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Automatic Detection of Disorientation among People with Dementia

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If I have seen further it is by standing on the shoulders of Giants

Sir Isaac Newton (1642–1727)

Acknowledgments

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List of Abbreviations

AD	Alzheimer's Disease Dementia
ADL	Activities of Daily Living
APP	Amyloid Precursor Protein
ATD	Assistive Technology Devices
CAVE	Cave Automatic Virtual Environment
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
DELCODE	DZNE – Longitudinal Cognitive Impairment and Dementia Study
FDA	Food and Drug Administration
GRAIL	Gait Real-Time Analysis Interactive Lab
IADL	Instrumental Activities of Daily Living
iVR	Immersive Virtual Reality
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
PwD	People with Dementia
rsFC	Resting-State Functional Connectivity
SCD	Subjective Cognitive Decline
VE	Virtual Reality Environment
VR	Virtual Reality

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List of Original Studies

Study 1:

Amaefule, C.O., Dyrba, M., Wolfsgruber, S.,...Teipel, S.J. & The DELCODE Study Group. (2021). Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum. Neuroimage Clinical, 29(2021), 102533.

Study 2:

Amaefule, C.O., Lüdtke, S., I., Kirste, T. & Teipel, S.J. (2020). Effect of Spatial Disorientation in a Virtual Environment on Gait and Vital Features in Patients with Dementia: Pilot Single-Blind Randomized Control Trial. JMIR Serious Games, 8(4):e18455.

Study 3:

Amaefule, C.O., Lüdtke, S., Klostermann, A., Hinz, C., Kampa, I., Kirste, T. & Teipel, S.J. At Crossroads in a Virtual City – Effect of Location-based Spatial Disorientation on Gait Variability among Healthy Older Adults. Gerontology, (in review).

Summary

Ageing is characterized by functional decline in selective cognitive domains such as visuo-spatial, executive and memory domains, which are necessary for independently carrying out instrumental activities of daily living (IADL). The onset of neurodegenerative diseases such as Alzheimer's disease dementia (AD) exacerbate this decline, leading to major challenges for the patients, and increased burden for the caregivers. An important function affected by this decline is orientation ability in wayfinding. Wayfinding and orientation difficulties have been observed as early symptoms of people with mild cognitive impairment (MCI) or AD. These deficits sustain a vicious cycle of inactivity and lack of cognitive stimulation, thereby leading to further cognitive decline.

Study 1 gives an overview of the neural correlates of domain-specific cognitive decline in the AD-spectrum by leveraging the combined advantage of a more representative and large multicentre sample, and composite measures of the most relevant cognitive domains in AD-spectrum. *Study 2* establishes the adequacy of the Gait Real-Time Analysis Interactive Lab (GRAIL), a virtual reality (VR) setup, for the assessment of orientation and wayfinding challenges among healthy older control and AD participants. Lastly, *study 3* shows that changes in the pattern of gait and psychophysiological arousal are indicative of instances of spatial disorientation, which occur mostly at crossings during wayfinding among older adults, and provide a good basis for automatic detection of spatial disorientation and the design of relevant interventions.

In summary, this work provides a comprehensive overview of the neural correlates of domain-specific cognitive decline in the AD-spectrum, with a focus on domains necessary for spatial orientation, while providing further insight into the substrates of real-world wayfinding challenges among older adults, with emphasis on viable features aiding the detection of spatial disorientation and the design of possible interventions.

Zusammenfassung

Das Altern ist durch einen funktionellen Rückgang in bestimmten kognitiven Bereichen wie dem visuell-räumlichen Bereich, dem exekutiven Bereich und dem Gedächtnis gekennzeichnet, die für die unabhängige Durchführung von instrumentellen Aktivitäten des täglichen Lebens (IADL) erforderlich sind. Das Auftreten neurodegenerativer Erkrankungen wie der Alzheimer-Demenz (AD) verschlimmert diese Verschlechterung, was zu großen Herausforderungen für die Patienten und zu einer erhöhten Belastung für die Pflegekräfte führt. Eine wichtige Funktion, die von diesem Rückgang betroffen ist, ist die Orientierungsfähigkeit bei der Wegfindung. Schwierigkeiten bei der Wegfindung und Orientierung wurden als frühe Symptome bei Menschen mit leichter kognitiver Beeinträchtigung (MCI) oder Alzheimer beobachtet. Diese Defizite halten einen Teufelskreis aus Inaktivität und mangelnder kognitiver Stimulation aufrecht und führen so zu einem weiteren kognitiven Abbau.

Studie 1 gibt einen Überblick über die neuronalen Korrelate des bereichsspezifischen kognitiven Abbaus im AD-Spektrum, indem sie den kombinierten Vorteil einer repräsentativen und großen multizentrischen Stichprobe und zusammengesetzter Messungen der wichtigsten kognitiven Bereiche im AD-Spektrum nutzt. *Studie 2* belegt die Eignung des Gait Real-Time Analysis Interactive Lab (GRAIL), eines Virtual-Reality (VR)-Systems, für die Bewertung von Orientierungs- und Wegfindungsproblemen bei gesunden älteren Kontrollpersonen und AD-Teilnehmern. Schließlich zeigt *Studie 3*, dass Veränderungen im Gangmuster und in der psychophysiologischen Erregung auf Fälle räumlicher Desorientierung hindeuten, die bei älteren Erwachsenen vor allem an Kreuzungen während der Orientierung auftreten, und eine gute Grundlage für die automatische Erkennung räumlicher Desorientierung und die Entwicklung entsprechender Interventionen bieten.

Zusammenfassend bietet diese Arbeit einen umfassenden Überblick über die neuronalen Korrelate des bereichsspezifischen kognitiven Abbaus im Alzheimer-Spektrum, wobei der Schwerpunkt auf den für die räumliche Orientierung notwendigen Bereichen liegt. Gleichzeitig werden weitere Einblicke in die Substrate der realen Orientierungsprobleme älterer Erwachsener gewährt, wobei der Schwerpunkt auf praktikablen Merkmalen liegt, die die Erkennung von räumlicher Desorientierung und die Entwicklung möglicher Interventionen unterstützen.

1 Introduction

1.1 Neurodegenerative diseases

A major barrier to healthy ageing is the occurrence of neurodegenerative diseases. Neurodegenerative diseases are a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the central nervous system or peripheral nervous system [1]. This progressive degeneration manifests in problems with movement referred to as *ataxias*, or cognitive functioning referred to as *dementias* [2]. Neurodegenerative diseases affect millions of people worldwide, with Alzheimer's disease dementia (AD) and Parkinson's disease being the most common types [1]. Although treatments may help relieve some of the physical or mental symptoms associated with neurodegeneration, there are currently no known cures [3]. In the case of AD, a very recent drug treatment "Aducanumab" aimed at reducing the build-up of Amyloid beta (Aβ) in people with mild cognitive impairment or mild dementia stage of disease, was approved by the United States Food and Drug Administration (FDA) in June 2021 [4]. Aducanumab has, however, been met with considerable criticisms concerning its efficacy, leading to the recommendation for further follow-up studies [4]. The absence of a well-established cure has motivated the quest to develop alternative, non-pharmacological treatments [5] to the debilitating effects of the irreversible neural cell death, with a considerable focus on those affecting cognitive functioning – dementias.

1.2 An overview of Alzheimer's type dementia

Dementia is any decline in cognition that is significant enough to interfere with independent, daily functioning. The causes of dementia are numerous and include primary neurologic, neuropsychiatric, and medical conditions [6]. Dementia can be classified into four most frequent subtypes (Alzheimer's, Vascular, Lewy body & Fronto-temporal), with associated neuropathological features (Figure 1). A shared disease neuropathology between two dementia types (e.g. plaques and tangles associated with AD are present along with blood vessel changes associated with vascular dementia), describes a mixed phenotype [7]. Dementias are responsible for the greatest burden of neurodegenerative diseases, with AD representing approximately 60-70% of dementia cases [2].

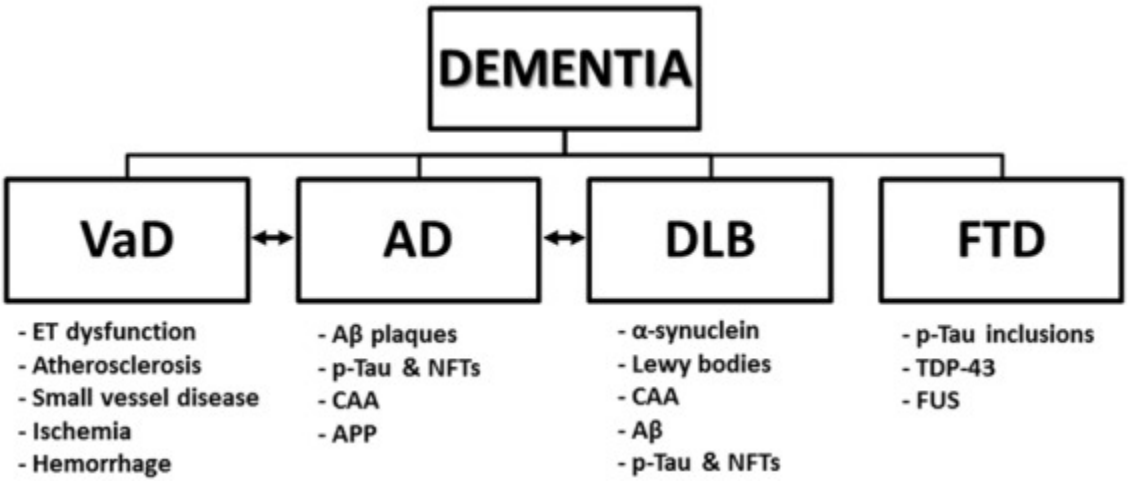

Figure 1. Classifications of dementia subtypes and associated neuropathological features

A mixed phenotype represented by double-sided arrows indicates a shared disease neuropathology between two dementia types. Aβ, amyloid-β; AD, Alzheimer's disease dementia; APP, amyloid precursor protein; α-synuclein, alpha-synuclein; CAA, cerebral amyloid angiopathy; DLB, Lewy body dementia; ET, endothelial; FTD, frontotemporal dementia; FUS, inclusions of fused in sarcoma; NFTs, neurofibrillary tangles; p-tau, hyperphosphorylated tau; TDP-43, transactive response DNA-binding protein-43; VaD, vascular dementia. Copyright approved image source: Raz et al. [7].

AD is the most common neurological cause of dementia in older adults above the age of 60 [8]. Three phases of AD as clinically described include: (a) a preclinical (presymptomatic) phase lasting many years prior to manifestation of cognitive symptoms; (b) the clinical prodromal stage lasting approximately two years with manifest, but still pre-demented symptoms, slight cognitive disorder or mild cognitive impairment; and (c) the stage of manifest AD dementia [9] (Figure 2).

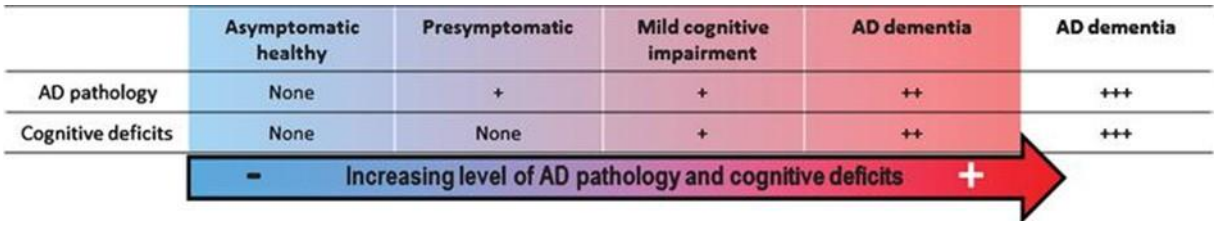

Figure 2. AD dementia continuum from cognitively intact individuals to AD dementia with degree of cognitive deficits and pathology

Each phase is characterized by the absence or presence and degree of corresponding AD pathology and cognitive deficits. Copyright approved image is adapted from Chételat [10].

A popular hypothesis put forward to explain the origin and cause of AD is the amyloid cascade hypothesis [11, 12]. According to this hypothesis, the excessive formation of amyloid-β is caused by the enzymatic cleavage of the amyloid precursor protein (APP) by the β- and γ-secretase as well as the aggregation of amyloid-β in the form of smaller oligomers and the extracellular deposition of larger plaques, which is the primary etiological factor in AD. Amyloid-β has a neurotoxic effect by inducing oxidative stress, increased influx of calcium ions and damage to the mitochondria [13]. Furthermore, these effects lead to changes in the phosphorus kinase activity and to hyperphosphorylation of the τ protein [14]. As a result, the τ proteins would detach from the microtubules and aggregate as neurofibrillary tangles [15]. Ultimately, this leads to the breakdown of the cytoskeleton, to disruption of cell metabolism and ultimately to cell death of the neuron [15] (Figure 3). This degenerative process thereafter transcends to increasing disruptions in higher cognitive functions, including memory, orientation, thinking, perception and the ability to learn [16]. The amyloid cascade hypothesis has, however, come under criticism in recent years due to the limited efficacy of drugs based on its theorem [12], thereby necessitating the consideration of alternative models of AD pathology.

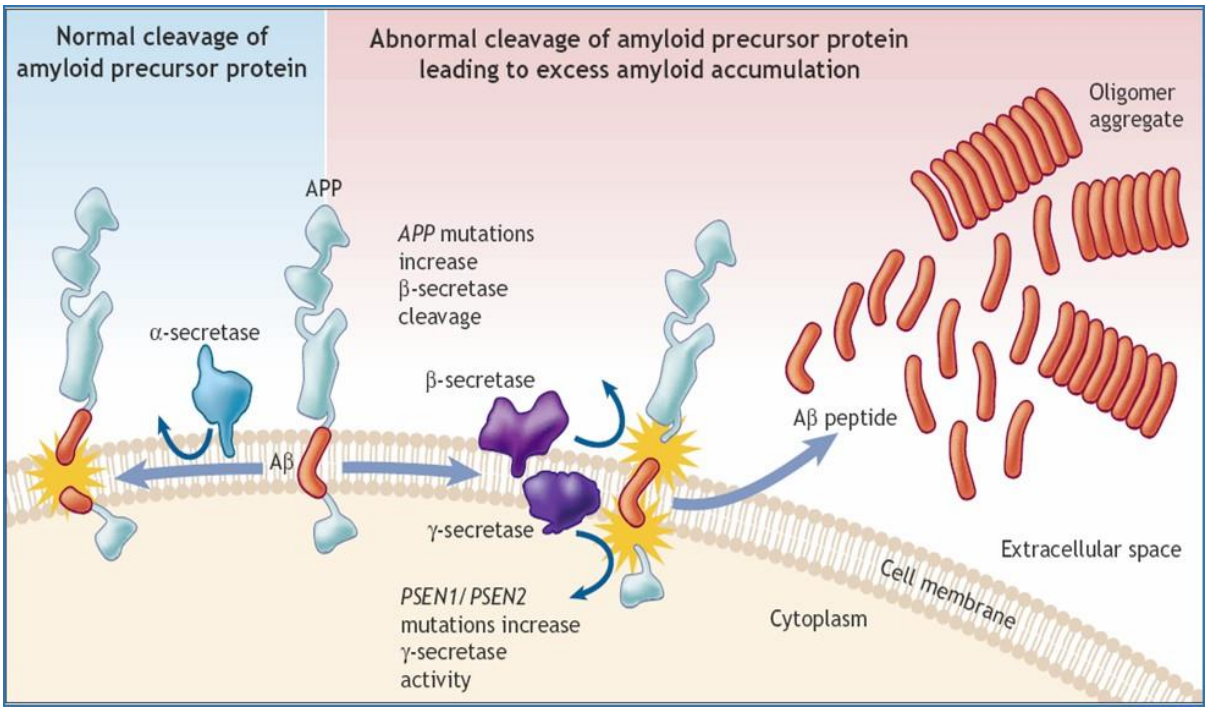

Figure 3. Illustration of the amyloid-β cascade hypothesis in AD dementia

The amyloid cascade hypothesis posits that the deposition of the amyloid-β peptide in the brain parenchyma is a crucial step that ultimately leads to AD. The APP is a transmembrane protein that can undergo a series of

proteolytic cleavage by secretase enzymes. When it is cleaved by α-secretase in the middle of the β-amyloid domain (Aβ), it is not amyloidogenic. However, when APP is cleaved by β- and γ-secretase enzymes, neurotoxic Aβ peptides are released, which can accumulate into oligomer aggregate. Mutations in the APP gene tend to inhibit cleavage by α-secretase and consequently enable preferential cleavage by β-secretase. Mutations in the presenilin-1 and presenilin-2 genes (PSEN1 and PSEN2), which are components of the γ-secretase complex, increase cleavage by γ-secretase at this site. In both situations, the result is excess Aβ peptide production. Over time, the subsequent oxidative stress and biochemical changes ultimately lead to neuronal death and the development of neuritic plaques typical of AD. Copyright approved image is adapted from Patterson et al. [11].

Over the years, several approaches have been adopted in studying the extent to which cognitive functioning is affected by the AD degenerative process. Two notable approaches include the Magnetic Resonance Imaging (MRI) and behavioural methods. Imaging studies of the neuronal underpinnings of cognitive functions have revealed links between functional and structural disruption, as well as patterns of cognitive decline in AD [17–20], using varying measures of cognition. The outcomes from these imaging studies have contributed considerably in advancing the understanding of the neural correlates of cognitive decline in AD. However, considering that most of these studies singled out and investigated certain cognitive functions using single test measures, a more comprehensive evaluation of cognitive domain functions becomes necessary, in order to avoid reaching unreliable conclusions due to measurement errors [21] or multiple comparisons [22], and to get a more holistic picture of affected cognitive domains. On the other hand, outcomes from behavioural studies have mainly provided real-world evidences and real-time readouts of the extent to which cognitive function is impaired by AD [23], which can also be observed in the execution of instrumental activities of daily living (IADL) [24], such as going shopping. Most of these studies have investigated links between changes in gait and cognitive function [25] or changes in gait and disease prognosis [26]. For instance, in a longitudinal study, Gillain et al. [26] investigated gait parameters as potential markers for early identification of mild cognitive impairment (MCI) patients at risk to develop AD in the future. Results of the study by Gillain et al. [26] showed that gait speed, symmetry and regularity were lower in MCI+ (i.e. MCI patients that progressed to AD) than in MCI− (i.e. MCI patients that did not progress to AD). Despite the existence of studies linking cognitive decline to impaired gait, a clearer understanding of how both factors affect day-to-day activities is still required. One crucial day-to-day activity is wayfinding.

1.3 Wayfinding and spatial disorientation in AD dementia: the possible role of assistive technology devices (ATD)

Wayfinding is the process of navigating from a current position to a desired destination [27]. The wayfinding process is essentially a problem-solving activity [28], which could be influenced by factors such as perception of the environment, availability of wayfinding information (e.g. route descriptions), ability to orientate, underlying cognitive and decision-making processes which determine the effectiveness of the wayfinding process [29]. AD is characterized by deficits in spatial cognition [30–32]. As a result of these deficits, people with AD and even people with MCI due to AD are prone to behavioural expressions of difficulties with the wayfinding process such as disorientation, wandering or getting lost [33–36]. Moreover, people with AD have been shown from previous research to experience profound difficulty in spatial navigation tasks, in which their performances have been argued to be related to the stage or progression of the disease [37, 38]. In order to avoid the psychological distress associated with spatial navigation failures [39, 40], many people with dementia (PwD) resort to staying inactive indoors or only walk outside if accompanied. This propagates a vicious circle of inactivity and further cognitive decline (Figure 4). Furthermore, the tendency to be disoriented, wander and get lost are contributing factors to institutionalization among community-based PwD [41, 42]. Contrary to staying inactive, being active has been highlighted as one of the mitigating factors against the progressive cognitive decline associated with dementia, as it acts as a source of cognitive stimulation, which is necessary to stay cognitively healthy [43, 44]. The ability to ambulate independently has also been suggested as a major contributor to well-being and autonomy in older individuals [25]. This highlights the importance of preserving wayfinding skills among people with AD.

Central to wayfinding difficulties among people with AD dementia is spatial disorientation. According to Algase [45], difficulty of AD patients in finding their way around is often triggered by spatial disorientation. It is one of the earliest symptoms in AD [31], characterized by the difficulty of knowing one's position within an environment and the inability to navigate to a destination [40, 46]. Spatial disorientation has been highlighted as one of the major features present in instances of spatial navigation failures among people with AD dementia [40]. The first symptoms of spatial disorientation in AD normally occur in unfamiliar surroundings, where individuals have difficulties in learning new routes [47], as is the case when newly

admitted to an institutional care setting. Subsequently, sudden moments of disorientation appear in familiar places [48] and cause difficulties for individuals with dementia to return back to their homes [49, 50]. Considering that instances of spatial disorientation are ubiquitous, detecting these instances in real time becomes a priority. However, for real-time detection to be achievable, patterns of change in behaviour (e.g. gait, psychophysiological response, interacting with environment), which co-occur with spatial disorientation, need to be adequately recognized.

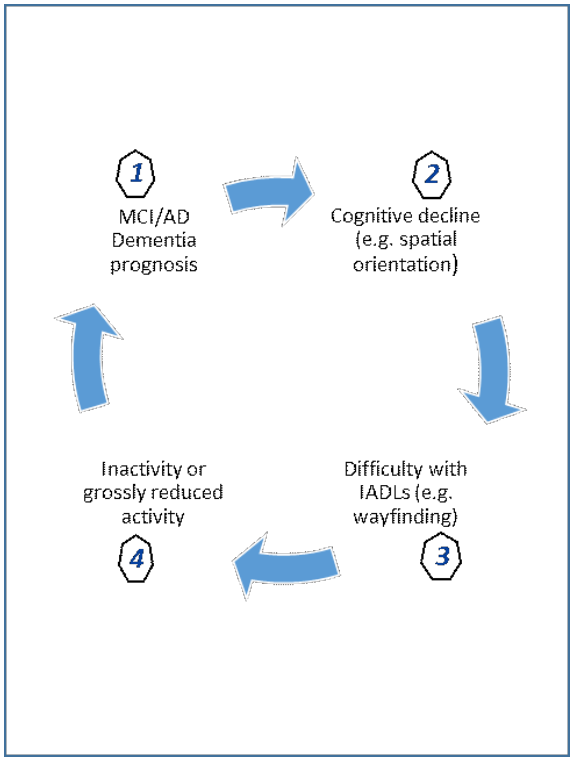

Figure 4. Illustration of the vicious cycle of cognitive decline and wayfinding-orientation difficulty in AD dementia

The vicious cycle of cognitive decline is propagated by difficulty in executing IADLs such as wayfinding due to disease onset and cognitive decline, which usually leads to reduced activity among people with AD. This reduced activity and lack of cognitive stimulation leads to further cognitive decline.

In the light of this, research and technological innovations have been driven by the need to support or assist PwD to be as autonomous as possible in navigation [51–57]. Adopting a user-centred design approach, Robinson et al. [52] described the development of an ATD, consisting of an armband and electronic notepad, which use Global Positioning System (GPS) tracking to locate users with dementia who are independently ambulatory in the community but at risk of getting lost. As an alternative to GPS tracking, ATDs have also been designed to

use information within the immediate environment to provide the user with context dependent directions. At the basic level, Chang et al. [53] used a series of tags, and Kirsch et al. [54] symbols in the environment, to provide the basis for context-dependent navigation using personal digital assistants. Liu et al. [56] also developed an assistive device that guides the user based on an internal pre-programmed map of the environment. Furthermore, on a more advanced level, Morris et al. [55] developed an intelligent robot navigation system which generates a representation of location based on probabilistic mapping and guides the user using sensors. Similarly, How et al. [57] developed an intelligent wheelchair which assists users with navigation and avoiding obstacles.

Taken together, the aforementioned ATDs share a common feature of being situation-aware [58], in the sense that they form some representation of where the user is and therefore support the user's self-awareness of their position in space. However, to assist optimally, it is important that these technologies are not only situation-aware, but also situation-adaptive and subsidiary [58]. This would entail that they are guided by a proper knowledge of the person's current emotional or cognitive state in relation to environmental context, and that assistance is only provided when needed in contrast to conventional navigation devices. In wayfinding, ATDs based on motion and physiological signals could support navigation based on the recognition of pertinent motion and physiological parameters indicative of the cognitive state of spatial disorientation during wayfinding. If the ATD is aware of phases of orientation and disorientation and adapts interventions to them dynamically, it could then improve assistance for a person with AD dementia [59].

1.4 Wearable sensors and immersive virtual reality (iVR) in the detection of spatial disorientation

The first step towards designing situation-adaptive and subsidiary ATDs for wayfinding and spatial orientation is the identification of predictive patterns or features that are indicative of the target cognitive or emotional state. Wearable sensors (Figure 5) have proven useful in several studies involving PwD [60, 61], providing a cost-effective and unobtrusive means of observation. In a previous field study concerned with wayfinding behaviour in persons with MCI and dementia [61], real-time instances of spatial disorientation were identified by means of the indicators developed in Yordanova et al. [62], and evaluated using machine learning

classifiers based solely on properties of the magnitude of motion from accelerometric data. The outcome of this study suggested that instantaneous detection of disorientation using wearable sensors is feasible, however, the accuracy was not sufficient to serve as a basis for an assistive device, due to the major study limitations – limited number of training features based only on properties of the magnitude of motion from accelerometric data and an uncontrolled environment.

