
Abteilung für Biomedizinische Magnetresonanz

Diffusion Tensor Imaging of white matter alterations in the aging population: Association with gait, cognition and risk of developing neurodegenerative disease

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von
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2025

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Tag der Disputation: 01.08.2025

Abbreviations

AD	Axial diffusivity
APOE	Apolipoprotein E
BDI-II	Beck Depression Inventory II
DAT	Dopamine transporter
DT	Dual-task(ing)
DTC	Dual-task costs
DTI	Diffusion Tensor Imaging
EF	Executive function(s)
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GM	Gray matter
LRRK2	Leucine-rich repeat kinase 2
MD	Mean diffusivity
MRI	Magnetic resonance imaging
PD	Parkinson’s disease
PD-RP	Parkinson’s disease risk persons
PFC	Prefrontal cortex
RBD	Rapid eye movement sleep behavior disorder
RBDSQ	Rapid eye movement sleep behavior disorder screening questionnaire
RD	Radial diffusivity
SOD1	Superoxide dismutase 1
ST	Single task
TMT	Trail Making Test
WM	White matter

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1. Introduction

1.1. Background

Neurodegeneration refers to a slow and progressive loss of neurons and their connections in the brain, leading to a decline in motor and cognitive functions. While aging naturally leads to some degree of neurodegeneration, pathological processes can accelerate this decline. Conditions like Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis are among the most prevalent neurodegenerative diseases, each with its unique clinical manifestations but often sharing common underlying mechanisms.

A hallmark feature shared by many neurodegenerative diseases, the so-called proteinopathies, is the accumulation of abnormal misfolded protein aggregates in the brain. This process is closely linked to advanced age, but the broader mechanisms contributing to this age-related phenomenon remain incompletely understood. In addition to protein misfolding, other processes such as oxidative stress, glymphatic dysfunction and neuroinflammation are believed to play crucial roles in the development and progression of these conditions (Wilson et al., 2023). While the exact etiology of neurodegenerative diseases is not understood entirely; however, it is believed that a combination of genetic and environmental factors may play a role.

As the global population continues to age, there has been a concerning rise in the incidence of neurodegenerative diseases, placing significant strain on healthcare systems and caregivers worldwide. As a consequence, significant efforts have been made towards early detection of neurodegenerative diseases, which include raising public awareness, advancement in imaging and development of biomarkers. Despite these efforts, there is still much to be done to fully understand and mitigate the impact of neurodegenerative diseases on the aging population. In particular, research in community-dwelling older adults and individuals at risk of developing neurodegenerative diseases to identify potential biomarkers and associated risk factors.

1.2. Early detection of neurodegenerative diseases

Most neurodegenerative diseases are characterized by specific symptoms that are crucial for clinical diagnosis. For instance, PD is typically identified by the presence of its cardinal motor symptoms: bradykinesia, resting tremor, rigidity, and postural instability. However, additional symptoms can manifest throughout different stages of disease, including cognitive impairments and changes in mood and behavior. In fact, some symptoms may appear before the clinical diagnosis, in the so-called prodromal phase. Given the progressive nature of neurodegenerative diseases, it is assumed that neurodegeneration starts long before a clinical diagnosis is made. In many cases, neuronal damage has already progressed by the time symptoms appear, which can take years or even decades. This is why early detection and diagnosis of neurodegenerative diseases are critical, as they allow for earlier interventions and treatments, potentially altering the disease's trajectory and improving patient outcomes.

So far, several clinical markers have been identified that suggest the presence of an early neurodegenerative process. Age is the most significant predictive risk factor for neurodegenerative diseases. The likelihood of developing these diseases escalates with age, with the majority of diagnoses occurring in individuals over the age of 60 (Hou et al., 2019). However, age is not a definitive indicator; not all older individuals will develop a neurodegenerative disease, nor are younger individuals entirely exempt. Consequently, other factors are also considered when assessing the risk of neurodegenerative diseases, including genetics. Indeed, mutations in several genes have been identified as potential biomarkers for the early detection of neurodegenerative diseases. These genes include APOE, presenilin-1, and presenilin-2 for Alzheimer’s disease; LRRK2, alpha-synuclein, and parkin for PD as well as SOD1 for amyotrophic lateral sclerosis (Bertram & Tanzi, 2005). With the exception of Huntington's disease, which is directly caused by a mutation in the Huntingtin gene, the vast majority of genetic mutations identified so far are only associated with an increased likelihood of developing certain neurodegenerative diseases, but are not known to directly cause them (Bertram & Tanzi, 2005). As such, genetic mutations only account for only a small fraction of cases, with the majority believed to result from a combination

of genetic predispositions and environmental factors. For example, studies have shown that exposure to pesticides, particularly the class of pesticides known as organophosphates, can cause damage to the substantia nigra and lead to the loss of dopaminergic neurons in this region, a key hallmark in the pathophysiology of Parkinson's disease. Moreover, exposure to heavy metals, such as mercury, lead, and aluminum as well as nanoparticles, has been linked to an increased risk of developing neurodegenerative diseases. These environmental pollutants are known to induce mechanisms of toxicity through the generation of oxidative stress, which in turn leads to common neurodegenerative markers, including inflammation and the formation of protein aggregates (Chin-Chan, Navarro-Yepes, & Quintanilla-Vega, 2015).
Further, several symptoms and clinical risk factors have been associated with an increased risk of developing neurodegenerative diseases. Since this research is part of a longitudinal study primarily focusing on early detection of Parkinson’s disease, the following discussion will highlight symptoms that have been associated with an increased risk of developing Parkinson’s disease, though it is important to note that these symptoms are not exclusive to Parkinson's and may also indicate other neurodegenerative conditions.

One of the strongest predictive markers for prodromal Parkinson’s disease, as well as other synucleinopathies, is rapid eye movement sleep behavior disorder (RBD). It is estimated that over 80% of individuals with RBD will eventually develop neurodegenerative disease. However, confirming a diagnosis of RBD requires polysomnography, a process that is both time-consuming and costly (Ronald B. Postuma & Berg, 2016). An alternative diagnostic approach involves using a questionnaire; however, this approach is limited by its low sensitivity, particularly in detecting subtle forms of RBD. Consequently, questionnaires might serve better as preliminary screening tools for the general population rather than definitive diagnostic measures (Halsband, Zapf, Sixel-Döring, Trenkwalder, & Mollenhauer, 2018; Ronald B. Postuma & Berg, 2016).

Olfactory impairment is another important prodromal feature of Parkinson's disease, as it can be the earliest sign of the disease, preceding clinical motor symptoms by years (Vaswani, Morley, Jennings, Siderowf, & Marek, 2022). In fact, evidence points to the early presence of histopathologic changes within the olfactory structures (Braak et al., 2003). As such, olfactory testing can be a useful tool to detect prodromal Parkinson's disease, particularly due to its low cost, non-invasiveness, and high sensitivity. However, olfactory impairment, while sensitive, is not a specific predictor of Parkinson's disease, as it can be a sign of other neurodegenerative disease, especially those associated with a Lewy body pathology, e.g. dementia with Lewy body (McShane et al., 2001). Consequently, studies focusing on early detection of PD were able to improve prediction rate by combining olfactory testing with modern imaging markers, such as dopamine transporter imaging (Jennings et al., 2017) and transcranial sonography of the substantia nigra (Berg et al., 2013).

Changes to mood and behavior are also common in neurodegenerative diseases even in the early or prodromal stages, and include depression, anxiety, apathy and disinhibition. It is well established that several cerebral regions, commonly affected by neurodegenerative processes, contribute to affective and behavioral regulation, such as the prefrontal cortex (PFC), the orbitofrontal cortex, the basal ganglia and the hippocampus. Therefore, the high prevalence of affective disorders, especially depression, among the elderly population and in individuals afflicted with neurodegenerative disease is not surprising. In fact, neurodegenerative diseases and major depressive disorder share some underlying mechanisms, including neuroinflammation, impaired neurogenesis in the hippocampus and a disruption of the frontostriatal network. Depression is observed in almost half the patients with PD and vice versa, individuals with depression are at a higher risk of developing PD (Jeong, Kim, Joo, Jang, & Park, 2021).

In the context of Parkinson's disease, it is frequently discussed as a risk factor, however, due to its low sensitivity and specificity as well as its high prevalence in the general population, it is unlikely to be useful as a marker of prodromal PD (R. B.

Postuma, Aarsland, et al., 2012). However, it could still be of value when assessed in addition to other risk factors, such as hyperechogenicity of the substantia nigra (Liepelt-Scarfone et al., 2011).

1.3. Motor and cognitive impairments in Early Neurodegeneration

Although discussions of prodromal PD often focus on nonmotor symptoms, the motor symptoms associated with Parkinsonism do not emerge abruptly, and mild motor signs can serve as early indicators of the disease. A study showed that that a score greater than 3 on the Unified Parkinson's Disease Rating Scale (part III) might signal prodromal parkinsonism in individuals with idiopathic RBD, with an estimated prodromal interval of 4.5 years (R. B. Postuma, Lang, Gagnon, Pelletier, & Montplaisir, 2012). Further evidence from the same study suggests that quantitative motor tests could detect parkinsonism even earlier, showing prodromal intervals comparable to those detected by most dopaminergic imaging markers.

Nevertheless, powerful compensatory mechanisms often obscure early gait abnormalities and other subtle motor signs in prodromal neurodegenerative syndromes, posing a challenge to the early detection of these conditions through motor biomarkers. In an effort to uncover latent motor deficits, alternative clinical tests were developed to push compensatory mechanisms beyond their limit. One effective method is gait assessment under challenging conditions, such as walking on a curved pathway or navigating obstacles. Another common approach that was utilized in this research is to assess gait under dual-tasking conditions. Introducing a secondary, particularly cognitive, objective to gait can diminish the brain's capacity to compensate for deficits compared to standard gait conditions. This is particularly evident in older adults with executive function (EF) impairments, as executive dysfunction is known to correlate with slower gait under dual-task conditions and may significantly contribute to the risk of falls (Yogev-Seligmann, Hausdorff, & Giladi, 2008). Additionally, the deterioration of EF often serves as one of the earliest signs of broader cognitive decline and increased frailty. In fact, declining EF are a significant early indicator of pathological neurodegeneration

(Kirova, Bays, & Lagalwar, 2015), presenting as the most affected cognitive domain in prodromal PD (Fengler et al., 2017).

The interplay between gait and cognition is well-documented; however, the underlying mechanisms remain somewhat elusive. Evidence suggests that complex gait situations demand the recruitment of additional cognitive resources (Boisgontier et al., 2013). Consequently, gait deterioration under dual-task conditions could reflect a decline in the shared cognitive and motor white matter (WM) pathways, especially those in the frontal lobes critical for EF and known to be susceptible to aging (Pfefferbaum, Adalsteinsson, & Sullivan, 2005).

Utilizing a cognitive-motor dual-tasking approach has revealed significant motor impairments in neurodegenerative diseases such as PD and Alzheimer's disease, exposing subtle deficits even in their prodromal stages (Longhurst et al., 2023). However, the relationship between brain structure, gait, and cognition is complex and has primarily been studied in patient groups and older individuals with dementia. Therefore, it is crucial to extend this research to non-demented adults and individuals at risk of neurodegenerative diseases to assess the potential of gait assessment under dual-task conditions as a valuable early marker of (frontal) WM deterioration. Further investigations are also necessary to explore the role of EF as a mediator of this relationship and the presence of shared pathways between motor and cognitive tasks.

1.4. Imaging as a marker for prodromal neurodegenerative disease

Imaging plays a crucial role in the diagnosis of neurodegenerative diseases by allowing visualization of structural and functional brain changes characteristic of these conditions. This capability aids in the differential diagnosis of various neurodegenerative diseases. However, standard imaging techniques often lack the sensitivity needed to identify early neurodegeneration. In the context of early detection of PD, dopamine transporter (DAT) imaging stands as one of the most validated imaging markers, showing a high likelihood for the presence of prodromal PD (Berg et al., 2015). This

technique has successfully identified abnormalities in the nigrostriatal dopaminergic system in individuals at risk for PD, including individuals with hyposmia (Jennings et al., 2014) as well as LRRK2 mutation carriers (Sossi et al., 2010). Despite its effectiveness, the high cost of DAT imaging limits its use as a primary screening tool for at-risk populations (Scherfler et al., 2007).

Another promising and extensively studied imaging marker for the early detection of PD is the hyperechogenicity of the substantia nigra, assessed using transcranial sonography. However, when used alone, it is not a strong risk marker for developing PD and is more effective when combined with other risk factors (Mahlknecht et al., 2020; Walter, 2011).

Recently, new sophisticated imaging techniques have been developed and used to better understand neurodegenerative diseases and aid in the early detection of neurodegenerative diseases. However, these methods have been mostly used in research settings and have not established themselves as a part of the clinical imaging routine. For example, using neuromelanin imaging and quantitative susceptibility mapping are able to detect pathological changes in the substantia nigra and have shown a lot of promise in the detection of prodromal PD (Sulzer et al., 2018; D. Zhang et al., 2022).

Diffusion Tensor Imaging (DTI) has also shown promising results in detecting early WM alterations suggestive of prodromal PD. In particular, a study used graph-theoretical analysis based on DTI to investigate WM connectome in a cohort suspected to be in the prodromal phase of PD. This cohort displayed greater subnetwork connectivity compared to PD patients and controls, suggestive of neural compensation in the early stages of the disease (Wen et al., 2017). Another study investigated structural alterations in the whole brain in individuals with risk factors for PD using DTI as well as morphometric methods, such as voxel-based morphometry and cortical thickness analysis. The latter methods could not reveal any abnormalities in gray matter (GM); however, DTI was able to detect microstructural alterations in WM in limbic and motor

regions, which correlated with hyperechogenicity in the substantia nigra (Heldmann et al., 2018).

1.5. Principles of DTI (Mori & Zhang, 2006)

Molecular diffusion, or simply diffusion, describes the random translational movement of particles (e.g. water) caused by thermal energy, also known as the Brownian motion. Within biological tissues, however, diffusion (of water molecules) is not random, as it is restricted by cell membranes and other macromolecules, making imaging of water diffusion a sensitive tool to investigate cellular and microstructural integrity. Diffusion-weighted imaging was conceptualized in the mid-1980s, since then it established itself as an integral part of the conventional MRI protocols, especially in the fields of stroke imaging, oncology and inflammatory diseases. Unlike isotropic diffusion in a glass of pure water, which would be equal in all directions, diffusion of water molecules within tissues with fibrous architecture, such as the axons that form the cerebral WM, is anisotropic. This means that water molecules diffuse more easily along the length of an axon than perpendicular to it. DTI makes use of this fact to provide information about the integrity and orientation of WM fibers.

So, how does DTI work? briefly, during an MRI scan, DTI introduces a pair of additional diffusion-sensitizing magnetic gradients. The first gradient selectively dephases the MR-signal from water molecules that have undergone diffusion in a specific direction. while the second gradient rephases the signal from those that have. The difference between the two signals provides a measure of the amount of diffusion that occurred during the time between the two gradients. These gradients are applied in three orthogonal directions (x, y, and z) to measure diffusion in each of the three dimensions. The diffusion-sensitizing gradients are a critical component of DTI, as they allow the measurement of water diffusion in different directions and provide the information needed to calculate the diffusion tensor and derive DTI parameters. The latter include fractional anisotropy (FA), which reflects the degree of directionality or anisotropy of water diffusion within tissue, and mean diffusivity (MD), which reflects average

magnitude of water diffusion within tissue. Both parameters are sensitive for changes to microstructural integrity, such as axonal damage, demyelination, or edema. However, they are still limited by their lack of specificity to the exact underlying pathology. For example, both axonal damage and demyelination lead to a decrease in FA and an increase in MD. Other less commonly used complementary parameters include axial (AD) and radial diffusivity (RD). AD reflects the magnitude of water diffusion along the principal axis of the diffusion tensor, which is typically aligned with the direction of axonal fibers. It is thought to be a sensitive measure of axonal integrity and can be affected by changes in axonal density, diameter, or myelination. RD on the other hand, reflects the magnitude of water diffusion perpendicular to the principal axis of the diffusion tensor, which is typically perpendicular to the direction of axonal fibers. It is thought to be a sensitive measure of myelin integrity and can be affected by changes in myelin thickness or spacing.

