Spatial Disorientation in Alzheimer's disease: The Role of Spatial Navigation Impairments and the Outdoor Environment

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Abstract

Spatial disorientation is one of the earliest and most distressing symptoms seen in Alzheimer's disease (AD) patients, and is associated with impairments to the spatial navigation domain. Although investigated from a virtual reality (VR) and real-world (RW) perspective, very little is known about the extent to which spatial navigation impairments in VR environments and whether any navigation-related factors associated with the outdoor environment relate to patients' risk for experiencing spatial disorientation in the community. The aim of this thesis is to study the role of spatial navigation impairments and the outdoor environment in contributing to spatial disorientation in AD. In the experimental Chapters 2 and 3, using police case records of dementia-related missing incidents, we show that increased outdoor landmark density and complex road network structure are potential environmental risk factors for spatial disorientation. In the experimental Chapter 4, using GPS tracking, we show that spatial disorientation has a negative impact on the outdoor mobility patterns of AD patients in the community. Lastly, in the experimental Chapter 5, we show that although AD patients exhibit spatial navigation impairments in both VR and RW settings, VR navigation tests did not predict patients that are at a high risk for experiencing spatial disorientation in the community. Our work offers insight into RW factors associated with spatial disorientation in AD and highlights the importance of relating VR navigation impairments of patients to their spatial disorientation in the community. Furthermore, our results also provide a platform for future studies to study and build a cognitive and demographic profile for patients at a high risk for experiencing spatial disorientation in the community.

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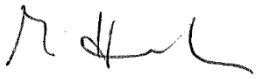
Supervisor Signature

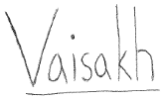
I, Michael Hornberger (primary supervisor), confirm that any required taught courses have been satisfactorily completed:

Signature: 

Author's Declaration

I, Vaisakh Puthusseryppady, declare that the work in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges the opinions, ideas and contributions from the work of others.

Parts of this work have been presented at conferences and published in academic journals.

Signature: 

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Oral Presentations Arising From This Thesis

1. "*Why Do Patients with Alzheimer's Disease Get Lost & Can We Predict Who is At High Risk?"* **Dementia Open Forum, University of East Anglia** (1st October 2020; held online). Available at https://www.youtube.com/watch?v=lcoZuGYCov8.

2. "*Dementia & Getting Lost in the Community: A Neuroscience Perspective*". **ICDW Summer Webinar Series 2020 #6: Research Perspective** (23rd July 2020; held online). Available at https://www.youtube.com/watch?v=xwe1uDFFOfQ.

3. "*Impact of Road Network Structure on Dementia-Related Missing Incidents – A Space Syntax Approach*". **ARUK East Network 2019 Annual Scientific Meeting and AGM** (22nd November 2019; University of Cambridge, UK).

4. "*Where am I? Spatial Disorientation in Alzheimer's Disease*". **Norfolk and Waveney Dementia Partnership Meeting** (9th September 2019; Costessey Centre, Norwich, UK).

5. ''*Geospatial Analysis of Missing Dementia Patients: Hotspots, Landmarks, and Road Network Connectivity''*. **Faculty of Medicine and Health Sciences Postgraduate Research Conference** (16th May 2019; University of East Anglia, UK).

6. "*Safeguarding Missing Dementia Patients in the Community: The Role of Technology*". **Future Tech Roadshow: Dementia Med Tech Showcase** (26th April 2019; Earlham Institute, Norwich Research Park, UK).

7. ''*Getting Lost and Landmarks: Missing Dementia Patients Police Data Analysis*''. **DZNE Interdisciplinary Symposium on Spatial Cognition in Aging and Neurodegeneration (**27th November – 29th November 2018; Magdeburg, Germany).

8. ''*Helping Alzheimer's Patients Find Their Way''*. **Manchester Medical Research Student Society National Undergraduate Conference** (17th February 2018; Manchester, UK).

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1. "*Alzheimer's Disease Patients Getting Lost in the Community – Is Road Network Structure a Significant Risk Factor?*" **Alzheimer's Association International Conference** (27th July – 31st July 2020; held online).

2. ''*Lost and Found: Missing Dementia Patients Police Data Study''*. **Faculty of Medicine and Health Sciences Postgraduate Research Conference** (17th May 2018; University of East Anglia, UK).

Publications Arising From This Thesis

1. **Puthusseryppady V**, Coughlan G, Patel M, Hornberger M. (2019) Geospatial analysis of environmental risk factors for missing dementia patients. *Journal of Alzheimer's Disease*, 71(3), 1005-1013. https://doi.org/10.3233/jad-190244.

2. **Puthusseryppady V**, Emrich-Mills L, Lowry E, Patel M, Hornberger M. (2020) Spatial disorientation in Alzheimer's disease: The missing path from virtual reality to real world. *Frontiers in Aging Neuroscience*, 12, 333. https://doi.org/10.3389/fnagi.2020.550514.

3. **Puthusseryppady V**, Manley E, Lowry E, Patel M, Hornberger M. (2020) Impact of road network structure on dementia-related missing incidents – a spatial buffer approach. *Scientific Reports,* 10, 18574. https://doi.org/10.1038/s41598-020-74915-y.

4. **Puthusseryppady V**, Patel M, Hornberger M. (2021) Outdoor mobility patterns of Alzheimer's disease patients in the community using GPS tracking – a spatial disorientation perspective. **In preparation**, to be submitted to *JMIR mHealth and uHealth* (tentative).

5. **Puthusseryppady V**, Patel M, Hornberger M. (2021). Predicting Alzheimer's disease patients' risk for spatial disorientation in the community using virtual reality navigation tests. **In preparation**, to be submitted to *JMIR Serious Games* (tentative).

Publications Not Related To This Thesis

1. Radakovic R, **Puthusseryppady V**, Flanagan E, Kiernan MC, Mioshi E, Hornberger M. (2018) Frontostriatal Grey Matter Atrophy in Amyotrophic Lateral Sclerosis: A Visual Rating Study. *Dementia & Neuropsychologia*, 12(4), 388-393, https://dx.doi.org/10.1590%2F1980-57642018dn12-040008.

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3. Pertesi S, Coughlan G, **Puthusseryppady V**, Morris E, Hornberger M. (2019) Menopause, cognition and dementia – a review. *Post Reproductive Health*, 25(4), 200-206, https://doi.org/10.1177%2F2053369119883485.

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7. Lowry E, **Puthusseryppady V**, Johnen AK, Renoult L, Hornberger M. (2021) Cognitive Markers of Preclinical Vascular Cognitive Impairment. Under review in *Cortex.*

List of Abbreviations

ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer's disease
aMCI	Amnestic Mild Cognitive Impairment
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
Aβ	Amyloid-beta
DNT	Detour Navigation Test
FDR	False Discovery Rate
GPS	Global Positioning System
HD	Head Direction
LSOA	Lower Layer Super Output Area
MPWD	Missing Patients with Dementia
RW	Real-World
SBSOD	Santa Barbara Sense of Direction
SHQ	Sea Hero Quest
SOS	Spatial Orientation Screening
UK	United Kingdom
VIF	Variance Inflation Factor
VR	Virtual Reality
VST	Virtual Supermarket Test

Chapter 1

General Introduction

Published Paper

Puthusseryppady V, Emrich-Mills L, Lowry E, Patel M, Hornberger M. Spatial Disorientation in Alzheimer's Disease: The Missing Path From Virtual Reality to Real World. Frontiers in Aging Neuroscience. 2020;12.

1.1 Introduction

Spatial navigation, along with episodic memory, is one of the earliest cognitive domains to be impaired in Alzheimer's disease (AD), resulting in affected individuals experiencing spatial disorientation [1]. Spatial disorientation is defined as moments where AD patients are unsure about their whereabouts and unable to navigate to an intended location [2]. It manifests behaviourally as patients making navigation errors when out in the community, which in turn can lead to a risk of them going missing in both unfamiliar and familiar environments [3].

It has been reported that up to 70% of dementia patients experience at least one missing incident over the course of the disease, with some even at risk for experiencing multiple missing incidents [4,5]. At present, it is estimated that there are approximately 40,000 dementia patients that go missing for the first time every year in the United Kingdom (UK) - a figure that is likely to grow in the coming years with the projected increase in the dementia population worldwide [6,7]. The occurrence of missing incidents have consequences not only for the patients themselves, but also their carers and the wider community in which they live in. For patients, consequences of missing incidents can include suffering from a reduced sense of autonomy, an increase in their likelihood of being admitted to a care home by up to seven times, sustaining various injuries and even death in the worst cases [4,8]. Moreover, missing incidents can also increase carer stress/burden as well as trigger the increasing involvement of law enforcement groups (i.e., Police) and community search resources [9–11]. Indeed, patients going missing in the community is so common and potentially

catastrophic in outcome that the Norfolk Police have developed the Herbert Protocol, which is a scheme used throughout the UK to help support the police in retrieving individuals once they have gone missing [12]. Due to these wide range of consequences, spatial disorientation is considered to be one of the most distressing symptoms seen in AD, in addition to being one of the earliest.

In recent years, the concept of spatial disorientation in AD has increasingly been studied using novel virtual reality (VR) paradigms in laboratory and clinical settings. However, despite exciting new findings from the VR studies of spatial disorientation that highlight underlying impairments in the spatial navigation brain processes, very little is known about which real-world (RW) factors in the community may contribute to this symptom. Furthermore, the extent to which VR tests of spatial navigation correlate with AD patients experiencing spatial disorientation in the community is also unclear. The work in this thesis aims to address these knowledge gaps by investigating the role of spatial navigation impairments and factors associated with the outdoor environment in causing spatial disorientation in AD.

The remainder of this chapter is organised as follows: We first introduce the current understanding of the underlying neuropathological causes of AD as well as the neural substrates of spatial navigation. We then examine VR studies of spatial disorientation which highlight how spatial navigation is affected in AD, and present evidence from RW studies of spatial disorientation, which relate more to demographic and situational risk factors for AD patients going missing in the community. We conclude this chapter by highlighting the missing link between the VR and RW studies, and how the work in this thesis will address this gap.

1.2 Alzheimer's Disease

Dementia is an umbrella term that refers to a set of symptoms including problems with memory, thinking, problem solving and language amongst others. Currently, it is estimated that there are over 850,000 people living with dementia in the UK, and with the increase in life expectancy, these rates are projected to increase to 1.5 million by 2040 [13].

AD is a neurodegenerative disease that is the most common cause of dementia in individuals above 60 years of age [5]. It is characterised by the formation and deposition of toxic amyloid-beta (Aβ) protein plaques as well as neurofibrillary tangles throughout the brain [14,15]. In terms of aetiology, genetic factors such as the E4 allele variant of the Apolipoprotein E gene as well as mutations to the Amyloid Precursor Protein and Presenilin-1/2 genes have been suggested to contribute to AD onset. Additionally, various modifiable lifestyle factors including poor diet, hypertension, smoking as well as environmental factors including air pollution and vitamin D deficiency have also been identified to contribute to the incidence of AD [16–20]. Although the exact factors are still unclear, it has been suggested that it may be the interaction between genetic, lifestyle, as well as environmental factors that could be contributing to the onset and progression of AD [5].

The pathological hallmarks of AD (i.e., Aβ plaques and neurofibrillary tangles) appear and spread throughout the brain in a specific spatiotemporal pattern. Neurofibrillary tangles precede the Aβ plaques, and their pattern of accumulation and spreading occurs in six stages. The tangles first appear in the medial temporal lobe, with the entorhinal cortex (Stage I) being the earliest region to be affected, followed by the hippocampus (Stages II & III). The tangles then appear in the limbic structures of the brain (i.e., amygdala, thalamus, claustram) (Stage IV), following which they continue to spread to all other regions of the brain, including the parietal and frontal lobe structures (Stages V-VI). Meanwhile, the Aβ plaques appear after the tangles and have a less predictable spreading pattern, appearing first in the

temporal lobe structures before spreading throughout the other cortical regions [21]. Overall, the changes induced by the plaques and tangles in the brain include increased atrophy and hypometabolism of affected regions over time [22], which results in patients suffering from a progressive loss to their cognitive abilities [23].

As a result of the disease, AD patients have impairments to various cognitive domains including working memory, attention, executive functioning, episodic memory, and spatial navigation [24]. However, due to the earliest brain regions affected by the AD pathology (i.e., anterior medial temporal lobe) forming part of the spatial navigation network of the brain, impairments to this cognitive domain are seen early in AD [1]. Indeed, it has been suggested that it is these impairments which fundamentally underlie spatial disorientation in AD, although impairments seen in other cognitive domains like episodic memory, executive function, and attention may also play a role [25].

Before examining how spatial navigation is affected in AD, we first explain how spatial navigation normally functions in the brain, and the brain structures that are critical for this.

1.3 Mechanisms of Spatial Navigation

Spatial navigation is defined as the ability to determine and maintain a trajectory from one location to another [26]. It is based on and guided by multimodal self-motion and environmental cues. Self-motion cues (i.e., motor, vestibular, and proprioceptive information) are combined to allow path integration, the process by which continuously updated estimates of one's position and orientation in space are made [27]. Meanwhile, environmental cues (i.e., visual, auditory, and tactile modalities) provide information on salient landmarks and extended boundaries, which are used to determine one's location and orientation in relation to the surrounding environment [28]. Both cues inform the two main types of navigation strategies – *egocentric* and *allocentric*.