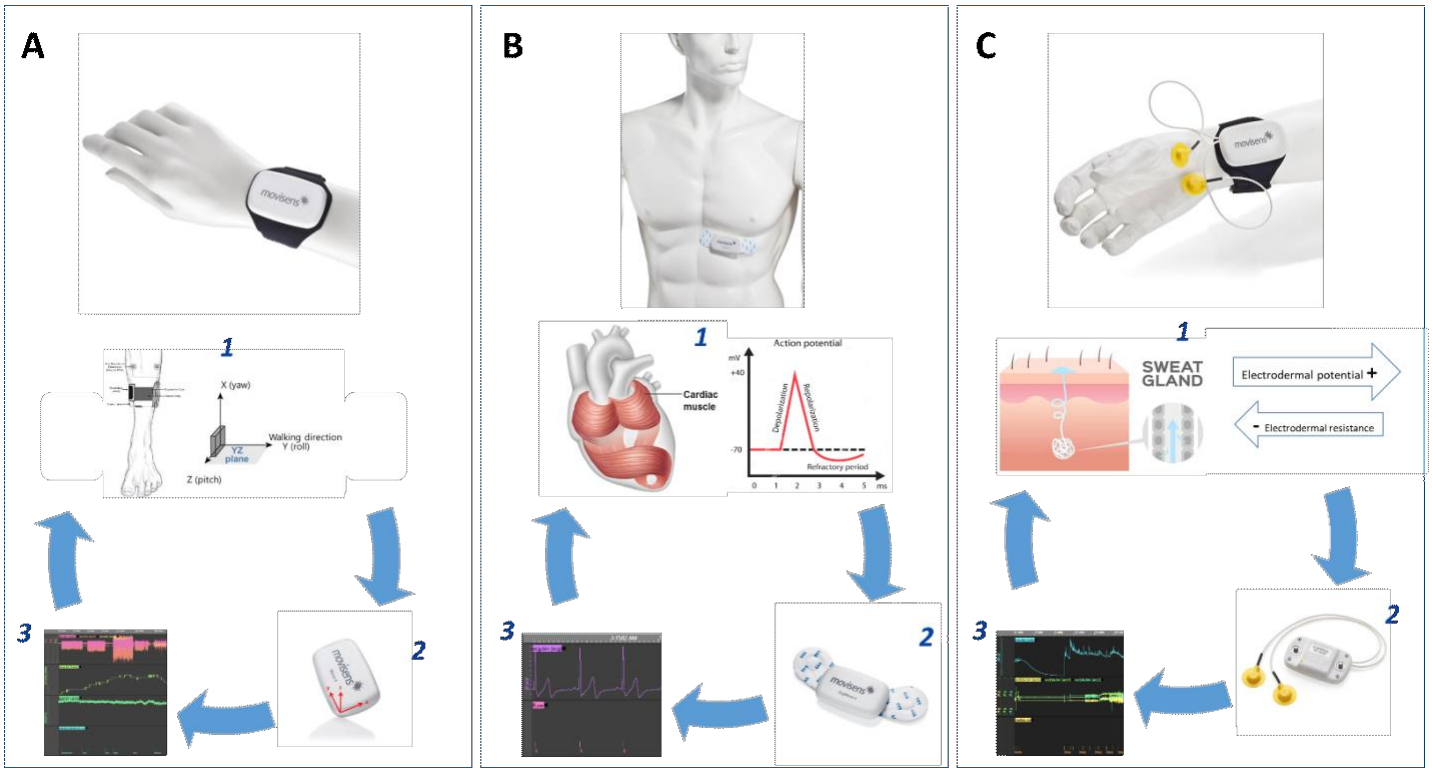

Figure 5. Wearable sensors for motion and physiological measurements

(A) Acceleration of a body in space is recorded from 3 axial coordinates by the accelerometer. The magnitude of acceleration is then stored as digital signals, (B) Sympathetic response by the cardiac muscle cells to stimuli, involves increase in depolarization followed by repolarization during each cardiac cycle (heartbeat). This results in electrical potential which is picked up by the 2-lead ECG electrode and stored as digital signals, (C) Sympathetic response by the sweat glands to stimuli, involves increase in sweat secretion, which contains water and electrolytes. This leads to an increase in electrical conductivity, thus lowering the electrical resistance of the skin. This change in skin conductivity is picked up by the EDA electrode and stored as digital signals. Sensor image source: movisens GmbH (www.movisens.com). Images are copyright approved.

An alternative to real-world navigation studies, which has gained popularity in recent times, is laboratory-based virtual reality (VR) and immersive virtual reality (iVR) studies (Figure 6) [63]. Cushman et al. [64] examined the feasibility of using VR to detect navigational deficits in people with AD. Participants had to navigate their ways through both a real hospital lobby and

a virtual hospital lobby. Following eight navigation subtests, the authors found that the use of virtual environments was an effective method to assess navigational skills, and that quantifying a virtual-world navigational performance is easier and less time-consuming than quantifying a real-world navigational performance. In another study [65] examining age- and AD-related differences in route learning and memory using iVR, participants were asked to navigate a virtual city and subsequently to recognize certain city buildings and objects. Young adults were quicker and more accurate than both older adults and individuals with AD, while individuals with AD had more difficulty with the recognition task than the older adult participants. In summary, navigation tasks posed in a virtual reality environment (VE) enjoy the advantage of having naturalistic interactive settings while ensuring a high degree of control and standardization [66]. This creates the enabling environment for accurately singling out the effect spatial disorientation might have on motion and psychophysiological behaviour.

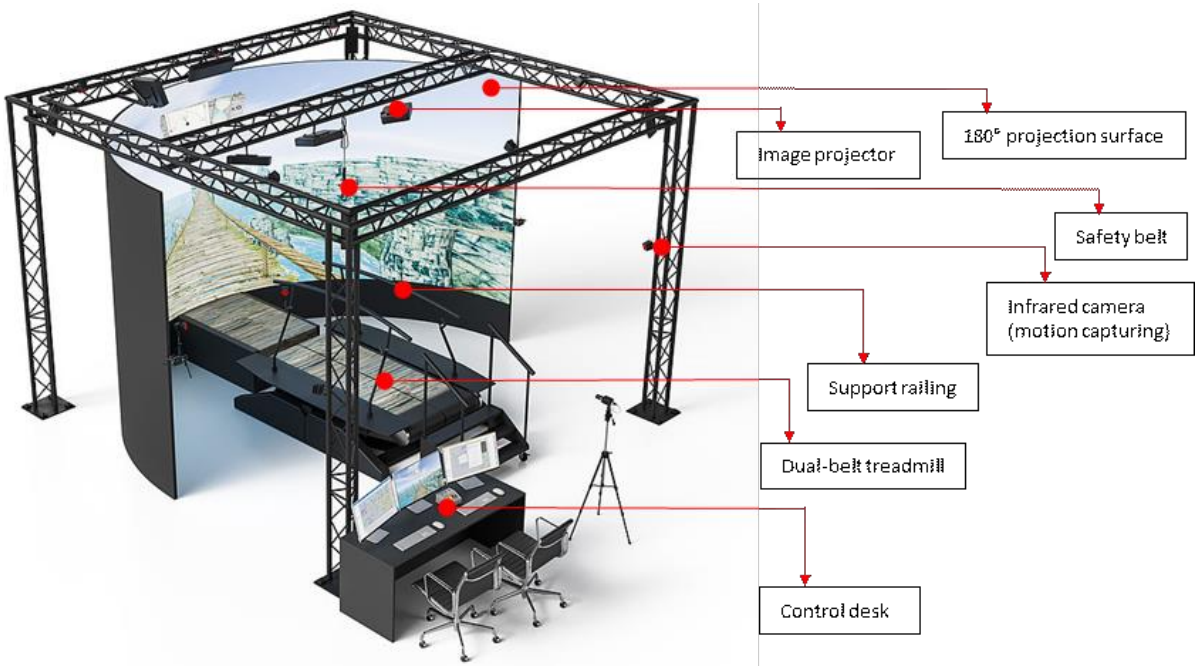

Figure 6. Depiction of a state-of-the-art immersive virtual reality setup

The Gait Real-time Analysis Interactive Lab (GRAIL) system displayed above majorly consists of a dual-belt treadmill, a large 180° projection screen, and an optical motion capturing system. Copyright approved image is adapted from Amaefule et al. [92].

1.5 Experimental aims and research questions

The purpose of this doctoral dissertation can be summarized as follows: (1) to advance the understanding of the neural correlates of domain-specific cognitive decline in the AD-spectrum, with a focus on domains necessary for spatial orientation, and (2) to provide further insight into the substrates of real-world wayfinding challenges among older adults, with emphasis on viable features aiding the detection of spatial disorientation and the design of possible interventions. The aims of this research project are divided in several objectives pursued through 3 different studies.

1. In the first study, using a multicentric and cognitive domain approach we explored the structural and functional correlates of key cognitive domains of AD, with a focus on the visuo-spatial domain. The study was motivated by the lack of research into the visuo-spatial domain in the AD spectrum, in comparison to more broadly studied domains such as memory and executive functions. We sought to establish the extent to which atrophy or disruptions in functional connectivity of corresponding brain regions and networks, respectively, are linked to cognitive decline in the AD spectrum.

2. Subsequently, we were interested in understanding how the cognitive deficits examined in the first study are expressed in real-world situations relevant to the execution of IADLs among our healthy older control and AD cohorts. To this extent, we implemented a real-world navigation task into an immersive three-dimensional VE. However, considering that our experimental setup was unprecedented in the study of wayfinding among the elderly, the second study was mainly geared towards establishing the feasibility and acceptability of our approach in capturing relevant behavioural correlates of wayfinding challenges among our healthy older control and AD cohorts.

3. Finally, adopting the setup established in the second study, we investigated the possible effect of spatial disorientation on gait and psychophysiological response among healthy older adults, with the aim of identifying coherent motion and psychophysiological features for spatial disorientation detection, which will aid the design of assistive interventional devices.

2 Methods

2.1 Study participants

To investigate the above mentioned research questions, three study cohorts were recruited. All participants or their relatives gave informed consent.

Study 1: To answer the first research question, data from an interim baseline release of the multicenter DELCODE study, conducted by the German Center for Neurodegenerative Diseases (DZNE) was used. The study sample consisted of 54 persons with AD, 86 persons with MCI, 175 persons with subjective cognitive decline (SCD) and 175 healthy controls (HC), which had both structural MRI, resting-state functional connectivity (rsFC) and cognitive domain composite scores from the nine study centers. The patient subgroup consisted of the AD, MCI and SCD participants. The demographic characteristics of the participants are given in Table 1.

Table 1. Study 1 sample characteristics (mean +/- standard deviation)

	HC (*n* = 175)	SCD (*n* = 175)	MCI (*n* = 86)	AD (*n* = 54)
Sex (% female)	58.0	49.0	41.0	57.0
Age (years)	69.0 ± 5.3	71.2 ± 5.8	72.5 ± 5.2	73.6 ± 6.4
Education (years)	14.7 ± 2.7	14.7 ± 3.2	13.8 ± 2.9	13.5 ± 3.3
GDS	0.6 ± 1.1	1.9 ± 1.9	2.1 ± 1.9	2.2 ± 1.8
MMSE (/30)	29.4 ± 0.8	29.2 ± 1.0	27.9 ± 1.7	23.5 ± 3.3

HC = Healthy Controls, SCD = Subjective Cognitive Decline, MCI = Mild Cognitive Impairment, AD = Alzheimer's Disease Dementia, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination.

Study 2: To answer the second research question, pilot data from the "Gait Analysis by Induced Disorientation in a VR Environment" study (ClinicalTrials.gov Identifier: NCT04134806) was evaluated. The study sample consisted of 9 healthy older participants (including 3 cognitively healthy older adults without memory complaints and 6 cognitively healthy older adults with subjective cognitive decline), and 4 patients with AD. The demographic characteristics of the participants are given in Table 2.

Table 2. Study 2 sample characteristics (mean +/- standard deviation)

	Healthy older adults (*n* = 9)	AD patients (*n* = 4)

Sex (% female)	56.0	50.0
Age (years)	70.0 ± 4.4	78.0 ± 2.3
Education (years)	14.5 ± 3.0	13.0 ± 2.3
MMSE (/30)	29.0 ± 0.7	20.5 ± 7.5

AD = Alzheimer's Disease Dementia, MMSE = Mini-Mental State Examination.

Study 3: To answer the third research question, subsequent data from the "Gait Analysis by Induced Disorientation in a VR Environment" study (ClinicalTrials.gov Identifier: NCT04134806) was evaluated. The study sample consisted of 10 young controls, 14 older controls and 14 older experimental participants. The young participants were mainly included as a first control group, enabling the investigation of possible age effects on gait with the older control participants. The older participants were randomly assigned to either the control or experimental group. The demographic characteristics of the participants are given in Table 3.

Table 3. Study 3 sample characteristics (mean +/- standard deviation)

	Young control (n = 10)	Older control (n = 14)	Older experimental (n = 14)
Sex (% female)	40.0	64.3	64.3
Age (years)	24.2 ± 2.7	69.5 ± 3.9	72.0 ± 5.3
Education (years)	13.3 ± 0.9	13.9 ± 2.9	14.9 ± 2.5
MMSE	-	28.9 ± 0.9	29.4 ± 0.6

MMSE = Mini-Mental State Examination.

2.2 Data collection and pre-processing

Study 1: The data were acquired from nine Siemens 3.0 Tesla MRI scanners using identical acquisition parameters and harmonized instructions across study sites. Data processing was carried out using Data Processing Assistant for Resting-State fMRI Advanced (DPARSFA 4.3) [67]. The T1-weighted anatomical images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the Statistical Parametric Mapping (SPM12) (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) New Segment toolbox implemented in Matlab 2015a (Mathworks, Natwick). The T1- weighted GM and WM partitions were normalized to the Montreal Neurological Institute (MNI) reference coordinate system using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm [68] and the default brain template included in CAT12 [69] as target.

Functional MRI preprocessing included removal of the first ten volumes of each fMRI scan, slice timing correction to the temporal middle, and realignment to the mean volume. The anatomical T1-weighted image for each participant was coregistered to the mean functional image such that the deformation fields generated by DARTEL from the anatomical T1-weighted images could be used to project the functional scans from each subjects' native image space into the MNI reference space. Subsequently, temporal bandpass filtering (0.01–0.1 Hz), and spatial smoothing with an 8 mm isotropic full-width-at-half-maximum (FWHM) Gaussian kernel were applied. The rsFC maps were calculated using the FSL melodic toolbox (Version 5.0.9, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/), resulting in 20 independent component analysis (ICA) maps. The resulting maps were then evaluated by experts to identify the four resting-state networks of interest, namely the visual (VIS), executive (EN), default mode (DMN) and language (LAN) networks, based on their spatial patterns as reported earlier [70–72]. Afterwards, subject-level rsFC z-maps were derived using FSL's dual regression, which generated subject-specific versions of the spatial maps and associated time series [73]. As a final step, network-specific explicit masks were derived, in order to clearly define the areas of cerebral activations which actually belong to each resting-state network. These masks were obtained from the group-based independent component maps of all study participants, by thresholding them based on the highest 10th percentile of intensities, leading to liberal masks for each of the four (VIS, EN, DMN, LAN) resting-state networks of interest.

Study 2 & 3: The gait data was sampled by means of the optical motion-capturing system of the GRAIL. Twenty six passive markers were placed on the participant's anatomical landmarks based on the Plug-in-Gait model of VICON (C7, T10, Sternum, Clavicle, 4 on the Pelvis; anterior and posterior superior iliac spine, 2 on the Thighs, 4 on the Knees, 2 on the Tibias, and 5 on each Foot; toe, 5th metatarsus, inner ankle, outer ankle and heel) and detected by 12 VICON infra-red cameras (www.vicon.com). The accelerometric, electrocardiographic and electrodermal data were collected by means of the movisens GmbH Move, EcgMove and EdaMove sensors (www.movisens.com) respectively. The video data was recorded using a GoPro Hero 7 action camera (www.gopro.com). The accelerometric, electrocardiographic and electrodermal data were exported using DataAnalyzer (www.movisens.com). Filtering and feature extraction for the electrocardiographic and electrodermal data was done using Kubios

HRV 3.3.1 (University of Kuopio, Finland) and Ledalab 3.4.9 (http://www.ledalab.de) respectively. All other procedures including synchronization, resampling and aggregation of all features were carried out in the R statistical software (R Core Team, 2018) using custom scripts. Figure 7 summarizes the pre-processing procedure.

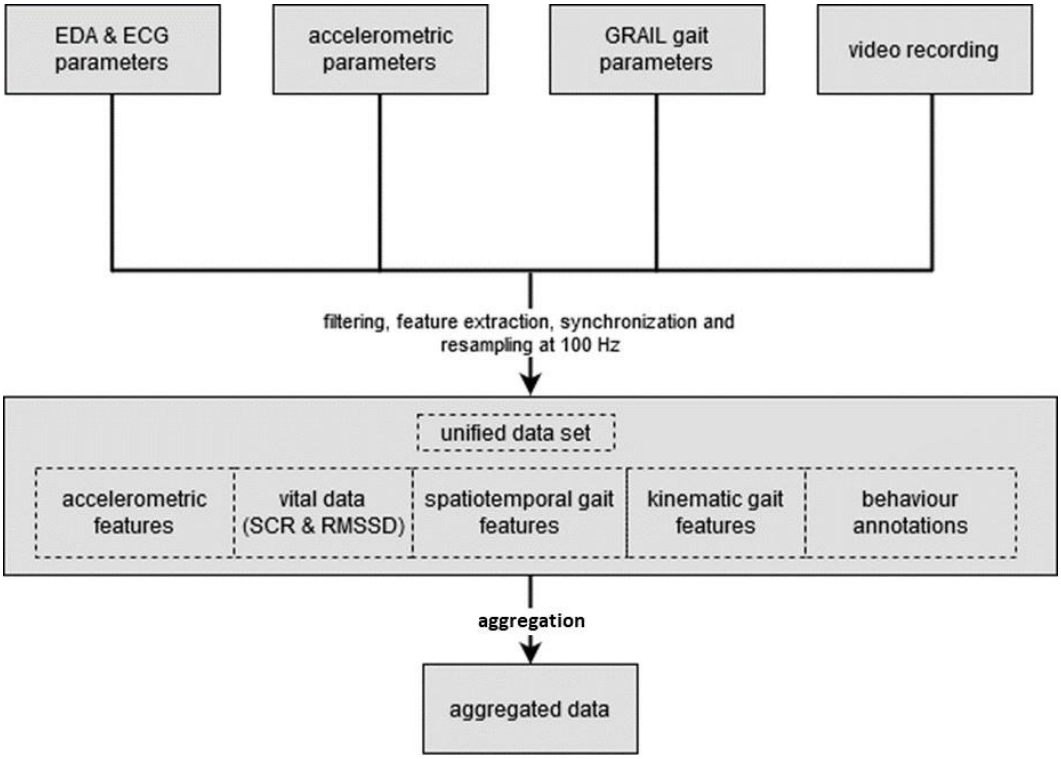

Figure 7. Overview of the gait, sensor and video data pre-processing procedure

EDA = electrodermal activity, ECG = electrocardiogram, SCR = skin conductance response, RMSSD = root mean square of successive differences of beat-to-beat intervals.

2.3 Statistical analyses

Study 1: Voxel-wise multiple regressions were used to explore the relationship between cognitive domain composite scores and both brain volume and functional connectivity. In the case of the volumetric analyses, we adopted an unbiased whole brain voxel-wise approach as similarly done in [74] by regressing each cognitive domain (executive, visuo-spatial, memory, working memory and language) composite score on the gray matter volume estimates. In the case of the rsFC analysis, we specifically regressed each cognitive domain composite score on the respective resting-state functional connectivity network (executive, visual, default mode and language), known to be associated with each function based in previous literature [75]. In so doing, executive and working memory scores were regressed on the executive network,

visuo-spatial scores on the visual network, memory scores on the default mode network and language scores on the language network. The regression models were controlled for age, sex, education, diagnosis and study site. In the volumetric analysis, the total intracranial volume was included as a global value.

Study 2: Given that this was a feasibility study, descriptive evaluations of the immersiveness of the VE, usability of the VR setup and frequency of disorientation instances were done. The extent of immersion was derived from participants' responses to the igroup Presence Questionnaire (IPQ) [76], usability of the VR setup was assessed based on participants responses to a usability questionnaire, while frequency of disorientation instances were derived from the video annotations.

Study 3: Mixed effects analyses of variance (ANOVAs) models within the generalized linear mixed model (GLMM) framework, having orientation (oriented, disoriented) as well as location (non-crossing, crossing) as within-subject variables, and group (older controls, older experimental) as between-subject variable were conducted. The young controls were excluded from the ANOVA models as they primarily served to investigate age effects with the older controls using unequal sample t-tests, and as well, had marginal instances of disorientation. More specifically, we assessed if: (1) spatial disorientation had an effect on gait and/or psychophysiological parameters, (2) the effect of spatial disorientation on gait and/or psychophysiological parameters depended on the location or group of the older participants and (3) if there was an effect of age (young controls vs. older controls) on gait. When statistically significant interactions were found, Bonferroni-corrected post-hoc tests were applied to identify the direction of effects

3 Results

3.1 Patterns of network-specific resting-state functional connectivity associated with distinct cognitive impairments in AD spectrum

Except for the visual network, patterns of network-specific resting-state functional connectivity were positively associated with distinct cognitive impairments among the patient subgroup in the AD-spectrum. Poorer cognitive performance scores for executive function were associated with reduced rsFC of areas within the executive network ($p < 0.05$, FDR corrected, $0.35 \leq d \leq 0.50$, Fig. 8A). We also found similar outcomes for the association of memory scores with connectivity of areas within the default mode network ($p < 0.05$, FDR corrected, $0.33 \leq d \leq 0.50$, Fig. 8C). When applying a more lenient significance threshold, we found that poorer cognitive performance scores for working memory were also associated with reduced rsFC of areas within the executive network ($p < 0.01$, uncorrected, $0.28 \leq d \leq 0.45$, Fig. 8B). The language scores were also associated with the rsFC of areas within the language network ($p < 0.01$, uncorrected, $0.24 \leq d \leq 0.50$, Fig. 8D).

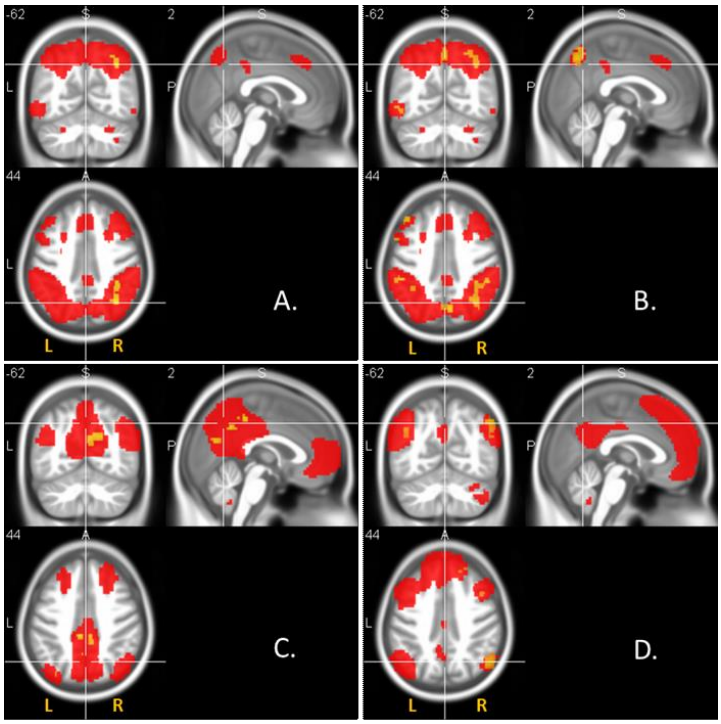

Figure 8. Network-specific resting-state functional connectivity

Showing associations with the (A) executive, (B) working memory, (C) memory, and (D) language functions respectively. Significance is reported at $p < .05$ FDR corrected for the executive and memory functions, and at $p < .01$ uncorrected for the working memory and language functions accordingly. Cluster size ≥ 20 voxels, $0.24 \leq d$

≤ 0.50. Red voxels represent group resting-state networks, yellow voxels show clusters of significant association between network-specific functional connectivity and cognitive domain scores. Association was restricted to the corresponding networks only by functional masks determined from the whole sample. Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain.