DTI provides the opportunity to analyze WM microstructure in the brain based on voxel-wise comparisons of diffusion tensor parameters. Unlike conventional MRI, this approach detects subtle differences in WM microstructure throughout the brain. Consequently, voxel-based DTI analysis can also be used to compare groups of subjects with different clinical or demographic characteristics, such as healthy controls versus patients with a neurodegenerative disease or risk factors thereof. Moreover, this method can test correlations between DTI parameters in WM tracts and behavioral or clinical measures.

1.6. Hypotheses and research questions

The aim of this dissertation is to utilize DTI to detect subtle WM alterations in the aging population that are not discernible with conventional MRI sequences.

Furthermore, this research investigates whether these alterations are associated with risk factors for developing neurodegenerative diseases, specifically Parkinson's disease, as well as with specific cognitive and motor impairments that could be considered early signs of neurodegeneration. Particular attention is given to the impairment of EF and gait deficits under dual-tasking conditions.

This dissertation investigates the following hypotheses:

1. Hypothesis:
Older individuals with risk factors for PD will exhibit subtle WM alterations that correlate with the severity of their risk factors and cognitive function.

2. Hypothesis:
Gait decline under dual-tasking conditions is associated with WM deterioration in the aging population, potentially signaling early signs of neurodegeneration. Furthermore, deterioration of neural pathways shared by both motor and cognitive tasks, particularly those involved in EF, might influence this interaction.

2. Results

2.1. Distinct Relationship Between Cognitive Flexibility and White Matter Integrity in Individuals at Risk of Parkinson's Disease

Alzaid H, Ethofer T, Hobert MA, Kardatzki B, Erb M, Maetzler W and Berg D (2020) Distinct Relationship Between Cognitive Flexibility and White Matter Integrity in Individuals at Risk of Parkinson's Disease. Front. Aging Neurosci. 12:250. doi: 10.3389/fnagi.2020.00250 (Alzaid et al., 2020)

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 13 August 2020
doi: 10.3389/fnagi.2020.00250

Distinct Relationship Between Cognitive Flexibility and White Matter Integrity in Individuals at Risk of Parkinson's Disease

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Background and Objective: Executive dysfunction is the most common cognitive impairment in Parkinson's disease (PD), occurring even in its early stages. In our study, we applied diffusion tensor imaging (DTI) to investigate white matter integrity and its association with a specific executive function such as cognitive flexibility in individuals with risk factors for PD.

Methods: We examined 50 individuals with risk factors for developing PD and 24 healthy controls from the TREND (Tübinger Evaluation of Risk Factors for Early Detection of Neurodegeneration) study including neuropsychological evaluation and DTI. Cognitive flexibility was assessed using the trail making test (TMT). Tract based spatial statistics (TBSS) were employed to assess white matter abnormalities and their correlation with cognitive flexibility.

Results: TMT performance correlated with mean and axial diffusivity in several white matter regions, predominantly in the frontoparietal white matter. These effects were stronger in PD risk persons (PD-RP) than in controls as evidenced by a significant group interaction. White matter integrity and TMT performance did not significantly differ across groups.

Conclusion: Based on our results, PD-RP do no exhibit white matter changes or impaired cognitive flexibility. However, specific executive functions in PD-RP are more related to white matter alterations than in healthy older adults.

Keywords: Parkinson's disease, prodromal phase, diffusion tensor imaging, white matter, cognitive flexibility

OPEN ACCESS

Edited by:
Xudong Huang, Massachusetts General Hospital and Harvard Medical School, United States

Reviewed by:
Deborah Lynn Harrington, University of California, San Diego, United States
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Received: *08 March 2020*
Accepted: *20 July 2020*
Published: *13 August 2020*

Citation:
Alzaid H, Ethofer T, Hobert MA, Kardatzki B, Erb M, Maetzler W and Berg D (2020) Distinct Relationship Between Cognitive Flexibility and White Matter Integrity in Individuals at Risk of Parkinson's Disease. Front. Aging Neurosci. 12:250. doi: 10.3389/fnagi.2020.00250

INTRODUCTION

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease characterized by an abnormal accumulation of misfolded α-synuclein protein in the brain. Clinically, it is diagnosed by the cardinal motor symptoms bradykinesia, resting tremor, and rigidity (Tolosa et al., 2006). It is well documented, that the motor symptoms of PD are caused by cell death in the substantia nigra. However, studies have shown that the onset of motor manifestations of PD, which is required for the clinical diagnosis, starts only after at least 50% of the neurons in substantia nigra have died

(Fearnley and Lees, 1991), and thus it has been suggested that neurodegeneration starts several years before the development of the cardinal motor symptoms (Miller and O'Callaghan, 2015). This time period preceding the clinical diagnosis is called the prodromal phase. During this phase, individuals at risk of developing PD can exhibit non-motor symptoms including hyposmia, rapid eye movement (REM)-sleep behavior disorder (RBD), depression, autonomic dysfunction, and mild cognitive impairment (Berg et al., 2015).

Mild cognitive impairment, in particular executive dysfunction, is commonly reported throughout all stages of PD (Litvan et al., 2011). Furthermore, a recent study revealed that executive function is the most affected cognitive domain in the prodromal phase of PD, and might be a useful non-motor biomarker for this phase (Fengler et al., 2017). There is cumulative evidence for the involvement of the frontoparietal network in executive functions (Collette et al., 2006) and it has been suggested that cortical "disconnection" through a disturbance of intra- and interhemispheric white matter connections, especially in the anterior white matter, represents a possible mechanism underlying age-related executive dysfunction (O'Sullivan et al., 2001) as well as disease-related alterations in PD (Bledsoe et al., 2018).

Although the death of dopaminergic neurons in the substantia nigra is considered a main pathomechanism of PD (Lees et al., 2009), several neuropathological studies revealed that axonal dysfunction and degeneration in diverse brain (Cheng et al., 2010), and even peripheral (Knudsen et al., 2018) regions are an additional important hallmark in the pathophysiology of PD. In fact, axonal degeneration may be the earliest sign of the disease, occurring long before the death of neuron cell bodies (Cheng et al., 2010). Consequently, diffusion tensor imaging (DTI; Basser et al., 1994) was successfully applied to detect alterations of structural fiber connectivity in PD (Atkinson-Clement et al., 2017; Koirala et al., 2018, 2019) including early stages (Zhang et al., 2015) and also identified candidate white matter structures for cognitive impairment in PD (Melzer et al., 2013; Zheng et al., 2014). Fractional anisotropy (FA) and mean diffusivity (MD) are the DTI-derived parameters that are primarily used to detect white matter microstructural alterations. FA is a measure of orientational coherence along the fibers, while MD is a measure of averaged diffusivity, representing the amount of diffusion in all directions (Pierpaoli and Basser, 1996). Typically, white matter pathology is associated with decreased FA and increased MD. In addition, axial diffusivity (AD) and radial diffusivity (RD) have been proven useful in detecting axonal damage and myelin loss, respectively (Song et al., 2002; Sun et al., 2006). AD reflects diffusion along the main axis (λ_1), whereas RD reflects perpendicular diffusion to the main axis (λ_2, λ_3).

In the current study, we investigated whether alterations of fiber connectivity as revealed by DTI are already detectable in individuals with risk factors for developing PD. Specifically, we utilized tract-based spatial statistics (TBSS) to investigate the following hypotheses:

1. White matter pathology is an early sign of PD and can already be detected in the prodromal phase.
2. Impairment of specific executive functions as assessed by the trail making test (TMT) are related to white matter pathology in individuals with risk factors for PD.

MATERIALS AND METHODS

Participants

This cross-sectional study investigated participants from the TREND study (Tübinger Evaluation of Risk Factors for Early Detection of Neurodegeneration), a prospective biannual follow-up study that aims at identifying risk factors for the development of PD. Sociodemographic and clinical data are presented in **Table 1**. Fifty individuals with well-known risk factors for developing PD (PD risk persons, PD-RP, 19 males, 31 females, and average age 66.1 ± 6.4 years), and 24 controls (controls, 14 males, 10 females, and average age 68.3 ± 6.5 years) from the TREND cohort were included in the current study. Study details and recruitment criteria have been previously published (Gaenslen et al., 2014). All participants were older than 50 years, were able to walk without aid, had no diagnosis of any neurodegenerative disease, no history of stroke, inflammatory diseases of the central nervous system, or polyneuropathy, were free of antipsychotic or other antidopaminergic drugs, and exhibited no significant impairment of vision or hearing. PD-RP had at least one of the following diagnoses:

- Hyposmia, assessed using Sniffin' sticks (Burghardt Medizintechnik, Wedel, Germany) with a set consisting of 16 different odors, identifying < 10 of odors is indicative of impaired sense of smell (Hummel et al., 2007).
- REM sleep RBD, assessed using the RBD Screening questionnaire (RBDSQ), a value of 5 out of 10 possible items was considered was a positive test result, which can

TABLE 1 | Demographics and clinical parameters of the cohorts.

	Control (n = 24)	PD-RP (n = 50)	P-Value
Gender (m/f)	14/10	19/31	0.1[a]
Age (y)*	68 ± 6	66 ± 6	0.19[b]
Years of education (range)	15 (10–20)	15 (10–21)	0.89[b]
Depression (prevalence)	0%	82%	–
Hyposmia (prevalence)	0%	28%	–
RBD (prevalence)	0%	32%	–
UPDRS-III (range)	1 (0–5)	1 (0–9)	0.75[c]
Sniffin' sticks (range)	13 (10–15)	10 (3–16)	0.003[c]**
RBDSQ (range)	2 (0–6)	4 (0–10)	0.006[c]**
BDI-II (range)	3 (0–9)	10 (0–42)	0.00009[c]**
MMSE (range)	29 (24–30)	29 (25–30)	0.55[c]
TMT A (s)*	34 ± 9	35 ± 11	0.65[c]
TMT B (s)*	76 ± 25	76 ± 28	0.94[c]
TMT B-A (s)*	42 ± 21	41 ± 24	0.78[b]

*Values are expressed as the mean ± standard deviation. **corrected for multiple comparisons. Abbreviations: BDI-II, Beck Depression Inventory II; MMSE, Mini Mental State Examination; TMT, Trail making test; and UPDRS-III, Motor part of the Unified Parkinson's Disease Rating Scale. [a]X^2-test. [b]Independent sample t-test. [c]Mann–Whitney-U test.

indicate the presence of RBD with a sensitivity of 96% and a specificity of 56% (Stiasny-Kolster et al., 2007).
- Depression, defined as current depression or the occurrence of at least one major depressive episode during their lifetime according to ICD-10 and DSM-IV criteria.

Individuals in the control group received the same screening and were explicitly chosen to not have any risk factors for PD.

Additionally, the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Beck Depression Inventory II (BDI-II; Beck et al., 1996) were administered to evaluate motor and depressive symptoms, respectively, though not considered in the selection of PD-RP.

Neuropsychology

All participants underwent testing of cognitive flexibility based on the TMT (Reitan and Skills, 1958) consisting of part A and B. In part A, subjects have to connect numbers from 1 to 25. It is used to test visual search ability and motor speed. In part B, subjects have to connect numbers and letters in an alternating way (1-A-2-B-3-C. . ..). In addition to the components from part A, part B also tests cognitive flexibility and working memory. We chose the derived score B-A as our parameter of interest, as (Sanchez-Cubillo et al., 2009) have recommended using B-A to minimize the influence of motor speed, visuospatial perception, and working memory demands to provide a more reliable indicator of cognitive flexibility. Additionally, the Mini-Mental State Examination (MMSE) was carried out in all participants (Folstein et al., 1975).

Image Acquisition

Structural T1-weighted images (TR = 2300 ms, TE = 4.18 ms, TI = 900 ms, and voxel size: 1 mm × 1 mm × 1 mm) were acquired with a 3 T scanner (Siemens PRISMA, Erlangen, Germany). Diffusion-weighted images were acquired using a "Stejskal-Tanner" sequence (TR = 6.0 s, TE = 69 ms, flip angle = 90°, 50 axial slices, and 2 acquisitions) with a voxel size of 1.7 × 1.7 × 2.5 mm^3 along 30 independent directions using a *b*-value of 1000 s/mm^2. Additionally, 12 images with a *b*-value of 0 s/mm^2 were acquired throughout the sequence.

DTI Data Analysis

Data preprocessing and DTI analysis were carried out using FSL 5.0.9 (FMRIB Software Library, http://fsl.fmrib.ox.ac.uk/fsl/). Preprocessing included correction of eddy current distortions and motion artifacts (Andersson and Sotiropoulos, 2016). Head motion was compared between groups across 6 direction (translation *x*/*y*/*z* and rotation *x*/*y*/*z*). The DTIFIT tool was used to fit a diffusion tensor model at each voxel and generate FA, MD maps, and the eigenvalues (λ_1, λ_2, λ_3). Axial (AD = λ_1) and radial [RD = $(\lambda_2 + \lambda_3)/2$] diffusivity maps were calculated from these eigenvalues. Voxel-wise statistical analysis of the FA data was carried out using TBSS included in FSL (Smith et al., 2004, 2006). FA data from each subject was aligned into a common space using the non-linear registration tool FNIRT (Andersson et al., 2007), which uses a *b*-spline representation of the registration warp field (Rueckert et al., 1999), and finally averaged to create a mean FA image. The mean FA image was then thinned to create a mean FA skeleton which represents the centers of all tracts common to the group; an FA threshold of 0.2 was used for the skeleton. Each subject's aligned FA data was then projected onto this skeleton. The same FA transformation was applied to MD, RD, and AD maps, and projected onto the same skeleton. Statistical models were set up to enable comparison across groups as well as correlation with TMT B-A and included age and gender as covariates of no interest. Additionally, we ran correlation analyses with the risk measures BDI-II, RBDSQ, and Sniffin' sticks across both groups and within each group to determine their influence on white matter integrity. Using the "Randomize" tool incorporated in FSL we ran non-parametric permutation-based statistical tests on the DTI maps with 10000 permutations and threshold-free cluster enhancement (Smith and Nichols, 2009) to correct for multiple comparisons across the whole brain at a significance threshold of $P < 0.05$ using family-wise error correction.

Analysis of White Matter Integrity and Cognitive Flexibility

The relationship between white matter integrity and cognitive flexibility was explored using the abovementioned tbss method. A correlation analysis between DTI parameters and TMT B-A was carried out to investigate overall correlation across both groups and within each group. Additionally, the group interaction effect was examined using the FSL GLM model "Two Groups with continuous covariate interaction" (see **Figure 1**). Age and gender were added as covariates of no interest in every correlation model. The same tbss settings as described above were applied in the correlation analyses. Clusters demonstrating a significant group interaction were defined based on Johns Hopkins University's Mori white matter atlas (Mori et al., 2008). DTI parameters in each significant cluster were than extracted from the skeletonized tbss image of each participant and plotted against their TMT B-A score. As a safeguard we ran all our analyses by leaving out the most extreme data point. While this obviously resulted in different statistical values it had no impact on statistical inference (i.e., whether results were statistical significant or not).

Statistical Analysis

Statistical analysis of the clinical and neuropsychological measures was carried out using SPSS version 25 software (SPSS Inc, Chicago, IL, United States). Independent sample *t*-tests as well as Mann–Whitney-*U* tests were used to compare mean/median scores between the groups for normally and non-normally distributed parameters, respectively. The X^2 test was used to assess potential differences in gender distribution. Partial Correlation analysis between TMT B-A, BDI-II, RBDSQ, and Sniffin' sticks scores controlling for age and gender was used to evaluate, whether TMT B-A performance was driven by one of the risk factors depression, RBD or hyposmia. A non-corrected *P*-value < 0.05 was considered significant. There was

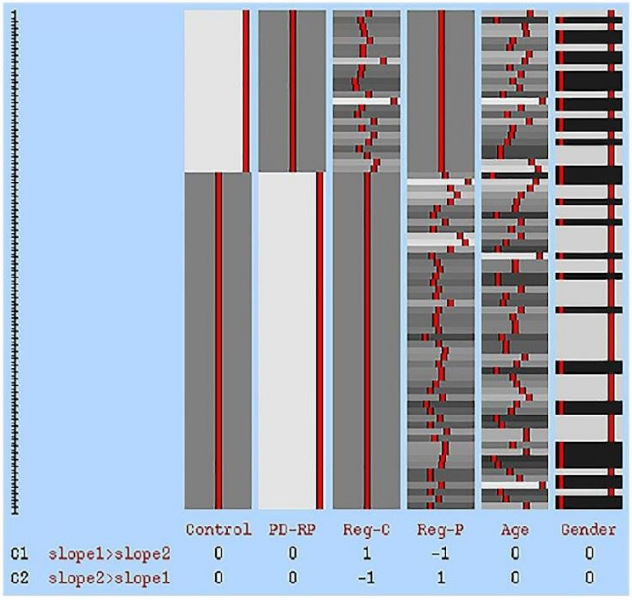

FIGURE 1 | GLM statistical model for group interaction effect. The first two columns represent tbss data of each group. Reg-C and Reg-P represent the regressor for the control group and PD-RP, respectively. Age and gender were added as covariates of no interest. C1: higher effect in control, C2: higher effect in PD-RP.

no significant difference in head motion between groups across all 6 directions (see **Supplementary Material**).