The egocentric navigation strategy is self-centred and involves encoding spatial representations in relation to the position of the navigator [29]. This strategy encompasses either the use of landmarks or recalling a sequence of direction changes to inform navigation turns [30]. This strategy is often used when navigating through familiar routes or in environments with a lack of distinct landmarks, and is associated with a brain network centred around the parietal lobe as well as subcortical structures [31,32]. On the other hand, the allocentric navigation strategy involves the use of non-self-centred cognitive maps which contain encoded representations of spatial layouts from a survey-like perspective, including the positions of landmarks and objects relative to one another [33]. This strategy is often used when we are required to be more flexible in our navigation (i.e., using alternative paths/shortcuts to a destination) and is associated with a brain network centred around the medial temporal lobe and particularly, the hippocampus [33,34]. It must be noted that it is not possible to completely dissociate both navigation strategies, as we rarely use purely one or the other. Rather, everyday navigation requires a seamless integration of both egocentric and allocentric strategies, as required by environmental demands. Indeed, the retrosplenial cortex has been identified as a key brain region allowing the integration of both strategies as it receives reciprocal information from the parietal and medial temporal lobe networks [35].

Overall, the brain regions sub-serving the egocentric and allocentric navigation strategies interact with different groups of spatial cells to perform navigation (Fig. 1.1). These include head direction (HD), grid, boundary, and place cells. HD cells are found in the circuit of Papez, and fire maximally when the head of an individual is facing a specific direction relative to the surrounding environment [36]. These cells have been suggested to function in angular path integration by acting as a neural compass for navigation [37]. Grid cells are found in the medial entorhinal cortex and fire in multiple locations, forming repeating triangular grids which tile the environment [38]. These cells encode distances for linear path

integration in navigation [38–41]**.** Boundary cells are also found in the medial entorhinal cortex, and fire in response to fixed boundaries in the environment. In navigation, these cells function in defining the spatial limits of the environment [42]. Place cells are found in the hippocampus and fire maximally when an individual enters restricted and specific locations of the environment, irrespective of what direction they are facing [43–45]. Place cells receive input from the HD, grid, and boundary cells, and use this to form cognitive maps [45,46].

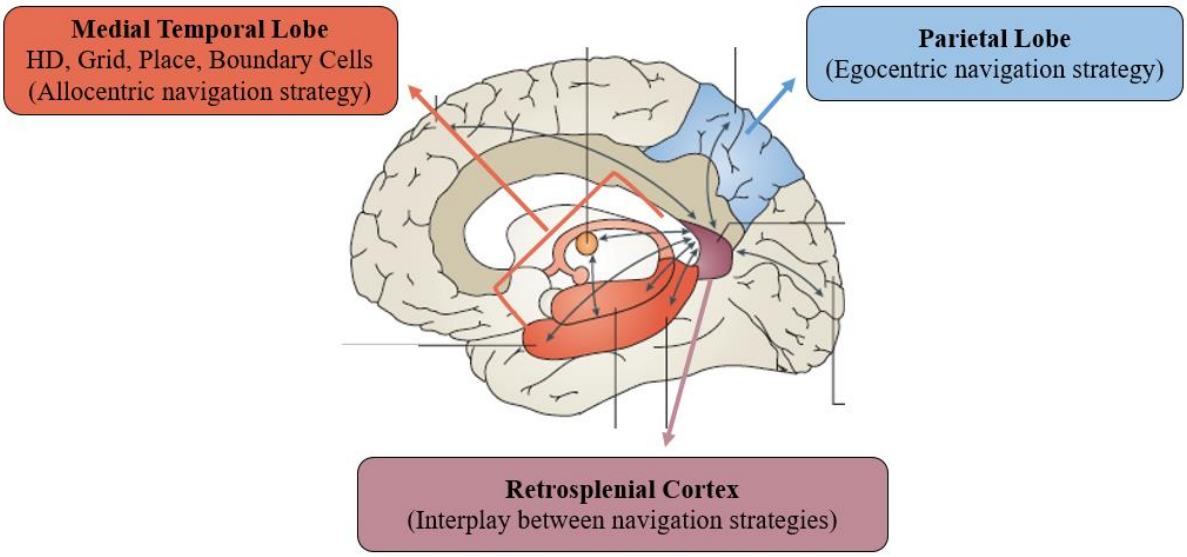

Figure 1.1: Overview of the brain regions (and spatial cell groups) involved in spatial navigation. The parietal lobe structures function in the use of an egocentric navigation strategy, while the medial temporal lobe structures (i.e., where the spatial cell groups are located) function in the use of an allocentric navigation strategy. The retrosplenial cortex functions in the interplay between both navigation strategies. Figure adapted from [35].

Overall, spatial navigation is underlined by the complex cellular and network interactions between the different spatial cell groups/brain regions, of which the exact dynamics for everyday navigation are still been explored. However, knowledge generated from animal and human navigation studies increasingly point in the direction of spatial representations converging on the hippocampus. As such, the following simplified model of spatial navigation can be considered (Fig. 1.2). When navigating in a novel environment, spatial representations are initially encoded in the egocentric reference frame, which is associated

with activity in the parietal cortex network. As one continues to move, the path integration system (i.e., HD and grid cells) provides information to maintain and update one's position and orientation [47]. Simultaneously, the transformation of spatial representations from an egocentric to an allocentric reference frame occurs via activity in the retrosplenial cortex. Here, the information regarding environmental boundaries (i.e., via boundary cells) are taken into account to help generate and store allocentric representations within the hippocampus (i.e., via place cells), in the form of a cognitive map [33].

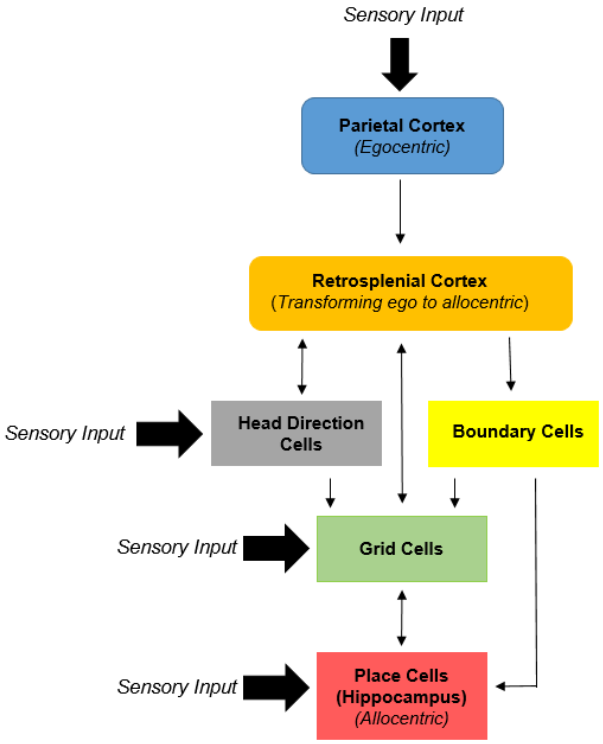

Figure 1.2: Interactions of cell groups and brain regions underlying spatial navigation. Novel environments are first encoded as egocentric representations by the parietal cortex network. As we continue to move, the HD & grid cells provide information for path integration. The egocentric representations are then transformed into allocentric representations by the retrosplenial cortex, and this is combined with information from the boundary cells to generate and store cognitive maps in the hippocampus (via the place cells). Figure adapted from [48].

1.3.1 Spatial Navigation Network and AD

The spread of the AD pathology throughout the brain unsurprisingly leads to changes in the brain regions and spatial cell groups of spatial navigation. Pathology related changes include

structural (i.e., reduction in volume) as well as metabolic (i.e., hypometabolism) deficits in the parietal and medial temporal lobe regions [22]. Furthermore, for the spatial cell groups, studies using transgenic mice models of AD have shown that the deposition of neurofibrillary tangles and Aβ plaques in the entorhinal cortex, hippocampus, and cortico-limbic regions alter the firing patterns of the grid, place, and HD cells, causing them to be less precise spatially [49–52]. These changes in the spatial navigation network of the brain affect AD patients' representation of space and more generally, their ability to use the egocentric and allocentric strategies for navigation. In the next section, we present studies which show in detail how the spatial navigation strategies are affected in AD.

1.4 Virtual Reality Studies of Spatial Disorientation

In recent years the advent of VR testing, either on a screen or via an immersive headset, has increasingly been used to study how spatial navigation is affected in AD. Indeed, VR environments offer many advantages for investigating spatial navigation. It allows testing of spatial navigation performance systematically and under controlled conditions, offering a viable and more ecologically valid alternative to standard table-top tests [33]. Moreover, navigation in VR environments has been shown to correlate highly with RW navigation, with navigation errors made in the former predicting errors made in the latter [53,54]. This, in addition to its ability to be easily administered and even be combined with various neuroimaging techniques, has led to VR being considered as an attractive tool to study the neural mechanisms underlying spatial navigation [33].

These advantages have led to a plethora of studies investigating spatial disorientation in AD using a variety of VR environments including a *supermarket*, *hospital lobby*, *museum*, and *town* amongst others [54–57], with some studies even combining VR environments with a RW analogue [54,58,59]. Overall, the VR studies of spatial disorientation have provided

insight into how the two spatial navigation strategies, egocentric and allocentric, are affected in AD.

1.4.1 Egocentric and Allocentric Navigation Strategies in AD

AD patients have been widely reported to be impaired in the use of both egocentric and allocentric navigation strategies, which is associated with pathology related changes in the parietal and medial temporal lobe structures respectively [22]. A common paradigm used in many VR studies to highlight these impairments is the Virtual Hidden Goal task [60]. This task is a human version of the Morris Water Maze used in animal model studies, and is designed to assess the use of the different navigation strategies. In this task, participants are placed inside a VR experimental arena and are asked to navigate to a hidden goal location under the following conditions: a) using only the relationship of the goal location to the starting position (egocentric strategy), b) using only the external landmarks to locate the goal, as the starting position varies (allocentric strategy), and c) using the relationship of the goal location to either the starting position or to external landmarks (egocentric and/or allocentric strategy).

Studies using this task in VR (and its RW analogue) environments have reported that mild AD patients are impaired in navigation performance under all conditions, suggesting difficulties in using both egocentric and allocentric navigation strategies, with the latter in particular being associated with reduced right hippocampus volume [58,59,61,62]. However, findings from another study suggested a more differential impairment for patients in the use of an allocentric strategy, with their performance on using an egocentric strategy being similar to healthy controls [60]. One study in particular expanded upon these allocentric deficits by employing a more ecological design of this task, using pictures of familiar landmarks in the participants' neighbourhood as external cues in the arena, and the location of their homes as the hidden goal location [63]. Findings from this study suggested that mild

AD patients have preserved cognitive maps for familiar surroundings, as measured by a test where the relative positions and spatial relationships of the landmarks to their home must be indicated on their neighbourhood map. However despite this, the patients were not able to apply these maps as effectively as healthy controls for navigation in the allocentric condition of the Hidden Goal Task.

Further to the Hidden Goal Task, VR studies using other paradigms have also highlighted impairments to the egocentric and allocentric navigation strategies in mild AD patients. Specifically, studies using virtual towns [64,65] and a Starmaze [66] (i.e., 5 alleys emanating from corners of pentagon) have reported impairments for patients in accurately recalling a sequence of turns required to reproduce a previously learned route (egocentric navigation strategy use), indicating the positions of landmarks in the navigation environment relative to one another on a map (cognitive map formation), and in applying their cognitive map of the environment to use the shortest path to navigate to a goal location (allocentric navigation strategy use). Two other studies have utilised a virtual supermarket to further highlight impairments to different aspects of navigation in AD patients. These studies show that after navigating through a route in the supermarket, patients are impaired on tests assessing their ability to use an egocentric strategy to correctly identify the direction of their starting location in relation to their own position, and this was associated with structural deficits in the retrosplenial cortex. Further, their ability to use an allocentric strategy to indicate their destination's position in relation to the starting location on a blank map on the supermarket was also impaired [57,67]. These findings however are in disagreement with another study that used the same task, which reported no significant differences in either test for AD patients when compared to controls [68].

Another group of VR studies have examined the interaction between the egocentric and allocentric navigation strategy use in AD. Specifically, it has been reported that mild AD

patients exhibit deficits in switching from an allocentric to an egocentric viewpoint when making spatial judgments using multiple objects [69,70]. These deficits were also seen in a navigation context, where patients were presented a visible map with a highlighted route (that they could not move or rotate) and asked to use this map to navigate this route (in a first person perspective) through a virtual maze [71]. In particular, impairments in the translation between the navigation strategies has been shown to be age related, being more apparent in early onset as opposed to late onset AD patients [72]. Indeed, it has been suggested that an inability to effectively switch from an allocentric to egocentric strategy during navigation, which is associated with alterations to the retrosplenial cortex, could be a key factor underlining why AD patients go missing in the community [57,73]. A more recent study reported that mild AD patients increasingly prefer to use an egocentric strategy to navigate in a virtual maze compared to controls, despite an allocentric strategy being required to correctly navigate to the goal location [74]. Further, this increasing preference of an egocentric strategy was associated with worse performance on a RW allocentric navigation task. The authors of the study speculated that AD patients may increasingly be adopting an egocentric strategy to compensate for deficits in their ability to use an allocentric strategy for navigation.

1.4.2 Landmark Recognition in AD

Landmarks are integral entities in spatial navigation, functioning as the building blocks for cognitive maps used in an allocentric navigation strategy as well as acting as reference points for us to orient ourselves in relation to the environment when using an egocentric navigation strategy [75]. As such, some studies have explored how the ability to recognise landmarks encountered during navigation in VR environments are altered in AD patients. These studies have reported AD patients as having deficits in landmark recognition, as they showed a tendency to indicate having seen new, previously un-seen landmarks before in a virtual town

[55]. In addition, mild AD patients were also shown to be impaired on tests of landmark identity, recall, location, temporal order, directional knowledge, as well as scene recognition [65]. However, results from another study showed that although AD patients had impaired recognition for landmarks encountered at decision points on a route, they still exhibited intact implicit recognition for landmarks encountered along non-decision points on this route [56] .

In summary, the VR studies of spatial disorientation have highlighted impairments to the use of the spatial navigation strategies as well as landmark recognition in AD patients. In the next section, we examine the findings shown from the RW studies of spatial disorientation.