3.2 Regional gray matter atrophy associated with distinct cognitive impairments in AD spectrum

Regional gray matter atrophy was positively associated with visuo-spatial and other cognitive impairments among the patient subgroup in the AD-spectrum. For visuo-spatial function, lower performance was associated with reduced gray matter volume in the middle temporal gyri, right temporal pole, right anterior cingulate gyrus, inferior parietal lobules, left inferior occipital gyrus, left premotor cortex, right fusiform gyrus and left superior parietal lobule (p < 0.01, FDR corrected, 0.41 ≤ d ≤ 0.60, Fig. 9A). In the case of executive function, lower performance was associated with reduced gray matter volume in the right posterior cingulate gyrus, left inferior frontal gyrus, prefrontal cortices, left premotor cortex, left middle frontal gyrus, left primary motor cortex, left superior parietal lobule, right inferior occipital gyrus and right inferior parietal lobule (p < 0.01, FDR corrected, 0.38 ≤ d ≤ 0.70, Fig. 9B). For working memory function, lower performance was associated with reduced gray matter volume in the left prefrontal cortex, inferior temporal gyri, right inferior occipital gyrus, left premotor cortex, middle frontal gyri, right inferior occipital gyrus, right inferior parietal lobule and left posterior cingulate gyrus (p < 0.01, FDR corrected, 0.38 ≤ d ≤ 0.65, Fig. 9C). When considering memory function, lower scores were associated with reduced gray matter volume in the middle temporal gyri, superior parietal lobule, inferior occipital gyrus, inferior parietal lobules, left insular cortex, right fusiform gyrus, left anterior and posterior cingulate gyri and right inferior temporal gyrus (p < 0.01, FDR corrected, 0.40 ≤ d ≤ 0.75, Fig. 9D). And lastly, for language function, lower performance was associated with reduced gray matter volume in the temporal poles, left posterior cingulate gyrus, left premotor cortex, inferior parietal lobules, prefrontal cortices, right insular cortex and left supplementary motor area (p < 0.01, FDR corrected, 0.39 ≤ d ≤ 0.70, Fig. 9E)

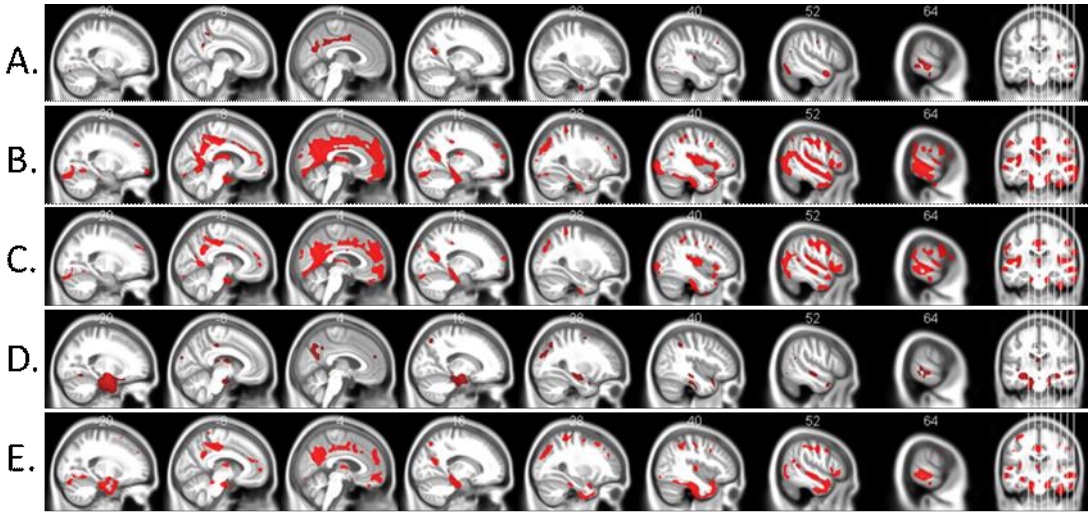

Figure 9. Regional gray matter volume

Showing associations with the (A) visuo-spatial, (B) executive, (C) working memory, (D) memory, and (E) language domains respectively. Voxel-wise multiple comparisons are thresholded at $p < .01$, FDR corrected, cluster size ≥ 50 voxels, $0.38 \leq d \leq 0.70$. Red voxels show clusters of significant association between gray matter volume and cognitive domain scores. Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain.

3.3 Immersiveness of the VE, usability of the VR setup and frequency of disorientation instances

Responses to the IPQ informed that the cognitively healthy older participants perceived an above-average degree of immersion; group mean item scores (between 1 and 7, where 7 means highest perceived presence/involvement/realism) were 4.60 for presence, 3.92 for involvement, and 4.42 for realism. The patients with dementia, on the other hand, while reporting lower mean scores relative to the cognitively healthy older participants, still perceived a considerable degree of immersion, with group mean item scores of 3.63 for presence, 3.31 for involvement, and 2.60 for realism. Of the 13 participants, only 1 (7%) of the participants reported simulator sickness.

Participants' responses to the usability questionnaire showed that the control over the chosen direction in the VR environment was perceived as functional for both the cognitively healthy older participants and patients with dementia (e.g., easy to learn; participants were able to move to where they wanted at their own pace), and adequately naturalistic.

The navigation setup was viable in inducing instances of disorientation. We observed an average of 21.40 instances of disorientation for the cognitively healthy older participants in the control group and 36.50 instances for the cognitively healthy older participants in the experimental group. For the patients with dementia, an average of 37.50 instances of disorientation was observed.

3.4 Spatial disorientation and gait variability

Significant main effects of orientation on gait were found for walking speed, walking speed CV, step length, stride time, stride time CV and stance time (Table 2), with slower walking speed, decreased step length, decreased stride time, decreased stride time CV, increased stance time and increased walking speed CV observed when spatial disorientation occurred. No significant main effect of spatial disorientation was found for step length CV and stance time CV. Significant main effects of location on gait were only found for walking speed, stride time, stride time CV and stance time CV, with increased walking speed, decreased stride time, decreased stride time CV and decreased stance time CV observed when participants were at crossings. Significant interaction effects of spatial disorientation x location were only observed for stride time and stride time CV (Table 2). Post-hoc analyses (Fig. 3) showed significantly higher stride time ($p < 0.01$) and stride time CV ($p < 0.05$) when disorientation occurred at crossings. On the contrary, stride time ($p < 0.05$) and stride time CV ($p < 0.01$) was significantly lower when disorientation occurred at non-crossings. No spatial disorientation x group interactions were found for gait variability (Table 2).

3.5 Spatial disorientation and psychophysiological response

Significant main effects of spatial disorientation on psychophysiological response were found for SCR amplitude and SCR count (Table 2), with increased SCR amplitude and SCR count observed when spatial disorientation occurred. No significant main effect of spatial disorientation was found for RMSSD. Furthermore, significant main effects of location on psychophysiological response were found for RMSSD and SCR count, with increased RMSSD and SCR count observed when participants were at crossings. A significant main effect of group was only found for SCR count, with increased SCR count observed for the older experimental participants. Significant interaction effect of spatial disorientation x location was observed for RMSSD, but not for the SCR amplitude and SCR count. In addition, a significant spatial disorientation x group interaction was found for SCR count, but not for RMSSD and SCR

amplitude (Table 2). Post-hoc analyses (Fig. 3) revealed that the RMSSD was only significantly lower when disorientation occurred at non-crossings ($p < 0.05$). In the case of SCR count (Fig. 3), a significant increase was observed when disorientation occurred for the older adults in the experimental group ($p < 0.001$).

Table 4. ANOVA outcomes for the significant main and interaction effects

	Orientation			Group			Location			Orientation × Group			Orientation × Location		
	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2
Gait parameters															
Walking Speed	15.297	0.000	0.200	-	-	-	5.600	0.021	0.099	-	-	-	-	-	-
Step Length	6.772	0.011	0.089	-	-	-	-	-	-	-	-	-	-	-	-
Stride Time	4.886	0.029	0.058	-	-	-	10.769	0.001	0.120	-	-	-	10.685	0.001	0.119
Stance Time	6.052	0.016	0.082	-	-	-	-	-	-	-	-	-	-	-	-
Walking Speed CV	10.289	0.001	0.115	-	-	-	-	-	-	-	-	-	-	-	-
Step Length CV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stride Time CV	5.951	0.016	0.070	-	-	-	6.526	0.002	0.108	-	-	-	10.423	0.001	0.117
Stance Time CV	-	-	-	-	-	-	4.053	0.048	0.061	-	-	-	-	-	-
Psychophysiological parameters															
HRV RMSSD	-	-	-	-	-	-	9.118	0.003	0.146	-	-	-	6.402	0.014	0.108
SCR Amplitude	5.399	0.023	0.074	-	-	-	-	-	-	-	-	-	-	-	-
SCR Count	13.891	0.000	0.161	10.733	0.002	0.204	6.309	0.014	0.097	11.526	0.001	0.138	-	-	-

CV = coefficient of variation; HRV = heart rate variability; RMSSD = root mean square of the successive differences of adjacent inter-heartbeat intervals; SCR = skin conductance response. Effect sizes are expressed as partial eta-squared η_p^2

4 Discussion

In the current chapter, I will discuss the major study findings in light of our research questions and integrate them into the existing literature in the field. Finally, I will present the limitations of the work while pointing out future research directions. The chapter will be wrapped up with a general conclusion.

4.1 Summary and evaluation of major findings

Deficits in major cognitive domains are reflected in both regional atrophy and functional connectivity in a multicentric cohort

Associations of cognitive domain composite scores with gray matter volume and network-specific rsFC among an SCD, MCI and AD patient subgroup were examined in study 1. Overall, results showed that regional gray matter atrophy was positively associated with visuo-spatial and other cognitive impairments within the AD-spectrum. Patterns of network-specific resting-state functional connectivity (except the VN) were also positively associated with distinct cognitive impairments within the AD-spectrum. The current study provides a comprehensive overview of the neural correlates of domain-specific cognitive decline in the AD-spectrum. Most importantly, the study also extends previous rsFC studies [18, 77, 78] by leveraging the combined advantage of a larger, more representative multicenter sample and composite measures of the most relevant cognitive domains in AD-spectrum.

When we assessed the association of cognitive domain composite scores with network-specific rsFC, we found consistent outcomes for the association of the executive domain scores with areas within the executive network, and the memory domain scores with areas within the default mode network, in agreement with previous studies which applied single test measures of cognitive function [18, 20, 78, 79]. Less consistent associations were found for the association of the working memory domain scores with areas within the executive network, and the language domain scores with areas within the language network. However, we could not find positive associations between visuo-spatial domain scores and the rsFC of the visual network. The finding of more consistent associations for the executive and memory domain is not surprising, as these domains are known from previous studies to be highly

affected earlier in the disease process at the onset of AD [80, 81]. The lack of a significant association of the visuo-spatial domain and the visual network in the current study could be the result of a more pronounced executive control influence of the single subtests (clock drawing, clock copying & CERAD figure copying) included in the visuo-spatial cognitive domain score. Performance on the clock drawing test as reported by Cosentino et al. [82] particularly appears to place an executive control demand on participants, thereby recruiting cognitive resources other than visuo-spatial resources. To test for this possibility, we performed post-hoc analysis, using the same method as performed earlier for the functional analysis. When associating the visuo-spatial domain scores with the rsFC of the executive network and default mode network, we expectedly found significant associations ($p < 0.01$, uncorrected), which buttresses a prominent role of executive dysfunction in visuospatial performance in the AD spectrum.

Our findings agree with the majority of previous studies that assessed the associations of regional gray matter volume with either single test measures of cognitive function, or composite measures of cognitive domains derived by averaging across standardized scores of single tests of cognitive function in both healthy elderly cohorts [74] and patients [77, 83, 84]. These previous and our findings differ from a previous magnetoencephalography and MRI study by Ranasinghe et al. [78] that found no correlation between gray matter atrophy and cognitive performance, however, the number of cases n = 27 in this previous study was very low. We found consistent associations for the volumetric analysis with the related composite scores of domain specific cognitive functions, which is indicative of the utility of our approach to deriving measures of cognitive function. When considering the pattern of atrophy for visuo-spatial function, we found that lower cognitive domain scores were associated with lesser gray matter volume in parietal, occipital and temporal regions. When we extended the association of atrophy patterns to the single measures of visuo-spatial function, we interestingly found that in the case of the clock drawing and clock copy test scores, the parietal and temporal areas similarly showed effects as was the case with the visuo-spatial domain score. The parietal, occipital and temporal regions are known to form part of the dorsal and ventral pathways responsible for the processing of visual stimuli [85], hence, atrophy in such regions have been shown to be associated with poorer visuospatial abilities in patients with MCI [83] and AD [77].

Virtual reality simulations provide a reliable basis for evaluating wayfinding and orientation challenges among healthy older adults and people with dementia

In recent times, iVR has proven useful in the assessment of PwD [63]. Previous iVR studies have generally employed various advanced VR setups, including head-mounted and CAVE [63] VR setups. However, one of the challenges of VR studies is the feasibility of using such setups for people with cognitive impairment and the inadequacy of immersion, which often leads to cybersickness [86]. Study 2 aimed at evaluating the feasibility and acceptability of our VR setup in capturing relevant behavioural correlates of wayfinding challenges among our healthy older control and AD cohorts. Similar to other iVR studies [63, 65], we were able to establish our GRAIL VR setup as adequate for the assessment of orientation and wayfinding challenges among our healthy older control and AD cohorts.

Sensor-based monitoring of instrumental activities of daily living in the evaluation of cognitive domain deficits among people with dementia

The onset of dementia is characterized by difficulty in independently carrying out activities of daily living (ADL), including iADL due to progressively declining cognitive capacities. In order to assess and identify the extent to which ADLs are affected by cognitive decline among people with dementia, a number of report and interview-based tools, such as the Barthel Index [24], have been generated. Tools such as the Barthel Index, however, may suffer from a number of limitations such as subjectivity, labor cost and lack of real-time observations necessary for prognosis and intervention. Sensor-based monitoring provides a cost-effective and reliable alternative to the use of report and interview-based tools. Similar to other sensor-based studies [60, 61], our findings from study 2 and 3 demonstrate that the wayfinding challenges and disorientation often experienced by people with dementia, could equally be objectively and reliably assessed using sensor-based observation. Furthermore, since wayfinding and orientation challenges are characteristic of the onset of dementia [33, 64], sensor-based monitoring also provides a means of detecting cognitive decline early enough among healthy older adults.

Gait variability and psychophysiological response provide unique information for spatial disorientation detection and intervention planning

An important aspect of improving wayfinding and orientation ability among PwD using ATDs, is the adequate detection of moments of spatial disorientation, which will inform individually-tailored interventions. In my final study, we sought to identify the possible effect of spatial disorientation on gait variability and psychophysiological response among healthy older adults during wayfinding in a controlled environment. We extended the literature on wayfinding challenges [31, 38, 40] and real-time spatial disorientation detection [32, 61], having shown that changes in the pattern of gait (walking speed, step length, stride & stance time) and psychophysiological arousal (skin conductance response) corresponds to instances of spatial disorientation during wayfinding among older adults. Additionally, we provided unique evidence showing that crossings are important "hotspots" for spatial disorientation occurrence, and that a unique pattern of gait change in stride time could be highly informative, as an indicator of possible instances of spatial disorientation while at crossings.

These outcomes encourage the use of a more adaptive approach in selecting relevant features for spatial disorientation detection and the designing of ATDs for navigation support, considering that while gait and psychophysiological features were reflective of spatial disorientation at non-crossings, only gait features remained indicative of spatial disorientation at crossings. In this case, a situation-adaptive ATD should be able to recognize and adapt to the user's location (derivable from GPS coordinates) in both detecting disorientation and providing assistance. A hypothetical ATD could then employ a combined evaluation of the user's gait and psychophysiological arousal level while at non-crossings, but prioritize evaluation of gait at crossings, as this proved more informative for spatial disorientation at crossings.

4.2 Limitations and future perspectives

Data-driven approach of deriving functional networks

A possible limitation of the first study is the data-driven approach employed in generating the rsFC networks using independent component analysis, in contrast to a seed-based approach

[87] in which regions of interest are defined a priori. It might be possible that the resulting independent components we defined as rsFC networks based on evidence in the literature such as [72] slightly differ from a few other studies. This indicates that despite the advantage of data-driven approaches in the automatic derivation of resting-state networks, heterogeneity in data-driven approaches still remains an open question.

Sample size and derivation of psychophysiological measures

A considerable limitation of the second and last studies are the limited sample sizes, due to the difficulty in recruiting a substantial amount of participants during the corona virus pandemic. Future studies with larger sample sizes will serve to replicate the findings from the both studies. An additional limitation of study 3 is the use of psychophysiological measures from the exact moment as the occurrence of spatial disorientation. Although this was done to ensure perfect temporal synchronization with the gait features, it might be a better approach to derive psychophysiological measures from a short duration after the occurrence of spatial duration, due to the required physiological latency between autonomic nervous system activation and changes in heart rate [88] or skin conductance response [89]. Nevertheless, deriving psychophysiological measures from a short duration after the occurrence of spatial duration poses a great challenge, especially when considering the potential difficulty in determining the exact offset time of disorientation.

Laboratory-based study

Laboratory-based studies enjoy the core advantage of control and standardization [66]. Nonetheless, it is important to keep in mind that the findings from laboratory-based studies may not completely model the real world [60], which could be more or less unstandardized and noisy. In the light of this, the findings from the second and last studies should be interpreted with caution, and inferences to real-world situations should be made while considering this limitation.

4.3 Conclusion

The aim of this thesis was to advance understanding of the neural correlates of domain-specific cognitive decline in the AD-spectrum, with a focus on domains necessary for spatial orientation, while providing further insight into the substrates of real-world wayfinding challenges among older adults, with emphasis on viable features aiding the detection of spatial disorientation and the design of possible interventions. Firstly, we provided a comprehensive overview of the neural correlates of domain-specific cognitive decline in the AD-spectrum, by leveraging the combined advantage of a more representative and large multicentre sample, and composite measures of the most relevant cognitive domains in AD-spectrum. Secondly, we established the adequacy of the GRAIL VR setup for the assessment of orientation and wayfinding challenges among healthy older control and AD cohorts. Lastly, we showed that changes in the pattern of gait and psychophysiological arousal are indicative of instances of spatial disorientation, which occur mostly at intersection, during wayfinding among older adults, and provide a good basis for automatic detection of spatial disorientation and the design of relevant interventions.

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Amaefule C.O., Dyrba M, Wolfsgruber S, Polcher A, Schneider A, Fliessbach K, Spottke A, Meiberth D, Preis L, Peters O, Incesoy EI, Spruth EJ, Priller J, Altenstein S, Bartels C, Wiltfang J, Janowitz D, Bürger K, Laske C, Munk M, Rudolph J, Glanz W, Dobisch L, Haynes JD, Dechent P, Ertl-Wagner B, Scheffler K, Kilimann I, Düzel E, Metzger CD, Wagner M, Jessen F, Teipel SJ (2021)
Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum.
Neuroimage Clinical 29(2021), 102533. doi: 10.1016/j.nicl.2020.102533. PMID: 33360018; PMCID: PMC7770965 (IF 4,35).

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Neurobiology of Learning and Memory, 169(2020), 107176, doi.org/10.1016/j.nlm.2020.107176 (IF 2,76).

Präsentationen auf nationalen und internationalen Fachkongressen

2021

Gait Changes among Older Adults during a Virtual Wayfinding Task: associations with Spatial Disorientation and Heart Rate Variability.
Alzheimer's Association International Conference (AAIC), Denver, USA. Virtuelle (Poster)

2020

Association of domain-specific cognitive functions with regional pattern of atrophy and functional connectivity across the Alzheimer's disease spectrum: An analysis from the DELCODE cohort.
Alzheimer's Association International Conference (AAIC), Amsterdam, Niederlande. Virtuelle (Poster)

Assessing Gait and Physiological Characteristics of Induced Disorientation in a VR Environment – First Results.
Jahrestagung der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), Berlin (Poster)

2019

Predicting Daytime Manifestations Of Challenging Behaviours In Advanced Stages Of Dementia Using Pre-Daytime Accelerometry: Post-Hoc Analysis Of The Dzne Rostock Insidedem Study.
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Appendix (Studies 1-3)

NeuroImage: Clinical 29 (2021) 102533

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Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum

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ABSTRACT

Background: Cognitive decline has been found to be associated with gray matter atrophy and disruption of functional neural networks in Alzheimer's disease (AD) in structural and functional imaging (fMRI) studies. Most previous studies have used single test scores of cognitive performance among monocentric cohorts. However, cognitive domain composite scores could be more reliable than single test scores due to the reduction of measurement error. Adopting a multicentric resting state fMRI (rs-fMRI) and cognitive domain approach, we provide a comprehensive description of the structural and functional correlates of the key cognitive domains of AD.

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2213-1582/© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Method: We analyzed MRI, rs-fMRI and cognitive domain score data of 490 participants from an interim baseline release of the multicenter DELCODE study cohort, including 54 people with AD, 86 with Mild Cognitive Impairment (MCI), 175 with Subjective Cognitive Decline (SCD), and 175 Healthy Controls (HC) in the AD-spectrum. Resulting cognitive domain composite scores (executive, visuo-spatial, memory, working memory and language) from the DELCODE neuropsychological battery (DELCODE-NP), were previously derived using confirmatory factor analysis. Statistical analyses examined the differences between diagnostic groups, and the association of composite scores with regional atrophy and network-specific functional connectivity among the patient subgroup of SCD, MCI and AD.

Result: Cognitive performance, atrophy patterns and functional connectivity significantly differed between diagnostic groups in the AD-spectrum. Regional gray matter atrophy was positively associated with visuospatial and other cognitive impairments among the patient subgroup in the AD-spectrum. Except for the visual network, patterns of network-specific resting-state functional connectivity were positively associated with distinct cognitive impairments among the patient subgroup in the AD-spectrum.

Conclusion: Consistent associations between cognitive domain scores and both regional atrophy and network-specific functional connectivity (except for the visual network), support the utility of a multicentric and cognitive domain approach towards explicating the relationship between imaging markers and cognition in the AD-spectrum.

1. Introduction

Cognitive decline in Alzheimer's disease (AD) has been associated with regional brain metabolic decline in fluorodeoxyglucose-positron emission tomography (FDG-PET) studies (Landau et al., 2011; Grothe et al., 2016; Ottoy et al., 2019), as well as structural and functional disruption of neural networks in structural and functional imaging studies (Agosta et al., 2012; Balachandar et al., 2015, 2017; Gardini et al., 2015). Blood-oxygen-level-dependent (BOLD) imaging during a defined resting state has been shown to reflect consistent functional networks, such as the default mode (DMN), visual (VIS) and executive networks (EN) (Rosazza and Minati, 2011). Different to task related functional MRI (fMRI), resting state fMRI is not confounded by the ability of patients to understand and memorize the instructions for fulfilling a specific task, rendering it advantageous for the study of people with cognitive decline (Cole et al., 2010). Additionally, conclusive evidence across the literature supports the use of resting-state connectivity as a biomarker of AD (Badhwar et al., 2017).

Resting-state fMRI studies in the AD-spectrum have progressively explored a large number of networks, including the DMN, EN, VIS, salience (SAL), language (LAN) and limbic (LIM) networks (Agosta et al., 2012; Balachandar et al., 2017; Zhou et al., 2010; Gour et al., 2014; Badhwar et al., 2017). A majority of studies which focused on the DMN found consistently decline of DMN connectivity in MCI and AD patients (Greicius et al., 2004; Agosta et al., 2012; Balachandar et al., 2015; Tam et al., 2015; Zhou et al., 2015). The same was observed for the VIS (Balachandar et al., 2015, 2017) in which overall a decrease in connectivity has been reported for AD patients. Studies on the SAL, on the other hand, reported increase in connectivity of the SAL for MCI and AD patients (Zhou et al., 2010; Wang et al., 2016). Similarly, an increase in functional connectivity of the LIM has also been reported for MCI and AD patients (Gour et al., 2014; Badhwar et al., 2017). For the EN, an increase in functional connectivity of the EN has mainly been observed in AD patients (Agosta et al., 2012; Balachandar et al., 2015). However, to the best of our knowledge, no study has so far reported any significant differences between HC and AD-spectrum patients for the connectivity of the LAN.

So far, most rs-fMRI studies linking pattern of cognitive decline with changes of functional networks have been conducted in monocentric cohorts, with observed case numbers substantially smaller than obtainable in a multicentric cohort. These studies have reported links between changes in functional connectivity and performance on cognitive tests of either global cognition (Ranasinghe et al., 2014; Zhou et al., 2015), or specific cognitive functions such as executive (Ranasinghe et al., 2014), memory (Dong et al., 2012; Ranasinghe et al., 2014; Balachandar et al., 2015; Gardini et al., 2015; Zhou et al., 2015; Brueggen et al., 2016) and visuo-spatial functions (Ranasinghe et al., 2014; Balachandar et al., 2017). More specifically, decreased connectivity in the VIS has majorly been associated with visuo-spatial deficits (Balachandar et al., 2017). In the study by Balachandar et al. (2017) involving 23 AD patients categorized as having mild or severe visuo-spatial deficits based on their performance on selected tests of visuo-spatial function, patients with severe visuo-spatial deficits showed more reduced connectivity in the bilateral lingual gyri and left supra-calcarine gyrus areas of the VIS. The authors, however, noted that a larger sample size would be required to confirm their findings. Further notable networks in which decreased rsFC has been associated with deficits in the respective cognitive domains in monocentric cohorts include the EN (Agosta et al., 2012; Ranasinghe et al., 2014) and DMN (Greicius et al., 2004; Dong et al., 2012). Additionally, a number of studies have also probed the possible associations between regional structural atrophy and cognitive deficits in both healthy elderly cohorts (Chee et al., 2009; Bruno et al., 2016; Cacciaglia et al., 2018) and AD-spectrum patients (Di Paola et al., 2007; Mitolo et al., 2013; Ranasinghe et al., 2014; Smits et al., 2014; Cacciaglia et al., 2018), using varying measures of cognition. Associations of course, do not only depend on the imaging methods employed but also on the way cognitive performance is being quantified.

Cognitive domain composite scores may allow to more comprehensively study structural and functional underpinnings of cognitive changes in AD compared to single test scores. They may be more reliable than single test scores due to the reduction of measurement error (Wolfsgruber et al., 2017) at the same time they allow restricting the number of comparisons and ensuing type 1 error (Clark et al., 2016). Three prominent approaches to obtaining cognitive composite scores include: (1) using tests of composite scores such as the Preclinical Alzheimer Cognitive Composite (PACC) (Donohue et al., 2014; Mormino et al., 2017) in neuropsychological assessment. As reported in the study by Mormino et al. (2017), results showed the ability of the PACC to capture both early and late cognitive decline during the preclinical stages of Alzheimer's disease. However, certain domains such as visuo-spatial function do not appear to be adequately covered by this composite score; (2) transforming raw scores of single tests to z-scores using the means and standard deviations (SDs), and further averaging the z-scores across single tests (Smits et al., 2014; Clark et al., 2016). This method, however beneficial, does not take into account the degree to which the different tests are similar in measuring the same construct; (3) combining single tests (indicators) into latent variables based on literature, and further obtaining confirmatory factor score estimates of these latent variables using the multivariate regression method (Grice, 2001; Dowling et al., 2010; Park et al., 2012; Wolfsgruber et al., 2017). This superior method of choice as already applied in the Wisconsin Registry for Alzheimer's Prevention (WRAP), Alzheimer's Disease Neuroimaging Initiative (ADNI), and DZNE – Longitudinal Cognitive Impairment and

Dementia (DELCODE) studies, especially has the advantage of taking close methodological relatedness of some indicators into account, by specifying residual correlations for these indicators and thereby avoiding overfitting the data.