RESULTS

Demographics and Clinical Features

Age, gender and education as well as UPDRS-III and MMSE scores were not significantly different between PD-RP and controls. As expected, BDI-II, RBDSQ, and Sniffin' sticks scores were significantly higher in PD-RP than in controls. The TMT B-A score was not significantly different between the groups and did not significantly correlate with BDI-II, RBDSQ or Sniffin' sticks scores.

TBSS Analysis

Voxel-wise TBSS whole brain analysis did not reveal any significant difference between both groups controlling for multiple comparisons across the whole brain. The correlation analysis between TMT B-A performance and diffusion parameters within the PD-RP group, however, revealed significant effects for MD and AD in several brain areas including, commissural tracts, e.g., corpus callosum, association tracts, e.g., superior longitudinal fasciculus and projection tracts, e.g., corona radiata (for full results see **Figures 2**, **3** and **Tables 2**, **3**). These effects were stronger in PD-RP than in controls as evidenced by a significant group interaction ($P < 0.05$ FWE-corrected, see **Figures 2**, **3**). The three risk measures BDI-II, RBDSQ and Sniffin' sticks scores did not significantly correlate with diffusion parameters in each group.

DISCUSSION

In recent years, enormous efforts have been devoted to better understand the time before motor symptoms allow clinical diagnosis of PD, i.e., the prodromal phase (Berg et al., 2015). Nevertheless, the number of neuroimaging studies on white matter alterations in this phase is still very limited with most studies focusing on idiopathic RBD as a predictor of α-synucleinopathies (Unger et al., 2010; Scherfler et al., 2011; Rahayel et al., 2015), and not the broad definition of prodromal PD (Berg et al., 2015). This study is, to our best knowledge, the first to reveal a correlation between white matter architecture and a cognitive function, such as cognitive flexibility, in PD-RP.

We found no significant differences between the two groups regarding the diffusion parameters arguing against a general application of the examined diffusion parameters as early marker for the development of PD. In contrast, a study on a PD-RP cohort with substantia nigra hyperechogenicity and/or hyposmia, revealed increased MD in the posterior thalamus, inferior longitudinal fasciculus, fornix and the corticospinal tract in the PD-RP group, but failed to demonstrate a significant difference between PD patients and controls (Heldmann et al., 2018). The authors suggested that PD-RP/PD patients with hyposmia could have a more severe disease course with a different pattern of neurodegeneration in comparison to those without hyposmia. This may explain the negative results in our study, since only 28% of our PD-RP cohort presented with hyposmia. On the other hand, a study on G2019S LRRK2 mutation carriers, an asymptomatic cohort generally considered at higher risk of PD, did not reveal any significant structural brain changes using DTI and VBM (voxel-based morphometry). However, a tendency for higher FA and lower MD in the mutation carriers was observed, which may hint at the involvement of a compensatory mechanism. Similarly, a recent study using graph-theory revealed greater local connectivity in regions relating to motor, olfactory, and sleep functions in PD-RP, suggesting neural compensation in the prodromal phase (Wen et al., 2017). This discrepancy between studies on PD-RP could be due to the application of different recruitment criteria, as it should be noted that our definition of the PD-RP group implicates that only part of this group will develop PD, so a true effect may be driven by a large proportion of non-converters. Based on this assumption it is even more interesting that our analysis revealed a significant correlation between TMT results and MD in the superior longitudinal fasciculus connecting the frontal and parietal cortex (Schmahmann et al., 2008), as well as the corpus callosum and multiple projection tracts, such as the corona radiata, while no such effects were observed for FA.

This observation is in line with MRI studies on early PD demonstrating that alterations of MD precede FA reduction (Melzer et al., 2013) as well as gray matter (Duncan et al.,

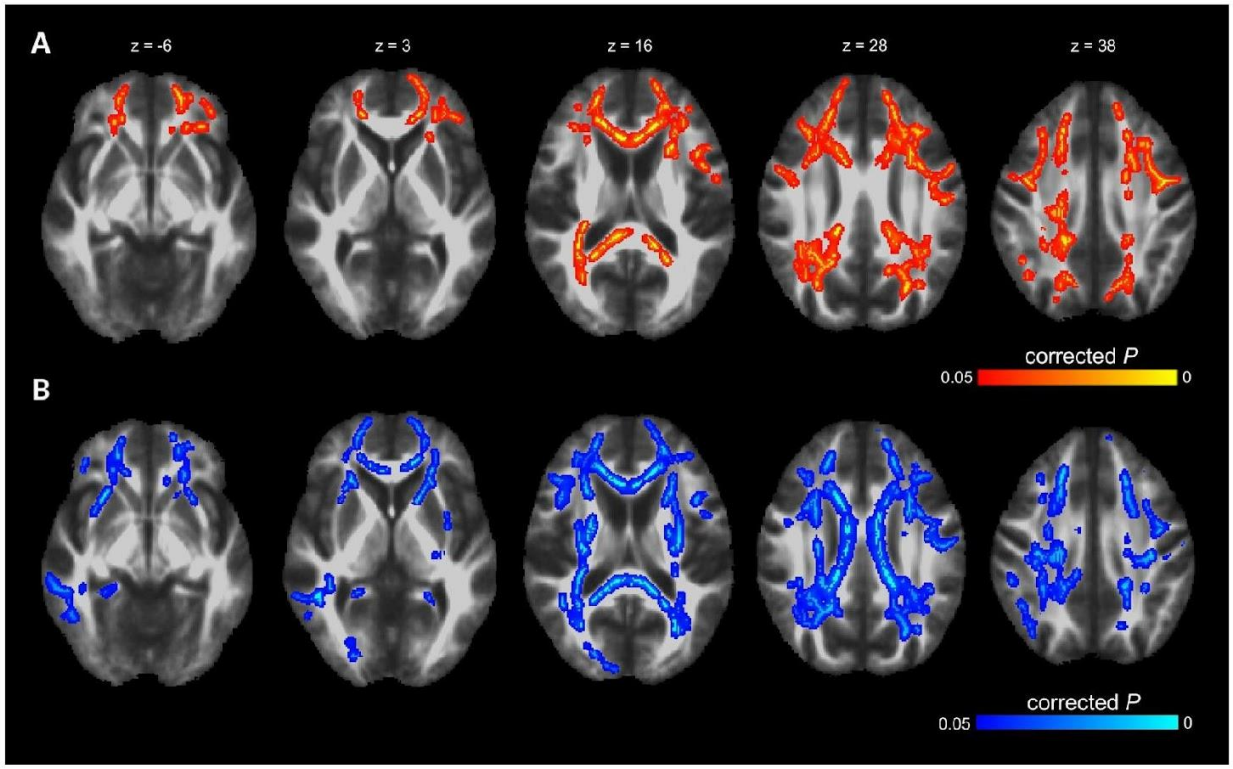

FIGURE 2 | The results of TBSS whole-brain regression analysis overlaid on mean FA (1 mm) template and presented in radiological convention. **(A)** Significant group interaction (PD-RP > controls) determined in the regression analysis between cognitive flexibility (TMT B-A) and mean diffusivity (MD). **(B)** Significant group interaction (PD-RP > controls) determined in the regression analysis between cognitive flexibility (TMT B-A) and axial diffusivity (AD).

TABLE 2 | MD clusters with a significant group interaction.

Region		Cluster size (voxels)	Individuals at risk of PD		Control group	
			MD ± SE (10^{-3} mm^2/s)	R^2/*P*	MD ± SE (10^{-3} mm^2/s)	R^2/*P*
ACR	Left	722	0.795 ± 0.006	0.168/0.003	0.793 ± 0.010	0.003/0.80
	Right	410	0.791 ± 0.007	0.200/0.001	0.797 ± 0.011	0.001/0.98
SCR	Left	153	0.786 ± 0.005	0.067/0.07	0.788 ± 0.010	0.027/0.44
	Right	220	0.778 ± 0.005	0.136/0.008	0.769 ± 0.008	0.014/0.59
PCR	Left	57	0.827 ± 0.006	0.130/0.01	0.810 ± 0.008	0.009/0.66
	Right	231	0.856 ± 0.007	0.166/0.003	0.847 ± 0.010	0.002/0.85
CC	Genu	435	0.802 ± 0.006	0.373/0.000002	0.804 ± 0.009	0.007/0.7
	Body	516	0.831 ± 0.007	0.301/0.000037	0.845 ± 0.011	0.055/0.27
	Splenium	884	0.758 ± 0.004	0.230/0.0004	0.755 ± 0.006	0.157/0.06
SLF	Left	206	0.784 ± 0.006	0.225/0.0005	0.773 ± 0.008	0.018/0.54
	Right	116	0.801 ± 0.008	0.149/0.0006	0.785 ± 0.008	0.002/0.82
ALIC	Left	22	0.757 ± 0.008	0.061/0.083	0.755 ± 0.013	0.009/0.66
RIC	Right	53	0.764 ± 0.006	0.156/0.0045	0.752 ± 0.008	0.044/0.32
EC	Left	33	0.801 ± 0.007	0.057/0.094	0.786 ± 0.012	0.015/0.56
SFOF	Left	7	0.795 ± 0.012	0.024/0.278	0.791 ± 0.020	0.018/0.53
PTR	Right	98	0.897 ± 0.009	0.216/0.0007	0.900 ± 0.010	0.020/0.51
T	Right	17	0.942 ± 0.013	0.163/0.0036	0.945 ± 0.019	0.003/0.79

All Values are expressed as the mean ± standard error (SE). Abbreviations: MD, mean diffusivity; ACR, anterior corona radiata; SCR, superior corona radiata; PCR, posterior corona radiata; CC, corpus callosum; SLF, superior longitudinal fasciculus; ALIC, anterior limb of internal capsule; RIC, retrolenticular part of internal capsule; EC, external capsule; SFOF, superior fronto-occipital fasciculus; PTR, posterior thalamic radiation; and T, tapetum.

TABLE 3 | AD clusters with a significant group interaction.

Region		Cluster size (voxels)	Individuals at risk of PD		Control group	
			AD ± SE (10^{-3} mm^2/s)	R^2/P	AD ± SE (10^{-3} mm^2/s)	R^2/P
ACR	Left	841	1.264 ± 0.007	0.126/0.011	1.268 ± 0.012	0.028/0.44
	Right	860	1.221 ± 0.007	0.161/0.0038	1.244 ± 0.014	0.024/0.47
SCR	Left	492	1.253 ± 0.009	0.052/0.112	1.250 ± 0.014	0.028/0.43
	Right	915	1.196 ± 0.008	0.045/0.137	1.191 ± 0.012	0.071/0.21
PCR	Left	271	1.349 ± 0.009	0.214/0.0007	1.338 ± 0.012	0.039/0.36
	Right	401	1.350 ± 0.010	0.152/0.005	1.342 ± 0.014	0.015/0.57
CC	Genu	812	1.627 ± 0.009	0.270/0.0001	1.647 ± 0.011	0.028/0.44
	Body	1404	1.755 ± 0.009	0.283/0.00007	1.759 ± 0.013	0.131/0.08
	Splenium	1647	1.684 ± 0.009	0.162/0.0038	1.684 ± 0.012	0.156/0.06
SLF	Left	304	1.210 ± 0.007	0.148/0.006	1.195 ± 0.008	0.078/0.19
	Right	468	1.285 ± 0.008	0.119/0.014	1.282 ± 0.009	0.095/0.14
ALIC	Left	177	1.372 ± 0.011	0.151/0.005	1.377 ± 0.014	0.016/0.56
	Right	91	1.306 ± 0.009	0.070/0.06	1.321 ± 0.012	0.025/0.46
PLIC	Left	76	1.411 ± 0.009	0.020/0.327	1.403 ± 0.011	0.036/0.37
	Right	125	1.414 ± 0.008	0.043/0.146	1.412 ± 0.009	0.080/0.18
RIC	Left	67	1.498 ± 0.007	0.026/0.26	1.495 ± 0.012	0.085/0.17
	Right	140	1.445 ± 0.011	0.061/0.08	1.472 ± 0.019	0.013/0.6
EC	Left	404	1.251 ± 0.007	0.066/0.07	1.243 ± 0.009	0.158/0.06
	Right	233	1.319 ± 0.007	0.093/0.03	1.311 ± 0.011	0.109/0.16
SFOF	Left	9	1.288 ± 0.002	0.066/0.07	1.283 ± 0.002	0.002/0.82
	Right	31	1.225 ± 0.010	0.063/0.08	1.236 ± 0.010	0.119/0.1
PTR	Left	88	1.672 ± 0.012	0.045/0.14	1.675 ± 0.014	0.231/0.02
	Right	205	1.622 ± 0.010	0.071/0.06	1.636 ± 0.015	0.184/0.04
T	Left	2	1.596 ± 0.002	0.101/0.024	1.590 ± 0.003	0.001/0.92
	Right	18	1.672 ± 0.015	0.121/0.013	1.665 ± 0.019	0.017/0.55
SS	Right	15	1.571 ± 0.012	0.006/0.6	1.607 ± 0.020	0.096/0.14
UF	Right	3	1.515 ± 0.014	0.054/0.1	1.512 ± 0.017	0.037/0.37
CG	Right	45	1.400 ± 0.009	0.063/0.08	1.410 ± 0.012	0.047/0.31
CH	Right	42	1.325 ± 0.013	0.075/0.055	1.317 ± 0.021	0.057/0.26

All Values are expressed as the mean ± standard error (SE). Abbreviations: AD, axial diffusivity; ACR, anterior corona radiata; SCR, superior corona radiata; PCR, posterior corona radiata; CC, corpus callosum; SLF, superior longitudinal fasciculus; ALIC, anterior limb of internal capsule; RIC, retrolenticular part of internal capsule; EC, external capsule; SFOF, superior fronto-occipital fasciculus; PTR, posterior thalamic radiation; T, tapetum; PLIC, posterior limb of internal capsule; CH, cingulum of hippocampus; CG, cingulate gyrus; UF, uncinate fasciculus; and SS, sagittal stratum.

2016). Also in line with our result, MD was found to be associated with executive function in PD, while no significant association was found for FA (Melzer et al., 2013). This is in contrast to studies on aging that demonstrated a positive correlation between FA and executive function (Perry et al., 2009; Halliday et al., 2019) and suggests that distinct white matter pathologies are responsible for cognitive impairments related to healthy aging and PD. A similar finding was also reported in individuals with traumatic brain injury (Kinnunen et al., 2011).

Our analyses also revealed a significant correlation between TMT performance and AD in several frontoparietal white matter regions. Although the mechanism causing increases of AD is not fully understood, it has been implicated as an early state-specific marker with a high sensitivity for early neurodegeneration and cognitive impairment (Acosta-Cabronero et al., 2012; Molinuevo et al., 2014). It has also been suggested that increased AD may represent an upstream event preceding axonal degeneration, e.g., inflammation (Acosta-Cabronero et al., 2012). In addition, the involvement of the frontoparietal network as an essential neurobiological correlate of executive functions concurs with previous DTI (Halliday et al., 2019) and functional magnetic resonance imaging (fMRI; Niendam et al., 2012) studies in healthy individuals as well as fMRI (Lewis et al., 2003) and DTI (Melzer et al., 2013) studies on neural substrates underlying impairments of executive functions in PD. Similarly, microstructural alterations in the corpus callosum and their association with mild cognitive impairment in PD including executive function impairments have been reported (Bledsoe et al., 2018), adding to the growing body of evidence suggesting both intra- and interhemispheric "disconnection" as a possible mechanism of executive dysfunction in PD (Melzer et al., 2013; Zheng et al., 2014).