1.5 Real World Studies of Spatial Disorientation in AD

Compared to VR studies, RW studies of spatial disorientation in AD are limited in number. A major reason for this stems from the fact that RW navigation occurs in complex large scale spaces that are usually explored from different viewpoints and over multiple viewings [76,77]. Hence compared to VR environments, there is a lack of experimental control over various contextual factors associated with RW environments (i.e., changing weather patterns, number of people in the area, level of noise etc.), which can make it challenging to keep these environments consistent over time for repeated navigation testing [78]. Another reason is that RW navigation tests are considered impractical to administer in clinical settings, as no two clinics will have the same RW environment, thereby making comparison of patient performance across clinics a challenge [64]. Nevertheless, with one of the main RW consequences of spatial disorientation being AD patients going missing in the community, the RW studies have mainly studied this symptom in the context of factors associated with these missing incidents. Moreover, studies have also investigated the ability of AD patients to use the different navigation strategies in RW environments.

1.5.1 Missing Incidents in AD

From a neurocognitive perspective, studies have attributed missing incidents to impairments in various cognitive domains seen in AD patients. Indeed, impairments to episodic memory, executive function, attention, and anosognosia (i.e., lack of insight) have all been associated with missing incidents [25]. Of more relevance to the spatial navigation domain, some studies have reported that impairments on neuropsychological tests of topographical memory and object recognition, as well as the modulation of visuospatial processing by working memory and executive functioning were all associated with missing incident history in patients [79,80]. To the best of our knowledge, only one study has directly related measures of spatial navigation, using questionnaire based information, to the occurrence of missing incidents measured longitudinally. This study reported that higher scores on the inattention subscale of a questionnaire measuring spatial navigation impairments (indicating higher impairment), predicts future incidence of missing incidents for the patients [81].

Studies have also identified some of the most common situational factors associated with missing incidents seen in patients. The main situational factor has been suggested to be when patients are alone and/or are temporarily not supervised by their carer. These situations most commonly occur when the patient performs a routine activity (i.e., going for neighbourhood walks), when they are temporarily left alone on purpose [3,10,82,83], or even during the night when the carer is sleeping [9,10,84].

Various studies have utilised case reports of missing patients in the community to further understand the circumstances in which they go missing, and these studies report demographic risk factors for these incidents. A common finding across multiple studies conducted in the US, UK, and Australia is that greater numbers of patients go missing from domestic residence settings when compared to care settings [3,85–87]. Additionally, higher age, longer duration of time missing, and cooler months have been reported as potential risk factors for sustaining

harm during the missing incidents [86,88]. Other studies have reported younger age as being a risk factor and the presence of a safety range (i.e., restricting navigation to only very familiar places) [81] as well as having lower mobility levels to be protective factors for the recurrence of missing incidents [9].

1.5.2 Real-World Navigation in AD

Few studies have investigated the ability of AD patients to navigate in an RW environment, both in controlled and more naturalistic conditions. Studies using a controlled environment have mainly employed navigation tasks akin to those used in the VR studies, and reported similar impairments in the use of navigation strategies in mild AD patients. Specifically, findings from studies using a two-dimensional floor maze suggested impairments to the use of an egocentric navigation strategy, with patients being reported to be impaired in learning and navigating a pre-determined route in the maze [89,90]. Other studies using university and hospital environments have also reported deficits in such route learning tasks, which was associated with decreased volumes of the right posterior hippocampus and parietal cortex, as well in tasks requiring the use of an allocentric navigation strategy (recalling the spatial layout and identifying the location of landmarks on a map of the test environment) [91–93]. Although two of these studies showed impairments for patients in the recognition of landmarks encountered on the route [91,92], this was in disagreement with findings from the study that suggested intact landmark recognition abilities for the patients [93].

Studies looking at the navigation of AD patients in naturalistic environments have mainly used a RW setting that is familiar to them, which was their neighbourhoods. Specifically, a pair of studies explored the strategies that patients used to help them navigate on a chosen route in their neighbourhood by observing their behaviour and through informal conversations with them on an accompanied walk [94,95]. These studies reported that patients were more likely than controls to exhibit spatial disorientation and get lost on the

chosen route, despite it being a highly familiar environment. Moreover, it was found that the most common strategy used by patients to help them navigate was to look for visible landmarks, and that the use of this strategy was particularly vulnerable to changes in the environment.

1.6 Conclusion – The Missing Path from Virtual Reality to the Real World

Overall, it can be seen that spatial disorientation in AD has been studied mainly through a VR as opposed to a RW perspective. The VR studies have provided useful insight into the neurocognitive factors that underlie spatial disorientation in AD. In particular, they highlight impairments to the use of the spatial navigation strategies in patients, and are increasingly being used to test these abilities in patients at different stages of the disease. However, there are some noteworthy limitations associated with this approach.

From a practical standpoint, AD patients can find it challenging to perform VR tasks on the computer and can often suffer from VR-induced motion sickness [96,97]. In addition, it must be noted that VR environments may not fully capture the vividness of complex RW settings in its entirety as they lack auditory and olfactory cues as well as often do not account for locomotion, a crucial feature of RW navigation [75,98], although recent studies are increasingly adopting VR paradigms incorporating RW walking [99,100]. Most importantly however, despite navigation tasks in VR environments being sensitive and specific to engaging the navigation systems of the brain, in design they are often not representative of the daily navigation challenges faced by AD patients in the RW. Hence, the extent to which findings from the VR studies relate to patients experiencing spatial disorientation in the community is at present unclear.

On the other hand, the RW studies of spatial disorientation focus much more on factors (neurocognitive, contextual, and demographic) associated with missing incidents as well as

how AD patients navigate in controlled RW environments. Here, studies have not related the missing incidents to the spatial navigation impairments seen in patients. Although some of these studies investigated neurocognitive factors, these findings were mostly based on neuropsychological tests which do not measure spatial navigation per se but more generally, visuospatial and other cognitive impairments. Moreover, although RW factors for missing incidents have been identified (i.e., demographic & contextual), factors that are specifically related to or associated with spatial navigation have in large not been explored. Meanwhile for studies looking at how AD patients navigate in RW environments, although they have related their findings to the spatial navigation brain processes, these studies largely used unfamiliar, controlled environments to measure navigation. Therefore, they suffer from the same limitations of VR studies in not accurately capturing RW situations where spatial disorientation may occur for patients.

Overall, it is clear that there is a missing link in the literature, with VR studies not relating the spatial navigation impairments of AD patients to their spatial disorientation in the RW and vice-versa for the RW studies (Fig. 1.3).

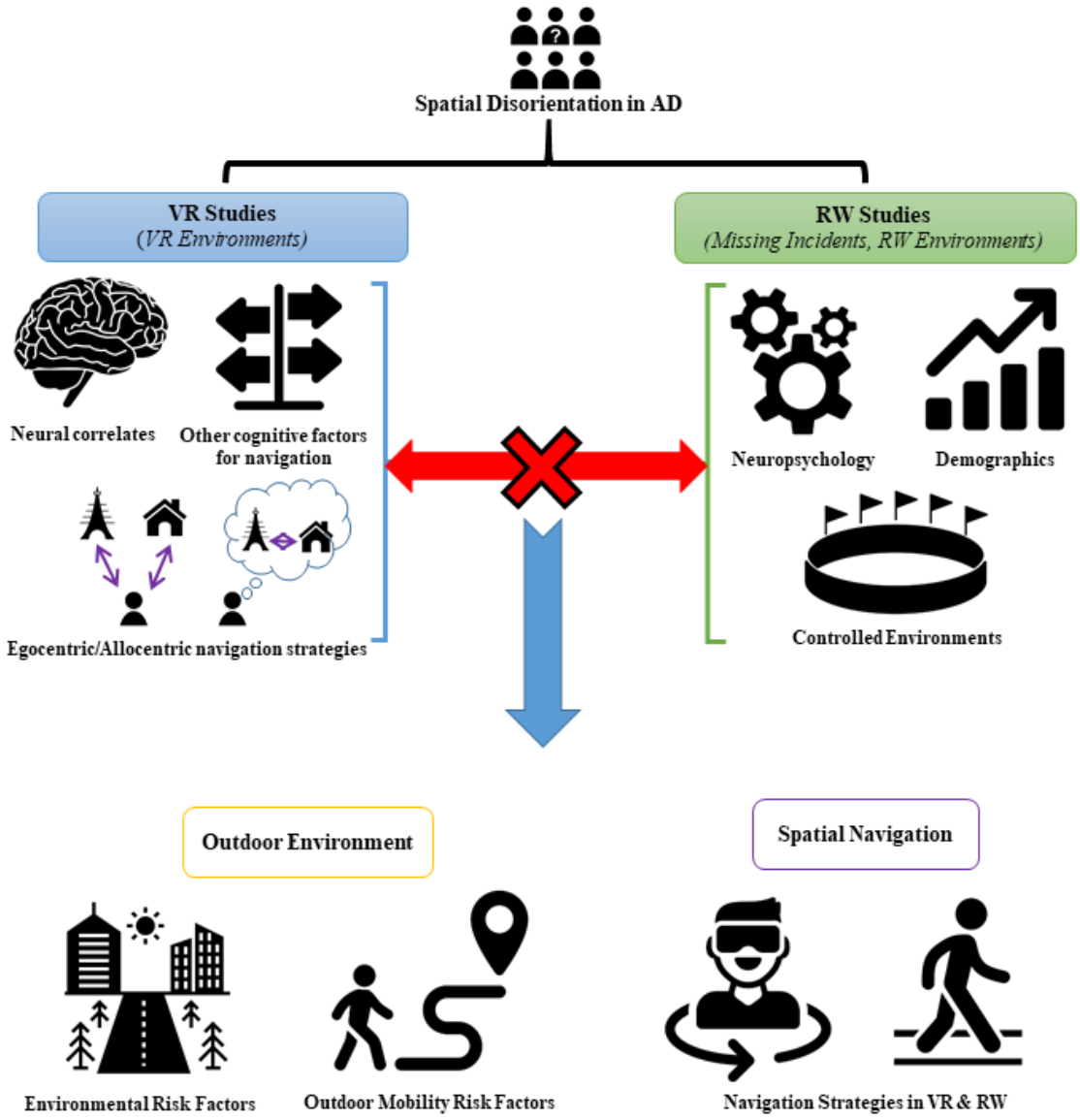

Figure 1.3: Summary of VR and RW studies of spatial disorientation in AD, including the current research gaps. VR studies have used VR environments to highlight the underlying neural correlates of navigation, impairments in the egocentric/allocentric navigation strategies, and other cognitive factors used in navigation (visuospatial memory, episodic memory, attention for landmarks etc.) in AD patients. RW studies have mainly studied missing AD patients in the community using case reports, questionnaires, interviews, and have identified neuropsychological and demographic risk factors for these incidences. Some studies have also studied how patients navigate in controlled RW environments, similar to the VR studies. At present, no studies have explored whether navigation-related factors in the outdoor environment may contribute to spatial disorientation. In addition, no studies have related the VR navigation impairments of patients to them experiencing spatial disorientation in the community[1].

[1] Icons used in the figure – "Missing" by Fahmi, "Brain" by Clockwise, "Navigation" by Jejen Juliansyah Nur Agung, "Person" by Support Designs, "House" by David, "Tower" by ibrandify, "Gears" by Daniel Shoreman, "Statistics" by Adrien Coquet, "Arena" by Kerry Webster, "Path" by Adrien Coquet, "Cityscape" by ProSymbols "Movement" by Adrien Coquet, "Pedestrian Crossing" by Andrew Doane – all from thenounproject.com

To help close this gap, it is important to identify if there are any RW factors for spatial disorientation that are associated with the outdoor environment, due to the impact that the environment has in influencing and guiding navigation [101]. Specifically, this includes studying more closely the locations where patients experience spatial disorientation to identify if specific features of the built environment might be contributing to this symptom. It also involves studying the more general patterns of how AD patients navigate and move outdoors in the community, to identify if any aspects of their outdoor mobility offer insight into spatial disorientation. In addition, it is also important for RW studies to study in more detail how AD patients use their egocentric/allocentric navigation strategies in the community by administering tests in a naturalistic setting, to more accurately simulate situations where spatial disorientation might occur. Here, spatial disorientation behaviour of the patients on the RW tests can then be related to more systematic measurements of spatial navigation made using VR environments to investigate the extent to which the two relate to one another.

In conclusion, addressing the current limitations of the literature could enhance our understanding of spatial disorientation in AD, specifically with regards to the role that spatial navigation impairments and the outdoor environment plays in this. Furthermore, with spatial disorientation being unpredictable in nature, understanding the relation between these factors could in turn enable us to predict patients at a high risk for experiencing spatial disorientation in the community.

1.7 Thesis Aims and Objectives

The aim of this thesis is to investigate the role that spatial navigation impairments and the outdoor environment plays in spatial disorientation in AD. Specifically, we aim to:

- Identify environmental risk factors associated with spatial disorientation in AD patients using retrospective police case records of dementia-related missing incidents (Chapters 2 and 3).
- Explore whether spatial disorientation in AD can be explained by examining patients' outdoor mobility patterns in the community over a 2 weeks period using global positioning system (GPS) tracking (Chapter 4).
- Investigate whether we can predict AD patients at a high risk for spatial disorientation in the community based on their performance on VR navigation tests (Chapter 5).

Each experimental chapter will include a set of hypotheses and detail the studies that were conducted to address these objectives. A brief discussion of the results is given at the end of each experimental chapter, followed by a more detailed discussion in the General Discussion (Chapter 6).

Chapter 2

Spatial Patterns and Impact of Outdoor Landmark Density for Dementia-Related Missing Incidents in the Community

Published Paper

Puthusseryppady V, Coughlan G, Patel M, Hornberger M. Geospatial Analysis of Environmental Risk Factors for Missing Dementia Patients. Journal of Alzheimer's Disease. 2019;71(3):1005–13.