In the current study, we provided a comprehensive description of the structural and functional correlates of the key cognitive domains of AD as determined by factor scores with a focus on visuo-spatial function. Patients with AD are known to be prone to experiencing impairment in visuo-spatial function during early stages of the disease (Quental et al., 2013). Impairments in visuo-spatial function in AD have mainly been attributed to posterior cortical atrophy (PCA) (Benson et al., 1988; Crutch et al., 2012), that affects the parieto-occipital areas which are equally relevant regions within the visual network (Beckmann et al., 2005; Castellazzi et al., 2014). These impairments in visuo-spatial function are not only precursors of MCI conversion to AD as has been indicated in (Didic et al., 2013) where performance on visual recognition predicted conversion to AD with a sensitivity of 80% and a specificity of 90.9%, but also relate to spatial disorientation (Henderson et al., 1989; Tetewsky and Duffy, 1999; Monacelli et al., 2003) which greatly impairs the daily life of patients. Nonetheless, there appears to be a relative lack of sufficient research into the visuo-spatial domain in the AD spectrum, in comparison to more broadly studied domains such as memory and executive functions (Park et al., 2012; Wang et al., 2015).

Using a multicentric and cognitive domain approach, our aim was to investigate associations between cognitive domain composite scores and both gray matter volume, and network-specific resting-state functional connectivity (rsFC), in patients in the AD-spectrum, ranging from memory clinic patients with subjective cognitive decline (SCD) through people with MCI to people with AD dementia, as well as in healthy controls. We tested two major hypotheses; firstly, that poorer cognitive domain composite scores would be associated with reduced regional gray matter volume, and secondly, that poorer cognitive domain composite scores would be associated with reduced rsFC of the related resting-state functional network.

2. Material and methods

2.1. Participants

We used data from an interim baseline release of the first ≠ 700 participants of the multicenter DELCODE study, conducted by the German Center for Neurodegenerative Diseases (DZNE) (Jessen et al., 2018). After proper quality control at the leading imaging site, we obtained data of 569 participants. However, only 490 participants; 54 Alzheimer's disease Dementia (AD), 86 Mild Cognitive Impairment (MCI), 175 Subjective Cognitive Decline (SCD) and 175 Healthy Controls (HC) were included in this study, which had both structural MRI, rs-fMRI and factor scores from the nine study centers (Jessen et al., 2018). The patient group consisted of the AD, MCI and SCD subgroup (Table 1). The DELCODE exclusion criteria ensured that no persons were included who had a current major depressive episode, past or present major psychiatric disorders, neurological diseases other than AD, or unstable medical conditions (Jessen et al., 2018).

SCD was defined as a persistent self-perceived cognitive decline in the absence of objective cognitive impairment as measured by the CERAD test battery, lasting at least for 6 months and being unrelated to an acute event (Jessen et al., 2014). The MCI patients met the core clinical criteria for MCI according to National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup guidelines (Albert et al., 2011). The AD patients had a clinical diagnosis of probable AD dementia according to the NIA-AA workgroups guidelines (McKhann et al., 2011). The HC participants had no objective cognitive impairment in cognitive tests, no history of neurological or psychiatric disease and did not report self-perceived cognitive decline. All participants or their representatives provided written informed consent. The study protocol was approved by the local institutional review boards and ethical committees of the participating centers. It was conducted in accord with the Helsinki Declaration of 1975.

2.2. Neuropsychological assessment

All participants (including healthy controls and patients) underwent a clinical assessment of their cognitive status, including the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and an extensive neuropsychological testing battery (Jessen et al., 2018). The neuropsychological test battery included tests which assess executive function, visuo-spatial ability, memory, working memory and language function (Jessen et al., 2018). Confirmatory factor analysis (CFA) based cognitive domain composite scores (Table 2) were derived from these tests using robust maximum likelihood (MLR) estimation (Wolfsgruber et al., 2017, 2020). The variance and mean of the latent factors were fixed to one and zero respectively, following the assignment of indicator variables to latent factors, which was guided by previous CFAs on similar test batteries of the ADNI and WRAP cohort studies focusing on preclinical and prodromal AD (Grice, 2001; Dowling et al., 2010; Park et al., 2012; Wolfsgruber et al., 2017). Resulting values were normally distributed (Shapiro-Wilk). Further to this, a 5-factor structure with intercorrelated factors of learning & memory, language ability, executive functions and mental processing speed, working memory and visuo-spatial abilities was tested, taking into account the close methodological relatedness of some indicators by specifying residual correlations. Factor score estimates of the latent variables were then extracted using the multivariate regression method (Grice, 2001; Dowling et al., 2010; Park et al., 2012; Wolfsgruber et al., 2017). The presence of depression among participants was assessed by means of the Geriatric Depression Scale (GDS) (Gauggel and Birkner, 1999).

Table 1
Patient demographics and clinical characteristics (mean +/- standard deviation).

	HC (n = 175)	SCD (n = 175)	MCI (n = 86)	AD (n = 54)
Sex (% female)	58	49	41	57
Age (years)	69.0 ± 5.3	71.2 ± 5.8	72.5 ± 5.2	73.6 ± 6.4
Education (years)	14.7 ± 2.7	14.7 ± 3.2	13.8 ± 2.9	13.5 ± 3.3
GDS	0.6 ± 1.1	1.9 ± 1.9	2.1 ± 1.9	2.2 ± 1.8
MMSE (/30)	29.4 ± 0.8	29.2 ± 1.0	27.9 ± 1.7	23.5 ± 3.3

The patient group includes a total of 315 patients with subjective cognitive decline (n = 175), mild cognitive impairment (n = 86), and alzheimer's dementia (n = 54). Numbers show means and standard deviations.
HC = Healthy Controls, SCD = Subjective Cognitive Decline, MCI = Mild Cognitive Impairment, AD = Alzheimer's Dementia, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination.

Table 2
Cognitive domain composite scores (mean +/- standard deviation).

Cognitive function	HC	SCD	MCI	AD	p
Visuo-spatial	0.39 ± 0.3	0.28 ± 0.4	−0.39 ± 0.7	−1.49 ± 1.3	< 0.001
Executive	0.52 ± 0.4	0.34 ± 0.5	−0.51 ± 0.7	−1.86 ± 0.8	< 0.05
Working memory	0.39 ± 0.3	0.31 ± 0.4	−0.46 ± 0.6	−1.52 ± 0.6	< 0.001
Memory	0.61 ± 0.3	0.36 ± 0.4	−0.59 ± 0.6	−1.98 ± 0.6	< 0.05
Language	0.52 ± 0.3	0.35 ± 0.5	−0.58 ± 0.6	−1.85 ± 0.7	

p values indicate the significance of one-way-ANOVA comparing the patient subgroup to HC.

2.3. Image acquisition and preprocessing

The data were acquired from nine Siemens 3.0 Tesla MRI scanners (4 Verio, 1 Skyra, 3 TimTrio and 1 Prisma system) using identical acquisition parameters and harmonized instructions. To ensure high image quality throughout the acquisition phase, all scans had to pass a semi-automated quality check during the study conduction, so that protocol deviations could be reported to the study sites, and the acquisition at the respective site could be adjusted. Functional MRI was based on a T2*-weighted echo-planar imaging (EPI) sequence using a 64 × 64 image matrix with 47 axial slices (thickness 3.5 mm, no gap) and interleaved acquisition. Of 180 acquired EPIs, the first 10 time points were excluded resulting in 170 EPI volumes for the analysis. The field of view was 224 × 224 × 165 mm, isotropic voxel size of 3.5 mm, echo time 30 ms, repetition time 2,580 ms, flip angle 80 °, and parallel imaging acceleration factor 2. The sequence took 7 min 54 s. High-resolution T1-weighted anatomical images were obtained using a sagittal magnetization-prepared rapid gradient echo (MPRAGE) sequence (field of view 256 × 256 mm, matrix size 256 × 256, isotropic voxel size 1 mm, echo time 4.37 ms, flip angle 7°, repetition time 2500 ms, number of slices 192, parallel imaging acceleration factor 2). The duration of the sequence was 5 min 8 s.

Data processing was carried out using Data Processing Assistant for Resting-State fMRI Advanced (DPARSFA 4.3) (Chao-Gan and Yu-Feng, 2010). The T1-weighted anatomical images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the Statistical Parametric Mapping (SPM12) (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) New Segment toolbox implemented in Matlab 2015a (Mathworks, Natwick). The T1- weighted GM and WM partitions were normalized to the Montreal Neurological Institute (MNI) reference coordinate system using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007) and the default brain template included in CAT12 (Kurth et al., 2015) as target. Functional MRI preprocessing included removal of the first ten volumes of each fMRI scan, slice timing correction to the temporal middle, and realignment to the mean volume. The anatomical T1-weighted image for each participant was coregistered to the mean functional image such that the deformation fields generated by DARTEL from the anatomical T1-weighted images could be used to project the functional scans from each subjects' native image space into the MNI reference space. Subsequently, we applied temporal bandpass filtering (0.01–0.1 Hz), and spatial smoothing with an 8 mm isotropic full-width-at-half-maximum (FWHM) Gaussian kernel. The rsFC maps were calculated using the FSL melodic toolbox (Version 5.0.9, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/), resulting in 20 independent component analysis (ICA) maps. The resulting maps were then evaluated by experts to identify the four resting-state networks of interest, namely the VIS, EN, DMN and LAN networks, based on their spatial patterns as reported earlier (Beckmann et al., 2005; Smith et al., 2009; Castellazzi et al., 2014). We further derived the subject-level rsFC z-maps using FSL's dual regression, which generated subject-specific versions of the spatial maps and associated time series. Technically, this was realized by a decomposition of each subject's 4D dataset using the group-spatial-maps to give a set of time courses, and then afterwards, decomposition of those time courses and the same 4D dataset to get a subject-specific set of spatial maps, one per functional network (Beckmann et al., 2009; Nickerson et al., 2017).

As a final step, network-specific explicit masks were derived, in order to clearly define the areas of cerebral activations which actually belong to each resting-state network. These masks were obtained from the group-based independent component maps of all study participants, by thresholding them based on the highest 10th percentile of intensities, leading to liberal masks for each of the four resting-state (VIS, EN, DMN, LAN) networks of interest. For clarity, we would like to point out here that our executive, visual and default mode ICA-derived networks corresponded to the executive control, visual, and default mode components mentioned in (Rosazza and Minati, 2011). As for the language network, the spatial pattern of our language network corresponded to the temporo-parietal and lateralized fronto-parietal components mentioned in (Rosazza and Minati, 2011). The temporo-parietal component is characterized by the engagement of regions typically associated to language processing, while the lateralized fronto-parietal components has been associated to different functions, one of which is language (Rosazza and Minati, 2011).

2.4. Statistical analysis

Statistical analyses were performed using SPM12 and R-statistics (R Core Team, 2018), respectively. SPM12 was used for voxel-based analyses, including *t*-test and multiple linear regressions, while R-statistics was used for analysis of variance (ANOVA) and post-hoc tests on the cognitive composite scores.

One way ANOVA and Tukey honest significant difference post-hoc tests were used to compare cognitive domain composite scores across diagnostic groups as done in (Ranasinghe et al., 2014). As a significance threshold, the one way ANOVA was tested at a family-wise confidence significance level of $p < 0.05$.

In voxel-wise analysis, two-sample *t*-tests with age, sex, education and study site included as nuisance variables, were used to compare both gray matter volumes, as well as the extent of functional connectivity of the different identified resting-state networks between the healthy control and individual patient groups. This statistical approach as already applied previously in (Ranasinghe et al., 2014; Brueggen et al., 2019) was applied to study extensive differences between each diagnostic group and the control group while controlling for the previously mentioned covariates of age, sex, education and study site. The directions of the comparisons were hypothesis-driven (Brain volume: HC > SCD/MCI/AD, Functional connectivity: HC > SCD/MCI/AD). A False Discovery Rate (FDR) of $p < 0.01$ was applied to control for multiple comparisons.

Voxel-wise multiple regressions were used to explore the relationship between cognitive domain composite scores and both brain volume and functional connectivity. In the case of the volumetric analyses, we adopted an unbiased whole brain voxel-wise approach as similarly done in (Cacciaglia et al., 2018) by regressing each cognitive function (executive, visuo-spatial, memory, working memory and language) composite score on the gray matter volume estimates. In the case of the rsFC analysis, we specifically regressed each cognitive domain composite score on the respective resting-state functional connectivity network (executive, visual, default mode and language), known to be associated with each function based on previous literature (Rosazza and Minati, 2011). In so doing, executive and working memory scores were regressed on the EN, visuo-spatial scores on the VIS, memory scores on the DMN and language scores on the LAN.

The regression models were controlled for age, sex, education, diagnosis and study site. In the volumetric analysis, the total intracranial volume was included as a global value. For the rsFC analysis, the network-specific explicit masks described in the previous subsection were applied. As our focus was on visuo-spatial function, we tested further post-hoc models investigating the association of the sub-tests of the visuo-spatial cognitive domain when positive associations were found at the composite level. As a significance threshold for the volumetric analysis, an FDR of $p < 0.05$ was applied a priori. However, this led to very extensive effects across the whole brain so that we decided post hoc to use a more strict significance threshold for the volumetric findings with an FDR of $p < 0.01$. In the case of the FC analysis, an FDR of $p < 0.05$ was applied to control for multiple comparisons. In addition, for exploratory purposes, we also report volumetric and rsFC results after applying a liberal statistical significance level of $p < 0.001$ and $p < 0.01$ respectively, uncorrected for multiple comparisons. Effect sizes (Cohen's d) are reported for all voxel clusters.

3. Results

3.1. Cognitive performance across diagnostic groups

As expected, we found that the SCD subgroup performed significantly better than all other patient subgroups on all cognitive domains ($p < 0.05$, one-way-ANOVA, Tukey post hoc). In turn, the MCI subgroup also showed significantly better composite scores than the AD subgroup on all cognitive functions ($p < 0.05$, one-way-ANOVA, Tukey post hoc). The AD subgroup showed the worst performance across the different cognitive domains (Table 2). Albeit performing in the normal range in the single cognitive tests (as required by the definition of SCD), the SCD cases performed significantly worse than the healthy controls in executive, memory, and language composite scores (Table 2).

All patient subgroups (SCD, MCI & AD) were significantly different from each other ($p < 0.001$, one-way-ANOVA, Tukey post hoc). Bold text further indicates the patient subgroups that were statistically different from healthy controls (HC) after Tukey post hoc comparison between the patient groups of subjective cognitive decline (SCD), mild cognitive impairment (MCI) and Alzheimer's disease (AD), with the significance threshold set to 0.05, for the visuo-spatial, executive, working memory, memory, and language domains respectively.

3.2. Regional gray matter atrophy associated with distinct cognitive impairments in AD spectrum

When comparing each patient group to healthy controls, we found that the MCI ($p < .01$, FDR corrected, $0.40 \leq d \leq 0.90$, Fig. 1A) and AD ($p < .01$, FDR corrected, $0.40 \leq d \leq 1.70$, Fig. 1B) subgroups, but not the SCD subgroup significantly differed from the control group in regard to hippocampus volumes. Additionally, the MCI subgroup also showed atrophy in the inferior frontal gyri, right superior temporal gyrus, left anterior cingulate gyrus, left middle frontal gyrus and right inferior parietal lobule. In the AD cases, further atrophy was found in the right premotor cortex, right prefrontal cortex, right putamen and superior parietal lobule (Fig. 1B). The SCD subgroup also did not differ from the HC subgroup when a lenient significance threshold of $p < .001$ uncorrected for multiple comparisons was applied.

Furthermore, across the whole sample of SCD, MCI and AD controlling for age, sex, site, and diagnosis, we found significant associations between the volume estimates and cognitive measures. For visuo-spatial function, lower performance was associated with reduced gray matter volume in the middle temporal gyri, right temporal pole, right anterior cingulate gyrus, inferior parietal lobules, left inferior occipital gyrus, left premotor cortex, right fusiform gyrus and left superior parietal lobule ($p < .01$, FDR corrected, $0.41 \leq d \leq 0.60$, Fig. 2A). In the case of executive function, lower performance was associated with reduced gray matter volume in the right posterior cingulate gyrus, left inferior frontal gyrus, prefrontal cortices, left premotor cortex, left middle frontal gyrus, left primary motor cortex, left superior parietal lobule, right inferior occipital gyrus and right inferior parietal lobule ($p < .01$, FDR corrected, $0.38 \leq d \leq 0.70$, Fig. 2B). For working memory function, lower performance was associated with reduced gray matter volume in the left prefrontal cortex, inferior temporal gyri, right inferior occipital gyrus, left premotor cortex, middle frontal gyri, right inferior occipital gyrus, right inferior parietal lobule and left posterior cingulate gyrus ($p < .01$, FDR corrected, $0.38 \leq d \leq 0.65$, Fig. 2C). When considering memory function, lower scores were associated with reduced gray matter volume in the middle temporal gyri, superior parietal lobule, inferior occipital gyrus, inferior parietal lobules, left insular cortex, right fusiform gyrus, left anterior and posterior cingulate gyri and right inferior temporal gyrus ($p < .01$, FDR corrected, $0.40 \leq d \leq 0.75$, Fig. 2D). And lastly, for language function, lower performance was associated with reduced gray matter volume in the temporal poles, left posterior cingulate gyrus, left premotor cortex, inferior parietal lobules, prefrontal cortices, right insular cortex and left supplementary motor area ($p < .01$, FDR corrected, $0.39 \leq d \leq 0.70$, Fig. 2E).

When applying a more lenient significance threshold, we additionally found performance on the clock copy (Fig. 2G) and clock drawing (Fig. 2F) tests to be the only sub-measures of visuo-spatial function significantly associated with gray matter atrophy; lower performance was similarly associated with reduced gray matter volume in the parietal, occipital and temporal areas, similarly as in the case of the visuo-spatial composite scores ($p < .001$, uncorrected, $0.38 \leq d \leq 0.50$).

3.3. Patterns of network-specific resting-state functional connectivity associated with distinct cognitive impairments in AD spectrum

When comparing each patient subgroup to healthy controls in the extent of rsFC for each network, we found that for the visual network, neither of the patient subgroups differed significantly from the healthy control subgroup, not even at a more lenient threshold of $p < 0.01$, uncorrected. For the executive network we found that only the AD subgroup ($p < .05$, FDR corrected, $0.39 \leq d \leq 0.60$) significantly differed from the healthy control subgroup (Fig. 3A). For the default mode network we found that both the MCI ($p < .05$, FDR corrected, $0.38 \leq d \leq 0.60$, Fig. 3B.i) and AD ($p < .05$, FDR corrected, $0.38 \leq d \leq 0.80$, Fig. 3B.ii) subgroup, but not the SCD subgroup differed significantly from the healthy control subgroup. When applying a more lenient significance threshold, we also found that for the language network, both the MCI ($p < .01$, uncorrected, $0.30 \leq d \leq 0.50$, Fig. 3C.i) and AD ($p < .01$, uncorrected, $0.31 \leq d \leq 0.65$, Fig. 3C.ii) subgroups, but not the SCD subgroup differed significantly from the healthy control subgroup.

Considering the whole patient sample of SCD, MCI and AD controlling for age, sex, site, and diagnosis, we found significant associations between the cognitive composite measures and the connectivity estimates. Poorer cognitive performance scores for executive function were associated with reduced rsFC of areas within the executive network ($p < .05$, FDR corrected, $0.35 \leq d \leq 0.50$, Fig. 4A). We also found similar positive outcomes for the association of memory scores with connectivity of areas within the default mode network ($p < .05$, FDR corrected, $0.33 \leq d \leq 0.50$, Fig. 4C). When applying a more lenient significance

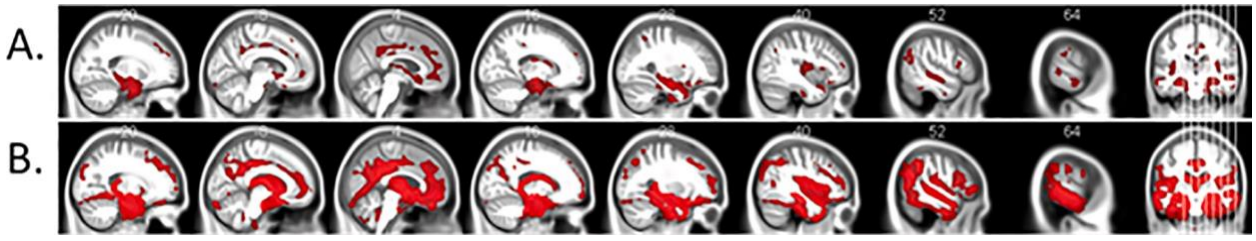

Fig. 1. Regional gray matter volume significantly differed between diagnostic groups in AD-spectrum, for the (A) MCI and (B) AD diagnostic groups respectively. Voxel-wise multiple comparisons are thresholded with $p < 0.01$, FDR corrected, cluster size ≥ 50 voxels, $0.40 \leq d \leq 1.70$. Red voxels show clusters of significantly reduced gray matter volume in patients with MCI and AD compared to HC subgroup. Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain. MNI coordinates and corresponding t values are provided in Supplementary Table 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

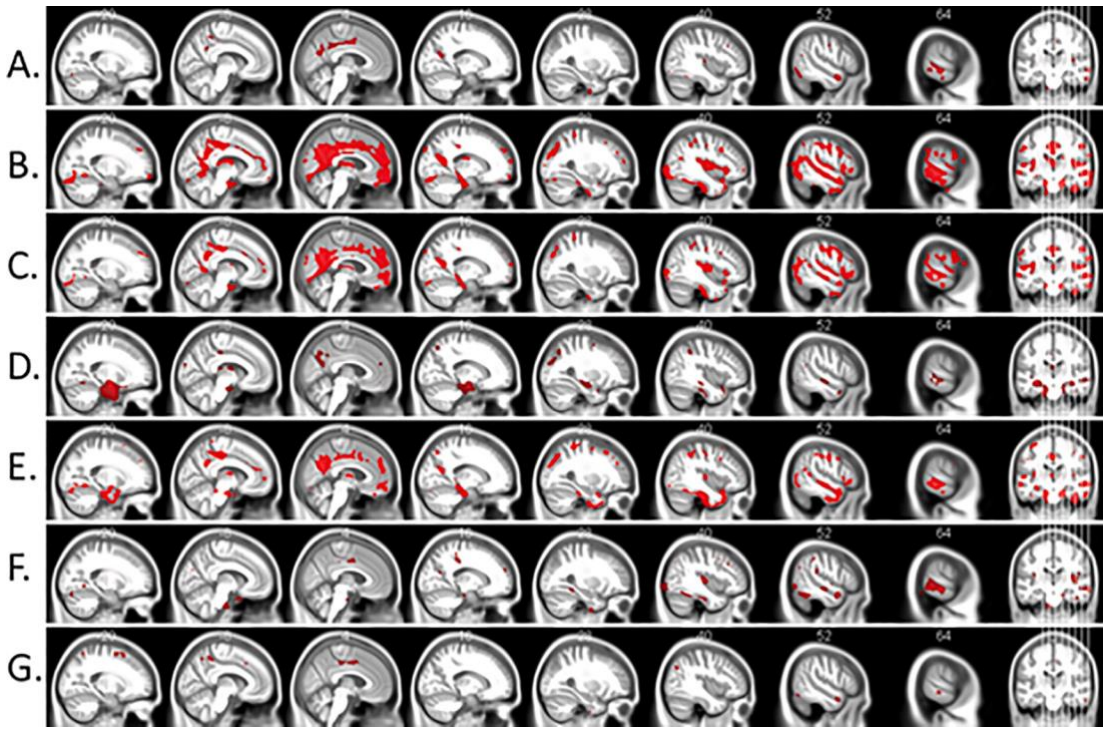

Fig. 2. Regional gray matter volume is associated with the (A) visuo-spatial, (B) executive, (C) working memory, (D) memory, and (E) language domains respectively. Figure (F) and (G) shows the association of gray matter volume with the clock drawing and clock copy subtest of visuospatial function respectively. Voxel-wise multiple comparisons are thresholded at $p < .01$, FDR corrected for only figures a-e, cluster size ≥ 50 voxels, $0.38 \leq d \leq 0.70$. Figures F and G are displayed at $p < .001$, $0.38 \leq d \leq 0.50$ uncorrected for multiple comparisons. Red voxels show clusters of significant association between gray matter volume and cognitive domain scores. Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain. MNI coordinates and corresponding t values are provided in Supplementary Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

threshold, we found that poorer cognitive performance scores for working memory were also associated with reduced rsFC of areas within the executive network ($p < .01$, uncorrected, $0.28 \leq d \leq 0.45$, Fig. 4B). The language scores were also associated with the rsFC of areas within the language network ($p < .01$, uncorrected, $0.24 \leq d \leq 0.50$, Fig. 4D). No significant effects were found for the association of the visuo-spatial function scores and the rsFC of the visual network.

4. Discussion

In this study, we tested differences in gray matter volumes, CFA-derived cognitive domain scores, as well as the extent of functional connectivity of the different identified resting-state networks across diagnostic groups involving 490 cases from the AD spectrum of the DELCODE multicenter study. We also examined associations of cognitive domain composite scores with gray matter volume and network-specific rsFC among our patient subgroup of SCD, MCI and AD. Overall, we found that cognitive performance, atrophy patterns and functional connectivity significantly differed between diagnostic groups in the AD-spectrum. Additionally, regional gray matter atrophy was positively associated with visuospatial and other cognitive impairments within the AD-spectrum. Patterns of network-specific resting-state functional connectivity (except the visual network) were also positively associated with distinct cognitive impairments within the AD-spectrum.

The current study makes an important contribution towards providing a comprehensive overview of the neural correlates of domain-specific cognitive decline in the AD-spectrum. Furthermore, extending Teipel et al. (2017) and Teipel et al. (2018) who primarily focused on the effect of multisite acquisition on rsFC and group separation, the current study further explored differences in cognitive performance, and also tested the association between composite cognitive function and alterations in specific rsFC in the AD-spectrum. Most importantly, our study extends previous rsFC studies (Ranasinghe et al., 2014; Smits et al., 2014; Balachandar et al., 2015) by leveraging the combined advantage of a more representative and large multicenter sample, and composite measures of the most relevant cognitive domains in AD-spectrum. We provide evidence for the viability of using CFA-derived cognitive composite scores in investigating structural atrophy and alterations in rsFC in the AD-spectrum. CFA-derived cognitive composite scores as already obtained in previous studies such as the ADNI and WRAP studies (Dowling et al., 2010; Park et al., 2012), provide a more reliable metric of cognitive function than single test measures (Wolfsgruber et al., 2017; Clark et al., 2016). Nonetheless, the association of CFA-derived cognitive domain composite scores with rsFC of underlying networks in a multricentric cohort has to the best of our knowledge not been previously studied.