It should be noted that the correlation between TMT performance and MD as well as AD was only found in the group of PD-RP, but not in the control group. An analogous

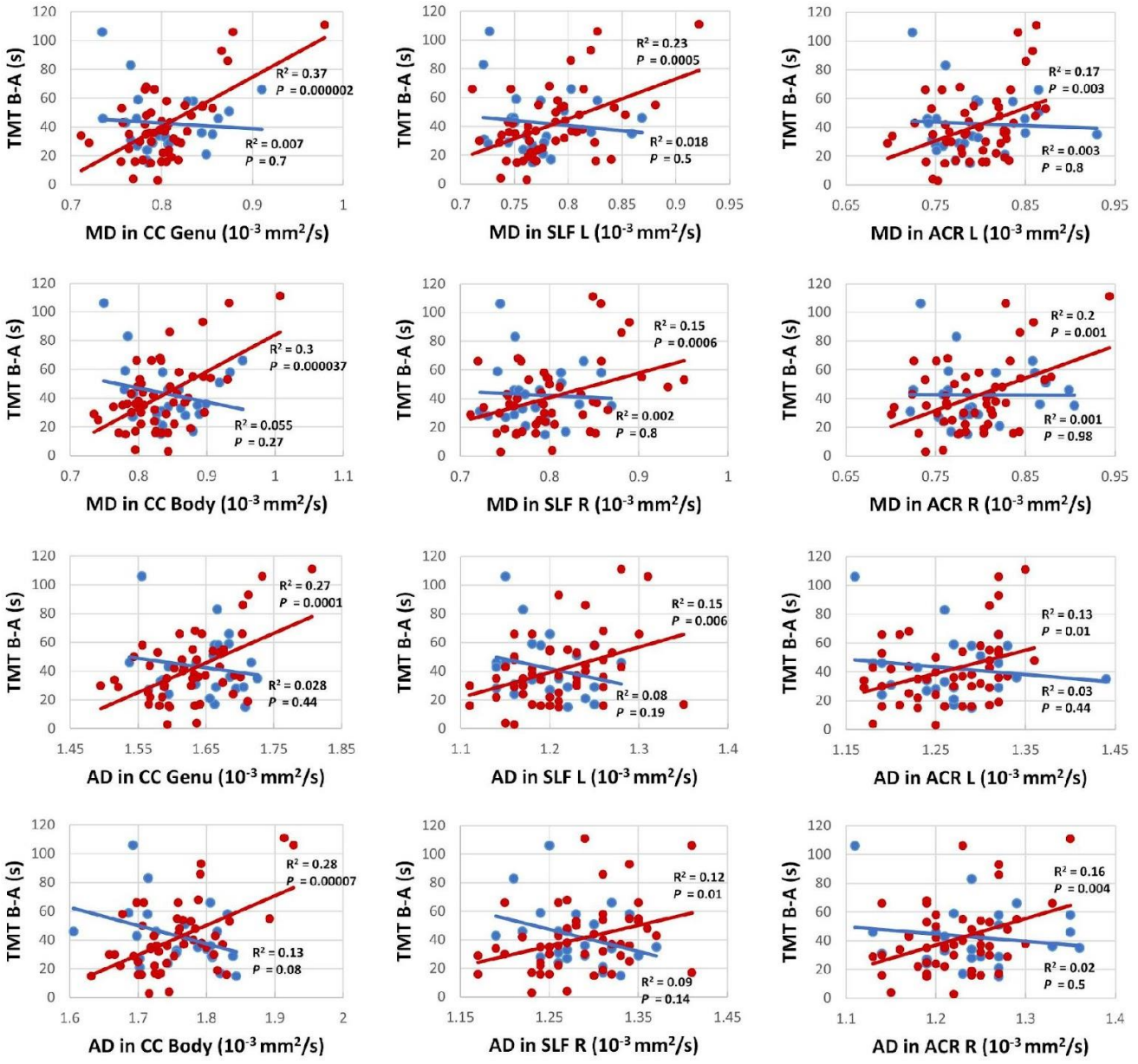

FIGURE 3 | Correlation analysis between TMT B-A and MD (upper six panels) as well as TMT B-A and AD (lower six panels) for persons with (red) and without (blue) risk factors for PD for the clusters with the highest correlation in commissural tracts: genu and body of the corpus callosum (CC), projection tracts: left and right anterior corona radiata (ACL), and association tracts: left and right superior longitudinal fasciculus (SLF).

finding has been reported in a DTI study on executive dysfunctions in individuals with traumatic brain injury with a significant correlation between TMT B-A performance and RD in frontoparietal areas which was restricted to the patient group, but not found in healthy individuals (Kinnunen et al., 2011). This distinct relationship may indicate that deficits in specific executive functions in PD-RP are more related to white matter pathology than in healthy older adults.

It is worth mentioning that PD-RP did not differ from the control group in regards to their TMT performance. While other imaging studies also failed to demonstrate cognitive deficits in PD-RP (Wen et al., 2017; Heldmann et al., 2018), a recent review reported the existence of executive function impairments in prodromal PD (Fengler et al., 2017). Hence, prospective longitudinal studies are still needed to determine the role of cognitive changes as a reliable biomarker for prodromal PD.

Interestingly, two fMRI-studies have reported a higher task-related activity in several cerebral regions in G2019S LRRK2 mutation carriers while maintaining an adequate executive function performance, suggesting a neural compensatory mechanism that enables intact cognitive performance (Thaler et al., 2013; Bregman et al., 2017).

Our study revealed no correlation between DTI measure and risk scores, such as sniffin' sticks and RBDSQ. This is in contrast to previous studies on PD-RP revealing structural correlates of olfactory tests (Wen et al., 2017; Heldmann et al., 2018) as well as RBDSQ (Wen et al., 2017). This is may be due to the lower prevalence of these risk factors in our PD-RP cohort.

This study faces some limitations. For example, this is a cross-sectional study and we do not have MRIs from the entire TREND cohort (which has already observed 16 PD converters within its lifetime). Thus, our results are built on a PD-RP cohort and it is not clear how many participants will eventually convert to PD. This limitation is shared with many other studies in the field. Due to this limitation we can also not exclude that the effect observed in this study is a constitutional factor, rather than a dynamic process indicating prodromal PD (Mirelman et al., 2011). This aspect has to be further investigated in longitudinal prospective cohorts. Another limitation is the relatively low specificity of our selected prodromal markers. Individuals with a positive score on RBDSQ and hyposmia may have prodromal PD with a likelihood of 2.8 and 6.4, respectively. While our most frequent risk factor, depression, has an estimated likelihood of only 1.6 (Heinzel et al., 2019). Thus, a prodromal risk score based on multiple prodromal markers would be a more appropriate approach to categorize PD-RP and yield a higher probability for prodromal PD.

To avoid a loss of sensitivity due to multiple testing we focussed on a single measure of executive functioning, namely the cognitive flexibility, which may be a plausible explanation for absence of a group difference in TMT. Therefore, future imaging studies on PD-RP should apply a more comprehensive executive function screening in addition to other cognitive domains to get a better understanding of the structural correlates of the cognitive deficits in prodromal PD.

The severity of depressive symptoms, as measured by BDI-II, did not correlate with TMT performance or white matter integrity in our analysis. Given that most of our PD-RP group have had at least one depressive episode during their lifetime, we cannot exclude the possibility that our result is a lingering effect of depression, which can be only partially accounted for by the severity of current depressive symptoms (Rock et al., 2014).

In summary, DTI and cognitive flexibility as assessed by TMT were not able to reliably differentiate PD-RP from healthy controls and thus may lack the needed sensitivity as biomarkers for the prodromal phase of PD. Nevertheless, DTI revealed frontoparietal white matter alterations related to a specific executive function only in PD-RP, which may indicate that deficits in specific executive functions PD-RP are more related to white matter alterations than in healthy older adults.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Medical Faculty at the University of Tübingen (Nr. 90/2009BO2). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB and WM contributed conception and design of the study. DB, MH, TE, and WM organized the study. HA performed data analysis. BK and ME provided analysis tools. HA wrote the first draft. DB, TE, and WM wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

We acknowledge support by Open Access Publishing Fund of University of Tübingen. The TREND-Study was supported by UCB, Teva, Janssen, Werner Reichardt Centre for Neuroscience, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Internationale Parkinson Fonds Deutschland, Hertie-Institut für klinische Hirnforschung, and the University of Tübingen.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2020.00250/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2.2. Gait decline while dual-tasking is an early sign of white matter deterioration in middle-aged and older adults

Alzaid H, Ethofer T, Kardatzki B, Erb M, Scheffler K, Berg D, Maetzler W, Hobert MA. Gait decline while dual-tasking is an early sign of white matter deterioration in middle-aged and older adults. Front Aging Neurosci. 2022 Sep 29;14:934241. doi: 10.3389/fnagi.2022.934241. (Alzaid et al., 2022)

frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 29 September 2022
DOI 10.3389/fnagi.2022.934241

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 02 May 2022
ACCEPTED 26 August 2022
PUBLISHED 29 September 2022

CITATION
Alzaid H, Ethofer T, Kardatzki B, Erb M, Scheffler K, Berg D, Maetzler W and Hobert MA (2022) Gait decline while dual-tasking is an early sign of white matter deterioration in middle-aged and older adults.
Front. Aging Neurosci. 14:934241.
doi: 10.3389/fnagi.2022.934241

Gait decline while dual-tasking is an early sign of white matter deterioration in middle-aged and older adults

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Loss of white matter integrity (WMI) is associated with gait deficits in middle-aged and older adults. However, these deficits are often only apparent under cognitively demanding situations, such as walking and simultaneously performing a secondary cognitive task. Moreover, evidence suggests that declining executive functions (EF) are linked to gait decline, and their co-occurrence may point to a common underlying pathology, i.e., degeneration of shared brain regions. In this study, we applied diffusion tensor imaging (DTI) and a standardized gait assessment under single- and dual-tasking (DT) conditions (walking and subtracting) in 74 middle-aged and older adults without any significant gait or cognitive impairments to detect subtle WM alterations associated with gait decline under DT conditions. Additionally, the Trail Making Test (TMT) was used to assess EF, classify participants into three groups based on their performance, and examine a possible interaction between gait, EF, and WMI. Gait speed and subtracting speed while dual-tasking correlated significantly with the fractional anisotropy (FA) in the bilateral anterior corona radiata (highest $r = 0.51/p < 0.0125$ FWE-corrected). Dual-task costs (DTC) of gait speed correlated significantly with FA in widespread pathways, including the corpus callosum, bilateral anterior and superior corona radiata, as well as the left superior longitudinal fasciculus (highest $r = -0.47/p < 0.0125$ FWE-corrected). EF performance was associated with FA in the left anterior corona radiata ($p < 0.05$); however, EF did not significantly mediate the effects of WMI on DTC of gait speed. There were no significant correlations between TMT and DTC of gait and subtracting speed, respectively. Our findings indicate that gait decline under DT conditions is associated with widespread WM deterioration even in middle-aged and older adults without any significant gait or cognitive impairments. However, this relationship was not mediated by EF.

KEYWORDS

diffusion tensor imaging, dual-task costs, gait, white matter, executive functions

Introduction

Gait impairments are common with aging and lead to major consequences, including falls, disability, and long-term institutionalization (Scheffer et al., 2008). However, many gait impairments are not apparent and are presumably masked by compensatory strategies. For instance, some gait impairments are only apparent in cognitively demanding situations, such as under cognitive-motor dual-tasking (DT) conditions (Lord et al., 2013). This is especially true in older people with executive function (EF) impairments, as executive dysfunction has been reported to be associated with slower gait under DT conditions and could be a possible mediator of falls (Yogev-Seligmann et al., 2008). In fact, the decline in EF appears to be an early sign of global cognitive decline and frailty. It is reasonable to assume a link between gait and cognition, as this has been consistently demonstrated in studies (Yogev-Seligmann et al., 2008; Montero-Odasso et al., 2009; Hobert et al., 2017); however, the mechanism behind it is not entirely clear. It has been theorized that gait in complex situations requires recruiting additional (primarily cognitive) resources (Boisgontier et al., 2013). In this regard, gait decline under DT conditions could reflect deterioration of shared white matter (WM) pathways, which are also involved in EF.

Previous evidence suggests the involvement of mostly frontal WM pathways in gait under DT conditions, including the corpus callosum (Ghanavati et al., 2018; Castro-Chavira et al., 2019; Snir et al., 2019), the anterior corona radiata (ACR)/anterior thalamic radiation (Pettit et al., 2013; Ruggieri et al., 2018; Castro-Chavira et al., 2019; Snir et al., 2019), and the left superior corona radiata (Hupfeld et al., 2022). However, this relationship has been mostly investigated in patient groups and older people with dementia. As frontal WM is particularly vulnerable to normal aging (Pfefferbaum et al., 2005), it is important to test this relationship in non-demented adults to assess the utility of gait assessment under DT conditions as an early indicator of WM deterioration. Moreover, further investigations into this relationship are needed, including the possible role of executive functions as a mediator and the existence of shared pathways between motor and cognitive tasks.

In this study, we applied Diffusion Tensor Imaging (DTI) to detect such alterations in the aging population and determine their influence on EF and gait under DT conditions. DTI is a modern neuroimaging method with a high sensitivity to detect WM alterations (Basser et al., 1994), which has been successfully applied to identify the WM correlates of gait (Bhadelia et al., 2009) and cognitive-motor dual-tasking (Snir et al., 2019) in older adults. Using this imaging method, researchers can obtain DTI-derived parameters to examine WM Integrity (WMI), such as fractional anisotropy (FA), which reflects diffusion orientation and coherence along the fibers. Low FA values generally indicate reduced WMI (Pierpaoli and Basser, 1996).

By assessing gait and cognitive function with a DT paradigm at the behavioral level and WMI using DTI, we examined whether gait decline under DT conditions is associated with early WM alterations in middle-aged and older adults without any significant gait or cognitive impairments. We then classified the participants into three groups based on their EF performance and compared WMI between the groups. Subsequently, a mediation analysis was conducted to assess whether EF mediates the interaction between WMI and gait under DT conditions. We hypothesize that the deterioration of widespread white matter contributes to gait decline while dual-tasking. Additionally, deterioration of shared pathways between the motor and cognitive tasks and pathways involved in executive functions might influence this interaction.

Materials and methods

Participants

This is a cross-sectional study as a part of the TREND study (Tübinger evaluation of Risk factors for Early Detection of Neurodegeneration), a prospective biannual follow-up study aimed at defining biomarkers for early detection of Parkinson's disease and Alzheimer's disease (Gaenslen et al., 2014). For this MRI cross-sectional study, we recruited 74 older adults from the whole cohort of the TREND study (41 women, mean age: 67 ± 6 years). All participants were middle-aged and older adults between 55 and 81 years of age and met the criteria of being community-dwelling without any significant gait or cognitive impairments. Specifically, all participants could walk without ambulatory aids or assistance, had a minimum score of 24 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and had no clinical signs of dementia. They also had no diagnosis of any neurodegenerative disease, a history of stroke, epilepsy, central nervous system inflammatory diseases, or polyneuropathy. They were free of antipsychotic or other antidopaminergic drugs and exhibited no significant impairment of vision or hearing. All participants gave written informed consent, and the study was approved by the ethical committee of the University of Tübingen (Nr. 90/2009BO2 and 370/2013BO2).

Trail making test

All participants underwent testing of EF based on parts A and B of the TMT (Reitan and Skills, 1958). In part A, participants have to connect numbers from 1 to 25 using a pen. It is used to assess visual search ability and motor speed. In part B, subjects have to connect numbers and letters alternatingly (1-A-2-B-3-C. . ..). In addition to the components from part A, part B also assesses cognitive flexibility and

working memory. We chose the derived score B-A as our parameter of interest, as previous studies have recommended using the derived score B-A to minimize the influence of motor speed and visuospatial perception and provide a more reliable indicator of EF (Sanchez-Cubillo et al., 2009). The participants were categorized based on their TMT B-A performance into three groups. TMT B-A values > 54 s defined poor performers (n = 17), values ranging from 35 to 54 s defined intermediate performers (n = 25), and values < 35 s defined good performers (n = 32). The cut-off values used are from a related analysis from the TREND study with a much larger and more representative sample size (N = 1054) (Salkovic et al., 2017).

Single- and dual-task assessment

In the single-task (ST) and DT assessments, the participants performed two ST and one DT trials. In the motor ST trial, participants were instructed to walk as fast as possible for 20 m on at least a 1.5-m wide corridor. Participants in the cognitive ST trial subtracted serial 7s as fast as possible from a random three-digit number until ten subtractions were made; the task was performed while standing. The time for subtracting was measured with a stopwatch, and the examiner took the number of subtractions in DT. The subtracting speed was defined as the number of subtractions divided by the time needed for the task (seconds).