2.1 Introduction

Spatial disorientation often leads to AD patients going missing in the community. Indeed, a dementia-related missing incident is defined as an instance when a patient is not at an expected location and their whereabouts are unknown to their carer [3]. Missing incidents have been suggested to arise fundamentally due to the impairments to spatial navigation seen in AD patients [1], which causes them to make navigation errors that they are ultimately unable to recover from when out in the community. Previous research has suggested that there may in fact be some external factors that interact with these impairments, specifically by acting as triggers for AD patients to make these navigation errors in the first place, which lead to them going missing [3]. Considering the key role that environmental factors play in influencing and guiding navigation in the RW [101], whether specific features of the environment act as such triggering factors for navigation errors made by patients warrants investigation.

Surprisingly however, there have been almost no studies which report RW environmental risk factors or geographic patterns for AD patients going missing in the community. Due to the unpredictable nature of missing incidents [3,10], identifying these factors are of importance as they can potentially help to identify or predict areas where patients may be more likely to go missing from. Clearly, this knowledge can further our understanding of why AD patients

go missing in the community as well as inform safeguarding guidelines to prevent them from going missing in the future.

In the current study, we investigate potential environmental risk factors that might contribute to AD patients going missing in the community, and more generally for spatial disorientation. We conducted a retrospective analysis of police records of missing incidents of dementia patients over a 3-year period. Here, we employ geospatial analytical techniques which are increasingly used in health and disease studies [102], to investigate the spatial patterns of patients going missing. Using the police records, we aim to: i) identify if there are any locations that patients are more likely to go missing from (i.e., hotspots) in our study area, and ii) explore the spatial configurations of the locations patients went missing from, to try and identify if particular built features of the environment may have contributed to patients going missing. For this work, the feature that we have chosen to examine is the density of outdoor landmarks, as landmarks represent important entities that are used for RW navigation, especially by AD patients [94,95,103]. We hypothesise that: i) there would be no 'hotspots' for missing incidents, once controlling for population density, as spatial disorientation (and hence missing incidents) are now seen as an integral part of AD [1], and ii) lower outdoor landmark density would be associated with/lead to higher incidence of missing incidents, as the relatively lower presence of landmarks will make it more difficult for patients to navigate safely to their intended destination.

2.2 Methods

2.2.1 Study Design

Records of missing patients with dementia (MPWD) were provided by the Norfolk Police force with a total of 210 anonymised cases covering dates from January 2014 to December 2017, for the Norfolk County (total population 898,390) in the UK.

For each missing case, the following data was provided - date missing, gender, age, location missing from (town and postcode), type of setting missing from (care home/hospital, domestic residence, public), location found (building name/road and town), case details (circumstances in which patient went missing/was found), time missing (minutes), and whether it was the first time missing (yes/no). Here, it is important to note that no clinical information was provided regarding the type or stage of dementia for the missing cases. However, considering that missing incidents are more likely to be seen in AD patients due to their specific navigation impairments, and more generally that AD makes up the largest proportion of dementia patients, we assume for this study that the majority of the cases had AD. From the location missing from/found information, the distance travelled by each MPWD was calculated in OpenStreetMap (https://www.openstreetmap.org/#map=5/54.910/-3.432) by using the shortest routes linking the two locations, which was determined by the mapping platform. Meanwhile, the locations patients went missing from were classified as urban or rural using the UK Office for National Statistic's 2011 rural urban classification guide [104]. Lastly, from the case details, we inferred whether the MPWD sustained harm (i.e., injuries/death) during the missing incident.

Ethical approval for this study was granted by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia (Ref. 2017/18 – 94), and all research was conducted in accordance with the relevant guidelines and regulations.

2.2.2 Demographics Analysis

The MPWD data contained a mixture of continuous and categorical variables. Shapiro-Wilk normality tests were conducted on the continuous variables (age, time missing, and distance travelled) to determine whether to use parametric or non-parametric statistics tests on the data. Meanwhile, Chi-Square and where appropriate, Fisher's Exact Test were used to

explore associations between the remaining, categorical variables. All demographics analysis were conducted via R software package version 3.4.2 [105].

2.2.3 Spatial Hotspot Analysis for Missing Incidents

Identification of spatial hotspots for the MPWD were conducted on ArcGIS software version 10.3.1 [106] with a map of the Norfolk County in the World Geodesic System 1984 geographic co-ordinate system. The Norfolk county was sub-divided into its lower layer super output areas (LSOAs) to provide specific spatial units for the analysis. LSOAs were chosen as they represent geographic units commonly used by the UK Office for National Statistics for reporting small area statistics (eg. neighbourhood population, income estimates, housing etc.) [107], and hence have good ecological validity by allowing to split the data into three main localities (urban, rural town and rural villages). For this analysis, we downloaded a shape file containing the UK sub-divided into its different LSOAs from the UK Office for National Statistics Open Geography Portal [108], and extracted only the LSOAs for the Norfolk region. In this shapefile, each LSOA was classified as being either urban or rural based on population density, and the latter were further sub-classified into rural towns and rural villages based on household density [104].

The locations patients went missing from were then plotted onto a map of Norfolk. As the locations were reported as postcodes in the dataset, for the purpose of this analysis the centroid of the reported postcodes were taken for these locations. In total, the 210 MPWD went missing from 168 different locations across the region (Fig. 2.1(i)), with there being 17 locations where multiple patients went missing. For patients that went missing multiple times, only one location (i.e., that of the most recent missing incident) was reported. In addition, there were 3 cases where the location the patient went missing from was not reported. All 168 MPWD locations were aggregated into the respective LSOAs in which they fell in. Of these 168 locations, 96 fell within urban LSOAs, 33 in rural town LSOAs, and 39 in rural village

LSOAs. To control for different population densities across Norfolk, the number of MPWD falling within each LSOA was normalised for the total population of that LSOA.

To identify the spatial hotspots for MPWD, a widely used geospatial analytical method known as global spatial autocorrelation (Moran's I) was used, which identifies potential spatial patterns evident across a region. This analysis explores the distribution of the normalised MPWD numbers across all LSOAs and tries to identify if the dataset exhibits spatial clustering (i.e., similar values occurring near each other) [109]. In this analytical approach, each LSOA is grouped together with its neighbouring LSOAs, forming what is termed as a 'neighbourhood'. Following standard practice in geospatial analysis, the K-nearest (i.e., solution = 8) neighbours approach was used to determine the neighbourhood for each LSOA unit, owing to the non-normal distribution of MPWD values across all LSOAs. This means that each LSOA along with its nearest 8 neighbours comprised a neighbourhood. The MPWD values in each respective neighbourhood across the region were then analysed to identify whether spatial clustering of similar values occurred in the dataset. The formula for calculating Moran's I [109] is given below:

$$I = \frac{n}{S_0} \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} w_{i,j} z_i z_j}{\sum_{i=1}^{n} z_i^2}. \qquad (2.1)$$

Here, n is the total number of spatial units (i.e., LSOAs); this formula uses a spatial weights matrix which defines the neighbourhood for each spatial unit; non-neighbouring units are assigned value of 0 whilst neighbouring units assigned a value of 1; $w_{i,j}$ are the spatial weights between spatial units i and j, z is the deviation of the MPWD value in spatial unit i/j from its mean, and S_0 is the aggregate of all spatial weights.

Any spatial dataset can exhibit one of three types of global spatial autocorrelation – positive (maximum value +1; clustering of values), zero (value of 0; completely random spatial

pattern of values), or negative (maximum value of −1; spatial pattern where dissimilar values appear near each other) (Fig. 2.1(iii)). In theory, if the dataset exhibits either positive or negative global spatial autocorrelation, a follow up local spatial autocorrelation (Anselin Moran's I) would have to be run [110]. In the case of the former, the follow up analyses would reveal the spatial locations and extents of the clusters as well as whether these clusters are significant hotspots (i.e., exhibit relatively higher values compared to rest of region) or coldspots (i.e., exhibit relatively lower values compared to rest of region). Typically, global spatial autocorrelation cannot be performed if there are spatial units exhibiting null values of a variable and consequently, all LSOAs not exhibiting MPWD locations were removed from the analysis region. A global spatial autocorrelation (Moran's I) analysis was then run on the remaining LSOAs (Fig. 2.1(ii)).

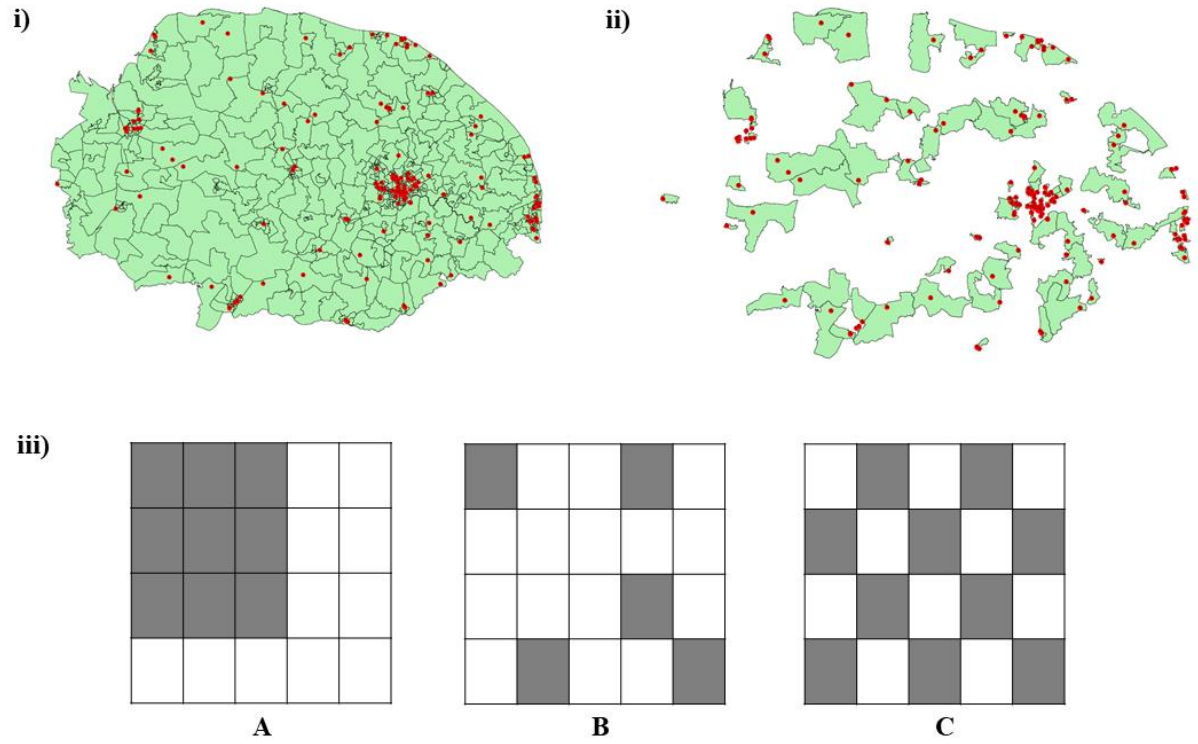

Figure 2.1 (i): Locations MPWD went missing from plotted on a map of Norfolk County, sub-divided into its LSOAs. **(ii)** Map of Norfolk county LSOAs after removing units with no MPWD. This map was used in the global spatial autocorrelation analysis. **(iii) A:** Positive Autocorrelation (maximum value +1). This suggests that the region of analysis is composed of LSOAs with similar MPWD values appearing near each other (i.e., spatial clusters). **B:** Zero Autocorrelation (0). This suggests that the region of analysis is composed of LSOAs exhibiting a completely random spatial pattern of MPWD values (i.e., no spatial clusters). **C:** Negative Autocorrelation (maximum value -1). This suggests that the region of analysis is composed of LSOAs with dissimilar MPWD values appearing near each other[2].

2.2.4 Outdoor Landmark Density and Missing Incidents

A spatial buffer analysis was conducted to explore the relationship of outdoor landmark density to the MPWD. This approach involves generating a buffer zone of a specific radius around each MPWD location and identifying the number of outdoor landmarks that fall within these zones. Since we do not have any trajectory data for the MPWD, employing a buffer zone enables us to take into account any direction that these individuals could have travelled and as such, allows us to estimate all potential landmarks that they could have encountered at the time and place they went missing. A radius of 1 kilometre was chosen for

[2] Reprinted from Journal of Alzheimer's Disease, Vol 71, no.3, Puthusseryppady V, Coughlan G, Patel M, Hornberger M, Geospatial Analysis of Environmental Risk Factors for Missing Dementia Patients, pp. 1005-1013, Copyright (2019), with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/https://doi.org/10.3233/JAD-190244.

the buffer zones as according to previous health geography studies [111–113], this has been suggested to be an appropriate distance to capture all environments accessible within a reasonable walking distance from a particular location.

To run this analysis, a dataset containing all the landmarks in the Norfolk region, in shape-file format, was downloaded from OpenStreetMap and imported into ArcGIS. This dataset contained any object or location that fell into the following five categories – Amenity & Leisure, Tourism, Traffic & Transport, Urban & Rural Furniture, and Historic (see supplementary table 2.1 for full breakdown of landmark categories, subcategories, and tags). For each landmark, details of its name (e.g., Riverside Leisure Centre), type (Swimming Pool), and map co-ordinates (X,Y; in the World Geodetic System 1984 geographic co-ordinate system) were provided in the dataset. The landmarks in the shape-file were overlaid onto a map of the Norfolk LSOAs. Both maps utilised the World Geodetic System 1984 geographic co-ordinate system.