Consistent with previous rsFC studies with smaller sample sizes (Ranasinghe et al., 2014; Smits et al., 2014; Balachandar et al., 2015), we showed differences between our healthy control and patient groups in a larger cohort. Nonetheless, difference of rs-FC between groups was spatially restricted, where areas of difference between groups were mainly found in small clusters. These differences, however, had moderate to large effect sizes. A possible explanation for the spatially restricted effects could owe to the notion that resting-state networks are made up of spatially distinct brain regions with underlying structures, some of which may be more susceptible to disease related alterations than the others (Greicius et al., 2004; Cai et al., 2017). For example, Greicius et al. (2004) studied hippocampal connectivity in relation to other brain regions within the DMN in AD patients, and reported that a deficit of functional connectivity was evident in the posterior cingulate and in the hippocampi, but not in other regions such as the mesial prefrontal cortex and lateral parietal cortex which also belong to the default mode network (Rosazza and Minati, 2011). Additionally, contrary to our expectation, none of the diagnostic groups showed

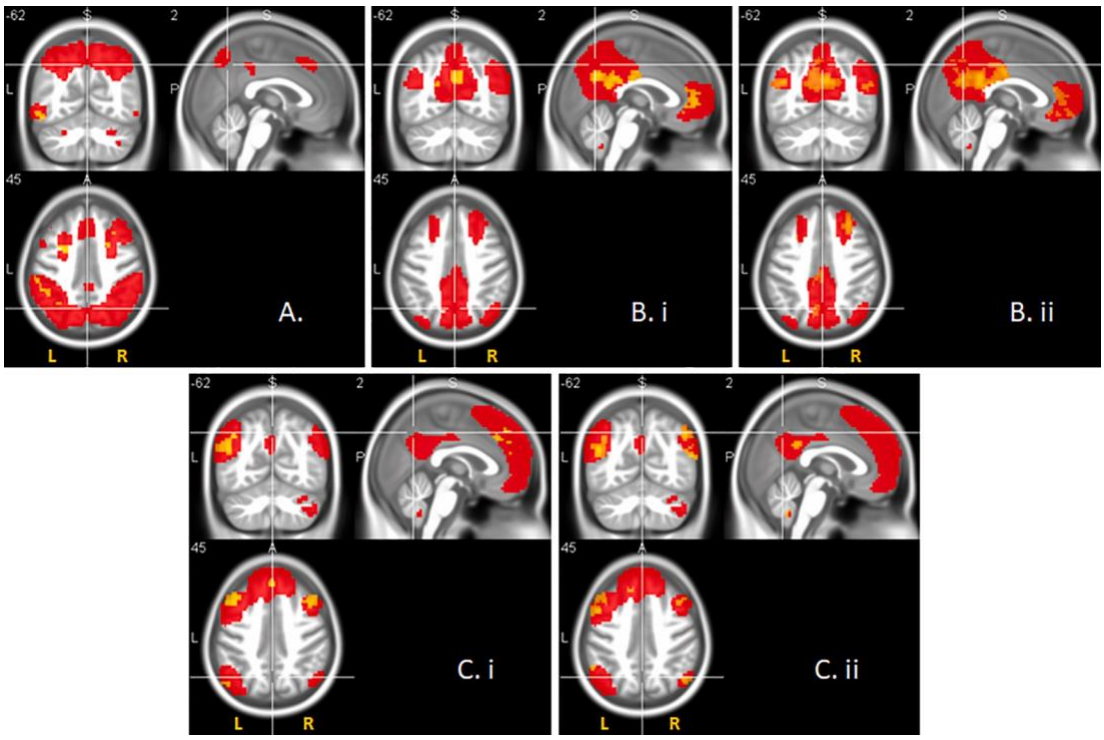

Fig. 3. Network-specific resting-state functional connectivity significantly differed between diagnostic groups in AD-spectrum, for the (A) executive, (B) default mode and (C) language networks respectively. Significance is reported at $p < .05$ FDR corrected for the executive and default mode networks, and at $p < .01$ uncorrected for the language network accordingly. Cluster size ≥ 20 voxels, $0.30 \leq d \leq 0.80$. Red voxels represent group resting-state networks, yellow voxels show clusters of significant difference between the patient and healthy control subgroups on network-specific functional connectivity. Statistical comparison was restricted to the corresponding networks only by functional masks determined from the whole sample (see Section 2.3). Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain. MNI coordinates and corresponding t values are provided in Supplementary Table 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significant differences for the connectivity of the visual network. A possible explanation for this can be found in the notion that the recruitment of the visual network may be more task dependent or external-stimuli-driven, as evidenced in a number of functional MRI studies focusing on the visual network (Stevens et al., 2010; Yang et al., 2015; Ruiz-Rizzo et al., 2018). For instance, Stevens et al. (2010) reported that VIS connectivity during resting-state fMRI was influenced by a prior visual stimuli exposure, suggesting that significant VIS activation leading to a possible difference between controls and patients, could more likely be observed when participants are subjected to a visual task or to visual stimuli in general.

When we assessed the association of CFA-derived cognitive domain composite scores with network-specific rsFC, we found consistent outcomes for the association of the executive domain scores with areas within the executive network, and the memory domain scores with areas within the default mode network, in agreement with previous studies which applied single test measures of cognitive function (Ranasinghe et al., 2014; Balachandar et al., 2015; Gardini et al., 2015; Zhou et al., 2015; Brueggen et al., 2016). Less consistent associations were found for the association of the working memory domain scores with areas within the executive network, and the language domain scores with areas within the language network. However, we could not find positive associations between visuo-spatial domain scores and the rsFC of the visual network. The finding of more consistent associations for the executive and memory domain is not surprising, as these domains are known from previous studies to be highly affected earlier in the disease process at the onset of AD (Seeley et al., 2009; Zhou et al., 2012; Quental et al., 2013; Lim et al., 2014; Rajan et al., 2015).

The lack of a significant association of the visuo-spatial domain and the visual network in the current study could be the result of a more pronounced executive control influence of the single subtests (clock drawing, clock copying & CERAD figure copying) included in the visuo-spatial cognitive domain score. Performance on the clock drawing test as reported by Cosentino et al. (2004) particularly appears to place an executive control demand on participants, thereby recruiting cognitive resources other than visuo-spatial resources. To test for this possibility, we performed post-hoc analysis, using the same method as performed earlier for the functional analysis. When associating the visuo-spatial domain scores with the rsFC of the executive network and default mode network, we expectedly found significant associations ($p < .01$, uncorrected), which buttresses a prominent role of executive dysfunction for visuospatial performance in the AD spectrum (Supplementary Fig. 1). Furthermore, our MCI and AD diagnostic subgroups differed significantly from the HC subgroup in extent of atrophy and rsFC patterns as expected, with the exception of the SCD subgroup. This agrees with previous studies which even after applying machine learning approaches to identifying the SCD subgroup have also reported classification accuracy below that of the MCI and AD subgroups (Liu et al., 2018; Yan et al., 2019), thereby further highlighting the difficulty in characterization and discrimination of the SCD subgroup relative to the HC subgroup. Nonetheless, some studies which overcome this particular limitation of the current study, have identified abnormal AD biomarkers in CSF and also brain correlates of AD pathology in SCD compared to HC (Wolfsgruber et al., 2020).

Our findings agree with the majority of previous studies that assessed the associations of regional gray matter volume with either single test measures of cognitive function, or composite measures of cognitive domains derived by averaging across standardized scores of single tests of cognitive function in both healthy elderly cohorts (Chee et al., 2009; Bruno et al., 2016; Cacciaglia et al., 2018) and patients (Di Paola et al., 2007; Mitolo et al., 2013; Ranasinghe et al., 2014; Smits et al., 2014; Cacciaglia et al., 2018). These previous and our findings differ from a

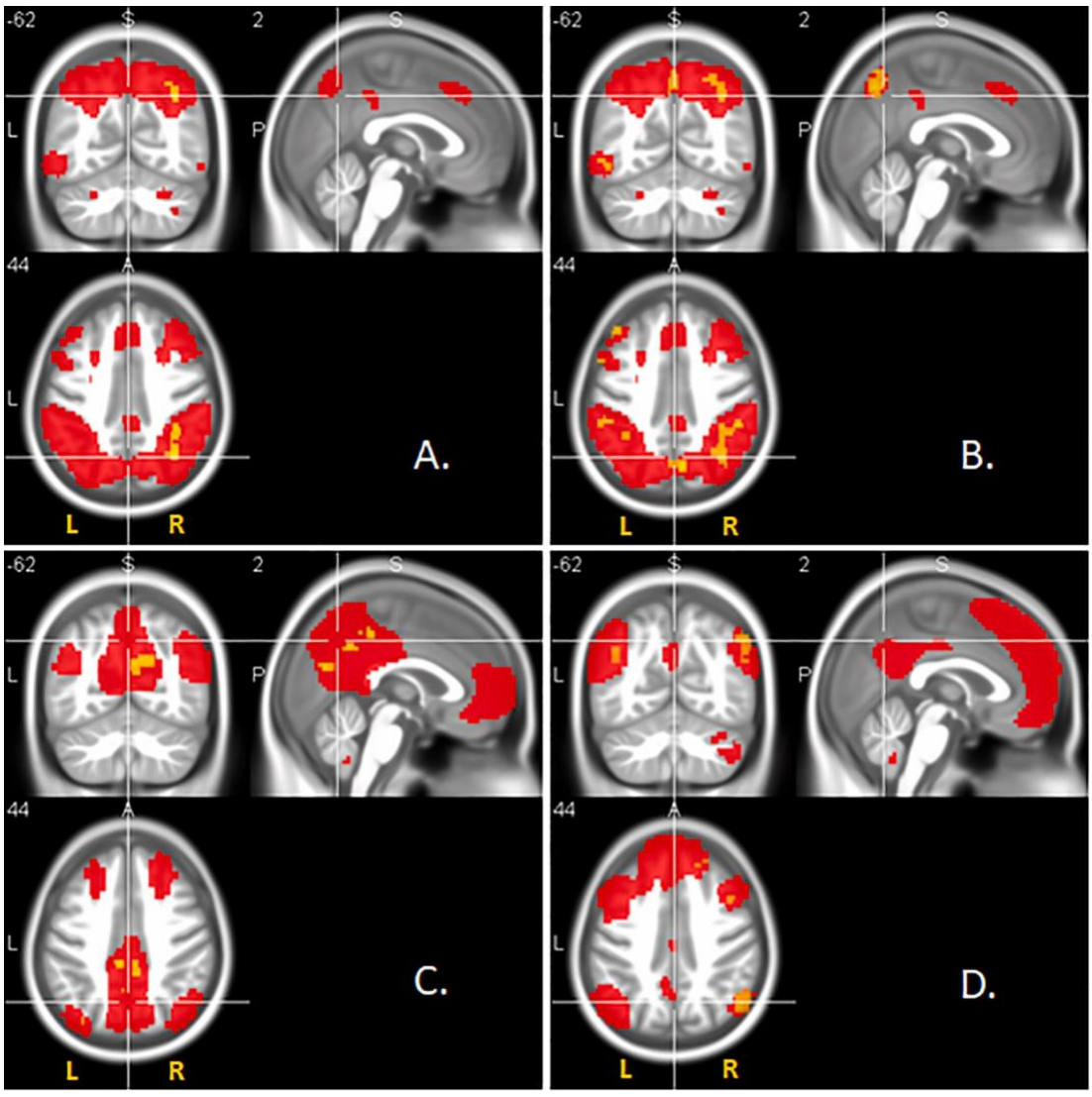

Fig. 4. Network-specific resting-state functional connectivity is associated with the (A) executive, (B) working memory, (C) memory, and (D) language functions respectively. Significance is reported at $p < .05$ FDR corrected for the executive and memory functions, and at $p < .01$ uncorrected for the working memory and language functions accordingly. Cluster size ≥ 20 voxels, $0.24 \leq d \leq 0.50$. Red voxels represent group resting-state networks, yellow voxels show clusters of significant association between network-specific functional connectivity and cognitive domain scores. Association was restricted to the corresponding networks only by functional masks determined from the whole sample (see Section 2.3). Statistical maps are superimposed on a rendering of the Montreal Neurological Institute template brain. MNI coordinates and corresponding t values are provided in Supplementary Table 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

previous MEG and MRI study Ranasinghe et al. (2014) that found no correlation between gray matter atrophy and cognitive performance, however, the number of cases n=27 in this previous study was very low. We found consistent associations for the volumetric analysis with the related composite scores of domain specific cognitive functions, which is indicative of the utility of our approach to deriving measures of cognitive function. When considering the pattern of atrophy for visuo-spatial function, we found that higher cognitive domain scores were associated with more gray matter volume in parietal, occipital and temporal regions. When we extended the association of atrophy patterns to the single measures of visuo-spatial function, we interestingly found that in the case of the clock drawing and clock copy test scores, the parietal and temporal areas similarly showed effects as was the case with the visuo-spatial domain score. The parietal, occipital and temporal regions are known to form part of the dorsal and ventral pathways responsible for the processing of visual stimuli (Mishkin et al., 1983), hence, atrophy in such regions have been shown to be associated with poorer visuospatial abilities in patients with MCI (Mitolo et al., 2013) and AD (Smits et al., 2014).

A possible limitation of the current study is the data-driven approach employed in generating the rsFC networks using ICA, in contrast to a seed-based approach (Brueggen et al., 2016) in which regions of interest (ROI) are defined *a priori*. Here, it might be possible that the resulting independent components we defined as rsFC networks based on evidence in the literature such as (Castellazzi et al., 2014; Rosazza and Minati, 2011) slightly differ from a few other studies, as we generated in total ~20 components compared to for instance generating ~44 components (Tie et al., 2014), which could lead to additional brain regions being considered in our study for certain networks. This indicates that despite the advantage of data-driven approaches in the automatic derivation of resting-state networks, heterogeneity in data-driven approaches still remains an open question.

In conclusion, the current study provides a comprehensive description of the structural and functional correlates of the key cognitive domains of AD, with a focus on the visuo-spatial domain. Our findings provide evidence for CFA-derived cognitive domain composite scores as

considerable proxy measures of the cognitive deficits associated with regional gray matter volume in the AD spectrum. The same is the case for the cognitive deficits associated with network-specific resting-state functional connectivity, however, with the exception of visuo-spatial cognitive deficits. We recommend the use of CFA-derived composite scores in future studies as they provide a more comprehensive measure of cognitive functions. The methodological approach applied by Balachandar et al. (2017) could be adopted, in terms of dividing the participant sample into those with severe or mild visuo-spatial deficits based on their visuo-spatial domain scores, while assessing the association with the rsFC of the visual network. This would provide the possibility to do within-diagnostic-group comparisons of the extent of rsFC with the extent of visuo-spatial deficit. As regards measuring visuo-spatial function, such future studies could then employ the usage of automated or simulated tests of visuo-spatial function, such as the computer-aided Visuo-spatial Cognitive-Performance Test (VCP-Test) (Matsubayashi et al., 1991), to provide performance metrics that are independent of rater abilities. Additionally, more robust measures of visuo-spatial function such as the Rey Complex Figure Test (Meyers and Meyers, 1995), could be considered while deriving the CFA-derived composite scores. More research focusing especially on the association of the rsFC of the visual network and visuo-spatial domain is required to confirm or extend these initial findings.

CRediT authorship contribution statement

Chimezie O. Amaefule: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Martin Dyrba:** Methodology, Data curation, Investigation, Writing - original draft. **Steffen Wolfsgruber:** Formal analysis, Investigation. **Alexandra Polcher:** Investigation. **Anja Schneider:** Investigation. **Klaus Fliessbach:** Investigation. **Annika Spottke:** Investigation. **Dix Meiberth:** Investigation. **Lukas Preis:** Investigation. **Oliver Peters:** Investigation. **Enise I. Incesoy:** Investigation. **Eike Spruth:** Investigation. **Josef Priller:** Investigation. **Slawek Altenstein:** Investigation. **Claudia Bartels:** Investigation. **Jens Wiltfang:** Investigation. **Daniel Janowitz:** Investigation. **Katharina Bürger:** Investigation. **Christoph Laske:** Investigation. **Matthias Munk:** Investigation. **Janna Rudolph:** Investigation. **Wenzel Glanz:** Investigation. **Laura Dobisch:** Investigation, Data curation. **John D. Haynes:** Investigation. **Peter Dechent:** Investigation. **Birgit Ertl-Wagner:** Investigation. **Klaus Scheffler:** Investigation. **Ingo Kilimann:** Investigation. **Emrah Düzel:** Investigation. **Coraline D. Metzger:** Investigation. **Michael Wagner:** Investigation. **Frank Jessen:** Investigation. **Stefan J. Teipel:** Conceptualization, Investigation, Writing - original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102533.

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Original Paper

Effect of Spatial Disorientation in a Virtual Environment on Gait and Vital Features in Patients with Dementia: Pilot Single-Blind Randomized Control Trial

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Abstract

Background: Orientation deficits are among the most devastating consequences of early dementia. Digital navigation devices could overcome these deficits if adaptable to the user's needs (ie, provide situation-aware, proactive navigation assistance). To fulfill this task, systems need to automatically detect spatial disorientation from sensors in real time. Ideally, this would require field studies consisting of real-world navigation. However, such field studies can be challenging and are not guaranteed to cover sufficient instances of disorientation due to the large variability of real-world settings and a lack of control over the environment.

Objective: Extending a foregoing field study, we aim to evaluate the feasibility of using a sophisticated virtual reality (VR) setup, which allows a more controlled observation of disorientation states and accompanying behavioral and physiological parameters in cognitively healthy older people and people with dementia.

Methods: In this feasibility study, we described the experimental design and pilot outcomes of an ongoing study aimed at investigating the effect of disorientation on gait and selected physiological features in a virtual laboratory. We transferred a real-world navigation task to a treadmill-based virtual system for gait analysis. Disorientation was induced by deliberately manipulating landmarks in the VR projection. Associated responses in motion behavior and physiological parameters were recorded by sensors. Primary outcomes were variations in motion and physiological parameters, frequency of disorientation, and questionnaire-derived usability estimates (immersion and perceived control of the gait system) for our population of interest. At this time, the included participants were 9 cognitively healthy older participants [5/9 women, 4/9 men; mean age 70 years, SD 4.40; Mini–Mental State Examination (MMSE) mean 29, SD 0.70) and 4 participants with dementia (2/4 women, 2/4 men; mean age 78 years, SD 2.30 years; MMSE mean 20.50, SD 7.54). Recruitment is ongoing, with the aim of including 30 cognitively healthy older participants and 20 participants with dementia.

Results: All 13 participants completed the experiment. Patients' route was adapted by shortening it relative to the original route. Average instances of disorientation were 21.40, 36.50, and 37.50 for the cognitively healthy older control, cognitively healthy older experimental participants, and participants with dementia, respectively. Questionnaire outcomes indicated that participants experienced adequate usability and immersion; 4.30 for presence, 3.73 for involvement, and 3.85 for realism of 7 possible points, indicating a good overall ability to cope with the experiment. Variations were also observed in motion and physiological parameters during instances of disorientation.

Conclusions: This study presents the first feasibility outcomes of a study investigating the viability of using a sophisticated VR setup, based on an earlier real-world navigation study, to study spatial disorientation among cognitively healthy older people and people with dementia. Preliminary outcomes give confidence to the notion that our setup can be used to assess motion and physiological markers of disorientation, even in people with cognitive decline.

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Trial Registration: ClinicalTrials.gov; https://clinicaltrials.gov/ct2/show/NCT04134806

(JMIR Serious Games 2020;8(4):e18455) doi: 10.2196/18455

KEYWORDS

spatial disorientation; activity recognition; wayfinding; wearable sensors; dementia; virtual reality; older adults

Introduction

Background

Challenges in wayfinding and orientation are early symptoms of people with mild cognitive impairment (MCI) or dementia. These deficits decrease mobility [1,2] and social interaction [3,4] of the affected people, which in turn may lead to further cognitive decline. Assistive technology devices (ATDs) can help reduce the burden of spatial disorientation by providing interventions (eg, by giving cues to the patients). For patients with cognitive impairment, an ideal ATD should fulfill 2 requirements: It should be situation-adaptive (ie, the device adapts to the situation and context, including the environment, user goal, and intention), and it should be subsidiary (ie, the device delivers assistance only in case of need, for example, if the user is disoriented). These requirements ensure that the device does not replace but rather leverages existing cognitive capabilities [5]. Technically, this means that the ATD needs to be able to detect instances of disorientation in real time from the available sensor data, like accelerometric, electrodermal (EDA), or electrocardiographic (ECG) data.

In a previous field study—Situation-Aware Navigation Assistance for Dementia Patients using Causal Behavior Models (SiNDeM) [6]—concerned with wayfinding behavior in MCI and patients with dementia through an urban environment, a machine learning classifier for disorientation based solely on accelerometric data led to a cross-validated area under the receiver operating characteristics curve (AUC) value of 0.75. The outcome of this study suggested that instantaneous detection of disorientation may, in principle, be possible; however, the accuracy was not sufficient to serve as a basis for individual support. Hence, additional signals, such as heart rate variability, may be needed to increase detection accuracy. However, performing such a study in a real-world environment requires a large effort in staff and resources. One of the limitations highlighted in the previous study [6] was that the recorded number of disorientation instances per subject was low, which can be problematic when training machine learning classifiers. This is due to the fact that, firstly, the experimenter could not influence whether (and when) subjects became disoriented. Secondly, the high level of inconsistency in the real-world environment did not enable the controlled observation of disorientation states that are not induced by experimental manipulation (eg, changing of landmarks) but rather by cognitive deficits, as in the case of the patients. Thus, a large effort is required to obtain only a small amount of data related to disorientation instances (which is the data that is most relevant in this context). A more robust approach to modeling real-time disorientation might rely on both a controlled environment as well as other more informative parameters in addition to motion. Gait features have recently been vastly explored as motion markers of disease progression [7-9] and fall detection [10], and could also be informative in identifying behavioral variations predictive of disorientation. Additionally, physiological parameters, including skin conductance response and heart rate variations, have also been previously shown to be influenced by the occurrence of spatial disorientation [11,12].

As an alternative to real-world studies, navigation tasks can be posed in a virtual-reality (VR) environment [13,14]. However, most experimental setups do not integrate a physical component—participants sit in front of a computer screen, and thus the physical manifestation of disorientation cannot be assessed. More generally, the need for physical locomotion might influence navigation behavior, as participants are in a dual-task situation where they have to simultaneously walk and navigate through the environment. Such dual-task conditions require cognitive resources such as attentional flexibility, which are depleted as disease progresses [15-18]. Therefore, a pertinent question would be, how can the navigation task be transferred to a safe and controllable VR environment while the participants still have to walk actively (like they would do in the real world), to allow for the investigation of the relationship between disorientation and physical motion? To this extent, we propose a VR-based experimental setup that allows realistic physical movement.

Specifically, we employed the GRAIL (Gait Real-time Analysis Interactive Lab; Motekforce Link) system, providing the opportunity to navigate on a treadmill through a virtual environment. Using such a virtual environment has several advantages: The setup is safe for the subjects, reproducible, and the experimental effort per subject is lower compared to a real-world study. Furthermore, the experimenters have full control over the environment; for example, the environment can be manipulated to induce disorientation to record a larger amount of disorientation instances. Also, disorientation states resulting from cognitive deficits can be properly observed.

Objectives

This study aims to evaluate the feasibility of using a complex virtual reality setup, which allows a more controlled observation of disorientation states, to study spatial disorientation among older cognitively healthy people and people with dementia, thereby validating the findings of the real-world SiNDeM study. This environment gives access to a broader set of sensor domains compared with the real-world setting, including gait, skin conductance, and heart rate variability in addition to accelerometry; it also allows for the examination of a larger sample size within a more controlled environment to build a more accurate disorientation detection and intervention model.