In the DT trial, participants simultaneously performed the subtracting the walking tasks. Both tasks had to be performed as fast as possible without any hints given by the investigator regarding the prioritization of any task. The time for walking and subtracting was measured with a stopwatch, and the examiner took the number of subtractions in DT.

Performing the trials at a fast walking pace as opposed to a preferred walking pace is meant to increase their difficulty level and reveal gait deficits masked by compensatory cognitive control of gait (Lord et al., 2013). There was only one dual-task trial to measure the "natural performance" without a chance to improve/change the strategy. For the familiarization, the two tasks were performed in a single task condition.

While there is no standardized protocol for testing gait under ST and DT conditions, the reliability of our protocol has been established in previous studies (Hobert et al., 2011, 2017; Salkovic et al., 2017).

To test the individual DT ability regardless of their ST performance, we derived the relative DT parameters, dual-task costs (DTC) of gait and subtracting speed, using the following formula (Baddeley et al., 1997).

$$DTC[\%] = [(ST\ speed - DT\ speed)/ST\ speed]^{*}100$$

Dual-task costs measure the change in DT compared to ST performance, expressed as a percentage of ST performance. Positive DTC describe a deterioration in DT, and negative DTC describe an improvement in DT compared to ST.

We decided to also include the absolute DT parameters in the analysis as an exploratory measure, as they could provide additional information needed to fully understand DT mechanisms (Plummer and Eskes, 2015).

We thus derived the following clinical parameters for the dual-task assessment:

(1) DT gait speed while subtracting.
(2) DT subtracting speed while walking.
(3) DTC of gait speed (while subtracting).
(4) DTC of subtracting speed (while walking).

Image acquisition

Structural T1-weighted images (TR = 2300 ms, TE = 4.18 ms, TI = 900 ms, voxel size: 1 × 1 × 1 mm^3) were acquired with a 3 Tesla scanner (Siemens PRISMA, Erlangen, Germany). Diffusion-weighted images were acquired using a "Stejskal-Tanner" sequence (TR = 6.0 s, TE = 69 ms, flip angle = 90°, 50 axial slices, 2 acquisitions) with a voxel size of 1.7 × 1.7 × 2.5 mm^3 along 30 independent directions using a b-Value of 1000 s/mm^2. Additionally, 12 images with a b-Value of 0 s/mm^2 were acquired throughout the sequence. The clinical tests and image acquisition were done in separate sessions.

Diffusion tensor imaging data analysis

Data preprocessing and DTI analysis were carried out using FSL 5.0.9 (FMRIB Software Library[1]). Preprocessing included correction of eddy current distortions and motion artifacts (Andersson and Sotiropoulos, 2016). Head motion was compared between groups across six directions. The DTIFIT tool was used to fit a diffusion tensor model at each voxel and generate the FA map. A voxel-wise statistical analysis of the FA data was carried out using the Tract-Based Spatial Statistics (TBSS) included in FSL (Smith et al., 2004, 2006). The FA maps from each subject were aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999), and finally averaged to create a mean FA image. The mean FA image was then thinned to create a mean FA skeleton, representing the centers of all tracts common to the group; an FA threshold of 0.2 was used for the skeleton. Each subject's aligned FA

1 http://fsl.fmrib.ox.ac.uk/fsl/

map was then projected onto this skeleton. The correlation between FA and the aforementioned dual-tasking parameters was set up using the GLM tool in FSL and included age and gender as covariates of no interest. Using the "Randomise" tool incorporated in FSL, we ran nonparametric permutation-based statistical tests on the DTI maps with 10,000 permutations and threshold-free cluster enhancement (Smith and Nichols, 2009) to correct for multiple comparisons across the whole brain at a significance threshold of $p < 0.05$ using family-wise error correction; the p-Value threshold was further reduced to $p < 0.0125$ ($p = 0.05$ divided by 4, Bonferroni corrected for four DT parameters). We then extracted the significant clusters within each tract based on Johns Hopkins University's Mori WM atlas to compare group FA values (Mori et al., 2008). The significant maps of DT gait speed and DT subtracting speed were multiplied to determine areas of overlap.

Statistical analysis

Statistical analysis of clinical and neuropsychological measures was carried out using SPSS version 25 software (SPSS Inc., Chicago, Illinois). A one-way ANCOVA (age and gender as covariates of no interest) and the *post hoc* Tukey-HSD or the Kruskal–Wallis and *post hoc* Dunn's tests were used to compare mean scores between the groups for normally and non-normally distributed parameters, respectively. The X^2 test was used to assess potential differences in gender distribution and the prevalence of relevant comorbidities. A non-corrected p-Value of <0.05 was considered significant for all clinical and neuropsychological tests. We compared FA values between the three groups in the clusters that showed a significant correlation with DTC of gait speed using a one-way ANCOVA adjusted for age, gender, and hypertension, followed up by *post hoc* analysis using Tukey's HSD test to assess pairwise differences while correcting for multiple comparisons. Group comparisons were only carried out in significant clusters of >30 voxels (6 ANCOVAs). Using PROCESS macro v.3.4.1 implemented in SPSS[2], we used the simple mediation model (model 4) to assess whether TMT B-A performance (i.e., EF) mediates the effects of FA (only in clusters with a significant group difference) on DTC of gait speed. The mediation was calculated using 95% confidence intervals with a bootstrapping sample size of 5,000. Age, gender, and hypertension were included as covariates of no interest.

Additionally, we ran a linear correlation analysis (Pearson) between TMT B-A and DTC of gait speed and subtracting speed. We performed a partial correlation analysis of the four DT measures adjusted for age and gender for descriptive purposes. A p-Value of <0.0125 was considered significant ($p = 0.05$ divided by 4, Bonferroni corrected for four DT parameters).

2 www.processmacro.org

Results

Demographic and clinical features

Gender distribution and years of education, as well as MMSE, were not significantly different between the groups (Table 1). There was also no significant difference in the prevalence of comorbidities. The poor TMT group was significantly older than the good TMT group ($p < 0.05$) and also older than the intermediate TMT group. However, the latter comparison did not reach statistical significance. ST subtracting speed significantly differed between good and poor performers, but all other ST and DT parameters and DTC scores did not. There were no significant correlations between TMT B-A and DTC of gait ($p = 0.1$, $r = 0.18$) and subtracting speed ($p = 0.15$, $r = -0.17$), respectively. There was a significant correlation between the four DT measures (Table 2).

Tract-based spatial statistics

The TBSS-based whole-brain correlation analysis revealed a significant correlation between FA and three dual-tasking parameters (positive correlation with DT subtracting speed while walking, positive correlation with DT gait speed while subtracting, and negative correlation with DTC of gait speed while subtracting) in several WM regions (see Figures 1, 2). Significant clusters with a voxel size of >5 are presented in Table 3. There was no significant correlation between FA and DTC of subtracting speed while walking using a threshold of $p < 0.0125$ corrected for multiple comparisons. There was an overlap between the correlation maps of DT gait speed and DT subtracting speed in the bilateral ACR (left ACR 88 voxels, right ACR 104 voxels).

Group comparisons

The one-way ANCOVA revealed a significant difference in FA values between the three TMT groups in the left ACR [$F(2,71) = 5,14$; $p < 0.05$, Bonferroni corrected for six clusters, see Figure 3]. The other five clusters showed a similar pattern, but the ANCOVAs obtained no significant results [all $F(2,71) < 2.2$; all $p > 0.05$]. Within the left ACR, the good TMT group had a significantly higher FA value than the intermediate TMT ($p < 0.05$) and poor TMT groups ($p < 0.01$). The FA value was higher in the intermediate TMT group compared to the poor TMT group, but this comparison failed to reach statistical significance. The mediation analysis was used to determine

TABLE 1 Demographic and clinical parameters of the groups.

	Whole cohort (SD)	Good TMT (SD)	Intermediate TMT (SD)	Poor TMT (SD)	*p*
N (female)	74 (41)	32 (20)	25 (12)	17 (9)	0.53
Age (years)	66.8 (6.5)	65.5 (5.4)[a]	65.9 (7.0)	70.4 (6.6)	<0.05
Education (years)	14.6 (2.6)	15.1 (2.8)	13.8 (2.0)	14.8 (2.6)	0.14
MMSE (0–30)	28.7 (1.4)	28.8 (1.4)	28.5 (1.5)	28.7 (1.5)	0.64
Osteoarthritis (%)	51.4	46.9	52.0	58.8	0.73
Osteoporosis (%)	5.4	9.4	0	5.9	0.29
Obesity (%)	14.9	18.8	16.0	5.9	0.47
Hypertension (%)	37.8	25.0	44.0	52.9	0.12
Diabetes (%)	6.8	9.4	8.0	0	0.44
TMT A (s)	34.5 (10.1)	33.4 (9.9)	32.8 (9.5)	39.2 (10.5)	0.23
TMT B (s)	76.0 (26.6)	56.3 (12.5)[b]	75.8 (10.2)[c]	113.4 (22.6)	<0.0001
TMT B-A (s)	41.5 (22.9)	22.9 (8.1)[b]	43.0 (6.3)[c]	74.1 (19.4)	<0.0001
ST gait speed (m/s)	1.67 (0.21)	1.64 (0.23)	1.72 (0.22)	1.66 (0.12)	0.30
ST subtracting speed (1/s)	0.34 (0.14)	0.39 (0.09)[d]	0.30 (0.16)	0.29 (0.13)	<0.005
DT gait speed while subtracting (m/s)	1.34 (0.20)	1.32 (0.19)	1.38 (0.22)	1.29 (0.19)	0.53
DT subtracting speed while walking (1/s)	0.29 (0.14)	0.32 (0.13)	0.26 (0.17)	0.28 (0.12)	0.14
DTC of gait speed while subtracting (%)	19.5 (12.0)	18.2 (12.8)	19.9 (11.2)	21.6 (12.0)	0.56
DTC of subtracting speed while walking (%)	12.0 (33.3)	15.6 (28.5)	15.2 (42.9)	0.84 (24.3)	0.26

Group comparisons were performed using a one-way ANCOVA and the *post hoc* Tukey-HSD test or the Kruskal–Wallis and the *post hoc* Dunn's test for normally and non-normally distributed parameters, respectively. SD, standard deviation; MMSE, Mini-Mental State Examination; ns, not significant, TMT, trail making test; DT, dual-task; DTC, dual-task costs.
[a]Significant difference ($p < 0.05$) compared to the poor TMT group.
[b]Significant difference ($p < 0.0001$) compared to the intermediate and poor TMT groups.
[c]Significant difference ($p < 0.005$) compared to the poor TMT group.
[d]Significant difference ($p < 0.005$) compared to the intermediate and poor TMT groups.

TABLE 2 Partial correlation between the dual-tasking parameters adjusted for age and gender.

Parameter	DT gait speed	DT subtracting speed	DTC of gait speed	DTC of subtracting speed
DT gait speed	–	0.29/0.013	−0.62/0.00001	−0.37/0.001
DT subtracting speed	0.29/0.013	–	−0.36/0.002	−0.56/0.00001
DTC of gait speed	−0.62/0.00001	−0.36/0.002	–	0.36/0.002
DTC of subtracting speed	−0.37/0.001	−0.56/0.00001	0.36/0.002	–

The values are expressed as *r*/*p*.
DT, dual-task; DTC, dual-task costs.

whether executive functions (TMT B-A performance) mediated the effects of FA in the left ACR on DTC of gait speed. However, the result was not significant (β = −0.0271, SE = 0.0485, 95% confidence interval [−0.1197, 0.0781]).

Discussion

We investigated the association between WMI and gait decline under DT conditions in middle-aged and older adults, and explored the possible role of EF in this interaction. The key findings of our study are that (i) gait decline while dual-tasking was associated with loss of WMI in frontoparietal pathways, including the corpus callosum, (ii) the bilateral ACR appears to be a shared pathway for the cognitive and motor tasks, and (iii) EF performance was associated with WMI in the left ACR; however, EF did not mediate the interaction between WMI and gait decline under DT conditions.

We demonstrated that DTC of gait speed was negatively correlated with FA predominantly in frontoparietal pathways, including the corona radiata, the corpus callosum, the superior longitudinal fasciculus, and the internal and external capsule. This finding suggests that gait decline under DT conditions is associated with widespread microstructural changes in cerebral WM in middle-aged and older adults. Previous DTI studies demonstrated similar findings in patients with amyotrophic lateral sclerosis (Pettit et al., 2013) and multiple sclerosis (Ruggieri et al., 2018), as well as individuals with mild cognitive impairment (Snir et al., 2019). WMI in these pathways is also associated with habitual gait speed in healthy older adults (Poole et al., 2018).

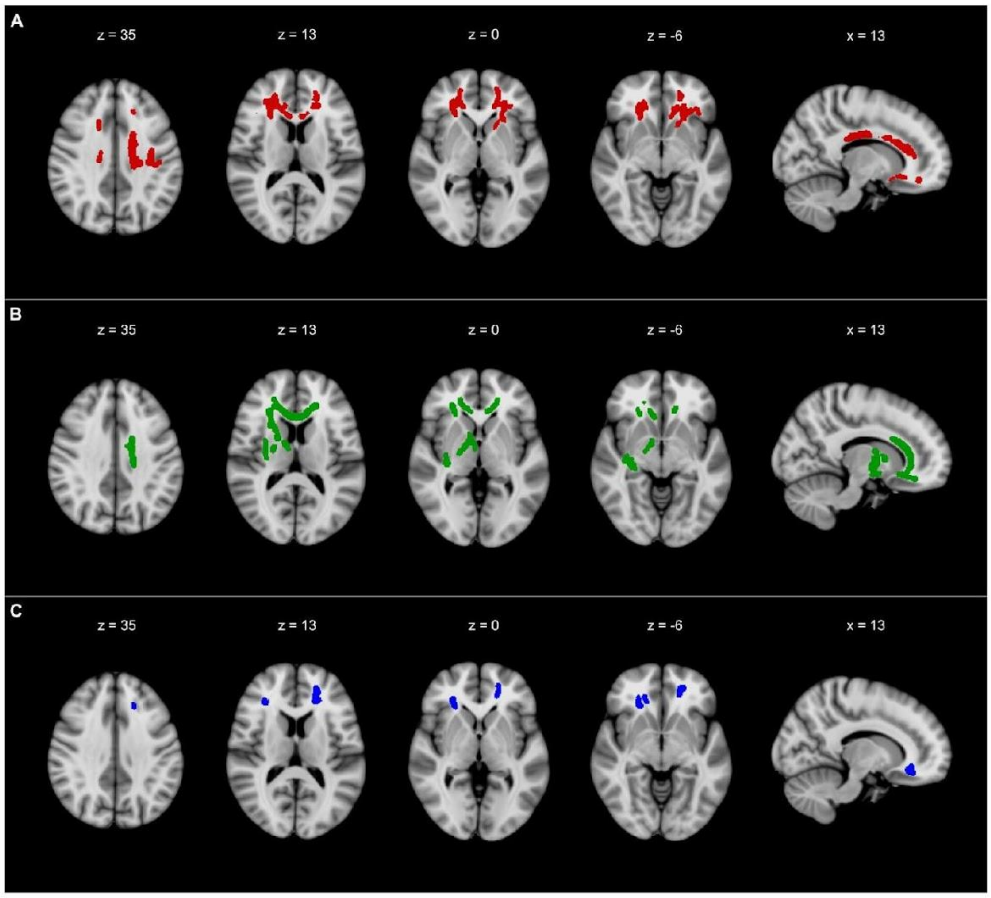

FIGURE 1
The results of TBSS whole-brain correlation analysis overlaid on MNI-152 T1 (1 mm) template and presented in radiological convention. **(A)** Negative correlation between FA and DTC of gait speed while subtracting. **(B)** Positive correlation between FA and DT gait speed while subtracting. **(C)** Positive correlation between FA and DT subtracting speed while walking. All TBSS results were thickened to improve visualization and are presented with a threshold of $p < 0.0125$ corrected for multiple comparisons. TBSS, tract-based spatial statistics; FA, fractional anisotropy; DT, dual-task; DTC, dual-task costs; x, x-coordinate; z, z-coordinate. Detailed description of the significant clusters, including cluster sizes and correlation coefficients, can be found in **Table 3**.