First, we searched and removed landmark duplicates in the dataset. Next, we wanted to ensure that our dataset captured only landmarks that were visible from open street view as an individual navigates in the community. To this end, landmarks that fell inside other landmarks were identified and their visibility from open street view was examined using Google Maps. If such landmarks were not visible from street view (e.g. individual shops falling inside a shopping mall), they were removed from the dataset, as it is unlikely that the MPWD would have used or been exposed to this landmark whilst navigating outdoors. Meanwhile, landmarks falling inside other landmarks that were visible from street view were examined to see if they were at least as salient as the landmark they fell within, using Google Maps. Although there are many features which render the perception of a landmark as being salient by dementia patients [114], for practical reasons we have chosen to focus here on the feature of size/scale with regards to assessing saliency. If the saliency condition was satisfied,

(e.g., bell tower as part of a church), then these landmarks were kept in the dataset, as it may have been just as likely for either of these landmarks to have caught the attention of the MPWD whilst navigating outdoors. If the saliency condition was not satisfied (e.g., recycling bin inside a large carpark), then the lesser salient landmarks were removed based on the assumption that they would not have caught the attention of the MPWD. After controlling for all factors listed above, we ended up with a total of 24,900 outdoor landmarks for analysis.

Next, for each of the 168 MPWD locations, a geodesic buffer zone with a radius of 1 kilometre was generated and the number of outdoor landmarks falling within each buffer zone was computed (Fig. 2.2(i), (iii)). Following this, a set of 168 random, control locations were generated across the entire Norfolk region using an in-built algorithm in ArcGIS (Fig. 2.2 (ii)). These random locations were generated in regions falling outside the MPWD location buffer zones, and controlled to have the same urban/rural distribution as the MPWD locations (96 urban locations, 33 in rural town, 39 in rural villages). The random locations were also controlled for the type of land they fell in. Of the 96 urban MPWD locations, 2 fell in industrial & retail lands, 69 in residential lands, and 23 in unclassified lands. Of the 33 rural town MPWD locations, 1 fell in forest lands, 25 in residential lands, 2 in retail lands, and the remaining 5 in unclassified lands. Lastly, of the 39 rural village MPWD locations, 29 fell in residential lands, 1 in commercial lands, and 9 in unclassified lands. The same number of random location points for each land use type were generated across Norfolk, for each respective locality (urban, rural town, rural village).

Once all 168 random locations were generated, geodesic buffer zones with a 1 kilometre radius were generated for each location and the number of outdoor landmarks falling within each location's buffer zone was computed (Fig. 2.2(iv)). As the number of outdoor landmarks in both the MPWD and random location buffer zones had a non-normal distribution, a Wilcoxon Rank Sum test was run to compare the number of outdoor landmarks falling within the buffer zones of both groups.

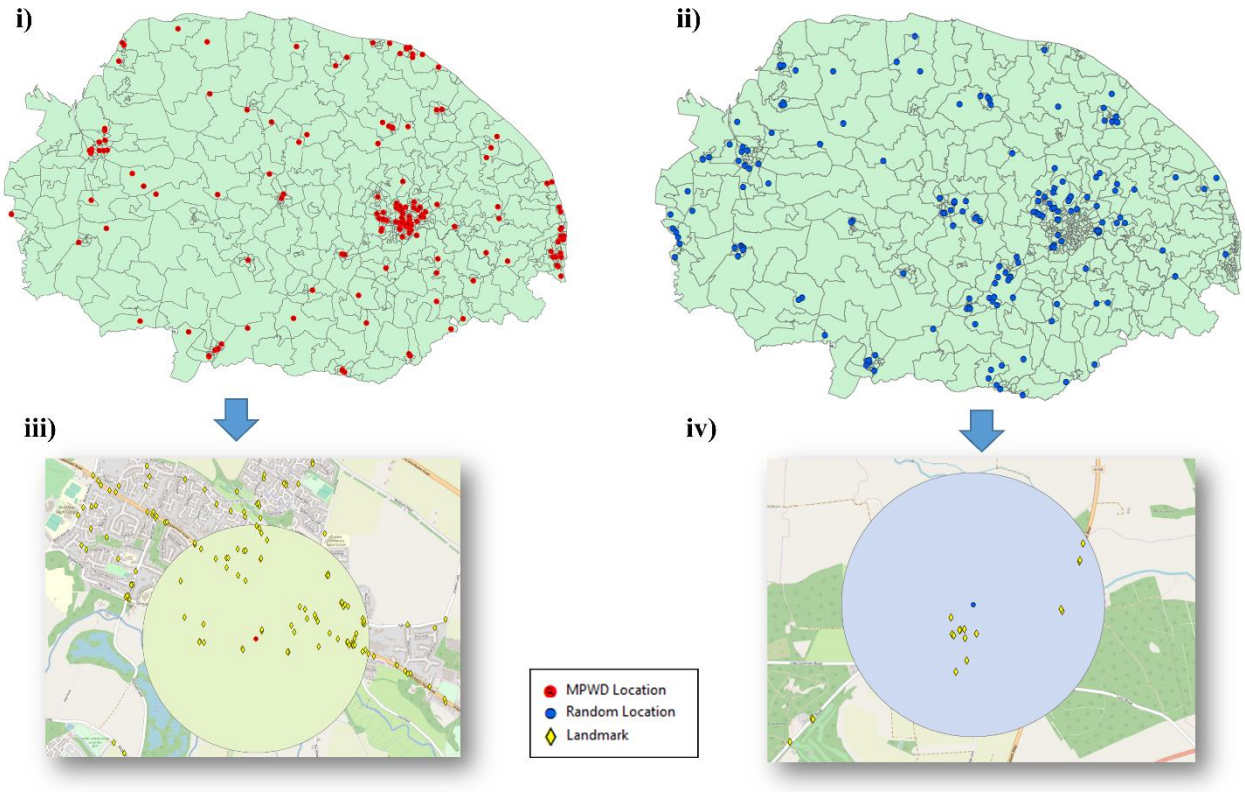

Figure 2.2 (i): Locations MPWD went missing from in Norfolk. **(ii):** Set of random control locations in Norfolk generated using an in-built algorithm in ArcGIS. **(iii):** Landmarks falling within a 1 kilometre radius buffer zone of a single MPWD location (residential land). **(iv):** Landmarks falling within a 1 kilometre radius buffer zone of a single random location (residential land)[3].

[3] Reprinted from Journal of Alzheimer's Disease, Vol 71, no.3, Puthusseryppady V, Coughlan G, Patel M, Hornberger M, Geospatial Analysis of Environmental Risk Factors for Missing Dementia Patients, pp. 1005-1013, Copyright (2019), with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/https://doi.org/10.3233/JAD-190244.

To explore the relationship between outdoor landmark density and MPWD on a more global scale, ordinarily least squares linear regression models were run where the number of MPWD in each LSOA were respectively regressed against the landmark density for each LSOA. In total, three independent regression models were run – one for urban, rural town, and rural village regions, respectively. All regression models were run in R software.

2.3 Results

2.3.1 Demographics Analysis

The MPWD demographics (Table 2.1) showed similar numbers of patients going missing across all 4 seasons, as well as similar numbers of males and females going missing. The majority of MPWD went missing from domestic residence settings (n = 134) when compared to care facilities (n = 52) or general public locations (n = 23). A total of 86 MPWD went missing on foot, 33 cases used some form of transport (taxi/bus/train/car), 2 cases used a combination of transport and foot, and the remaining 87 cases did not have sufficient information provided to infer their mode of transportation. Subgroups of MPWD that went missing multiple times (n = 52), as well as those that sustained harm whilst missing (n = 10), were also identified. All MPWD were found alive except for one case.

Table 2.1: Demographics of the Missing Dementia Patients

	Total	**Males**	**Females**	**Significance**
Cases	210	114	96	-
Age (Mean)	78.43	77.85	79.12	ns
Season Lost				
Summer	51	22	29	ns
Autumn	52	29	23	
Winter	52	31	21	
Spring	55	32	23	
Setting Missing From				
Domestic Residence	134	63	71	*
Care Facility	52	36	16	
Public Place	23	15	8	
Locality Missing From				
Urban	134	75	59	ns
Rural	73	37	36	
Unspecified	3	2	1	
Distance Travelled (Mean; Kilometres)	20.45	21.60	19.15	ns
Time Missing (Mean; Minutes)	186.73	238.89	124.80	**
Missing Multiple Times	52	37	15	**
Sustained Harm	10	5	5	ns

ns = not significant; *p < 0.05, **p < 0.01

There is often a general assumption that spatial navigation might be different between males and females [115,116]. We therefore explored associations between the missing incident variables and gender as a factor. For the type of location MPWD went missing from, the results showed that patients missing from domestic residences were more likely to be female than male (X^2=8.644, p = 0.013). By contrast, patients who went missing multiple times were more likely to be male than female (X^2=7.701, p = 0.005). Results also showed that male MPWD went missing for significantly longer periods of time than females (W = 4293, p = 0.007).

Finally, we explored potential demographic risk factors for patients who went missing multiple times as well as for those who sustained harm. When comparing the patients missing

multiple times to those that went missing only once, no significant differences were seen in any variable. However, a statistical trend was observed for age, with patients missing multiple times being younger than patients that only went missing once (W= 4804, p = 0.056). A statistical trend was also observed for distance travelled, with patients missing multiple times travelling a lower distance than those that only went missing once (W= 3766.5, p = 0.058). Meanwhile, no significant differences were observed in any variable when comparing patients which sustained harm to the unharmed patients.

2.3.2 Spatial Hotspots Analysis for Missing Incidents

The global spatial autocorrelation (Moran's I) analysis revealed no significant spatial autocorrelation in our dataset (Global Moran's I = − 0.011, p = 0.911). Considering that the global trend can potentially mask subtle underlying cluster like patterns present in specific regions, a follow up local spatial autocorrelation (Anselin Local Moran's I) analysis was run to identify possible underlying clusters. Here, a False Discovery Rate (FDR) was used to correct for multiple comparisons. The results of the follow-up analysis confirmed the global spatial autocorrelation results, signifying that the MPWD exhibits a random spatial pattern across Norfolk and as such, there are no significant hotspots (or cold spots) for MPWD in the examined region.

The spatial autocorrelation analyses listed above were run on values of MPWD normalised for the total population values of the respective LSOAs in which they fell in. To account for the fact that there may be differences in the densities of the elderly population across Norfolk, as a second measure we ran these analyses again, this time normalising the MPWD values for the LSOA population values of individuals equal to/above 65 years of age only. Using these new normalised MPWD values, our global spatial autocorrelation analysis this time revealed a significant positive spatial autocorrelation in our dataset (Global Moran's I = 0.128, p < 0.001). However, our follow up local spatial autocorrelation analysis (using FDR to correct

for multiple comparisons) did not identify any significant hotspots (or coldspots) for MPWD in the examined region.

2.3.3 Spatial Buffer & Regression Analysis

The Wilcoxon Rank Sum Test revealed that there is a significantly higher number of outdoor landmarks falling within a 1 kilometre buffer zone of the MPWD locations when compared to the random locations ($W = 21312$, $p < 0.001$).

Our first set of regression models showed that increased outdoor landmark density significantly predicted higher MPWD in urban ($p < 0.001$, $R^2=0.15$) and rural village regions ($p < 0.001$, $R^2= 0.69$) (Fig. 2.3), but no significant relationship was found in rural town regions ($p = 0.770$). Similar to the spatial autocorrelation analyses, we ran a second set of regression models, this time by using the MPWD values which were normalised for the total elderly population of their respective LSOAs. Here, we found the same results – increased outdoor landmark density significantly predicted increased MPWD in urban ($p < 0.001$, $R^2=0.19$) as well as rural village regions ($p < 0.001$, $R^2=0.65$) (Fig. 2.4), but not in rural town regions.

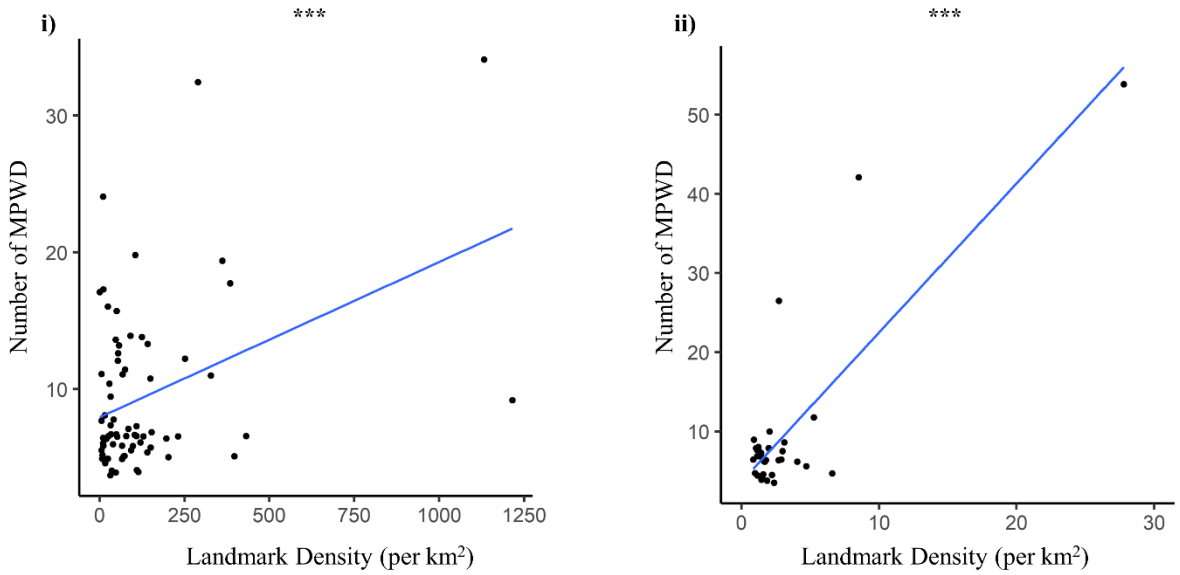

Figure 2.3: Plots showing first set of significant regression models for relationship between landmark density and number of MPWD in **(i)** Urban and **(ii)** Rural Town regions.