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Research Questions

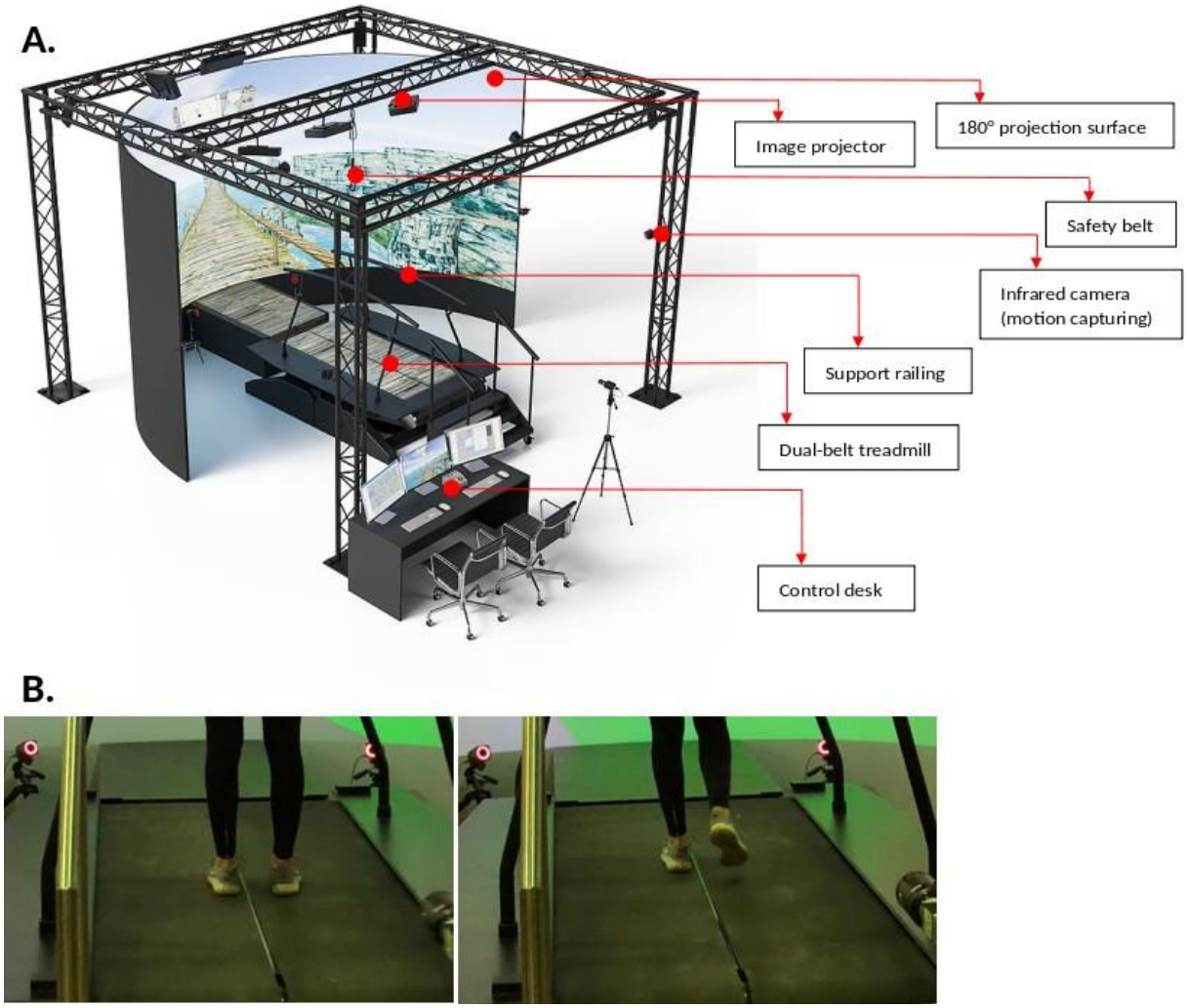
The study is based on the following core research question: Is our setup feasible for investigating states of disorientation during active navigation among cognitively healthy older participants and people with dementia? This is motivated by the reported overall effectiveness of VR in assessing spatial navigation [19], spatial navigation memory for predementia screening [20], and improving cognitive functioning among individuals with neurocognitive disorders [21,22]. Evaluation of the feasibility of our setup is further guided by the following research questions: (1) Is the virtual environment adequately immersive? (2) Are we able to reliably induce disorientation through the manipulation of the virtual environment? (3) Do the participants feel comfortable with the walking pattern change due to our navigation mechanism? (4) Are we able to adequately measure motion and physiological parameters?

Methods

Study Design and Setting

This is a single-blind randomized experiment currently taking place in Rostock, Germany. The experiments are carried out in the Gait Real-time Analysis Interactive Lab (GRAIL; Motekforce Link; Figure 1), which is a Class I medical system (according to the Medical Device Directive 93/42/EEC) and is specially designed to ensure the safety of participants for clinical gait analysis and training. This is achieved through a safety belt and side railings, which serve to support the participant and prevent falls. The GRAIL further consists of a treadmill, a large 180° projection screen, and an optical motion capturing system (Vicon Motion Systems Ltd). A virtual environment that models a city center is shown onscreen, and subjects can navigate through the environment by walking on the treadmill. Gait kinematics and kinetics, as well as spatio-temporal gait parameters, can be derived from the motion capturing data [23]. The system has been used, for example, for rehabilitation exercise [24] or for gait analysis in different settings [25-27].

Figure 1. (A) The GRAIL system, consisting of a dual-belt treadmill, 180° projection surface, and optical motion capturing system (figure sourced from Motek Medical); (B) plantar figures.



The 3D virtual environment used in this study was generated from OpenStreetMap (OSM) data of the Rostock city center, using the OSM2World tool [28]. This data includes building heights and rudimentary 3D models of landmark buildings

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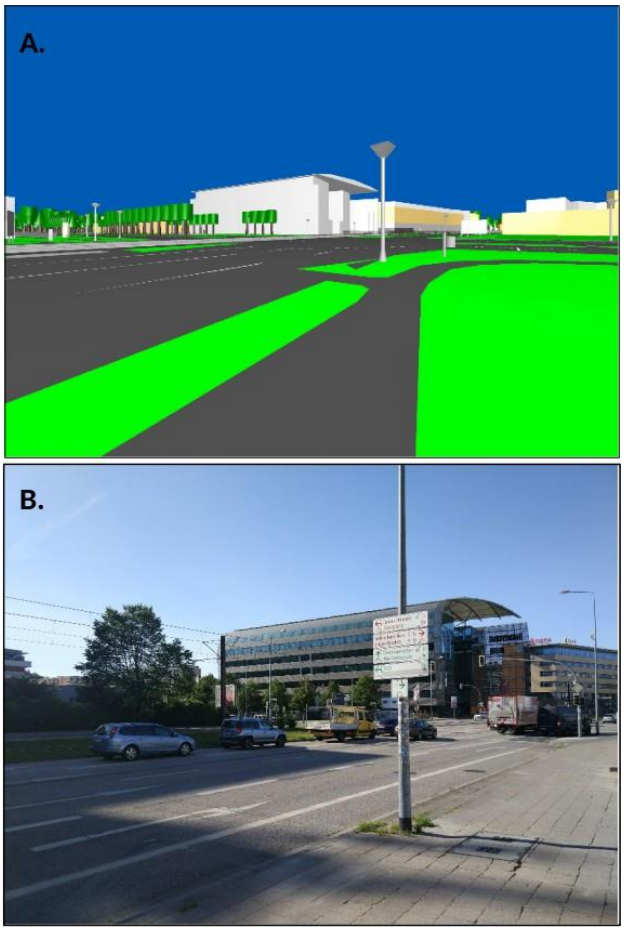
(Figure 2). The resulting VR environment is a low-detail replication of the real city, but does not contain moving objects like cars or pedestrians. The treadmill speed is feedback-controlled, which allows participants to walk with their preferred walking speed. This is achieved by adapting the belt speed according to the subject position (measured by motion capturing) in relationship to the center of the belt [29]. The movement speed through the VR is synchronized with the belt speed (ie, the current speed of the participant). An important constraint of the GRAIL system is that a change in walking direction (eg, turning left or right) is not supported by the treadmill; it does not rotate. Thus, it was necessary to provide an alternative means for voluntary direction change: participants can choose their walking direction by walking on either side of the treadmill. Walking on the left side of the treadmill will result in a left turn in the VR environment, and vice versa. We are aware that this is not identical to naturalistic walking: subjects still walk a straight line on the treadmill, whereas the movement in the VR describes a curve. Therefore, as part of the current study reports, we observed the movement behavior of participants and asked them about their experiences.

Figure 2. (A) The OpenStreetMap (OSM)–generated virtual environment containing some notable landmarks from (B) the real world.



Recruitment and Eligibility

Participants were recruited in 3 groups: (1) mobile, physically and cognitively healthy, younger (18-40 years of age) adults; (2) mobile, physically healthy older [60-85 years of age; Mini–Mental State Examination (MMSE) scores≥28] adults, including cognitively healthy older adults without memory complaints and cognitively healthy older adults with subjective cognitive decline (SCD) in the absence of any clinical evidence of cognitive impairment; and (3) physically healthy older adults with diagnosed MCI or mild dementia due to Alzheimer disease (60-85 years of age; MMSE 15-27). People with dementia and cognitively healthy older adults are recruited from the memory clinic of the University Medicine, Rostock, while the healthy young adults are recruited from within the University of Rostock student community. Exclusion criteria for all groups include other neurological conditions besides dementia, an inability to understand task instructions and questionnaire items, and deaf-mutism and blindness.

As the focus of this feasibility study was on cognitively healthy older adults and people with dementia, 9 cognitively healthy older participants (5/9 women, 4/9 men; 6/9 with SCD; mean age 70 years, SD 4.40; MMSE mean 29, SD 0.70) and 4 people with dementia (2/4 women, 2/4 men; mean age 78 years, SD 2.30; MMSE mean 20.50, SD 7.54) have been included so far. Of the 9 cognitively healthy older participants, 4 participants (2/4 women, 2/4 men) were randomly assigned to the experimental group. Informed consent was given by all participants.

Study Procedure and Data Collection

Participants were guided along a path in the VR environment (Figure 3). Afterward, they were set back to the starting location

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and asked to walk the same path again, this time unguided. For half of the healthy young or older subjects (the experimental group), phases of disorientation were induced by changing landmarks or decision points in the VR environment (Figure 4) while subjects were required to walk the path on their own. The changes were (1) moving a landmark from one intersection to the next intersection, (2) adding a decision point (ie, an intersection), (3) blocking a road, or (4) moving the goal indicator to a different location. Overall, 5 locations have been manipulated. For the patients with dementia, the environment was not changed, as we assume that these participants would show phases of disorientation already without such changes due to existing cognitive deficits. Based on the experience with the first patient with dementia, we adapted the route for the other patients by shortening it due to earlier observed fatigue while navigating the route (Figure 3).

Figure 3. Map of the routes of (A) cognitively healthy older participants and (B) patients with dementia. Red crosses denote locations where the environment is changed in the experimental run. The environment is unchanged for the patients with dementia; however, the route is shortened (image: Google Maps).

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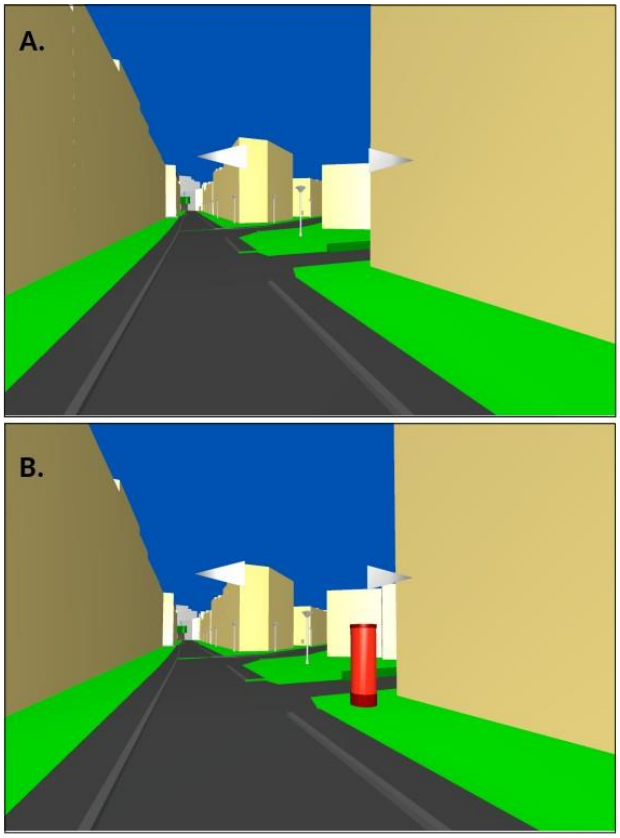
Figure 4. Example of changes in the environment to induce disorientation. (A) Original environment shown in the guided walk (note the red landmark at the far end of the road, to the right). (B) Manipulated environment used in the experimental run; in this case, the landmark is moved to a different intersection.



The participants were familiarized with the depicted city center by briefly showing them a map, such that problems in wayfinding will be due to disorientation instead of exploration in an unknown environment. In addition to recording kinematic and kinetic gait parameters as provided by the GRAIL system, participants are also equipped with 3 wearable sensors on the left wrist, right ankle, and chest, each of which contain a 3-axes accelerometer and 3-axes gyroscope sampled with 64 Hz. Additionally, the chest sensor records an electrocardiogram (ECG; 1024 Hz), and the wrist sensor records electrodermal activity (EDA; 32 Hz). Wearable sensor data and data provided by the GRAIL system are synchronized by an event-based mechanism (ie, participants perform a distinctive movement at the beginning of the recording, which can be easily located in all sensors) and are resampled to 100 Hz. All wearable sensors have been used in previous studies [6,30] and validated [31-33].

After the orientation task, participants filled out the igroup Presence Questionnaire (IPQ) [34], a questionnaire on the functionality and realism of the interaction with the VR environment, as well as questions regarding engagement in the study, hobbies and activities, technical device usage, and demographics. Additionally, participants provided answers to open questions on (1) problems that occurred in controlling the direction, (2) suggestions for improving the controlling mechanism, (3) which properties in the VR they used for orientation, (4) orientation problems they had, and (5) suggestions for enabling better self-orientation in the VR environment. Table 1 displays the experimental procedure in phases.

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Table 1. Experimental procedure for the cognitively healthy older participants (n=9) and patients with dementia (n=4). The patient group followed the procedure of the control group.

Phase		Experimental group (n=4)	Patients with dementia (n=4) and control group (n=5)
1	Preparation (90 min)	Study information, informed consent, assessment of physical and cognitive status, blood draw, fixing of markers and electrodes, and practice walking on treadmill	
2	Task 1 (20 min)	Learning the route: accompanied walk (route: Figure 3)	
3	Task 2 (20 min)	Autonomous navigation (modified environment)	Autonomous navigation (unchanged environment)
4	Questionnaires (20 min)	Presence, navigation, orientation, experience with technical devices	

Randomization

Randomization of the healthy younger and older participants into the experimental or control group was carried out using the program Research Randomizer (Social Psychology Network) [35]. In contrast, the patients with dementia are only assigned to the control group (ie, with the adapted route), as we expect a sufficient number of episodes of disorientation in people with MCI or dementia even without interfering with their environment.

Behavior Annotation

An offline annotation procedure was applied to the video data recorded during the orientation task, for assessing the observable orientation behavior of the participants using the ELAN 5.8 tool (The Language Archive) [36]. As a coding scheme, we used an adequate adaption of the coding scheme provided by Yordanova et al [30]. The same scheme has been used in the SiNDeM field study [6]. This coding scheme was developed both by domain experts and assistive systems designers, based on interviews, video logs, data from a systematic literature review, and concepts from existing ontologies, for the purpose of providing assistance to people with dementia during their outdoor mobility. Hence, it covers aspects of orientation behavior that are beyond the scope of wayfinding in our VR setup (eg, behaviors associated with attention to traffic). For this reason, we adapted the coding scheme to capture exactly those behaviors that are obtainable within our virtual reality setup.

Specifically, to identify instances of disorientation, we annotated when participants show wandering behavior (ie, nongoal-directed walk), communication behavior (ie, asking for help when disoriented), topological orientation (ie, trying to orient themselves based on the surrounding environment), or spatial orientation (ie, trying to orient themselves based on landmarks). In addition, different types of errors that are associated with disoriented behavior were annotated (ie, initiation, realization, sequence, and completion errors). The annotations are being evaluated based on the level of agreement between annotators (ie, interrater reliability in terms of Cohen kappa [37]).

Ethical Approval

This study has been reviewed and approved by the Ethics Commission of the University Medicine Rostock (Approval number: A 2019-0062).

Outcome Measures

The study is estimated to run until the end of 2021. The outcome measures to be collected are included in Table 2. However, for this pilot study, we focused on the feasibility and usability (level of immersion, perceived control of the gait system) as primary outcomes, and on measures of motion variations (walking speed), physiological variations (heart rate, skin conductance response), and spatial disorientation (frequency of occurrence) as secondary outcomes.

Table 2. Study outcome measures.

Outcome Measure	Measurement	Modality	Status
Feasibility and usability	Level of immersion, usability feedback	igroup Presence Questionnaire (IPQ), usability questionnaire	Ongoing
Heart rate variability	Rate of change in heart rate	Electrocardiographic sensor	Ongoing
Skin conductance	Rate of change in electrodermal response	Electrodermal activity sensor	Ongoing
Spatial disorientation	Incidences of disorientation	Customized annotation scheme in ELAN	Ongoing
Gait variability	Incidences of change in gait pattern	Gait capturing system of the GRAIL	Ongoing
Accelerometry	Incidences of change in motion pattern	Accelerometers	Ongoing
Apolipoprotein E4 status	Presence of the variants Apo-E2, -E3, and -E4 in the blood samples	7.5 ml blood samples	Ongoing

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Data Analysis

Analysis of both the quantitative and qualitative data collected during the course of the study will take place in accordance with predetermined analysis plans; however, for this feasibility study with a limited sample size, we reported basic descriptive statistics (mean and standard deviation as well as frequencies) applied to the quantitative and qualitative data for evaluation purposes using R statistical software (version 3.6.0; R Core Team).

Results

Immersiveness of the Virtual Environment

All participants could complete the experiment. Responses to the IPQ informed us that the cognitively healthy older participants perceived an above-average degree of immersion; group mean item scores (between 1 and 7, where 7 means highest perceived presence/involvement/realism) were 4.60 for presence, 3.92 for involvement, and 4.42 for realism. The patients with dementia, on the other hand, while reporting lower mean scores relative to the cognitively healthy older participants, still perceived a considerable degree of immersion, with group mean item scores of 3.63 for presence, 3.31 for involvement, and 2.60 for realism. Of the 13 participants, only 1 (7%) of the participants reported simulator sickness.

Inducing Disorientation Through the Manipulation of the Virtual Environment

Our setup was viable in inducing instances of disorientation. We observed an average of 21.40 instances of disorientation for the cognitively healthy older participants in the control group and 36.50 instances for the cognitively healthy older participants in the experimental group. For the patients with dementia, an average of 37.50 instances of disorientation was observed. A number of these instances of disorientation were observed either at points where the virtual environment was manipulated or at subsequent points afterward, where the participants had to reorient themselves due to the altered virtual environment (Figure 4). This amounted to a good proportion of the data being annotated as disoriented. Furthermore, regarding properties used for orientation, participants mentioned the landmark shown in Figure 4, houses, intersections, and trees.

Comfortability With the Walking Pattern Change due to our Navigation Mechanism

Participants' responses to the usability questionnaire show that the control over the chosen direction in the VR environment was perceived as functional for both the cognitively healthy older participants and patients with dementia (eg, easy to learn; participants were able to move to where they wanted at their own pace), and adequately naturalistic. Table 3 shows the answer scores on the questionnaire items regarding usability and navigation control. When asked about problems that occurred, only 2 (22%) of the 9 cognitively healthy older participants mentioned initial difficulty with controlling the direction of movement, while 1 (25%) of the 4 patients with dementia mentioned that it felt unusual. Of the 9 cognitively healthy older participants, 2 (22%) also mentioned that the right and left movement felt a little rapid. Additionally, in the case of the first patient with dementia sampled, we observed early fatigue while navigating the route, leading to an adaptation of the patient's route (Figure 3). Also, due to a temporary technical fault at the time of recording, we could not obtain gait information for the first patient with dementia sampled. However, all other data were collected for this patient, and complete data could be collected for the 3 subsequent patients with dementia sampled.

Table 3. Questionnaire regarding the usability of controlling movement in the virtual-reality environment for the cognitively healthy older participants (n=9; group mean score) and patients with dementia (n=4; group mean score). The scale ranged from 1 (fully disagree) to 7 (fully agree).

Questionnaire item	Cognitively healthy older participants (n=9), mean score	Patients with dementia (n=4), mean score
1. Learning to navigate was easy.	4.9	4.0
2. After a while, I did not have to think about how to navigate.	4.3	3.0
3. I was able to move where I wanted.	5.8	3.6
4. I was able to move how I wanted	4.9	3.0
5. I was able to stop at a specific place when I wanted.	5.9	4.0
6. I did not feel limited in my freedom of movement.	5.8	3.3
7. I felt tired after navigating.	3.3	2.5
8. Navigation felt natural.	4.7	3.3

Measuring Motion and Physiological Parameters

Variations in walking speed, heart rate, and skin conductance response were observed among our pilot participants. Figures 5A, B, and C, respectively, show a sample of the recorded walking speed, accelerometry, heart rate variability, and skin conductance response amplitude for a participant in the control group (where the environment was not manipulated), a participant in the experimental group (where the environment was manipulated, as described above), and for a patient with dementia (where the environment was not manipulated). Relative decrease in motion (walking speed and accelerometry) and an increase in heart rate variability and skin conductance response amplitude can be observed during instances of disorientation.

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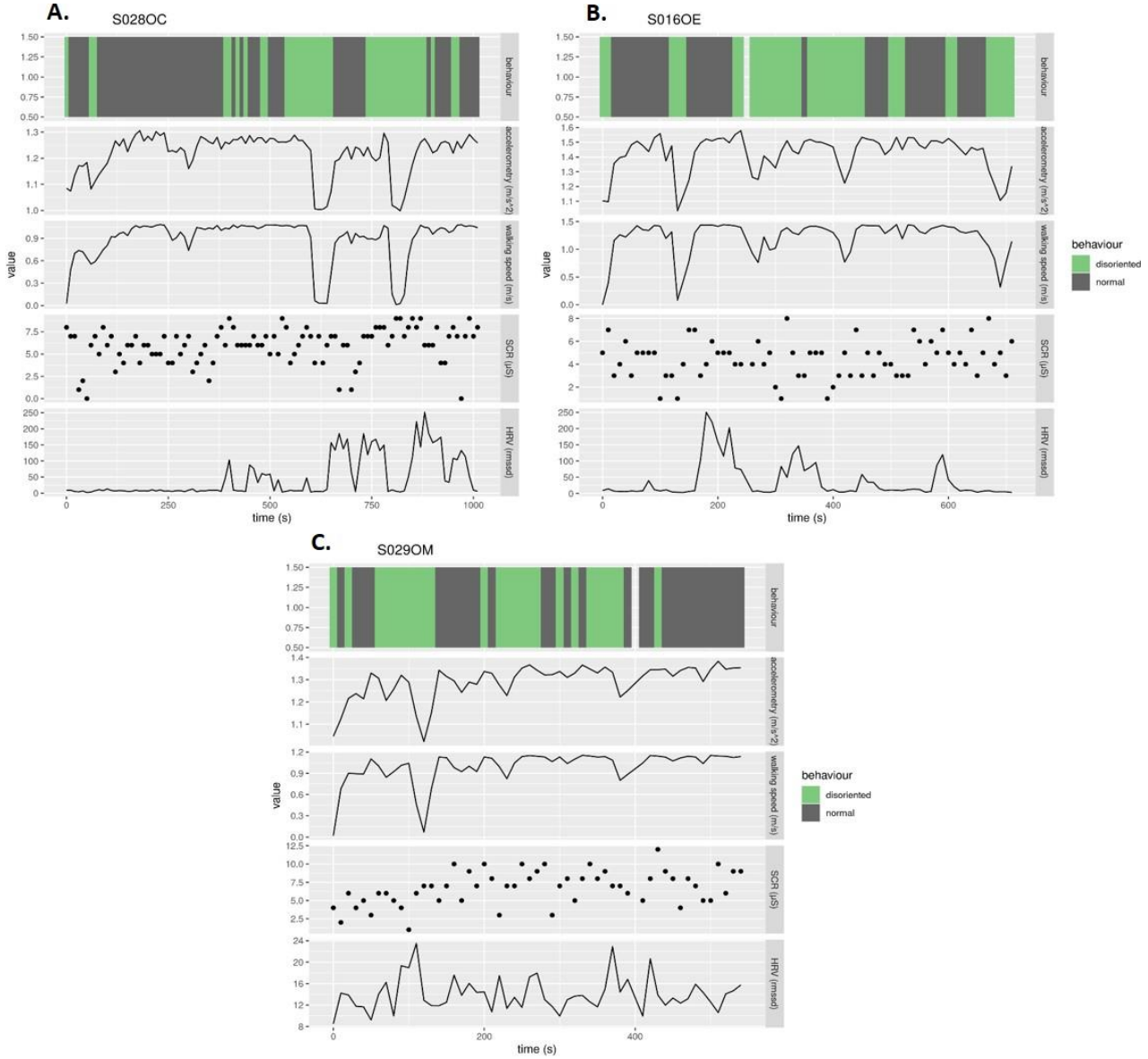
Figure 5. Sample of motion and physiological data showing variations in walking speed, accelerometry, heart rate, and skin conductance of participants occurring during instances of disorientation (green bars in the first row) from the unguided walk for (A) an older control participant (environment not manipulated), (B) an older experimental participant (environment was manipulated), and (C) a patient with dementia (environment not manipulated).



Discussion

In this paper, we presented the design for a study investigating the effect of spatial disorientation on physical motion and physiological features, as well as the initial outcomes of the pilot sample. The combined usage of a fully instrumented treadmill, wearable sensors, and an adequately immersive VR system to investigate real-time disorientation among older participants and patients with dementia during active navigation is, to the best of our knowledge, unprecedented. Previous studies that investigated spatial orientation [38-40] and navigation memory [20,41] have relied mostly on VR systems in which navigation or interaction with the VR environment was passively based on the use of control objects (eg, joystick, mouse). This, however, further limits the ecological validity of such setups, as the locomotion aspect of real-world navigation was apparently lacking.

Our patient and cognitively healthy older participant dyad reported a noticeably varying degree of immersion. While the older healthy participant group reported a higher level of immersion [42], the patient group reported a relatively lower level of immersion compared to the cognitively healthy older participant group. However, this is not surprising as we also expect cognitive and perceptual abilities to play a significant role in the evaluation of the VR setup, as people with dementia are known to experience visuoperceptual difficulties [43,44], which may influence this judgment. Nonetheless, participants' responses to the usability part of the questionnaire indicated an overall confidence that our setup is effective in investigating manifestations of disorientation among cognitively healthy older adults and people with dementia. Furthermore, the first patient with dementia sampled experienced fatigue while navigating the route (akin to the finding of Behrens et al [27]), which suggests that dual-task conditions can be mentally exhausting among older participants. Therefore, this effect could be

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exacerbated by the increased difficulty of multitasking as a result of cognitive deficits [45]. Hence, we adapted the route of the patients by shortening it relative to the original route.