The strongest correlations with FA were found in the corpus callosum and anterior corona radiata. The corpus callosum is a hub for interhemispheric communication to relay motor and cognitive information (Van Der Knaap and Van Der Ham, 2011). Evidence from earlier studies suggests that WMI in the corpus callosum is essential for maintaining gait under ST (Bhadelia et al., 2009; Poole et al., 2018; Snir et al., 2019) and DT conditions (Pierpaoli and Basser, 1996), in addition to its important role in EF (Halliday et al., 2019). Similarly, the ACR is a pathway known for its crucial role in maintaining adequate DT performance (Pettit et al., 2013; Ruggieri et al., 2018; Snir et al., 2019). Furthermore, the ACR is also involved in key components of EF, i.e., working memory and cognitive flexibility (Schmahmann et al., 2009; Macpherson and Hikida, 2019). This pathway is a part of the basal ganglia-thalamocortical circuitry connecting the prefrontal cortex (PFC) and the anterior cingulate cortex with subcortical structures, such as the thalamus and the basal ganglia. Interestingly, a recent paper revealed a positive association between DTC of gait speed and gray matter volume in the PFC and the cingulate cortex in a cohort of 139 healthy older adults (mean age = 75 years) (Tripathi et al., 2019). The authors interpreted their findings as an increased importance of these regions as DT performance worsens, e.g., as a compensatory mechanism. Another study investigating 55 healthy older adults (mean age = 75 years) showed that lower gray matter volume in frontal areas leads to over-activation of the frontal lobe during a cognitively demanding walking task, which supports the notion of neural inefficiency in aging (Wagshul et al., 2019). Numerous studies measured brain activity using different techniques and reported

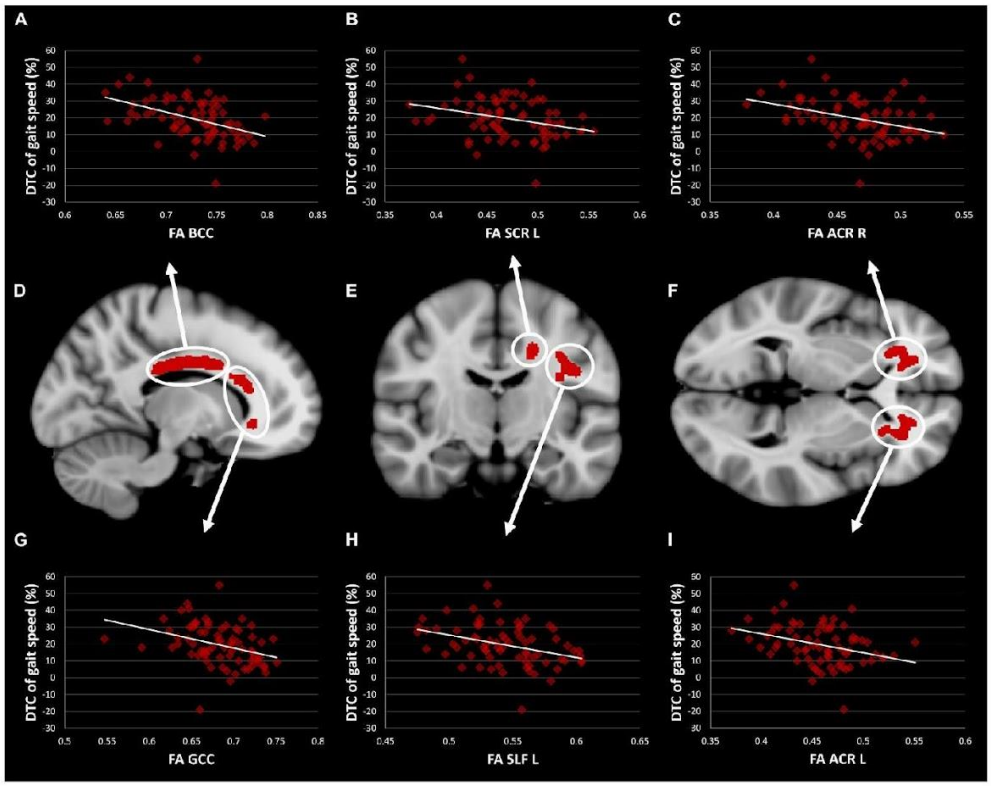

FIGURE 2
TBSS Clusters with a significant correlation between DTC of gait speed while subtracting and FA **(D–F)** displayed on T1 MNI-152 template (1 mm). Scatter plots showing a correlation between FA and DTC of gait speed while subtracting in body **(A)** and genu **(G)** of the corpus callosum, left superior corona radiata **(B)**, left superior longitudinal fasciculus **(H)**, right **(C)** and left **(I)** anterior corona radiata. TBSS, tract-based spatial statistics; FA, fractional anisotropy; DTC, dual-task costs; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; ACR, anterior corona radiata; SCR, superior corona radiata; SLF, superior longitudinal fasciculus.

increased brain activity in these regions for gait under DT conditions compared to ST conditions (Leone et al., 2017). The increased neural activity also compensates for prefrontal WM deterioration, i.e., less wiring and more firing (Daselaar et al., 2015; Lucas et al., 2019). With respect to these studies, our findings highlight the importance of frontal regions in maintaining gait under DT conditions. However, DTC of gait speed might be more sensitive to WM alterations, as gray matter areas can functionally and/or structurally compensate for changes in DTC of gait speed.

Corresponding to the results of the DTC of gait speed, our exploratory analysis of the absolute DT parameters revealed a significant correlation between FA in predominantly frontal WM and the absolute parameters of gait speed and subtracting speed in DT conditions. Interestingly, the WM correlates of both the cognitive and the motor tasks in DT conditions overlapped in the ACR (**Figures 1B,C**), thus indicating that both the motor and the cognitive tasks share WM pathways. Some authors suggest that gait under challenging conditions requires the recruitment of additional mainly cognitive brain regions, most notably the PFC, which becomes increasingly difficult with aging (Boisgontier et al., 2013). As previously mentioned, the ACR represents the primary connections of the PFC, thereby concurring with previous findings. However, some pathways correlated significantly with DT gait speed but not with DT subtracting speed, including the corpus callosum and the internal and external capsule. In light of these findings, gait decline under DT conditions might only partially be explained by the deterioration of shared WM pathways.

Our group comparison demonstrated a markedly lower FA in the left ACR in the poor and intermediate TMT groups compared to the good TMT group. Similar patterns were observed in the other WM regions associated with increased DTC of gait speed; however, they did not reach statistical significance. This result concurs with a previous study demonstrating an association between damage to left-lateralized frontal areas and EF deficits on four neuropsychological tests (including TMT) (Barbey et al., 2012).

TABLE 3 Group differences in clusters with a significant partial correlation between dual-task parameters and FA adjusting for age, gender, and hypertension.

Parameter	Region	Cluster size (voxels)	*r*/*p*	FA				*p*
				Whole cohort	Good TMT	Intermediate TMT	Poor TMT	
DTC of gait speed while subtracting	GCC	309	−0.40/0.0006	0.683 ± 0.004	0.692 ± 0.005	0.681 ± 0.007	0.667 ± 0.012	0.188
	BCC	1073	−0.47/0.00003	0.727 ± 0.004	0.736 ± 0.005	0.724 ± 0.008	0.715 ± 0.009	0.184
	ACR L	631	−0.41/0.0003	0.458 ± 0.004	0.473 ± 0.005	0.451 ± 0.008	0.442 ± 0.008	0.008*
	ACR R	693	−0.44/0.0001	0.466 ± 0.004	0.475 ± 0.005	0.462 ± 0.008	0.457 ± 0.008	0.308
	SCR L	267	−0.36/0.002	0.471 ± 0.005	0.484 ± 0.005	0.467 ± 0.009	0.454 ± 0.009	0.096
	SLF L	190	−0.39/0.0008	0.543 ± 0.004	0.552 ± 0.005	0.535 ± 0.007	0.539 ± 0.008	0.162
	SCC	29	−0.36/0.01	0.843 ± 0.004	0.845 ± 0.005	0.838 ± 0.007	0.846 ± 0.011	0.697
	ALIC L	18	−0.28/0.02	0.468 ± 0.007	0.475 ± 0.012	0.472 ± 0.012	0.450 ± 0.017	0.546
	CG L	12	−0.35/0.003	0.628 ± 0.007	0.631 ± 0.012	0.619 ± 0.011	0.635 ± 0.013	0.359
	EC L	15	−0.28/0.02	0.481 ± 0.004	0.480 ± 0.007	0.482 ± 0.007	0.482 ± 0.010	0.587
	EC R	23	−0.41/0.0004	0.450 ± 0.004	0.450 ± 0.006	0.450 ± 0.006	0.454 ± 0.009	0.338
	SCR R	13	−0.20/0.09	0.444 ± 0.007	0.460 ± 0.009	0.434 ± 0.012	0.430 ± 0.015	0.186
DT gait speed while subtracting	GCC	864	0.47/0.00004	0.725 ± 0.004	0.730 ± 0.005	0.727 ± 0.006	0.715 ± 0.010	0.480
	BCC	823	0.46/0.00006	0.727 ± 0.004	0.734 ± 0.005	0.726 ± 0.009	0.713 ± 0.009	0.306
	ACR L	364	0.37/0.002	0.483 ± 0.005	0.497 ± 0.006	0.477 ± 0.009	0.467 ± 0.011	0.065
	ACR R	699	0.46/0.00005	0.500 ± 0.004	0.503 ± 0.005	0.501 ± 0.007	0.492 ± 0.007	0.875
	SCR L	151	0.36/0.002	0.501 ± 0.005	0.511 ± 0.006	0.498 ± 0.010	0.483 ± 0.009	0.257
	ALIC R	213	0.38/0.001	0.645 ± 0.004	0.640 ± 0.006	0.650 ± 0.006	0.647 ± 0.008	0.627
	EC R	247	0.45/0.00007	0.504 ± 0.003	0.514 ± 0.004	0.495 ± 0.006	0.497 ± 0.007	0.021
	RIC R	26	0.30/0.01	0.601 ± 0.004	0.608 ± 0.007	0.598 ± 0.008	0.589 ± 0.009	0.493
	SCR R	352	0.46/0.00006	0.575 ± 0.003	0.583 ± 0.004	0.566 ± 0.005	0.573 ± 0.007	0.022
	PLIC R	272	0.37/0.001	0.690 ± 0.003	0.690 ± 0.005	0.688 ± 0.006	0.695 ± 0.007	0.811
	SS R	14	0.25/0.04	0.574 ± 0.006	0.585 ± 0.009	0.559 ± 0.011	0.574 ± 0.011	0.139
	FST R	39	0.30/0.01	0.608 ± 0.006	0.612 ± 0.007	0.619 ± 0.011	0.584 ± 0.010	0.274
	CG L	43	0.35/0.003	0.634 ± 0.006	0.638 ± 0.009	0.632 ± 0.011	0.631 ± 0.012	0.551
DT subtracting speed while walking	ACR L	174	0.44/0.0001	0.438 ± 0.005	0.447 ± 0.007	0.435 ± 0.009	0.424 ± 0.010	0.354
	ACR R	166	0.51/0.00001	0.514 ± 0.004	0.521 ± 0.004	0.512 ± 0.009	0.504 ± 0.009	0.488

All values are expressed as the mean ± standard error. FA, fractional anisotropy; TMT, trail making test; DT, dual-task; DTC, dual-task costs; GCC, genu of the corpus callosum; BCC, body of the corpus callosum; SCC, splenium of the corpus callosum; ACR, anterior corona radiata; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; ALIC, anterior limb of the internal capsule; RIC, retroarticular part of the internal capsule; PLIC, posterior limb of the internal capsule; CG, cingulum (cingulate gyrus); EC, external capsule; SS, sagittal stratum; FST, fornix/stria terminalis. Only clusters with a voxel size > 5 are presented. *Significantly higher FA value in the good TMT group compared to the intermediate ($p < 0.05$) and poor TMT groups ($p < 0.01$).

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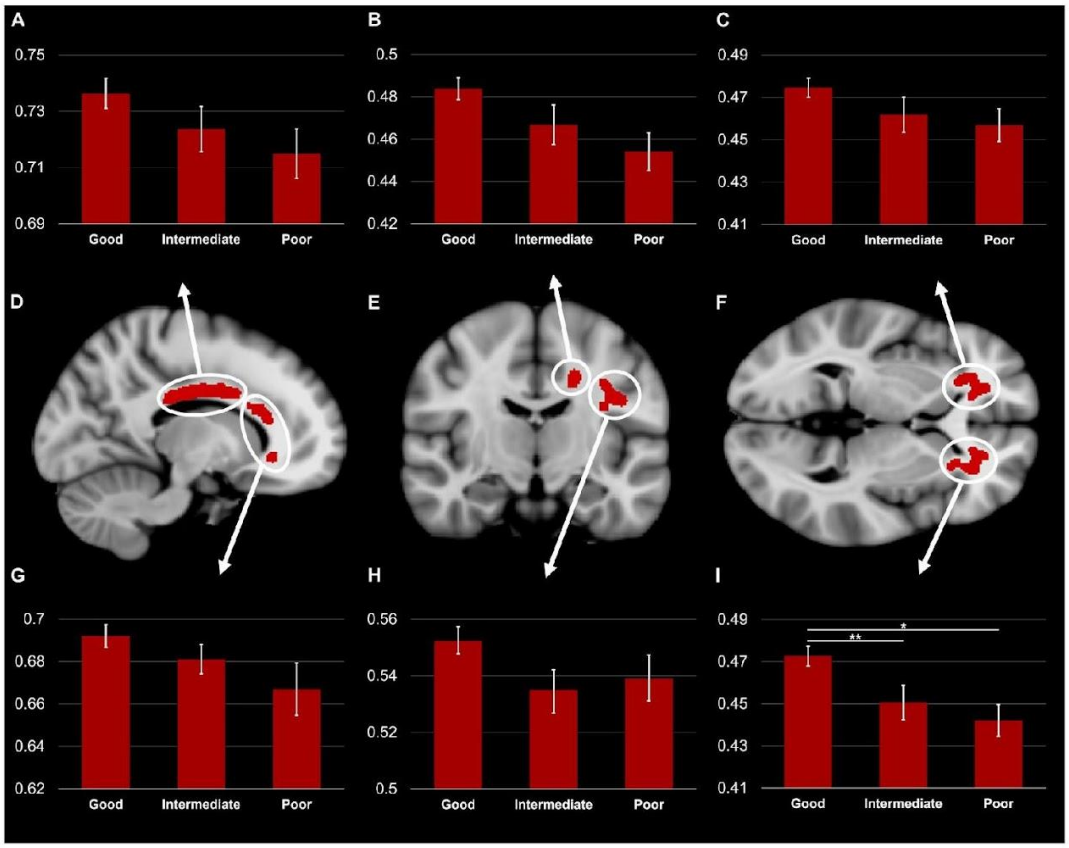

FIGURE 3
TBSS Clusters with a significant correlation between DTC of gait speed while subtracting and FA **(D–F)** displayed on T1 MNI-152 template (1 mm). Group comparison of FA in body **(A)** and genu **(G)** of the corpus callosum, left superior corona radiata **(B)**, left superior longitudinal fasciculus **(H)**, right **(C)** and left **(I)** anterior corona radiata. Error bars represent standard error of the mean. TBSS, tract-based spatial statistics; FA, fractional anisotropy; DTC, dual-task costs. *Significant difference between the good and poor TMT groups ($p < 0.01$). **Significant difference between the good and intermediate TMT groups ($p < 0.05$).

While it may be intriguing to assume a direct relationship between low EF and increased DTC of gait speed based on shared substrates, the correlation analysis we ran between TMT B-A and DTC of gait speed revealed an insignificant and weak positive correlation ($p = 0.1$, $r = 0.18$). Furthermore, our mediation analysis did not reveal any significant results. In other words, TMT B-A performance did not mediate the effects of FA on DTC of gait speed.

A similar imaging study revealed a significant correlation between TMT B-A and normal gait speed but not with the DTC of gait speed. However, the authors reported an association between DTC of gait speed and episodic memory performance, implying that ST and DT gait are supported by different brain networks (Tripathi et al., 2019). However, this finding has not been replicated and contradicts the findings of many clinical studies. It is also plausible that these inconsistent results are due to the relatively small sample size in MRI studies, as a related clinical study from TREND with a much larger sample size ($N = 661$) revealed a highly significant and slightly stronger correlation between TMT B-A and DT gait speed while subtracting ($p < 0.0001$, $r = 0.27$) (Hobert et al., 2017). In addition to the well-recognized critical role of EF in complex gait situations, e.g., walking over an obstacle course (Ble et al., 2005) or walking under DT conditions (Yogev-Seligmann et al., 2008; Hobert et al., 2017). Nevertheless, EF is only one factor affecting a complex multifactorial mechanism such as gait (Jayakody et al., 2018), especially under DT conditions, which could also explain the relatively weak correlation in our study.