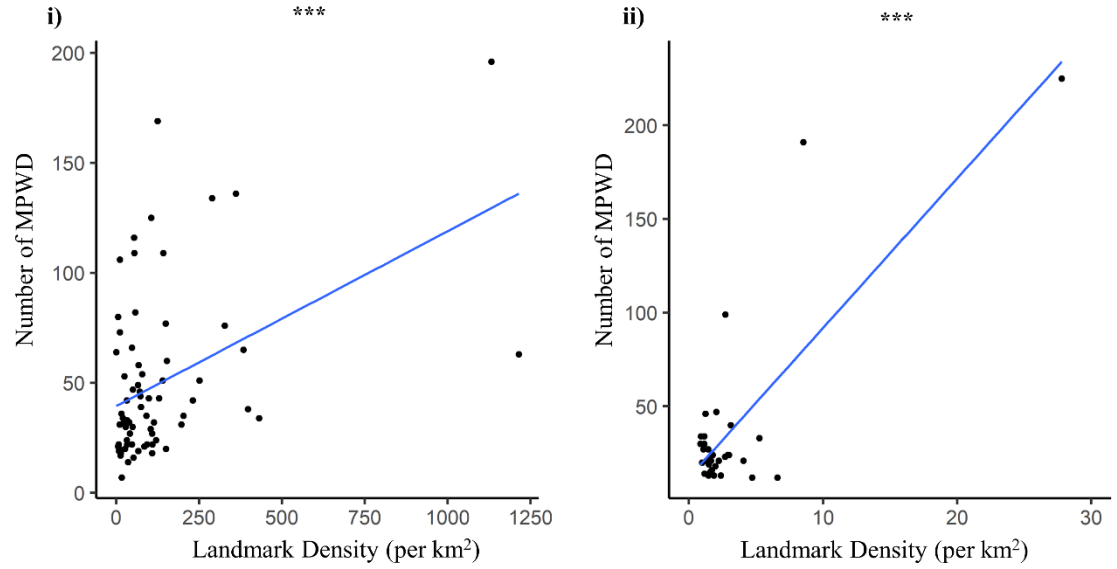

Figure 2.4: Plots showing second set of significant regression models for relationship between landmark density and number of MPWD in **(i)** Urban and **(ii)** Rural Town regions.

2.4 Discussion

In this chapter, we aimed to identify whether there were any hotspot locations for dementia-related missing incidents in our study area as well as explore whether outdoor landmark density was an environmental risk factor for these missing incidents.

On a demographic level, we found that rates of missing incidents were not dependant on season, as similar numbers of patients went missing across all four seasons. We also found that the majority of patients went missing from domestic residence settings as opposed to care facilities, which replicates findings from multiple similar studies [3,85,86]. Although similar numbers of male and female patients went missing, replicating previous findings [85,86], gender differences were seen in 3 of the missing incident variables. Specifically, patients going missing from domestic residences were more likely to be female than male. Furthermore, male patients went missing for significantly longer and were associated with being more likely to go missing multiple times when compared to females. In addition to gender, a statistical trend for younger age as being a risk factor for multiple missing incidents was also observed, which was consistent with a previous study [81]. Finally, we also found a very small group of MPWD who sustained harm whilst lost, however we did not identify any risk factors for this.

In line with our hypothesis, we did not find any hotspot locations for the MPWD, indicating that the distribution of missing incidents is widespread and similar in the study region. The global spatial autocorrelation analysis we used for this have so far only been used to establish the frequency and mortality of dementia across regions [117,118], but to our knowledge, this is the first study to use this geospatial technique for dementia-related missing incidents. Contrary to our hypothesis however, we found that at the spatial buffer level, increased outdoor landmark density was associated with the missing incidents. Further, at a LSOA level, our findings showed that increased outdoor landmark density predicted higher

incidence of MPWD in urban and rural village locations. However, for our findings at the LSOA level, it must be noted that the regression models in both urban/rural village regions seem to be influenced by LSOAs with relatively high landmark density values. Nevertheless, our results overall suggest that regardless of location, the increased presence of outdoor landmarks is an environmental risk factor that could be contributing to patients going missing in the community. Previous studies have thus far only assessed landmark knowledge and recognition in AD patients during navigation in VR settings [55,65] and using qualitative accounts from patients, how these entities are used to aid their navigation in the community [94,95,114,119]. To the best of our knowledge, this is the first time that the impact of outdoor landmark density on patients going missing in the community has been explored.

In conclusion, our results replicate and extend previous demographic findings for dementia-related missing incidents. Moreover, our results also suggest increased outdoor landmark density as being one potential environmental risk factor for AD patients going missing in the community. Our work in this chapter has shown that geospatial analytical techniques provide an exciting opportunity to determine systematic RW factors that are associated with spatial disorientation in AD. In the next chapter, we continue to explore environmental risk factors for dementia-related missing incidents using the same police records dataset, this time by investigating the road network structure in the locations where patients went missing.

Chapter 3

Impact of Road Network Structure for Dementia-Related Missing Incidents in the Community

Published Paper

Puthusseryppady V, Manley E, Lowry E, Patel M, Hornberger M. Impact of road network structure on dementia-related missing incidents: a spatial buffer approach. Scientific Reports. 2020;10(1).

3.1 Introduction

In the previous chapter, we investigated and found that outdoor landmark density may be a potential environmental risk factor for AD patients going missing in the community, using police records of dementia-related missing incidents. In this chapter, we focus on the role that another environmental variable may play in causing AD patients to go missing, which is the structure of road networks.

Forming the backbones of built environments, road networks play an important role in guiding and influencing human navigation behaviour in the RW. Specifically, previous studies have shown that road intersections prompt the spatial decision making process during navigation and that individuals tend to choose well-connected roads when navigating to a particular location [120,121]. In the context of spatial disorientation in AD, two previous studies have reported that patients get disoriented at road intersections, especially at those with many route options, and when navigating through road networks with complex layouts [103,122]. However, these findings were based on observations from a relatively small sample of dementia patients, during accompanied walks with the researcher. In the current study, we aim to explore further the role that road network structure may play in causing AD patients to go missing in the community when they are alone, and using a relatively larger participant sample. Informed by findings from the studies described above, we focus here on

three key features of the network: i) road intersection density, ii) road intersection complexity, and iii) road orientation entropy (i.e., measure of road network layout in a given area by looking at the orientation of the roads).

To this end, we conducted a retrospective analysis using the same set of police case records of dementia-related missing incidents as in the previous chapter. We hypothesise that: i) higher road intersection density would lead to increased missing incidents, as the more frequently patients have to make critical navigation decisions, the more likely they are to make an error and wrong turn, ii) higher road intersection complexity would lead to increased missing incidents, as the more route options an intersection has, the harder it will be for the patients to identify and select the correct route, and iii) higher road orientation entropy would also be associated with increased missing incidents, as road networks with a high entropy would be less ordered in structure and hence more complex to navigate through.

3.2 Methods

3.2.1 Study Design

This study was conducted using the same case records of dementia-related missing incidents provided by the Norfolk Police as in the last chapter (total records = 210, covering dates from January 2014 to December 2017). It is important to mention again that apart from having a diagnosis of dementia, no further clinical information was provided regarding the type/stage of dementia for the missing cases. However, we are assuming that the majority of the reported cases had AD, for the purpose of this study.

As mentioned in detail in Chapter 2, each MPWD case contained a mixture of continuous and categorical missing incident variables (eg. date missing, gender, age, location missing from, etc.). For each case, the location the patients went missing from was classified as urban or rural using the UK Office for National Statistic's 2011 rural urban classification guide [104].

Using the above variables, we investigated retrospectively if there were any demographic risk factors for the MPWD and the impact of outdoor landmark density on these individuals going missing in Chapter 2. Here, using the same dataset, we are investigating the impact of road network structure on these individuals going missing.

Ethical approval for this study was granted by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia (Ref. FMH2017/18 – 94), and all research was conducted in accordance with the relevant guidelines and regulations.

3.2.2 Missing Incidents & Road Intersection Density

For our first measure, we explored the impact of road intersection density on the patients going missing. For this we first plotted out all 168 different locations that the patients went missing from onto a map of Norfolk, in shape-file format, on ArcGIS software version 10.6.1 [106] (Fig. 3.1a). As the locations were reported as postcodes in the dataset, for the purpose of this analysis the centroid of the reported postcodes were taken for these locations. The road network data used in this study was the Ordnance Survey Open Roads layer (https://www.ordnancesurvey.co.uk/business-government/products/open-map-roads), which is a publicly available dataset containing all the roads (major & minor) and intersections in the UK. In this dataset, road intersections are represented as vertices and the roads themselves are represented as edges connecting the vertices (Fig. 3.1c). Here, all roads and intersections for the Norfolk region were extracted and overlaid onto the map of Norfolk (Fig. 3.1b). In this dataset, road ends are labelled as intersections; since these do not represent true road intersections, we removed all intersections that were labelled road ends. The data analysis was then conducted using all remaining road intersections.

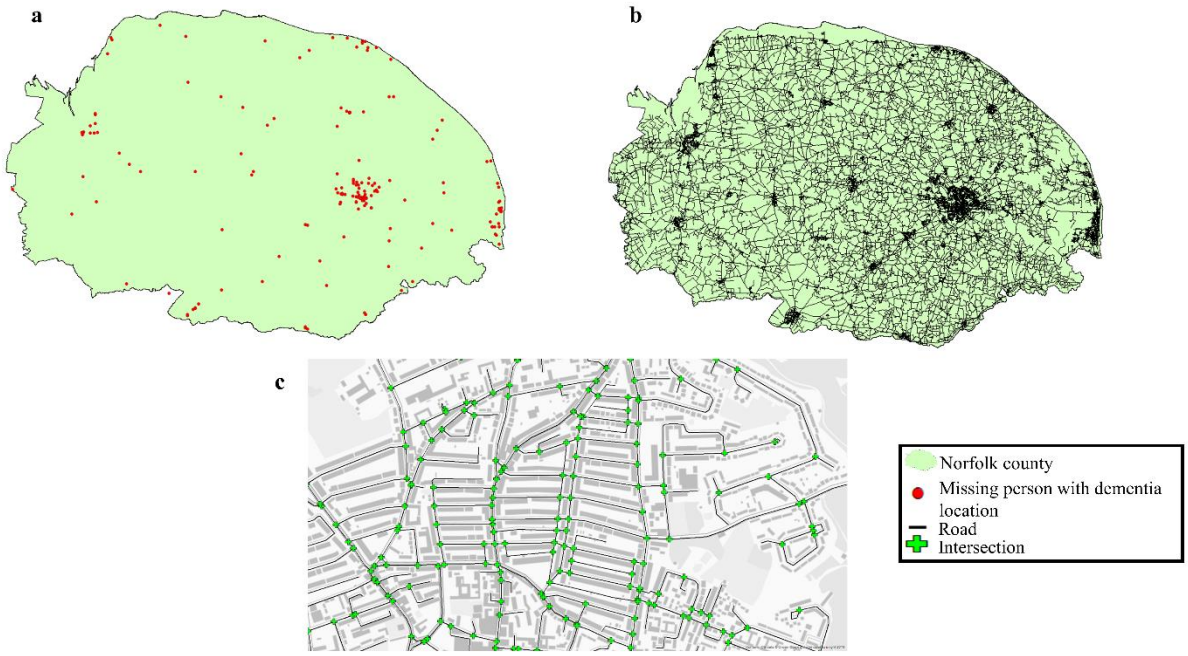

Figure 3.1 (a): MPWD locations in Norfolk. **(b):** Road network dataset overlaid onto map of Norfolk. **(c):** Roads and intersections in the road network dataset.

The measure of road intersection density was employed using the same methodology as in the previous chapter - spatial buffers. In short, this approach involves generating a buffer zone of a specific radius around each MPWD location and identifying the number of road intersections that fall within these zones. Owing to the lack of trajectory data for the MPWD, employing a buffer zone enables us to take into account any direction that these individuals could have travelled and as such, allows us to estimate all potential road intersections that they could have encountered at the time and place they went missing. To keep in line with our work in the previous chapter, we continued to use a radius of 1 kilometre for the buffer zones.

Here, geodesic buffer zones with a radius of 1 kilometre were generated for each of the 168 MPWD locations (Fig. 3.2a), and the road intersection density within each buffer zone was computed. Following this, we used the same set of 168 random, control locations generated across the entire Norfolk region as in the previous chapter, which had a similar urban/rural

distribution as well as fell in the same types of land as the MPWD locations (Fig. 3.2b). Similar to the MPWD locations, we generated geodesic buffer zones with a radius of 1 kilometre for each of the 168 random locations, and computed the road intersection density within these buffer zones.

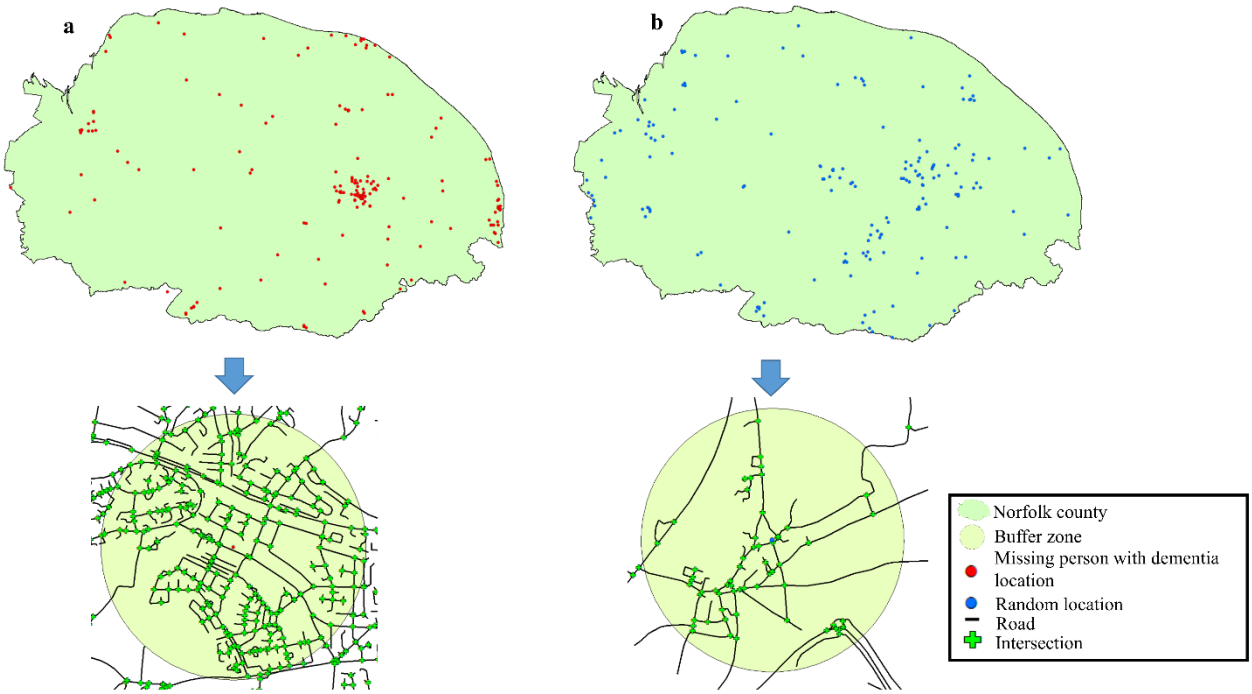

Figure 3.2 (a): Road intersections falling within a 1 kilometre radius buffer zone of a single MPWD location (urban region, residential land). **(b):** Road intersections falling within a 1 kilometre radius buffer zone of a single random location (urban region, residential land).