Considering the number of instances of spatial disorientation, we confirmed our expectation of finding more disorientation events among the participants in the experimental group (changed environment) compared to the participants in the control group (unchanged environment). This preliminary observation gives credence to the validity of our setup in inducing the target behavior of disorientation. We also observed that the patients with dementia expressed a considerable amount of disorientation. This was the case even though the environment remained unchanged, thereby indicating that moments of disorientation accruing to cognitive deficits can also be reliably observed among patients with dementia in our setup. The variations in motion and physiological data observed among our pilot participants illustrates that we are able to adequately obtain the relevant motion and physiological parameters within our approach. As building situation-adaptive devices for supporting navigation among people with dementia relies on the adequate detection of disorientation [6], our setup therefore provides a promising approach to acquiring the needed data.

We acknowledge that there are multiple alternatives to using the GRAIL system for the goal of investigating the effect of spatial disorientation on gait in a lab environment. An alternative to projecting the VR to a screen would be to use a VR headset, like the Oculus Rift (Facebook Inc) or the Samsung Gear VR (Samsung Electronics). A main advantage of the GRAIL over the Oculus Rift and Samsung Gear VR lies in the relative ease of use, safety, and closeness to reality for our study sample, which consists of cognitively healthy older adults and people with dementia who may not be as apt as younger participants at learning to navigate with a VR headset. To participate in the navigation task on the GRAIL, the participant walks freely on the treadmill without any headset or hand gear and observes the virtual environment as one normally would in a real-life situation. In contrast, with the Oculus Rift and Samsung Gear VR, a remarkable difference to the real-world situation is observed the moment one has to put on a headset and navigate with the use of controllers. Additionally, such devices can quickly cause simulator sickness, especially if participants have to move through the environment and when synchronization of head movement and VR movement is not optimal [46]. In this study, simulator sickness was only reported by 1 of the participants so far. Moreover, virtual reality games [such as serious games for dementia care (SGDC)] in which participants interact with the virtual environment using their body movements in the absence of controllers have also reported positive effects on patients' mental and physical health [47]; these include improvement in memory and motivation, through the performance of mental and physical activities that are carried out while using various physical motions.

A major experience reported by a few of the participants, which also serves as a limitation to the current study, was the fact that control over left/right movement felt somewhat challenging. Possible alternatives to the current direction control mechanism used in this study include using a game controller to choose directions [19], or leaning in the respective direction [48]. However, we expect that this would be perceived as even more unrealistic in terms of how well the experimental setup models the real-world situation in which we are very much interested, as this would require movements that are not representative of real-world locomotion. For instance, Kizony et al [19] acknowledged that the combination of the joystick and treadmill may have posed an additional challenge to the older adults, although no discomfort was reported. This could have been further confirmed if participants were asked about their experience using structured measures such as the IPQ and usability questionnaires as employed in this study. Nonetheless, usability and immersion in VR studies remains an open topic. Further studies replicating the setup employed in this study could serve to provide further testing and data for evaluating this setup. Omnidirectional treadmills [49,50] (that allow free movement in all directions) could be a promising alternative for this purpose. However, such systems are still research prototypes and are not commercially available.

In conclusion, our GRAIL setup allows us to collect a rich dataset: most prominently, the motion capturing system can be used to assess spatio-temporal gait parameters (eg, walking speed). Results from this feasibility study suggest that our setup is sufficient in investigating sensor-derived features of spatial disorientation, even in patients with dementia, in a safe and controlled environment that is comparable to the real world. This is evident in the fact that we observed a considerable amount of disorientation among our participants, which also corresponded to the sensor data and questionnaire responses. Based on the full data set, in the future, we will focus on training machine learning classifier models for discriminating instances of disorientation from moments of orientation, with the aim of coming up with a relevant feature set for developing an interventional device. This classifier subsequently will be tested with real-world data (ie, perform transfer of learning). This feasibility study encourages further investigations on the possibility of more robust real-time detection of spatial disorientation, with the aim of coming up with adequate situation-aware interventions.

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Authors' Contributions

COA and SL contributed to the conception of the work, acquisition and analysis of the data, and wrote substantial parts of the manuscript. COA reviewed and adapted the annotation scheme used for the study. TK, SJT, SL, and COA provided substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work. TK, SJT, SL, and COA participated in drafting the work, revising it critically for important intellectual content, and approved the version to be published; these authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ATD: assistive technology device
BPM: beats per minute
ECG: electrocardiography
EDA: electrodermal activity
GRAIL: Gait Real-time Analysis Interactive Lab
IPQ: igroup Presence Questionnaire
MCI: mild cognitive impairment
MMSE: Mini–Mental State Examination
OSM: OpenStreetMap
SiNDeM: Situation-Aware Navigation Assistance for Dementia Patients using Causal Behavior Models
VR: virtual reality

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At Crossroads in a Virtual City – Effect of Location-based Spatial Disorientation on Gait Variability among Healthy Older Adults

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Short Title: Crossroads in Virtual City - Effect of Location-based Spatial Disorientation

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Keywords: Spatial Disorientation, Gait Analysis, Older Adults, Virtual Reality, Wayfinding

Abstract

Background: Aging has been associated with decline in cognitive and motor performance, often expressed in dual-task walking situations, which could include wayfinding. A major challenge to successful wayfinding is spatial disorientation, occurring mostly at crossings. Although gait changes have been observed in various dual-task conditions, little is known about the effect of disorientation on gait variability in wayfinding among older adults.

Objectives: Identify the effect of location-based spatial disorientation on gait variability and psychophysiological response among healthy older adults during wayfinding in a controlled environment.

Method: We analyzed data of 38 participants (22 female) consisting of young controls ($n = 10$), older controls ($n = 14$) and older experimental ($n = 14$). Participants performed a wayfinding task consisting of 14 major decision points (7 intersections) within a virtual environment (VE) projected on a 180° screen, while walking on a self-paced treadmill equipped with a marker-based optical motion-capture system. The VE was held constant for the controls, and manipulated for the experimental participants. Disorientation was identified based on a customized annotation scheme. Variability in gait was measured as the primary endpoint. Psychophysiological response measures, including heart rate and skin conductance were continuously monitored as secondary endpoints, and estimates of cognitive effort. Mixed Effects ANOVAs were applied to hypothesis-driven outcome measures extracted from decision points.

Results: We found main effects of disorientation on gait (walking speed, step length, stance time and stride time), and psychophysiological response (skin conductance response). Interaction effects were observed for disorientation and location (crossing vs. non-crossing) on gait (stride time) and psychophysiological measures (heart rate variability). A disorientation by group (control vs. experimental) interaction was only observed for psychophysiological response (skin conductance response), among older participants. Age effects on gait were significant for walking speed and stance time.

Conclusions: Results provide evidence for the impact of spatial disorientation on changes in gait pattern and cognitive effort among older adults during wayfinding. Being at crossings also had implications for the effect of disorientation on gait and cognitive effort. This gives further insight into the substrates of real-world navigation challenges among older adults, with emphasis on viable features for designing situation-adaptive interventional devices aiding independent mobility.

Introduction

Healthy aging and Independent mobility

The World Health Organization (WHO) defines healthy aging as the process of developing and maintaining the functional ability that enables wellbeing in older age. This includes a person's ability to meet their basic needs, learn, grow and make decisions, be mobile, build and maintain relationships, and contribute to society [1]. As a key aspect of maintaining functional ability, independent mobility is highly dependent on the individual's ability to successfully navigate their

spatial environment. Aging is, however, associated with functional decline in selective cognitive domains (e.g. executive and memory function) [2] required for successful navigation. As adults advance in age, they experience serious problems in spatial navigation, often leading to getting lost [3]. As a result, they avoid unfamiliar routes and places, which limits their personal autonomy and in turn diminishes their quality of life [4]. This becomes a cause for concern, given that the ability to ambulate independently has been suggested as a major contributor to wellbeing and autonomy in older individuals [5]. Moreover, declines in spatial navigation can be among the earliest indicators of a progression from healthy aging to Alzheimer's dementia (AD) [6], which further necessitates more exploration into the contributing factors to navigation difficulties among older adults.

The wayfinding Process

According to Darken et al. [7], an important cognitive component of spatial navigation is wayfinding. Wayfinding involves deliberate navigation between two or more points of interest and can take place in both familiar (e.g. near home) and unfamiliar (e.g. on vacation) environments [8]. The wayfinding process is essentially a problem-solving activity [9], and could be influenced by factors such as perception of the environment, availability of wayfinding information (e.g. route descriptions, landmarks), ability to orientate, cognitive and decision-making processes, which determine the effectiveness of the wayfinding process [10]. Cognitive models that have been put forward to explain the wayfinding process have made reference to the iterative processes of route planning and plan execution [11]. Route planning describes the process of reviewing internal (memory) and/or external (such as maps) information to plan a sequence of navigation actions from an origin to a destination. During route planning, individuals tend to identify potential routes that satisfy their goals and then use several implicit and explicit strategies to quickly reduce options and settle on a route [8]. Following, route planning is the execution of the plan, which manifests in physical actions such as walking in a goal-oriented manner [12]. Walking alone (not only in a goal-oriented manner), is a task requiring cognitive input and this input is even greater in older adults [13]. In this sense, the wayfinding process is established as a dual-task process (planning and physically moving the body), involving a strong emphasis on two aspects of the environment: landmarks and intersections [8]. Brunyé et al. [8] describes landmarks as environmental features that prompt familiarity, resolve locational ambiguity, and cue sequences of actions. Studies show that wayfinders often focus on landmarks positioned within particular intersections, employing them both for recognition and to cue appropriate actions such as continuing forward or taking a turn [14]. In light of this, intersections have frequently been implicated as critical decision points, considering that they place a demand on wayfinders to make decisions regarding how to continue their journey (e.g. continue straight, turn right or left) [15]. Support for this argument can be derived from the findings of previous studies which have equally shown that, overall, more errors (indicative of disorientation) were observed at intersections (i.e. crossings) [16, 17].

Spatial disorientation and Wayfinding

A term which has been coined to express the difficulty in wayfinding, experienced mostly by cognitively impaired older adults, and often leading to getting lost is spatial disorientation [18]. Spatial disorientation detection has met considerable attention in the study of Alzheimer’s disease (AD) pathology [16, 19]. Considering that instances of spatial disorientation are ubiquitous, detecting

these instances in real time becomes a priority. However, for real-time detection to be achievable, patterns of change in behavior (e.g. gait, psychophysiological response, interacting with environment), which co-occur with spatial disorientation, need to be recognized. Following the outcome of a previous field study [20], a clear set of behaviors considered to be indicative of disorientation were identified. An example of such behaviors is “surveying the surrounding”, which according to Yordanova et al. [20] is indicative of the process of trying to re-orient oneself during moments of disorientation (e.g. taking the wrong turn). In a subsequent field study concerned with wayfinding behavior in persons with mild cognitive impairment (MCI) and dementia [16], real-time instances of spatial disorientation were identified by means of the indicators developed in Yordanova et al. [20]. Further analysis of these disorientation instances, using machine learning classifiers based solely on properties of the composite acceleration amplitude, was able to yield good but insufficient accuracy for individual prediction, which was determined by the area under the receiver operating characteristics curve (AUC) value of 0.75; representing the accuracy of the accelerometric features in discriminating between moments of orientation and disorientation. The outcome of this study suggested that instantaneous detection of disorientation is feasible, however, the accuracy was not sufficient to serve as a basis for individual support due to the major study limitations – limited number of training features based only on properties of the composite acceleration amplitude from accelerometric data and an uncontrolled environment. An alternative to real-world navigation studies, which has gained popularity in recent times, is laboratory-based virtual reality (VR) studies [6]. In summary, navigation tasks posed in a virtual-reality environment (VE) enjoy the advantage of having naturalistic interactive settings while ensuring a high degree of control and standardization [21]. This creates the enabling environment for accurately singling out the effect spatial disorientation might have on motion and psychophysiological behavior.

The current Study

Extending the study by Schaat et al. [16], the current study sought to investigate the possible effect of spatial disorientation on gait and psychophysiological response among healthy older adults in a more controlled setting involving the Gait Real-Time Analysis Interactive Lab (GRAIL). The GRAIL has been reliably used by a number of previous studies in measuring gait performance with satisfactory outcomes [16, 36]. It was intended that undertaking a wayfinding task would place similar cognitive demands on the participants as other dual-task conditions (e.g. mental fatigue), and that moments of disorientation will lead to heightened cognitive workload, as participants try to re-orient themselves. To ensure that adequate instances of disorientation are observed among the healthy older adults whom are the focus of the current study, and thereby overcoming the limitation of an earlier field study [16], disorientation was systematically induced for half of the older participants. Hence, this study was motivated by two major questions: (1) does spatial disorientation have an effect on gait and/or psychophysiological parameters, and (2) does the effect of spatial disorientation on gait and/or psychophysiological parameters depend on one’s location (i.e. non-crossing vs. crossing) among healthy older participants in a VE. The focus on healthy older participants is motivated by the importance of detecting correlates of spatial disorientation earlier on in older participants before any neurodegeneration occurs. This will enable the prospect of early detection and intervention using assistive technology devices (ATD). Furthermore, the gait and psychophysiological parameters were chosen as primary and secondary outcomes respectively, considering that they have been well explored in different dual-task [22, 23] walking conditions, and have appeared to produce significant

age effects [22], including indications of cognitive effort [22] or deficit [24]. Additionally, psychophysiological parameters are reliable measures of associated stress response even in non-ambulatory conditions [25, 26]. An additional rationale for focusing on gait and psychophysiological measures lies in the high potential for evaluating real-time changes in these parameters by a wearable assistive navigation device. Lastly, the emphasis on location (non-crossing vs. crossing) is motivated by the proven influence of intersections on wayfinding behavior [8, 16, 17] . We therefore hypothesized that: (1) spatial disorientation will impair gait outcomes among older adults; (2) the impairment of gait outcomes by spatial disorientation among older adults will be more pronounced at intersections; (3) spatial disorientation will also lead to increased psychophysiological response among older adults, and (4) the increase in psychophysiological response due to spatial disorientation among older adults will also be more pronounced at intersections.

Materials and Methods

Participants

The 38 volunteers consisted of young controls ($n = 10$), older controls ($n = 14$) and older experimental ($n = 14$) participants. The younger participants constituted of young adults between ages 18 and 45, while the older participants constituted of older adults between ages 60 and 85. The young participants were mainly included as a first control group, enabling the investigation of possible age effects on gait with the older control participants. As a first control group, the younger participants were not the focus of the current study, but primarily served as a yardstick for investigating age-related outcomes among the older control participants. The older participants were randomly assigned to either the control or experimental group. The younger volunteers were students of the University of Rostock. The older participants were community-dwelling volunteers. Prescreening for the older participants comprised the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) cognitive battery, which included the Mini-Mental State Examination (MMSE) test [27]. Exclusion criteria for all participants were past or present unstable medical conditions, major psychiatric disorders or neurological diseases and musculoskeletal injuries. All participants had either normal or corrected-to-normal vision. Table 1 shows demographic characteristics of the participants. All volunteers were informed about the experimental procedures and possible risks associated with the experiment before giving their written consent. The study followed the guideline of the declaration of Helsinki [28], and was approved by the ethics committee of the University Medicine Rostock (Approval number: A 2019-0062).

Materials

The experiments were carried out in the GRAIL (Motek Medical B.V). The GRAIL-system consisted of a treadmill, a large 180° projection screen and an optical motion-capturing system. Twenty six passive markers were placed on the participant's anatomical landmarks based on the Plug-in-Gait model of VICON (C7, T10, Sternum, Clavicle, 4 on the Pelvis; anterior and posterior superior iliac spine, 2 on the Thighs, 4 on the Knees, 2 on the Tibias, and 5 on each Foot; toe, 5th metatarsus, inner ankle, outer ankle and heel) and detected by 12 VICON infra-red cameras (www.vicon.com). A low-detail 3D virtual model of the Rostock city center was projected onscreen. The virtual environment was generated from OpenStreetMap data of the city, using the OSM2World tool (osm2world.org). This data includes building heights and rudimentary 3D models of landmark buildings. The resulting VR

environment is a low-detail replication of the real city, but does not contain moving objects like cars or pedestrians (see Appendix A of supplementary material). Participants navigated through the virtual environment by walking on a self-paced treadmill. Additionally, participants were equipped with three wearable sensors (Movisens GmbH) on the left wrist, right ankle and chest that each contain a three-axes accelerometer with a sampling rate of 64 Hz. In addition to accelerometry, the chest sensor also recorded electrocardiographic activity (ECG, 1024 Hz), while the wrist sensor recorded electrodermal activity (EDA, 32 Hz). Participants' orientation behavior was further unobtrusively recorded using a GoPro Hero 7 action camera (www.gopro.com). The camera was placed facing the treadmill and projection screen at a distance of about 2 meters to the left side of the treadmill, and at a height of about 0.5 meters. Figure 1 shows a depiction of the experimental setup. The ECG and EDA data were preprocessed using Kubios HRV Premium (University of Kuopio, Finland) and LEDALAB (www.ledalab.de) respectively. As for the video data, annotation by 2 trained annotators was carried out using the ELAN software (ELAN Linguistic Annotator 5.6.0.; Max Planck Institute for Psycholinguistics Nijmegen, The Netherlands). Further specific details about the study setup can be found in [17].

Study design and Procedure

The current study employed a 2 (*orientation:* oriented vs. disoriented) x 2 (*location:* crossing vs. non-crossing) x 3 (*group*: young controls vs. older controls vs. older experimental) mixed-factorial design. Orientation and location were manipulated within participants. Participants performed a wayfinding task consisting of 14 major decision points (7 crossings) within the virtual environment (VE). A crossing was defined as a point where movement in 4 directions was possible, while a non-crossing was defined as a point where movement was only possible in less than 4 directions for the decision points (DP). Movement through the VE was achieved by walking on the treadmill. Participants chose their walking direction by walking in the center or on either side of the treadmill. Walking on the left side of the treadmill resulted in a left turn in the VE, and vice versa. Walking in the center resulted in a linear forward progression. Prior to the wayfinding task, participants underwent a training session in which they were properly familiarized with navigating using the setup. The study only proceeded upon oral confirmation from the participants that they were comfortable in using the setup. Additionally, comfortability of the setup has previously been explored in an earlier feasibility study [17]. The wayfinding task consisted of two trials. For the first trial, participants were *guided* along a path (start to goal position) in the VE (shown in Fig. 1). The participants were instructed to learn the path during the guided walk, and were familiarized with the wayfinding route, by briefly showing them a map (Fig. 1). The map (excluding details about the DPs) was shown to participants on a printed out A4-size paper for approximately 1 minute. In comparison to some previous navigation studies [29, 30] in which route maps were shown for 5 minutes, we deemed 1 minute sufficient for 2 reasons: 1). Participants were additionally led along the route in the first (learning) trial in addition to being shown a map. Hence, in contrast to Meneghetti et al. [30] and Beni et al. [29] the map served as an additional reference in explaining the task, but was not the primary means of route learning. 2). The focus of the current study was on establishing motion and psychophysiological correlates of navigation errors and not on the dynamics of route learning or visuo-spatial and other cognitive factors affecting navigation ability. The study instructions can be found in Appendix B of the supplementary material. This ensured that errors during the wayfinding task were mainly due to disorientation, instead of exploration in an unfamiliar environment [16]. In the second trial,

participants were set back to the starting position, and asked to walk the same path again, this time *unguided*. For half of the healthy older subjects (the experimental group), phases of disorientation were induced by changing landmarks or decision points in the VE during the unguided walk. The changes included – moving a landmark from one intersection to the next intersection, adding a DP, blocking a road, or moving the goal indicator to a different location. Overall, five locations were manipulated (shown in Fig. 1). More specifically, the DPs were altered as follows: DP4 – a red pillar was moved to DP4 from DP7; DP9 – the road was blocked; DP11 – a new path was introduced; DP13 – the color of the pillar was changed to red; DP14 – the goal location was moved a little further away. The essence of inducing disorientation among the experimental group was to allow enough instances of navigation errors, enabling the sufficient observation of the effect of disorientation on gait and psychophysiological response. Additional depiction of the changes can be found in Appendix A of the supplementary material. The changes were always the same for all older participants in the experimental group. The experiment lasted an average duration of 40 minutes.

Outcome Measures

Primary outcome measures from the unguided trial included spatio-temporal gait parameters – walking speed, step length, stride time and stance time derived from the VICON markers as described in [31]. Furthermore, the coefficient of variation (CV) of all gait parameters, an index of gait variability, which has been shown to be affected by cognitive effort in dual-task walking conditions [22] among healthy older adults was derived. The CV was calculated for each gait parameter as the ratio of the standard deviation to the mean multiplied by 100 ($\mathrm{CV} = \text{standard deviation} \times \text{mean}^{-1} \times 100$). Secondary outcome measures included psychophysiological parameters – root mean square of the successive heartbeat interval differences (RMSSD) which is a measure of heart rate variability (HRV), and skin conductance response (SCR, amplitude and count; both representing magnitude and frequency of changes in electrodermal conductivity respectively) that were continuously monitored using the sensors on the chest and wrist respectively. Changes in both psychophysiological measures (i.e. reduction in RMSSD and increase in SCR) have also been associated with cognitive effort [22, 32]. All resulting data were synchronized by an event-based mechanism (participants perform a distinctive movement at the beginning of the recording, which can be easily located in all sensors), and resampled to 100 Hz. Additional outcome measures included if participants were oriented or disoriented (orientation), and if the decision point which they were at was a crossing or non-crossing (location). In order to identify instantaneous disorientation, the video data from the unguided walk was annotated using a customized scheme, which was an adequate adaptation of the scheme earlier employed in [16]. More specifically, we annotated when participants show wandering behavior (i.e., non-goal-directed walk), communication behavior (i.e., asking for help when disoriented), topological orientation (i.e., trying to orient themselves based on the surrounding environment), or spatial orientation (i.e., trying to orient themselves based on landmarks). In addition, four different types of errors that are associated with disoriented behavior were annotated [17]. These included initiation (i.e., failure to commence the task), realization (i.e., failure to make a correct turn leading to the goal location at decision points), sequence (i.e., failure to proceed continuously with the task), and completion (i.e., failure to locate the goal point) errors. Following, all outcome measures for each participant were segmented according to the decision points along the wayfinding route, and each outcome measure was computed for each segment.

Statistical Analysis

The resulting data were assessed for normality by inspection of histograms and the Shapiro-Wilk test. The Fisher's exact test, with Bonferroni correction for multiple comparison when applicable, was used to evaluate if the observed frequency of disorientation instances differed between locations (non-crossing, crossing), and between all groups (young control, older control, older experimental). Due to the scarcity of disorientation instances among the young controls, as expected, the Fisher's test was chosen over the popular chi-square test, as it is more suitable for smaller sample sizes [33]. To determine if there were differences between all groups for the distribution of gender, the Fisher's exact test was equally applied. Differences in age and education years of participants between all groups were evaluated using a one-way ANOVA with Bonferroni-corrected post-hoc tests to identify where the difference lay, while difference in MMSE score between the older control and older experimental participants was evaluated by an independent samples t-test. Using the R package VCD, the reliability of the video annotations between the 2 annotators (i.e. inter-rater reliability) was assessed based on the Cohen's kappa, which in comparison to percent agreement, is especially robust against agreement by chance [34]. Mixed effects analyses of variance (ANOVAs) models within the generalized linear mixed model (GLMM) framework, having orientation (oriented, disoriented) as well as location (non-crossing, crossing) as within-subject variables, and group (older controls, older experimental) as between-subject variable were conducted for the average of each outcome measure using the LMER and LMERTEST R packages. Again, the young controls were excluded from the ANOVA models as they primarily served to investigate age effects with the older controls, and as well, had marginal instances of disorientation. More specifically, we assessed if: (1) spatial disorientation had an effect on gait and/or psychophysiological parameters, and (2) the effect of spatial disorientation on gait and/or psychophysiological parameters depended on the location or group of the older participants. When statistically significant interactions were found, we conducted Bonferroni-corrected post-hoc tests to identify the direction of effects. Effect sizes were expressed as partial eta-squared (η_p^2). The level of statistical significance was set at $p < 0.05$. Further exploratory analyses focused on investigating if there was an effect of age (young controls vs. older controls) on gait using unequal sample t-tests. We also explored if there was any relationship between the gait parameters analyzed and accelerometric parameters (i.e. the individual magnitude of acceleration of the chest, wrist and ankle sensors), which have also been shown to be relevant in real-time disorientation detection [16] using the Pearson product-moment correlation with only the older participants (i.e. older control and older experimental) included and corrected for multiple comparisons using the Holm–Bonferroni method. All analyses were conducted using the R statistical software (R Core Team, 2018).

Results

Descriptive Analyses

A descriptive evaluation of the participants' orientation behavior showed that a significantly higher number of disorientation instances occurred mainly at crossings (Fisher's exact test, $p < 0.001$). Additionally, participants in the experimental group showed, overall, more instances of disorientation (Fisher's exact test, $p < 0.001$). The young controls did not differ from the older controls in the number of disorientation instances (Fisher's exact test, $p = 1.0$). Figure 2 shows an

overview of the ratio of disoriented behavior instances per participant. As regards the reliability of the video annotations, we found a substantial level of agreement, Cohen's $\kappa = 0.61$ (95% CI, 0.379 to 0.858), $p < 0.001$). Furthermore, differences in all other demographic variables (shown in Table 1) only turned out significant for the comparison of ages of participants; the young controls were significantly younger than the older control and older experimental group participants ($p < 0.001$).

Spatial Disorientation and Gait variability

Significant main effects of orientation on gait were found for walking speed, walking speed CV, step length, stride time, stride time CV and stance time (Table 2), with slower walking speed, decreased step length, decreased stride time, decreased stride time CV, increased stance time and increased walking speed CV observed when spatial disorientation occurred. No significant main effect of spatial disorientation was found for step length CV and stance time CV. Significant main effects of location on gait were only found for walking speed, stride time, stride time CV and stance time CV, with increased walking speed, decreased stride time, decreased stride time CV and decreased stance time CV observed when participants were at crossings. Significant interaction effects of spatial disorientation x location were only observed for stride time and stride time CV (Table 2). Post-hoc analyses (Fig. 3) showed significantly higher stride time ($p < 0.01$) and stride time CV ($p < 0.05$) when disorientation occurred at crossings. On the contrary, stride time ($p < 0.05$) and stride time CV ($p < 0.01$) was significantly lower when disorientation occurred at non-crossings. No spatial disorientation x group interactions were found for gait variability (Table 2).