It is worth mentioning that despite the apparent difference in FA values across the groups in clusters associated with DTC of gait speed, only a slight gradual increase in the DTC value between the good TMT (18%), intermediate TMT (20%), and poor TMT groups (22%) was observed, although it was not statistically significant. While this may contradict one of

the most cited papers regarding the association between EF and gait in complex situations (Ble et al., 2005), the authors used much higher TMT B-A thresholds in older subjects (mean age = 75 years); some of whom have global cognitive impairment. As a result, we conclude that an association between DTC of gait speed and EF might only be apparent with a high degree of EF impairments and/or global cognitive impairments.

Interestingly, two recent studies provide a plausible explanation for this phenomenon, as they have shown that compromised WM microstructural integrity (Lucas et al., 2019) and reduced frontal gray matter volume (Wagshul et al., 2019) were accompanied by an increase in oxygenated hemoglobin in the PFC during dual-task walking. This could be able to, at least partly, compensate for the increasing cognitive demands of locomotion and perhaps decrease gait deterioration under DT conditions. It is worth mentioning that some studies have found an association between DTC and other cognitive functions, namely episodic (Montero-Odasso et al., 2014) and working memory (Montero-Odasso et al., 2009), suggesting the potential involvement of temporal regions. Accordingly, future studies should investigate the structural correlates of DTC and their association with multiple cognitive domains. In summary, this result suggests that EF and gait performance in DT conditions share common neural substrates. However, the effect of WM alterations on DT gait impairments might be compensated by other mechanisms in the early stages of cognitive impairments.

Even though our cohort did not have any significant gait impairments, their gait performance declined under the more challenging DT conditions, as measured by DTC. Moreover, gait decline was associated with a lower FA value, i.e., lower WMI, in widespread WM pathways. Our findings thus suggest that the decrement of gait performance under DT conditions could be an early sign of WM deterioration. In this regard, testing DTC of gait might be of clinical importance in the aging population, as it provides opportunities for early therapeutic, preventive, and behavioral interventions.

This study has some limitations. For example, the study did not include T2-FLAIR images to estimate the burden of microvascular associated WM changes, i.e., WM hyperintensities, which can influence DTI measures such as FA (Vangberg et al., 2019), and have also been associated with gait impairments (Bolandzadeh et al., 2014), and executive dysfunction (Murray et al., 2010) in community-dwelling older adults. Nevertheless, our cohort exhibits a relatively low cardiovascular burden, corresponding to normal aging in this age group.

Furthermore, we assessed the effects of only one secondary cognitive task on gait impairments under dual-tasking. Existing evidence suggests that different cognitive tasks involving internal interfering factors (e.g., mental tracking and verbal fluency tasks) disturb gait and posture equally, regardless of their nature (Bloem et al., 2003; Al-Yahya et al., 2011). A DTI study revealed distinct WM correlates of gait speed under dual-tasking conditions depending on the nature of the paired cognitive task (subtracting 7s, counting, naming animals) (Snir et al., 2019). This could, however, be a consequence of using a fairly unspecific parameter that does not take into account task prioritization, i.e., "walking speed while dual-tasking," instead of the more specific parameter we applied here: DTC of gait speed. Additionally, we only evaluated the gait parameter gait speed and did not consider DTC changes related to other gait parameters. While other gait parameters, such as stride length and cadence, are also susceptible to dual-task-related changes, gait speed appears to be the most sensitive parameter to these changes and also the most utilized gait parameter in DT studies (Al-Yahya et al., 2011).

Conclusion

Our findings indicate that gait decline under DT conditions is an early sign of WM deterioration, even in middle-aged and older adults without any significant gait or cognitive impairments. Some of the affected WM pathways were shared between the cognitive and motor tasks, indicating that gait decline under DT conditions might be partially explained by the deterioration of shared WM pathways. However, this relationship was not mediated by EF.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the University of Tübingen (Nr. 90/2009BO2 and 370/2013BO2). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HA, MH, and TE contributed to the conception and design of the study. DB, KS, TE, MH, and WM organized the study.

HA performed data analysis and wrote the first draft. BK and ME provided analysis tools. MH and TE wrote sections of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Funding

We acknowledge support by the Open Access Publishing Fund of the University of Tübingen. The TREND-Study was supported by the UCB, Teva, Janssen, Werner Reichardt Centre for Neuroscience, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Internationale Parkinson Fonds Deutschland, Hertie-Institut für klinische Hirnforschung and the University of Tübingen.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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3. Discussion

In the present cumulative dissertation, a voxel-wise DTI analysis was used to investigate 1. the presence of WM alterations in individuals with risk factors for neurodegenerative diseases, more specifically Parkinson's disease, and their association with specific cognitive impairments (1st publication), as well as 2. the association between WM alterations and specific gait and cognitive impairments in community-dwelling older adults (2st publication). The following main results were found:

- Individuals with risk factors for PD did not exhibit any statistically significant differences in DTI-parameters in the whole brain WM compared to controls. There was also no significant correlation between DTI-parameters and the severity of individual PD risk scores, i.e., depression (BDI-II-score), hyposmia (sniffin' sticks score) and RBD (RBDSQ-score). While individuals with risk factors for PD did not exhibit a reduced EF performance, based on Trail Making Test (TMT) B-A, there was a significant positive correlation between TMT B-A performance and the DTI-parameters MD and AD in frontoparietal pathways within the risk cohort, but not in the control group.

- Dual-task costs (DTC) of gait speed correlated significantly with FA in widespread pathways, including the corpus callosum, bilateral anterior and superior corona radiata, as well as the left superior longitudinal fasciculus. Gait speed and subtracting speed while dual-tasking correlated significantly with the FA in the bilateral anterior corona radiata (ACR). EF performance was associated with FA in the left ACR; however, EF did not significantly mediate the effects of WM integrity on DTC of gait speed.

3.1. White matter alterations and the risk of developing neurodegenerative disease

3.1.1. Absence of white matter alterations in PD-RP

A pivotal aspect of the findings is the absence of significant WM alterations when comparing PD-RP with healthy controls across the whole brain. This observation is crucial as it challenges some existing presumptions about the early manifestation of neurodegenerative changes in WM structures among PD-RP. In comparison, a study found increased MD in specific brain regions in PD-RP who presented with substantia nigra hyperechogenicity and/or hyposmia (Heldmann et al., 2018). The difference in findings might be attributed to the specific clinical features of the cohorts examined. In fact, the same study did not observe any difference between healthy controls and patients with PD, in contrast to PD-RP, attributing this to the higher rates of hyposmia in PD-RP compared to their PD-Group. The presence of hyposmia in a larger subset of the PD-RP group, as in Heldmann et al.'s study, might indicate more active or pronounced neurodegenerative processes that are detectable by DTI, suggesting that neurodegenerative patterns could vary substantially based on specific clinical presentations. Similarly, another study evaluated imaging abnormalities in prodromal and early-stage PD based on the presence of RBD and found differing disease trajectories in idiopathic RBD and PD patients with RBD compared to those without RBD, suggesting the existence of different disease subtypes (Horsager et al., 2020). As such, the lower prevalence of hyposmia (28%) in our PD-RP cohort might explain our inability to detect notable differences at the group level, illustrating how variations in clinical presentations within at-risk groups can crucially influence neuroimaging outcomes.

Building upon the exploration of potential explanations for the negative results of our study, another intriguing perspective involves the concept of compensatory mechanisms in PD-RP. For instance, a study focusing on LRRK2 mutation carriers, an asymptomatic cohort recognized as having a heightened risk of PD, did not uncover any significant structural brain changes using DTI and voxel-based morphometry (Avner Thaler et al.,

2014). However, this study revealed an intriguing trend of higher FA and lower MD in the mutation carriers, which is particularly striking as it contradicts the typical neurodegenerative pattern of lower FA and higher MD. Together with results from fMRI studies that showed an increased functional connectivity in mutation carriers (A. Thaler et al., 2013; van Nuenen et al., 2012), these findings suggest the activation of compensatory neural mechanisms that may help maintain normal function despite underlying pathological changes. This phenomenon aligns with findings from another study utilizing graph theory, which demonstrated greater local connectivity in regions associated with motor, olfactory, and sleep functions in PD-RP, which might also suggest neural compensation during the prodromal phase (Wen et al., 2017).

Following the observation of no significant WM alterations in PD-RP, our study further explored the relationship between DTI-measures and the severity of employed risk factors, specifically evaluating the olfactory score, RBDSQ and BDI-II. Contrary to our expectations and previous research, we found no correlation between these risk scores and DTI-measures. Previous studies have identified structural correlates between olfactory score, RBDSQ, and brain structure within PD-RP cohorts (Heldmann et al., 2018; Wen et al., 2017). Specifically, one study observed reduced structural connectivity between the supplementary motor area and the putamen correlating with the severity of RBD symptoms (Wen et al., 2017). Similarly, another study found that higher degrees of hyposmia were associated with reduced microstructural integrity in the cerebrospinal tract and the thalamus (Heldmann et al., 2018).

The absence of similar correlations in our study could be attributed to several factors. One potential explanation is the lower prevalence of pronounced risk factors such as hyposmia and RBD within our cohort. If fewer individuals exhibit high severity of these symptoms, it might reduce our study's power to detect significant correlations across the group. This is especially relevant in neurodegenerative conditions like PD, where the heterogeneity of symptom presentation can greatly influence the outcomes of population-based analyses.

3.1.2. Association Between executive function and white matter integrity in PD-RP

There is evidence of cognitive impairments in PD-RP, with a recent review highlighting that EF are particularly affected (Fengler et al., 2017). Motivated by these findings, our aim was to delve into the neurobiological correlates of these EF deficits, seeking a deeper understanding of the underlying mechanisms contributing to cognitive decline in PD-RP. We employed the TMT B-A, a well-established measure of EF, particularly cognitive flexibility (Sánchez-Cubillo et al., 2009). In exploring PD-RP, our study brought to light intriguing findings about the neurobiological underpinnings of cognitive impairments. Notably, the analysis identified a significant correlation between performance on the TMT B-A and MD across several key neural pathways for EF, including the superior longitudinal fasciculus, corpus callosum, and corona radiata.

This correlation is particularly interesting, as no significant effects for FA were noted. The observed pattern of MD alterations preceding changes in FA aligns with trends identified in PD-RP (Heldmann et al., 2018) and early-stage PD (Duncan et al., 2016; Melzer et al., 2013), indicating a progressive microstructural degradation that may start with subtle diffusivity changes before more evident anisotropy alterations emerge. A similar correlation pattern was also observed between TMT B-A and AD in PD-RP. While the mechanisms driving AD elevation are not fully understood, it has been implicated as a state-specific highly sensitive marker for early neurodegeneration and cognitive impairment, potentially linked to mechanisms like inflammation that precede overt axonal damage (Acosta-Cabronero, Alley, Williams, Pengas, & Nestor, 2012; Molinuevo et al., 2014). Moreover, the lack of a correlation with FA contrasts with previous studies on aging that demonstrated a positive correlation between FA and EF (Halliday, Gawryluk, Garcia-Barrera, & MacDonald, 2019; Perry et al., 2009), suggesting that distinct WM pathologies are responsible for cognitive impairments related to healthy aging and PD. This discrepancy is especially significant given that the correlation was observed only in PD-RP and not in controls, indicating a specific vulnerability in this group to the type of WM deterioration associated with executive dysfunction. The unique neurobiological profile of PD-RP suggests that even minor lapses in EF might be rooted in early neurodegenerative processes, a notion supported

by similar observations in traumatic brain injury research where specific cognitive deficits align closely with WM pathologies in affected individuals (Kinnunen et al., 2011).

The engagement of the frontoparietal network, as observed through our DTI-metrics, aligns with its well-documented role in mediating EF (Collette, Hogge, Salmon, & Van der Linden, 2006). The findings from our study are corroborated by previous imaging research, which illustrates how disruptions in this network's integrity are pivotal in the cognitive decline seen in neurodegenerative conditions such as PD (Lewis, Dove, Robbins, Barker, & Owen, 2003; Melzer et al., 2013). The observed microstructural alterations in the corpus callosum further suggest a pattern of intra- and interhemispheric disconnection, potentially contributing to the observed EF impairments (Bledsoe, Stebbins, Merkitch, & Goldman, 2018; Zheng et al., 2014).

Despite these findings, PD-RP did not exhibit discernible differences in their TMT B-A performance compared to the control group. This aligns with other imaging studies that similarly failed to reveal cognitive deficits in PD-RP cohorts (Heldmann et al., 2018; Wen et al., 2017). One plausible explanation for this could be neural compensation, as fMRI studies in LRRK2 mutation carriers reported increased task-related activity in various cerebral regions while maintaining adequate EF performance (Bregman et al., 2017; A. Thaler et al., 2013). However, it's important to note that a review suggested the presence of EF impairments in prodromal PD (Fengler et al., 2017), indicating the need for prospective longitudinal studies to ascertain the role of cognitive changes as a reliable biomarker for prodromal PD.

In summary, our study did not find evidence of reduced WM integrity or impaired EF in PD-RP, arguing against the utility of DTI and TMT B-A as biomarkers for the prodromal phase of PD. However, DTI did reveal frontoparietal WM alterations in association with EF, specifically cognitive flexibility, exclusively in PD-RP. This suggests that EF deficits in PD-RP may have a stronger association with white matter alterations than in healthy older adults. This finding together with the absence of a discernible difference in EF between PD-RP and healthy controls may indicate the presence of compensatory

mechanisms in the former group, warranting further investigation into neural compensation strategies in prodromal PD.

3.2. White matter alterations and gait impairments in the aging population

Building on the findings from our initial research, which revealed a relationship between EF deficits and WM alterations in PD-RP (Alzaid et al., 2020), we extended our analysis to focus on cognitive-motor dual-tasking. This analysis encompassed both the PD-RP and the control group, considering that PD-RP, while at risk, have not been clinically diagnosed with a neurodegenerative disease. Notably, all participants were community-dwelling older adults with no significant gait or cognitive impairments, thus providing a baseline for assessing subtle, subclinical changes.

Gait impairments, although common in this age group, are often not apparent due to compensatory strategies that mask their presence. To reveal potential hidden gait impairments, we tested gait under cognitively demanding conditions, particularly cognitive-motor dual-tasking. The analysis focuses on DTC of gait speed, as in the measure of change in DT compared to ST. Positive DTC describe a deterioration in DT, and negative DTC describe an improvement in DT compared to ST. Since gait under DT conditions are particularly common in older adults with EF impairments, we therefore explored the relationship between these gait impairments, EF and WM integrity

Given that dual-task gait deficits are frequently observed in neurodegenerative diseases and mild motor symptoms alongside EF impairments are among the early signs of PD, this approach could prove essential in the early detection of neurodegenerative conditions. The assessment of gait under dual-task conditions as well as EF helps to highlight potential degradation in shared WM pathways that support both functions, offering valuable insights into early patterns of neurodegeneration.

3.2.1. Dual-task gait impairments as a sign of white matter deterioration

We demonstrated that the DTC of gait speed is negatively correlated with FA, primarily in frontoparietal pathways, including the corona radiata, corpus callosum, superior longitudinal fasciculus, as well as the internal and external capsules. Similar patterns have been observed in previous DTI studies involving neurological conditions such as amyotrophic lateral sclerosis, multiple sclerosis, and mild cognitive impairment. However, our findings indicate that gait decline under dual-task conditions is linked to a widespread reduction in WM integrity, even among middle-aged and older adults with no significant gait or cognitive impairments. This aligns with large-scale clinical studies that show dual-task gait performance begins to deteriorate in the sixth decade of life. Based on these findings, testing gait under dual-task conditions can serve as a sensitive method for detecting early neurodegeneration, potentially making it a valuable tool for the early detection of neurodegenerative diseases.

The most notable correlations with FA were observed in the corpus callosum and ACR, which are crucial for relaying motor and cognitive information across hemispheres and supporting gait stability during both single and dual-task activities. The ACR is also integral to EF and plays a vital role in dual-task performance due to its involvement in the basal ganglia-thalamocortical circuitry, linking the PFC and anterior cingulate cortex with subcortical regions. Moreover, evidence suggests that as the structural integrity of these pathways degrades, compensatory mechanisms may increase WM volume (Tripathi, Verghese, & Blumen, 2019) and brain activity (Wagshul, Lucas, Ye, Izzetoglu, & Holtzer, 2019) in the prefrontal and anterior cingulate cortices. This compensatory response helps sustain gait performance under DT conditions amidst early degeneration of WM (Lucas, Wagshul, Izzetoglu, & Holtzer, 2019), emphasizing the pivotal role of frontal brain regions in managing dual-task challenges. Consequently, subtle gait abnormalities, such as increased DTC of gait speed might be a more sensitive indicator to WM rather than GM alterations, as GM areas are able to functionally and/or structurally compensate for changes in DTC of gait speed. Considering that microstructural disruption of WM may precede GM atrophy (Hong et

al., 2016), these findings highlight the usefulness of DTI in investigating early neurodegeneration.