As the road intersection density within the buffer zones of both the MPWD and random locations groups had a non-normal distribution, a Wilcoxon Rank Sum Test was run to compare this variable in both groups.

3.2.3 Missing Incidents & Road Intersection Complexity

Our second measure was exploring the complexity of the road intersections at the MPWD and random locations. Here, road intersection complexity refers to the number of route options that branch out from a single intersection. For example, road intersections with 5

route options would be considered to be more complex than road intersections with only 2 route options. For this, we computed the average road intersection complexity exhibited in each of the MPWD and random location buffer zones. Owing to the non-normal distribution of this variable in both groups, Wilcoxon Rank Sum Tests were run to compare the group differences in this variable.

3.2.4 Missing Incidents & Road Orientation Entropy

For our last measure, we explored the impact of road orientation entropy on the MPWD. Here, road orientation entropy refers to a measure of how ordered or disordered the overall layout of a road network within a given area is.

We first calculated the angular orientation of each road in the MPWD and random location buffer zones. Since each road is bidirectional in nature, this was done by measuring the angle between compass North and the start/end points of the road respectively. Hence for each road this yielded two angles that were reciprocals of one another (i.e., If start point of road had orientation angle of 60º, the end point would have angle of 300º). After calculating the orientation of all roads in the MPWD and random location buffer zones, we group these values into 36 bins, with each bin representing incremental ranges of 10º (i.e., 0-10, 11-20, 21-30…351-360) (Fig. 3.3).

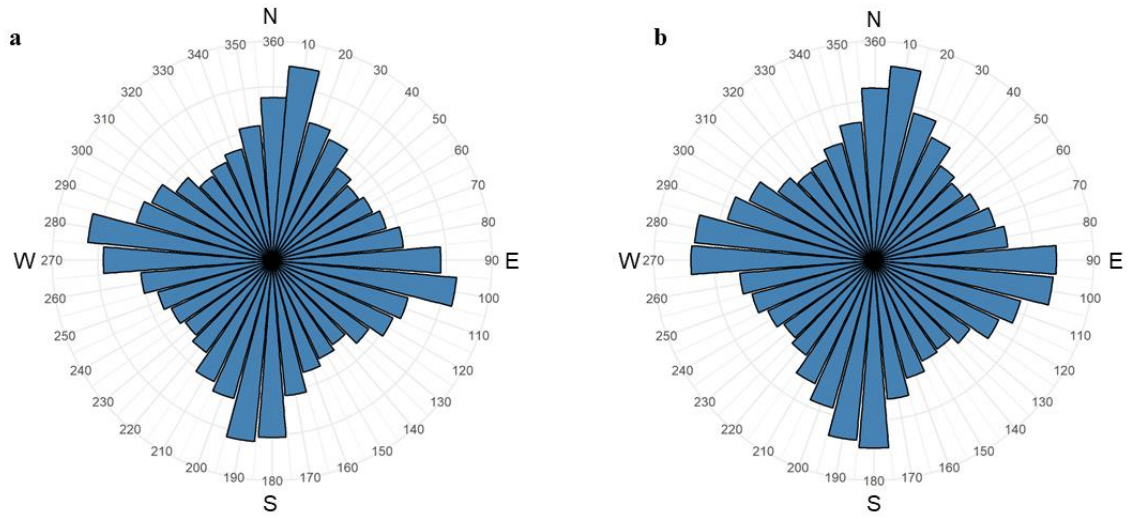

Figure 3.3: Rose diagrams showing the orientations of roads in a single **(a)** MPWD location buffer zone (urban, residential area) and **(b)** random location buffer zone (urban, residential area). The direction of the bars represent the orientation of the roads, whilst the height of the bars represent the frequencies of roads exhibiting that orientation.

We next calculated Shannon's entropy (H) [123] for the distribution of road orientations across all bins for the MPWD and random location buffer zones, using the formula:

$$H = -\sum_{i=1}^{n} P(0_i) \log_e P(0_i), \qquad (3.1)$$

where n is the total number of bins, i is the bin number, and $P(0_i)$ is the probability of a randomly selected road from the sample falling in bin number i. In essence, the entropy measure tells you how ordered the layout of the roads in each buffer zone are, with higher entropy indicating low order and lower entropy indicating high order.

3.2.5 Missing Incidents & Road Intersection Density, Intersection Complexity, and Orientation Entropy – Multiple Regression Modelling

To explore whether road intersection density, intersection complexity, and orientation entropy predicted MPWD across Norfolk, we ran ordinarily least square multiple regression models.

To provide specific spatial units for the analysis, the Norfolk County was sub-divided into its LSOAs (Fig. 3.4). We continued to use LSOAs as our spatial units of analysis to keep in line

with our work in the previous chapter. For this, we downloaded a shape-file containing the UK sub-divided into its different LSOAs from the UK Office for National Statistics Open Geography Portal [108], and extracted only the LSOAs covering the Norfolk region. In this shape-file, each LSOA was classified as being either urban or rural based on population density and the latter were further sub-classified into rural towns and rural villages based on household density [104]. All the 168 MPWD locations were then aggregated into the respective LSOAs in which they fell in (96 locations in urban LSOAs, 33 in rural town LSOAs, and 39 in rural village LSOAs). Here, LSOAs that did not exhibit a MPWD were removed from the analysis (Fig. 3.4).

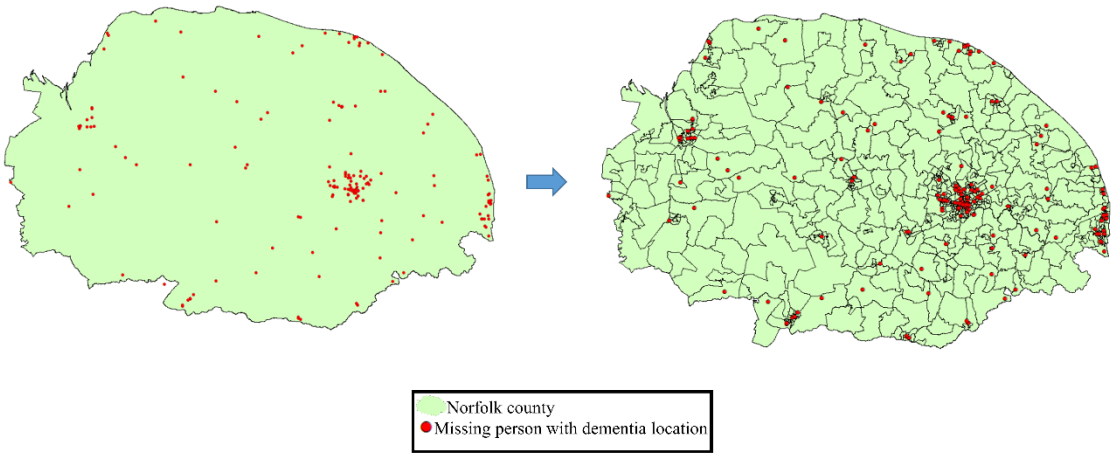

Figure 3.4: Map of Norfolk containing all the MPWD locations, sub-divided into its different LSOAs.

To control for the distribution of population densities across Norfolk, the number of MPWD falling within each LSOA were firstly normalised for the total population of that LSOA. Ordinary least squares multiple regression models were then run where the number of MPWD in each LSOA were regressed against the road intersection density, average intersection complexity, and road orientation entropy of each LSOA. In total, three multiple regression models were run – one for urban, rural town, and rural village regions, respectively. Following this, we ran a second set of multiple regression models for each

locality, this time by normalising the number of MPWD in each LSOA for the elderly population (≥ 65 years of age) values for that LSOA, instead of the total population. All regression models were run in R software package version 3.4.2 [105].

3.3 Results

3.3.1 Demographics Risk Factors

All results of the demographics analysis were conducted and reported in the previous chapter. However, in summary and of relevance to this study, it is important to note that a similar number of males and females went missing. Moreover, most of the patients went missing from domestic residence settings (*n = 134)*, followed by care facilities (*n = 52)* and general public locations (*n = 23)*. Subgroups of patients that went missing multiple times (*n = 52)*, as well as those that sustained harm during the missing incident (*n = 10*) were also identified. All MPWD were found alive except for one case.

3.3.2 Missing Incidents & Road Intersection Density, Complexity

Our results showed that there was a significantly higher road intersection density within the MPWD location buffer zones when compared to the random location buffer zones ($W = 21425$, $p < 0.001$). In addition, the average intersection complexity in the MPWD location buffer zones were also significantly higher when compared to that of the random location buffer zones ($W = 16522$, $p = 0.006$).

3.3.3 Missing Incidents & Road Orientation Entropy

Our results showed that there were no significant differences in the road orientation entropy in the MPWD location buffer zones when compared to that of the random location buffer zones ($W= 15482$, $p = 0.081$). However, considering that this p-value of 0.081 indicates a statistical trend towards significance, we speculate that the threshold of 1 kilometre may have the limitation of being too small a radius (for the buffer zone) to fully capture differences in

the orientation of roads between locations. Hence as an exploratory measure, we expanded the buffer zone radius to 2 kilometres for all MPWD and random locations, and ran the analysis again. Here, we found that the roads in the MPWD location buffer zones had a significantly higher orientation entropy than the roads in the random location buffer zones ($W= 16352$, $p = 0.012$).

3.3.4 Missing Incidents & Road Intersection Density, Intersection Complexity, and Orientation Entropy – Multiple Regression Modelling

Our first set of multiple regression models showed that in urban regions, increased road intersection density was a significant predictor for increased MPWD ($\beta= 0.03$, $p = 0.01$) whilst neither road intersection complexity nor orientation entropy were significant predictors ($p = 0.184$; $p = 0.949$) ($r^2 = 0.05$, $p = 0.07$). Meanwhile, neither road intersection density, intersection complexity, nor orientation entropy were significant predictors for MPWD in either rural towns or villages. To ensure that our models did not violate the fundamental assumption of multiple regression modelling regarding whether the predictor variables exhibited multi-collinearity (i.e., correlate with one another), we calculated the variance inflation factor (VIF) for each predictor variable in the three models (i.e., urban, rural town, and rural villages). All predictor variables in all three models had VIFs that fell close to 1 (i.e., well below the recommended thresholds of 5 or 10), which indicates the absence of any problematic multi-collinearity [124].

From our first set of regression models, we found that higher road intersection density was a significant predictor for higher incidence of MPWD in urban regions. In the previous chapter, we found that higher outdoor landmark density also significantly predicted higher incidence of MPWD in urban regions. Hence, we ran an additional multiple regression model for urban regions where we regressed the number of MPWD against road intersection density and outdoor landmark density. Our results for this model show that only higher outdoor landmark

density significantly predicts higher incidence of MPWD in urban regions (β= 0.009, p = 0.008), with road intersection density no longer being a significant predictor (p = 0.375) (r^2 = 0.13, p = 0.002).

Our second set of regression models (i.e., using values of MPWD normalised for the elderly population densities across Norfolk) showed the same results as the first set – in urban regions, increased road intersection density was a significant predictor for increased incidence of MPWD (β = 0.25, p < 0.001) whilst neither of the other two variables (i.e., road intersection complexity and orientation entropy) were significant predictors (p = 0.424; p = 0.545) (r^2 = 0.19, p < 0.001). Meanwhile, neither of these three variables were significant predictors for MPWD in rural town or village regions. Again, none of the three variables in all three models exhibited any problematic multi-collinearity.

Since in the previous chapter the second set of linear regression models showed that increased outdoor landmark density was also a significantly predictor for higher incidence of MPWD in urban regions, here for urban regions we regressed the number of MPWD against road intersection density and outdoor landmark density. Our results here show that both increased road intersection and outdoor landmark density (β = 0.19, p = 0.003; β = 0.05, p = 0.020) significantly predict higher incidence for MPWD in urban regions (r^2= 0.26, p < 0.001).

3.4 Discussion

In this chapter, we aimed to explore the role that road network structure may play in causing AD patients to go missing in the community by specifically focusing on the variables of road intersection density, intersection complexity, and orientation entropy. In line with the hypothesis, our results showed that increased road intersection density and complexity were associated with the missing incidents. However, our hypothesis that increased road

orientation entropy would also be associated with the missing incidents was true only when using a 2 kilometre radius buffer zone, and not 1 kilometre.

Our results overall suggest that increased road intersection density, intersection complexity, and orientation entropy may all be environmental risk factors contributing to AD patients going missing in the community. To date, only two previous studies have looked into the relationship between road network structure and spatial disorientation in AD. Importantly, our results support the findings of these studies that dementia patients experience disorientation at road intersections, have difficulties using intersections with many route options, and get lost in areas with complex road layouts [103,122]. We here replicate and extend these findings using a relatively larger sample of AD patients, and by associating dementia-related missing incidents seen in the community to these properties of the road network structure.