Spatial Disorientation and Psychophysiological response

Significant main effects of spatial disorientation on psychophysiological response were found for SCR amplitude and SCR count (Table 2), with increased SCR amplitude and SCR count observed when spatial disorientation occurred. No significant main effect of spatial disorientation was found for RMSSD. Furthermore, significant main effects of location on psychophysiological response were found for RMSSD and SCR count, with increased RMSSD and SCR count observed when participants were at crossings. A significant main effect of group was only found for SCR count, with increased SCR count observed for the older experimental participants. Significant interaction effect of spatial disorientation x location was observed for RMSSD, but not for the SCR amplitude and SCR count. In addition, a significant spatial disorientation x group interaction was found for SCR count, but not for RMSSD and SCR amplitude (Table 2). Post-hoc analyses (Fig. 3) revealed that the RMSSD was only significantly lower when disorientation occurred at non-crossings ($p < 0.05$). In the case of SCR count (Fig. 3), a significant increase was observed when disorientation occurred for the older adults in the experimental group ($p < 0.001$).

Exploratory Analyses

Significant differences in gait variability between the young control and older control participants (Table 3) was only observed for walking speed, stance time and stance time CV. All other gait parameters did not differ between the young control and older control participants. We found significant moderate to strong correlations between certain gait parameters analyzed (walking speed, walking speed CV, stance time and stance time CV) and accelerometric parameters

(acceleration magnitude of the chest and ankle accelerometers). Figure 4 shows an overview of the correlation outcomes.

Discussion

The present study investigated the effect of location-based spatial disorientation on gait variability and psychophysiological response among healthy older adults during wayfinding in a VE. Firstly, results from this study indicate that spatial disorientation was successfully induced even among healthy older adults, judging by the significantly higher instances observed among the experimental participants, which is a step forward compared to previous studies that have mostly investigated disorientation among cognitively impaired individuals [16, 35]. Secondly, results showed a significant effect of spatial disorientation, most of which were observed at crossings, on gait variability and psychophysiological response. This adds new insights to the existing literature on the detection of spatial disorientation [16, 19], and to the associated changes in gait [22, 36] and psychophysiological response [22] resulting from the cognitive demands posed by dual-task walking. As regards the VE used in the current study, considering that it was a low-detail replication of the Rostock city center (with landmarks from the real-world presented in a highly degraded form), we do not expect extent of familiarity outside the context of the study to play any considerable role in performance outcomes.

Impact of Location-based Spatial Disorientation on Gait Variability

As expected and predicted by Hypothesis 1, spatial disorientation had an effect on gait variability among the healthy older adults. Gait measures such as speed, stride length, and stance time have been investigated previously in other dual-task conditions involving older adults [22, 36]. Behrens et al. [22] for instance, investigated the effect of a state of heightened cognitive demand (mental fatigue) on gait variability. Results from the study by Behrens et al. [22] showed significantly increased variability in speed, stride length and stance time among the older participants following mental fatigue in the dual-task walking condition. Similarly, Kizony et al. [37] have also reported significant decrease in gait speed among older participants following a cognitive task in a VE. In context of the current study, we intended that the wayfinding task would place similar cognitive demands on the participants as other dual-task conditions (e.g. mental fatigue), and that moments of disorientation will lead to heightened cognitive workload, as participants try to re-orient themselves, which could be observed in the variability of their gait patterns. This was the case, as increases in older participants' stride time and stride time coefficient of variation were observed following instances of spatial disorientation at crossings, thereby also confirming Hypothesis 2. These outcomes are consistent with the well-known fact that aging is characterized by functional decline in selective cognitive domains [2] required for successful navigation, due to anatomical alterations in the aging brain. One of such critical functions is executive function, which can be divided into different components, each having unique effects on gait [38]. Of particular importance to this discourse is the attention/dual tasking component. Models put forward to explains the role attention/dual tasking may have on gait generally revolve around the capacity-sharing theory, the bottleneck theory or the multiple resource models theory [38]. The capacity-sharing theory [39], for instance, posits that attentional resources are limited in capacity, and so the performance of two attention-demanding tasks will cause deterioration of at least one of the tasks. In other words, the

performance of an additional task (i.e. wayfinding) during walking alters gait (e.g., stability, speed) or the execution of the wayfinding task or both. These alterations in gait and secondary task performance have mainly been studied in the context of falls [22, 40]; however, in the current study we were able to show that such alterations could also be indicative of moments of spatial disorientation in the absence of fall risks. Furthermore, the observation of an interdependence between spatial disorientation and location also lends further evidence in support of the notion that intersections are critical decision points in the wayfinding process [8], with strong implications for successful navigation. Lastly, the lack of significant main or interaction effects of group suggests that the effect of disorientation on gait parameters among the older adults did not depend on if the older participants were in the normal group (i.e. older control) or the group with the altered VE (i.e. older experimental), but rather on the location (i.e. crossing vs. non-crossing).

Impact of Location-based Spatial Disorientation on Psychophysiological Response

In confirmation of Hypothesis 3, spatial disorientation had an effect on psychophysiological response among the healthy older adults. Changes in the autonomic nervous system (ANS) activity in response to highly challenging situations has been observed in various conditions [22]. In principle, when faced with challenging situations, the ANS and hypothalamic-pituitary-adrenal (HPA) axis are two major systems that respond in an attempt to re-establish balance on a psychophysiological level, through changes in cardiac activity, sweat gland activity, and skin temperature [26]. Two popular estimates of psychophysiological response are the HRV and SCR measures. In non-walking conditions, HRV has been associated with performance in a range of cognitive domains, including, but not limited to executive and attention functions, memory function, and visuospatial skills [41]. As for SCR, changes have been informative in the occurrence of spatial disorientation among pilots [32], and for algorithm-based detection of stress [26]. More importantly, in dual-task walking, Behrens et al. [22] reported a stronger psychophysiological workload response and a higher cognitive effort during a mental fatiguing task in the older adults, based on reduction in the RMSSD HRV measure. In the current study, similar changes in RMSSD was observed during moments of spatial disorientation. However, contrary to our expectation (Hypothesis 4), a significantly lower RMSSD was only observed when disorientation occurred at non-crossings; when disorientation occurred at crossings, a higher RMSSD was rather observed. A possible explanation could be that due to the physiological latency [26, 42] between activation of the ANS and changes in heart rate variability (about 1 second) or skin conductance response (1 – 5 seconds) detected by the worn sensors, activations resulting from instances of spatial disorientation at crossings may have only been picked up “post facto” in moments after which the participant could have already traversed the crossing. Lastly, we found significantly more SCR counts when disorientation occurred in the experimental group irrespective of location. To a fair extent, this supports the earlier notion that disorientation was successfully induced by manipulating the environment in the experimental group.

Implication for Independent mobility and Assistive Technology

A central aim of gerontological research in recent times is to identify markers for designing effective intervention. In the area of assistive technology, this means, firstly, identifying the most relevant indicators of the challenging situation (i.e. spatial disorientation), and secondly, designing situation-adaptive and subsidiary assistive devices, which could leverage upon existing cognitive resources by only providing assistance when needed [43]. In the current study, results showed that changes in the

pattern of gait (walking speed, step length, stride and stance time) and psychophysiological arousal (skin conductance response) corresponds to instances of spatial disorientation during wayfinding among older adults. Additionally, we were able to show that crossings are important "hotspots" for spatial disorientation, and that a unique pattern of gait change in stride time could be very informative as an indicator of possible instances of spatial disorientation while at crossings. These outcomes suggest that in designing ATDs for navigation support, a more adaptive approach might be needed in selecting relevant features for detecting spatial disorientation, considering that while gait and psychophysiological features were reflective of spatial disorientation at non-crossings, only gait features remained indicative of spatial disorientation at crossings. In this case, a situation-adaptive ATD should be able to recognize and adapt to the user's location (derivable from global positioning system coordinates) in both detecting disorientation and providing assistance. A hypothetical ATD could then employ a combined evaluation of the user's gait and psychophysiological arousal level while at non-crossings, but prioritize evaluation of gait at crossings, as this proved more informative for spatial disorientation at crossings.

Exploratory Analyses

The purposes of the exploratory analyses were to investigate the replicability of the effect of age on gait observed in previous studies [36], and to explore if there was any relationship between the gait parameters analyzed and the recorded accelerometric parameters which have also been shown to be relevant in real-time disorientation detection [16]. Similar to the findings from a dual-task study [36], our young controls significantly differed from the older controls on walking speed, stance time and stance time CV, thereby providing further evidence to support the existence of an age-associated increase in the dual-task effect on gait variability within a wayfinding paradigm. We also found significant moderate to strong correlations between certain gait parameters analyzed and accelerometric parameters, which were employed in a previous field study [16]. Firstly, this indicates that the optical-marker-based gait parameters are reliable measures of the effect of spatial disorientation, and can therefore, be employed in training machine learning models of spatial disorientation detection, with the potential for more accurate classification outcomes. Secondly, considering that such fine-grained gait parameters may be difficult to obtain in the real world, in comparison to accelerometric gait data that is available in most smart devices, a considerable amount of correlation between gait and acceleremotric parameters, therefore, gives further support to the viability of accelerometers for disorientation detection in real-world settings, where optical-marker-based gait parameters might be difficult to obtain.

Strengths and Limitations

A key strength of the current study is the combined setup of an adequately immersive VE and a well-instrumented treadmill [17]. This gives the advantage of a naturalistic interactive setting while ensuring a high degree of control and standardization. With the current setup, we were able to explore associated changes in gait and psychophysiological features resulting from instances of spatial disorientation among older adults during wayfinding, while overcoming two major challenges: (1) the lack of control and standardization in real world environments, and (2) the limited ecological validity in non-ambulatory VR navigation studies. This gives confidence to the validity of the study findings. On the contrary, a major limitation of the current study is the limited sample size. Further studies with larger sample sizes are still recommended to confirm the findings of the current study. A

455 further limitation is the use of psychophysiological measures from the exact moment as the
456 occurrence of spatial disorientation. Although this was done to ensure perfect temporal
457 synchronization with the gait features, it might be a better approach to derive psychophysiological
458 measures from a short duration after the occurrence of spatial duration, due to the required
459 physiological latency between ANS activation and changes in heart rate or skin conductance
460 response. Nevertheless, deriving psychophysiological measures from a short duration after the
461 occurrence of spatial duration poses a great challenge, considering the potential difficulty in
462 determining the exact offset time of disorientation. Another limitation worth acknowledging is the
463 exclusion of the younger control participants in the ANOVAs. This limits the applicability of the
464 findings when making comparisons between younger and older adults. Lastly, a different way of
465 examining gait and psychophysiological parameters at the periods of interest (i.e.
466 oriented/disoriented, at crossings/non-crossings) is recommendable. Perhaps, the standard way of
467 calculating dual-task costs could be more informative, thus looking at each individual's change in
468 behavior rather than the absolute values themselves.

469 ## *Conclusion*

470 In conclusion, the successful induction of spatial disorientation even among healthy older adults for
471 the first time, is a step forward compared to previous studies that have mostly investigated
472 disorientation among cognitively impaired individuals. Furthermore, findings of unique variations in
473 gait and psychophysiological response following moments of spatial disorientation (most of which
474 were observed at crossings), provides valuable insight into the behavioral substrates of navigation
475 challenges among older adults, thereby highlighting viable features for designing situation-adaptive
476 interventional ATDs.

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480 ## *Statement of Ethics*

481 The study followed the guidelines of the declaration of Helsinki [28]. All participants have given their
482 written informed consent before participating in any study related activity. The study protocol has
483 been approved by the ethics committee of the University Medicine Rostock (Approval number: A
484 2019-0062).

485 ## *Disclosure Statement*

486 Part of the presented material arises from the doctoral theses of A. Klostermann, C. Hinz and I.
487 Kampa.

488 ## *Data Availability Statement*

489 The data that support the findings of this study are available from the corresponding author, C.O.
490 Amaefule, upon reasonable request.

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Author Contributions

C.O. Amaefule, S. Lüdtke, A. Klostermann, C. Hinz and I. Kampa contributed towards data acquisition. C.O. Amaefule analyzed the data and wrote substantial parts of the manuscript. S.J. Teipel, T. Kirste, S. Lüdtke and C.O. Amaefule provided substantial contributions to the conception and design of the work, analysis, and interpretation of data for the work. C.O. Amaefule, S. Lüdtke, A. Klostermann, C. Hinz, I. Kampa, T. Kirste and S.J. Teipel participated in drafting the work and revising it critically for important intellectual content and finally approved the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Fig. 1. Depiction of the experimental setup (top left and right). Image is used with permission of the participant. Wayfinding route (bottom left). Red crosses denote locations where the virtual environment was manipulated in the experimental group. DP1 to DP14 indicate the decision points from start to finish. The changes as described earlier were always the same for all older participants in the experimental group.

Fig. 2. Ratio of disoriented behavior instances per participant. A. All groups at non-crossings and crossings; B. different groups at non-crossings and crossings, ns, not significant, *** $P < 0.001$.

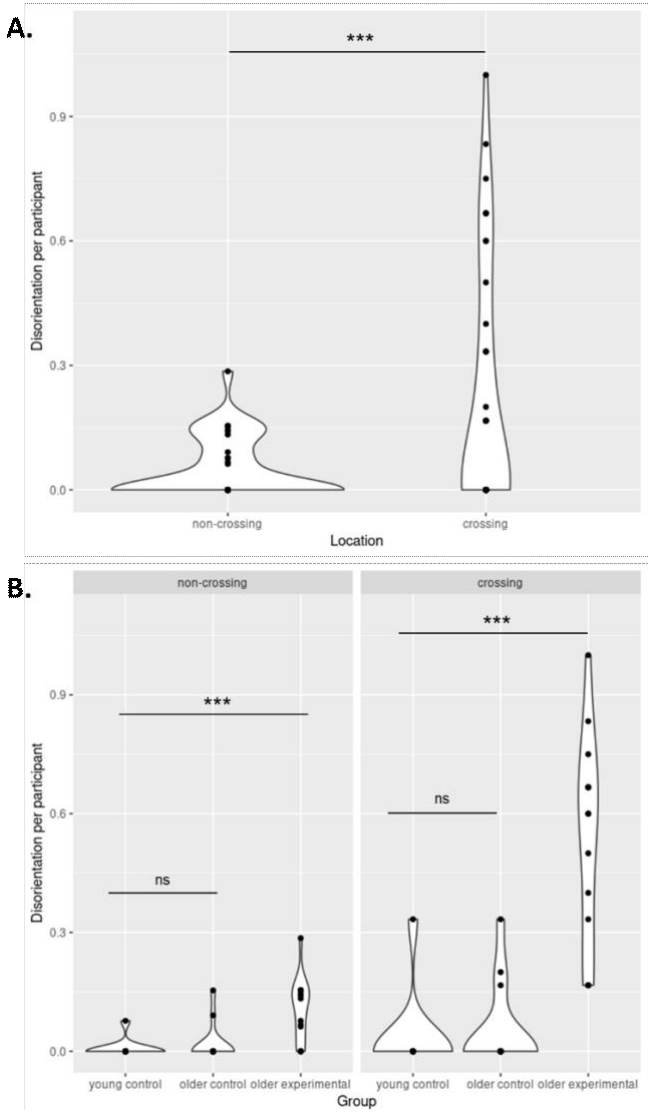

Fig. 3. Direction of interaction effects. A. stride time mean, B. stride time CV. C. heart rate variability (RMSSD). D. skin conductance response. CV, coefficient of variation; RMSSD, root mean square of the successive differences of adjacent inter-heartbeat intervals; SCR, skin conductance response; ns, not significant, * $P < 0.05$, ** $P < 0.01$, **** $P < 0.001$.

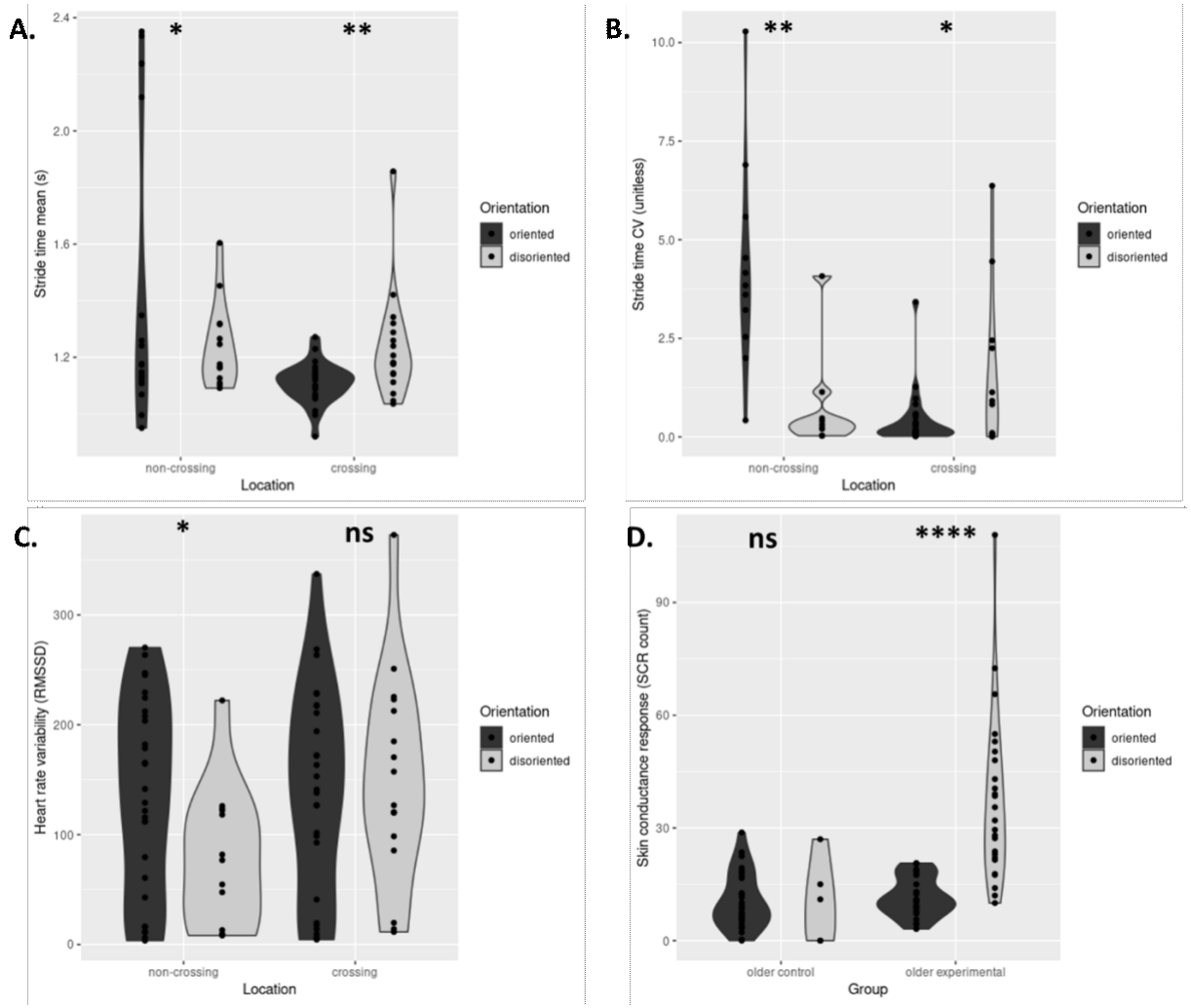

Fig. 4. Pearson r correlation of gait and accelerometric parameters showing moderate to strong correlations between the chest, ankle acceleration magnitude and walking speed, walking speed CV, stance time and stance time CV. Color scale represents strength and direction of correlation. CV, coefficient of variation. Crossed cells are non-significant $p < 0.05$.

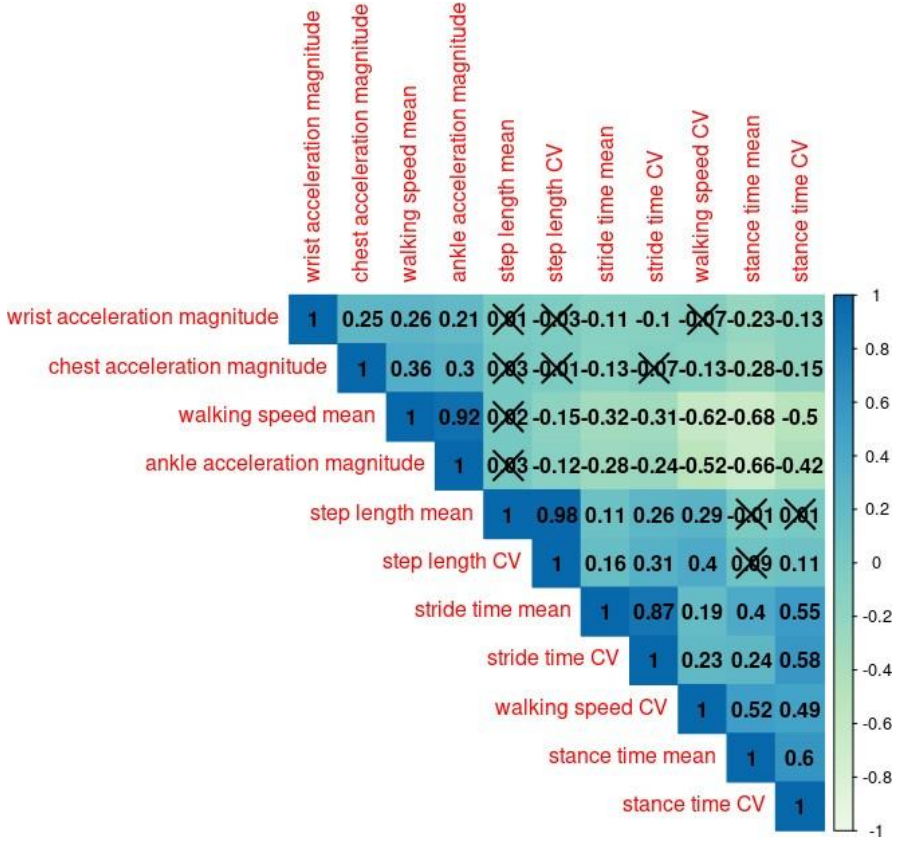

Table 1. Demographic characteristics of the young control, older control and older experimental participants.

	Young control (n = 10)	Older control (n = 14)	Older experimental (n = 14)
Females	4 (40.0%)	9 (64.3%)	9 (64.3%)
Age (yrs)	24.2 ± 2.7[a,b]	69.5 ± 3.9	72.0 ± 5.3***
Education (yrs)	13.3 ± 0.9	13.9 ± 2.9	14.9 ± 2.5
MMSE	-	28.9 ± 0.9	29.4 ± 0.6

Data are presented as mean ± standard deviation. * denotes a significant difference between groups (*** $P < 0.001$). [a] denotes different to older control participants, [b] denotes different to older experimental participants. MMSE, mini-mental state examination.

Table 2. ANOVA outcomes for the significant main and interaction effects.

	Orientation			Group			Location			Orientation × Group			Orientation × Location		
	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2	F	*P*	η_p^2
Gait parameters															
Walking Speed	15.297	0.000	0.200	-	-	-	5.600	0.021	0.099	-	-	-	-	-	-
Step Length	6.772	0.011	0.089	-	-	-	-	-	-	-	-	-	-	-	-
Stride Time	4.886	0.029	0.058	-	-	-	10.769	0.001	0.120	-	-	-	10.685	0.001	0.119
Stance Time	6.052	0.016	0.082	-	-	-	-	-	-	-	-	-	-	-	-
Walking Speed CV	10.289	0.001	0.115	-	-	-	-	-	-	-	-	-	-	-	-
Step Length CV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stride Time CV	5.951	0.016	0.070	-	-	-	6.526	0.002	0.108	-	-	-	10.423	0.001	0.117
Stance Time CV	-	-	-	-	-	-	4.053	0.048	0.061	-	-	-	-	-	-
Psychophysiological parameters															
HRV RMSSD	-	-	-	-	-	-	9.118	0.003	0.146	-	-	-	6.402	0.014	0.108
SCR Amplitude	5.399	0.023	0.074	-	-	-	-	-	-	-	-	-	-	-	-
SCR Count	13.891	0.000	0.161	10.733	0.002	0.204	6.309	0.014	0.097	11.526	0.001	0.138	-	-	-

CV, coefficient of variation; HRV, heart rate variability; RMSSD, root mean square of the successive differences of adjacent inter-heartbeat intervals; SCR, skin conductance response. Effect sizes are expressed as partial eta-squared η_p^2.

Table 3. Gait characteristics of all participant groups.

	Young control	Older control	Older experimental
Walking Speed	1.45 ± 0.16	1.07 ± 0.19***	0.99 ± 0.11
Step Length	0.74 ± 0.07	0.64 ± 0.26	0.56 ± 0.05
Stride Time	1.61 ± 0.64	2.30 ± 1.10	1.59 ± 0.68
Stance Time	0.69 ± 0.03	0.75 ± 0.07**	0.79 ± 0.08
Walking Speed CV	2.52 ± 1.55	3.02 ± 1.86	5.41 ± 2.33
Step Length CV	0.75 ± 0.82	2.10 ± 6.46	2.66 ± 1.68
Stride Time CV	269.0 ± 298.0	537.0 ± 513.0	203.42 ± 335.0
Stance Time CV	1.20 ± 1.06	3.90 ± 3.48**	4.80 ± 4.12

Data are presented as mean ± standard deviation of the parameter for the respective group. * denotes a significant difference between the young control and older control groups (** $P < 0.01$, *** $P < 0.001$). The older experimental participants were not included in the age effects analysis considering that the VE was changed. CV, coefficient of variation.