In addition to our primary analysis of WM correlates of DTC of gait speed, we conducted an exploratory analysis of the absolute DT parameters of both the cognitive and motor tasks, i.e. gait and subtraction speed. This investigation aimed to explore the potential involvement of shared WM pathways between both tasks. Notably, our analysis revealed a significant correlation between FA in predominantly frontal WM and the absolute parameters of gait speed and subtracting speed in DT conditions. Interestingly, the WM correlates of both the cognitive and the motor tasks in DT conditions overlapped in the ACR, indicating shared WM pathways between these tasks. This result is particularly interesting as the ACR represents the primary connections of the PFC, with evidence showing that gait under challenging conditions requires the recruitment of additional cognitive brain regions, especially the PFC. This adaptive strategy becomes increasingly difficult with aging as neurodegeneration progresses (Boisgontier et al., 2013). As such, gait decline under DT conditions might only partially be explained by the deterioration of shared WM pathways, possibly hindering the brain's ability to recruit additional cognitive resources.

3.2.2. Link between gait and executive function

Given the recognized impact of EF on gait (Yogev-Seligmann et al., 2008) and our observation of an association between the DTC of gait speed and the microstructural integrity of frontoparietal WM pathways, indicative of the executive network, we proceeded to explore this relationship further. To achieve this, we divided the entire cohort into three groups based on their TMT B-A performance and compared the FA values among these groups in regions significantly linked to the DTC of gait speed. Our group analysis revealed decreased FA in most of the aforementioned regions, with statistical significance observed particularly in the left ACR when comparing the poor and intermediate TMT groups with the good TMT group. This finding concurs with a prior investigation demonstrating a connection between damage to left-lateralized frontal areas and EF deficits across various neuropsychological tests, including the TMT

(Barbey et al., 2012). Although the causal link between EF and gait remains uncertain, our findings hint at EF potentially mediating the impact of WM degeneration on gait. However, our complementary mediation analysis failed to produce significant results, and we found no notable correlation between TMT B-A performance and DTC of gait speed.

In light of the cohort's lack of significant cognitive impairments, we opted for relatively lenient thresholds on the TMT to categorize groups based on their EF performance (Hobert et al., 2017). Consequently, we observed no notable difference in the DTC of gait speed between these groups, contrasting with findings from previous studies involving older and more severely impaired cohorts, which displayed markedly worse TMT performance (Ble et al., 2005). Thus, our results suggest that despite the well-documented influence of EF on DTC of gait speed, this association may only become evident in the presence of considerable EF impairments and/or global cognitive deficits. Moreover, considering evidence indicating an increase in oxygenated hemoglobin in the PFC during dual-task walking alongside compromised WM microstructural integrity (Lucas et al., 2019) and reduced frontal WM volume (Wagshul et al., 2019), it appears that the brain's ability to recruit additional cognitive resources from the PFC could offer a plausible explanation for this phenomenon.

3.3. Limitations

The study utilized three relatively unspecific risk factors: hyposmia, history of depression, and RBD-diagnosis based on RBDSQ. The latter, while useful as a screening tool, primarily serves as an initial assessment and may not reliably differentiate RBD from other conditions such as sleepwalking or epilepsy (Stiasny-Kolster et al., 2007). Importantly, its positive likelihood ratio for predicting PD is only 2.8, compared to a much higher likelihood ratio of 130 when using polysomnography-proven RBD as a marker (Heinzel et al., 2019). Although hyposmia exhibits a higher positive likelihood ratio of 6.4 for predicting PD (Heinzel et al., 2019), it is still considered nonspecific as it can also manifest in other neurodegenerative diseases or result from

trauma or sinus infections (Barresi et al., 2012; Saltagi et al., 2021). Moreover, with over 80% of our cohort having experienced at least one depressive episode and given the notably low positive likelihood ratio of 1.6 for depression as a predictor of PD (Heinzel et al., 2019), distinguishing whether the neuroimaging changes observed are indicative of neurodegenerative processes or merely residual effects of depression becomes particularly challenging. Using these less specific markers might not provide a comprehensive view of an individual's risk of developing PD. However, this approach allows us to examine whether brain alterations are also detectable with less specific risk factors, compared to already established risk factors like polysomnography-proven RBD (Unger et al., 2010), thereby expanding the scope early detection of neurodegenerative diseases. This can be particularly useful in broader clinical settings where more specific, expensive diagnostic tools, such as polysomnography might not be available. Future studies could benefit from adopting a more holistic approach by integrating multiple risk factors into a cumulative score. This could enhance the specificity and sensitivity of risk predictions, offering a more robust framework for identifying individuals at higher risk of developing PD (Berg et al., 2015).

The inability to detect significant differences in WM integrity between the PD-RP group and controls may suggest limitations in the sensitivity of standard DTI model used in our study. More advanced neuroimaging techniques, such as Neurite Orientation Dispersion and Density Imaging, might offer higher sensitivity for detecting subtle neurodegenerative changes that DTI fails to capture (Chouliaras & O'Brien, 2023). Employing more refined imaging modalities could potentially aid in the early detection of neurodegenerative diseases.

Another limitation of this study is the limited range of cognitive and gait parameters analysed. Specifically, we only assessed cognitive flexibility as a measure of EF, which might not adequately capture the full spectrum of cognitive impairments associated with PD or other neurodegenerative diseases. This narrow focus may constrain our understanding of the associations between WM changes and other cognitive domains, such as memory, which are likely to be affected as well (Fengler et al., 2017). Similarly,

the only gait parameter assessed in the DT trial was gait speed. Future research should incorporate a more comprehensive battery of cognitive and gait tests. This expanded approach would enable a more detailed examination of the relationships between neuroimaging markers and the various aspects of cognitive and gait decline, thereby enhancing early detection of neurodegenerative diseases.

3.4. Conclusion

The findings of the present studies reveal an interplay between WM integrity and both motor and cognitive deficits in the aging population. While DTI did not reliably differentiate between PD-RP and healthy controls based on risk factors alone, it successfully identified an association between WM alterations and EF deficits within the PD-RP group. Moreover, we observed that gait decline under dual-task conditions is a significant indicator of WM deterioration, evident even in community-dwelling older adults without apparent cognitive or motor impairments. This gait decline is likely interconnected with impairments in EF, reflecting degeneration in common WM pathways that support both gait and EF. These findings highlight the potential of using EF and gait testing under dual-task conditions as tools for the early detection of neurodegenerative diseases. Furthermore, integrating DTI with these behavioural assessments provides valuable insights into subtle neurodegenerative changes, establishing DTI as an essential tool not only for detecting these changes but also for delineating the specific neural pathways involved. This approach enhances our ability to identify early neurodegenerative signs and could lead to more targeted interventions.

4. Summary

Neurodegenerative diseases progress slowly, often taking years before clinical diagnosis. In the prodromal phase preceding diagnosis, individuals may exhibit subtle signs of neurodegeneration, including gait and cognitive impairments. Identifying these early signs is crucial for effective intervention and disease management, as it provides valuable insights into early disease mechanisms. This dissertation employs DTI to explore the complex interplay among WM alterations, motor and cognitive deficits, and the risk of developing neurodegenerative disease in the aging population.

In the first analysis we focused on individuals with risk factors for PD (Parkinson's disease risk persons, PD-RP), specifically hyposmia, RBD and history of depression. The analysis revealed no significant differences in DTI-parameters across the whole-brain WM compared to the control group. Also, no correlation was found between DTI-parameters and the severity of the utilized risk factors. However, based on evidence of cognitive impairment in the prodromal phase of PD, particularly EF impairment, we conducted an additional correlation analysis between TMT B-A and DTI-parameters. Despite no significant difference in TMT between groups, a positive correlation between TMT B-A performance and DTI-parameters was observed in frontoparietal pathways within PD-RP group, indicating that deficits in EF in PD-RP might be more related to WM alterations than in healthy older adults.

The second analysis expanded upon the findings of the first and included both the PD-RP and the control group as a whole cohort. This approach was based on the fact that PD-RP, while at risk, have not been clinically diagnosed with a neurodegenerative disease. The cohort thus consisted of community-dwelling older adults with no significant gait or cognitive impairments. Given that gait deficits are common in the age group and can serve as an early indicator of neurodegeneration, albeit often concealed by compensatory strategies, we sought to uncover potential hidden impairments using cognitive-motor dual-tasking. Our investigation aimed to determine whether gait impairments under DT conditions were associated with WM alterations. Considering the

frequent occurrence of dual-task gait impairments in individuals with EF deficits and the presumed involvement of common cognitive-motor WM pathways, we also explored the role of EF and the possibility of shared WM pathways. The analysis revealed significant correlations between gait impairment under DT conditions and FA in widespread WM pathways. Moreover, the performance of motor and cognitive tasks under DT conditions correlated significantly with FA in the bilateral ACR. While EF performance was associated with FA in the left ACR, it did not effectively mediate the effects of WM integrity on DTC of gait speed.

In summary, the findings demonstrate an interplay between WM integrity and motor-cognitive deficits in aging. DTI did not differentiate PD-RP from controls based on risk factors alone, but revealed an association between WM alterations and EF deficits in PD-RP. Moreover, gait decline under DT conditions appears to be an early sign of WM deterioration, even in older adults without apparent cognitive or motor impairments. This can be partly attributed to the deterioration of shared WM pathways between the cognitive and motor tasks and pathways involved in EF. These insights highlight the utility of EF and DT gait testing for early neurodegenerative disease detection, with DTI offering crucial insights into early neurodegenerative changes and specific neural pathways involved.

5. Zusammenfassung (German summary)

Neurodegenerative Erkrankungen schreiten langsam voran und werden oft erst Jahre nach dem Beginn klinisch diagnostiziert. In der prodromalen Phase vor der Diagnose können Individuen subtile Anzeichen von Neurodegeneration zeigen, darunter Gang- oder kognitive Defizite. Die Identifizierung dieser frühen Anzeichen ist für eine wirksame Intervention und Krankheitsmanagement entscheidend, da sie wertvolle Einblicke in frühe Krankheitsmechanismen bietet. Diese Dissertation untersucht mit Hilfe von DTI das komplexe Zusammenspiel von Veränderungen der weißen Substanz, motorischen und kognitiven Defiziten sowie dem Risiko, eine neurodegenerative Krankheit zu entwickeln.

In der ersten Analyse konzentrierten wir uns auf Personen mit Risikofaktoren für die Parkinson-Krankheit (PD-RP), insbesondere Hyposmie, REM-Schlafstörung und Depression in der Vorgeschichte. Die Analyse ergab keine signifikanten Unterschiede in den DTI-Parametern der gesamten weißen Substanz im Vergleich zur Kontrollgruppe. Es wurde auch keine Korrelation zwischen den DTI-Parametern und der Schweregrad der verwendeten Risikofaktoren gefunden. Aufgrund von Hinweisen auf kognitive Beeinträchtigungen in der prodromalen Phase von Parkinson, insbesondere Beeinträchtigungen der exekutiven Funktionen, führten wir eine zusätzliche Korrelationsanalyse zwischen TMT und DTI-Parametern durch. Obwohl zwischen den Gruppen kein signifikanter Unterschied im TMT festgestellt wurde, wurde eine positive Korrelation zwischen der TMT-Leistung und den DTI-Parametern in frontoparietalen Bahnen innerhalb der PD-RP-Gruppe beobachtet, was darauf hindeutet, dass Defizite in den exekutiven Funktionen bei PD-RP stärker mit Veränderungen der weißen Substanz zusammenhängen als bei gesunden älteren Erwachsenen.

Die zweite Analyse erweiterte die Ergebnisse der ersten und umfasste sowohl PD-RP als auch die Kontrollgruppe als Gesamtkohorte. Dieser Ansatz berücksichtigte, dass PD-RP zwar einem Risiko ausgesetzt sind, jedoch noch keine klinische Diagnose einer neurodegenerativen Krankheit erhalten haben. Die Kohorte bestand somit aus

selbstständigen älteren Menschen, die keine signifikanten Gang- oder kognitiven Defizite aufwiesen. Angesichts der Tatsache, dass Gangdefizite in dieser Altersgruppe häufig auftreten und als früher Indikator für Neurodegeneration dienen können, jedoch oft durch Kompensationsstrategien verdeckt sind, versuchten wir, potenzielle verborgene Beeinträchtigungen mithilfe kognitiv-motorischer Dual-Task-Aufgaben aufzudecken. Unsere Untersuchung zielte darauf ab, festzustellen, ob Gangstörungen unter Dual-Task-Bedingungen mit Veränderungen der weißen Substanz verbunden waren. Angesichts des häufigen Auftretens von Dual-Task-Gangstörungen bei Personen mit EF-Defiziten und der vermuteten Beteiligung gemeinsamer kognitiv-motorischer WM-Bahnen haben wir auch die Rolle der EF und die Möglichkeit gemeinsamer WM-Bahnen untersucht. Die Analyse ergab signifikante Korrelationen zwischen Gangstörungen unter Dual-Task-Bedingungen und FA in weit verbreiteten WM-Bahnen. Darüber hinaus korrelierte die Leistung motorischer und kognitiver Aufgaben unter Dual-Task-Bedingungen signifikant mit FA in der bilateralen ACR. Während die EF-Leistung mit FA in der linken ACR assoziiert war, vermittelte sie nicht effektiv die Auswirkungen der Integrität der weißen Substanz auf die Gangstörung unter Dual-Task-Bedingungen.

Zusammenfassend zeigen die Ergebnisse ein Zusammenspiel zwischen WM-Integrität und motorisch-kognitiven Defiziten beim Altern. DTI unterschied PD-RP nicht allein anhand von Risikofaktoren von Kontrollen, sondern offenbarte eine Assoziation zwischen WM-Veränderungen und EF-Defiziten bei PD-RP. Zunehmende Gangstörung unter DT-Bedingungen ist ein frühes Anzeichen für eine WM-Verschlechterung, selbst bei älteren Erwachsenen ohne offensichtliche kognitive oder motorische Beeinträchtigungen. Dies kann teilweise auf die Verschlechterung gemeinsamer WM-Bahnen zwischen kognitiven und motorischen Aufgaben sowie Bahnen zurückgeführt werden, die an EF beteiligt sind. Diese Erkenntnisse unterstreichen die Nützlichkeit von EF- und DT-Gangtests für die frühzeitige Erkennung neurodegenerativer Erkrankungen, wobei die DTI wichtige Einblicke in frühe neurodegenerative Veränderungen und spezifische betroffene neuronale Bahnen bietet.

6. References

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7. Author contribution

The conception of the MRI study as part the TREND study was developed in collaboration by Prof. Thomas Ethofer, Prof. Klaus Scheffler, Prof. Daniela Berg and Prof. Walter Maetzler. Recruitment of the study participants was done by Dr. Markus Hobert, Prof. Daniela Berg and Prof. Walter Maetzler. Acquisition of MRI data was done by Prof. Thomas Ethofer and Dr. Michael Erb. For each publication I selected the specific methods and approach in cooperation with Prof. Thomas Ethofer. The majority of the data analysis for each publication was conducted by me, with assistance from Bernd Kardatzki and Dr. Michael Erb. Interpretation of the results was done in cooperation with Prof. Thomas Ethofer, Prof. Daniela Berg and Prof. Walter Maetzler for the first Publication, and also in cooperation with Markus Hobert for the second Publication. For each publication I wrote the first draft of the manuscript; Prof. Thomas Ethofer, Prof. Daniela Berg and Prof. Walter Maetzler revised the manuscripts; Markus Hobert revised the second manuscript.

8. Acknowledgements

I would like to express my gratitude to my advisor, Prof. Thomas Ethofer, for his invaluable guidance and support throughout the course of this research. I am also grateful to my lab colleagues, Bernd Kardatzki and Michael Erb, for their assistance throughout this project. Special thanks also go to our collaborators from the Department of Neurology at Kiel University Hospital: Daniela Berg, Walter Maetzler, and Markus Hobert, for their contribution to the project.