Despite our results showing a significant association for road intersection density, intersection complexity, and road orientation entropy at a buffer level, at a LSOA level we found that increased road intersection density was the sole significant predictor for increased missing incidents, and that too only in urban regions and not in rural towns or villages. Indeed, there may be other, more significant variables that may be predictive of missing incidents in rural regions, which requires further investigation. In urban regions however, after removing the non-significant predictors (road intersection complexity, orientation entropy) and adding outdoor landmark density as a predictor, our results first showed that road intersection density ceased to be a significant predictor for MPWD. However, when regressing against values of MPWD normalised for the elderly population densities, our results showed that both increased road intersection and outdoor landmark density were significant predictors for increased MPWD in urban regions.

In conclusion, our findings suggest that pockets of regions with a high road intersection density, intersection complexity, and orientation entropy could represent likely locations where a missing incident could occur for AD patients. Hence in addition to increased outdoor landmark density, our results suggest that complex road network structure may also be an important environmental risk factor for AD patients going missing in the community. On top of shedding light on the role that built features of the outdoor environment may play in spatial disorientation in AD, the results of our studies in Chapters 2 and 3 provide a platform for future studies to investigate these variables more systematically, using more sophisticated geospatial analytical techniques.

Chapter 4

Outdoor Mobility Patterns of AD Patients in the Community – A GPS Tracking Study

Paper under Preparation

Puthusseryppady V, Patel M, Hornberger M. Outdoor mobility patterns of Alzheimer's disease patients in the community using GPS tracking – a spatial disorientation perspective. To be submitted to *JMIR mHealth and uHealth*.

4.1 Introduction

In Chapters 2 and 3, we investigated and presented evidence for increased outdoor landmark density and complex road network structure as being potential environmental risk factors for dementia-related missing incidents, and more generally for spatial disorientation in AD. However, due to the retrospective nature of the data and the unavailability of trajectory data for the missing dementia patients, the true extent to which these factors contribute to spatial disorientation is unclear. Validation of our results using collected trajectory data from AD patients is warranted to examine if these built features of the environment do play a role in contributing to spatial disorientation.

In addition to examining built features of the environment that influence navigation, investigating more general patterns of how AD patients move in the community could offer further insight into their spatial disorientation. To date, only very few studies have investigated the outdoor mobility patterns of AD patients in the community [125–128], however none of these studies have related the measured mobility patterns of these individuals to their spatial disorientation. Exploring this relationship can potentially offer insight into variables that are associated with spatial disorientation, specifically mobility risk

factors, which can then be used to identify individuals that may be at a high risk for going missing in the community.

In this work, we conducted a 2 weeks GPS tracking study on a sample of community-dwelling AD patients and healthy controls. Using their collected trajectories, our first aim was to understand the outdoor mobility patterns of AD patients in the community over an extended time period and under naturalistic conditions. Specifically, we wanted to investigate differences seen between controls and a) patients overall, b) patients when they are alone vs. accompanied, and c) patients who did/did not experience spatial disorientation during the tracking period. Our second aim was to test whether we could validate our findings from Chapters 2 and 3, by retrospectively investigating whether AD patients experienced spatial disorientation when navigating through environments with a high outdoor landmark density and/or complex road network structure.

For our first aim, we hypothesise that AD patients will exhibit reduced outdoor mobility in the community when compared to controls, based on findings from previous studies [125,127] and more specifically, due to their impairments in spatial navigation. Here, we expect this to especially be true when patients are alone compared to when they are accompanied. We also hypothesise that we will identify mobility patterns which reflect risk factors for spatial disorientation in patients. Specifically, higher distance travelled from home (i.e., venturing into unfamiliar environments) and increased night-time outings into the community will show as being such risk factors, as these variables reflect common situations where spatial disorientation occurs for AD patients. For our second aim, we hypothesise that patients who experienced spatial disorientation during the tracking period will have navigated through environments with a high outdoor landmark density and/or complex road network structure, based on our findings from Chapters 2 and 3.

4.2 Methods

4.2.1 Participants

A total of 16 community-dwelling AD patients and 18 age matched healthy controls were recruited to participate in our research study at the University of East Anglia (see supplementary material 4.1 for details). Prior to study participation, all participants underwent an initial telephone screening procedure to assess eligibility for the study. Inclusion criteria was being between 50-80 years of age, living at home and if a patient, a clinical diagnosis of AD as well as having a carer (relative/spouse) that knows them well and who is willing to assist in the study. The exclusion criteria was having a previous history of alcohol or substance abuse, presence of a psychiatric condition, any other significant medical condition that may be likely to affect participation in the study (head injury, loss of vision, mobility issues), and if a patient, the presence of a comorbid neurological condition not related to AD.

Signed informed consent was obtained from all participants prior to undergoing the experimental protocol. Ethical approval for the study was provided by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia (FMH2017/18 – 123) as well as the National Health Service Health Research Authority (project ID 205788; 16/LO/1366).

4.2.2 Experimental Protocol

All participants underwent an experimental protocol consisting of a cognitive testing session and 2 weeks GPS tracking (detailed below).

4.2.2.1 Cognitive Testing Session

The cognitive testing session for healthy controls took place in a quiet testing room on the university campus and for patients, in a quiet room in their own home. In this testing session,

the background demographics of the participants including their age, gender, level of education, and whether they had any previous history of missing incidents were collected from their carers. In addition, the participants completed a range of cognitive tests and spatial navigation questionnaires. Of relevance to this study, the participants completed the Mini-Addenbrooke's Cognitive Examination (Mini-ACE) and the Santa Barbara Sense of Direction (SBSOD) Scale. The Mini-ACE is a sensitive, validated cognitive screening test for dementia, with lower scores indicating higher cognitive impairment whilst the SBSOD is a self-report scale that measures RW environmental spatial abilities, with higher scores indicating higher spatial ability [129,130]. Since patients may lack insight into their own navigational abilities as a result of AD [131], we also got the carers of the patients to complete the Spatial Orientation Screening (SOS) questionnaire. This is a newly developed screening tool that assesses the carer's reports of their loved one's navigational impairments in the community, with higher scores indicating higher impairments [132] (see supplementary material 4.2 for copy of SOS questionnaire).

Of the 16 recruited AD patients, 3 had a clinical diagnosis of amnestic Mild Cognitive Impairment (aMCI). However, as aMCI patients are highly likely to go on to develop AD [133] and with their scores on the Mini-ACE test falling below the upper cut-off score of ≤ 25 which indicates the likely presence of dementia [129], we considered these 3 patients as having AD for the research purposes of this study.

4.2.2.2 GPS Tracking

Following the cognitive testing session, all participants underwent GPS tracking of their outdoor mobility patterns in the community for a 2 weeks period, under naturalistic conditions. Here, outdoor mobility in the community is defined as any movement that occurs outside of the participant's home and includes movement inside indoor locations in the community (eg. shopping malls, supermarkets, etc.). An exploratory period of 2 weeks was

chosen for the tracking period in order to capture participants' mobility patterns over repeated weekdays/weekends and to account for potential day-to-day fluctuations in these patterns. With a set of only 3 GPS trackers, participants were at a time tracked in parallel, in groups of 3, with the entire data collection period spanning from November 2018-2019.

All participants were visited at home and provided with a GPS tracker (Trackershop Pro Pod 5). They were instructed to wear the tracker (i.e., by placing it in their coat/trouser pockets) whenever they left the house during the tracking period. All participants were asked to wear the tracker regardless of whether they were alone or accompanied and regardless of the mode of transport used when outside. The GPS devices for the first batch of 22 participants (13 controls, 9 AD patients) recorded data at a sampling frequency of every 3 seconds, whilst for the remaining 12 participants (5 controls, 7 AD patients), data was recorded data at a sampling frequency of every 5 seconds. The differences in sampling frequencies are as a result of the GPS Company changing the lowest sampling frequency (from 3 to 5 seconds) of the devices online, midway through data collection.

In addition to wearing the tracker, participants were also instructed to log all outings made in the tracking period in a navigation diary. For each outing, participants were asked to record the date/time of the outing, mode of transport used, and whether they were alone or accompanied during the outing.

4.2.2.3 Disorientation Behaviour in Tracking Period

Following the GPS data collection, we retrospectively obtained information about the disorientation behaviour of the AD patients during the tracking period from their carers. The carers were asked if there were any instances (that they knew of) in this period where the patients experienced: a) a missing incident and, b) a more subtle instance of spatial disorientation behaviour, where the carers had to intervene and correct the navigation of the

patients. Based on their carer's responses, a simple yes or no for each disorientation behaviour during the tracking period was recorded for all patients.

4.2.3 Data Analysis

4.2.3.1 GPS Trajectory Data Pre-Processing

Pre-processing of the collected GPS trajectory data was carried out in MATLAB® R2017b, and consisted of data cleaning, smoothing, and transportation mode classification.

For each participant, the data cleaning procedure involved identifying and removing days with no outdoor mobility from their data. Here, we identified one patient with almost no recorded data, due to a faulty GPS tracker; this patient was removed for the analysis, leaving a total of 15 AD patients. Following data cleaning, the data smoothing procedure was run on the remaining data of all participants, which involved identifying and removing spikes (i.e., big signal jumps) in the data. Following recommendations in the literature, data points representing spikes were identified and removed using distance thresholds set between every consecutive pair of recorded data points (i.e., the hypothetical distance that an individual could cover, assuming a set maximum speed, in the time difference between the data points) [134,135].

We next classified each participant's trajectory data points into three transportation modes – stationary, by foot, and in vehicle. As a first step, we grouped all trajectory data points into time windows. For participants with data recorded every 3 seconds, each time window had a duration of 9 seconds and for participants with data recorded every 5 seconds, each time window had a duration of 10 seconds. For both sets of participants, we set a duration for the time windows which was similar but also as small as possible, to ensure consistency and to increase the accuracy of our transportation mode classification. Each time window was then

classified into transportation modes (*i.e., stationary, by foot, in vehicle*) based on set mean and maximum speed values of the data points in that time window.

For further details of pre-processing, see supplementary material 4.2.

4.2.3.2 Outdoor Mobility Variables Analysis of GPS Trajectories

To explore the outdoor mobility patterns of the participants, we chose to investigate 8 different variables. The following 5 variables were chosen as they have been suggested to represent important aspects of outdoor mobility in previous GPS tracking studies of dementia patients [125–127] – total outings made, distance travelled (total and by foot), time spent moving outside, and distance travelled from home. In addition, with findings from one of these studies showing that the outings of dementia patients are dependent on time of day [125], we also chose to look at total day-time and night-time outings made to explore this pattern further. Additionally, since qualitative findings from a previous study suggested that dementia patients stick to familiar routes when navigating in their neighbourhood [103], we chose similarity of trajectories as our final variable of interest to investigate this pattern quantitatively.

4.2.3.2.1 Outings Made (Total, Day-time, Night-time)

From each participant's trajectories, we identified the total number of outings they made. Here, an outing is defined as a journey which starts when the participant leaves their home and ends when they return home. Outings were identified by firstly calculating the distance of all recorded data points to the centroid of the participant's home address. In line with previous research, all data points within 30 metres (i.e., 3 times the standard deviation of the GPS device's measurement error, allowing 97% confidence for determining true position) of the home address centroid were considered to reflect the participant being at home [136]. An outing was then identified whenever the participant's trajectory left home and covered a

minimum distance of 100 metres, which has been shown to be a reasonable threshold to identify outings by a previous study [137]. The total number of outings made by each participant over the tracking period were computed, and normalised for the total number of days of recorded data.

Due to the influence that time of day has on outdoor mobility in dementia patients [125], we were particularly interested in the total number of day-time (6:00am-6:00pm) and night-time (6:01pm-5:59am) outings made. Here, we recognise that these time bands will vary according to season, however to keep things simple we decided to use the same time bands for all participants, despite different individuals being tracked at different times of the year. The values of these variables were normalised for the total number of days that the GPS data was recorded.

4.2.3.2.2 Time Spent Moving Outside

We next computed our second variable of interest, time spent moving outside home, for each participant. The GPS devices used in this study automatically stop recording data when no movement is detected for a maximum of 2 minutes. Hence for this variable, we calculated the sum of the total duration of each of the participant's outings, excluding the periods of time where the participant was not moving. This variable was then normalised for the total number of outings made by the participant.

4.2.3.2.3 Distance Travelled (Total, By Foot & From Home)

To compute total distance travelled, we summed the distance between each pair of consecutive data points across all the participant's outings, and normalised this value for the total outings made. The same method was used to calculate the distance travelled by foot, this time by using only the portions of each participant's trajectories where they were walking (i.e., walking trajectories). Again, this value was normalised for total outings made.

Meanwhile, to compute the distance travelled from home, we calculated the mean distance of the data points in each outing to the participant's home, and averaged this value across all outings.

4.2.3.2.4 Similarity of Trajectories

To compute our final variable of interest, similarity of trajectories, we used a metric known as Fréchet distance. Fréchet distance is a metric that measures how similar two curves are in their shape, taking into account the location and ordering of the data points that make up the curve [138]. This metric is used for various purposes including handwriting recognition [139], investigating the alignment of protein structures [140], and for assessing the similarity of trajectories. A common example used to explain the concept of Fréchet distances is that of a man walking his dog on a leash, where the man will be on one trajectory (A) and the dog on another trajectory (B). The Fréchet distance refers to the minimum length of a leash that is required to connect the man on trajectory A to the dog that is on trajectory B, with both walking forwards simultaneously. Here, the more similar the two trajectories are to each other, the lower the Fréchet distance. The Fréchet distance between two separate trajectories, T_1 and T_2, is calculated using the formula below [141]:

$$d_{\text{Fréchet}}(T_1, T_2) = \inf \max_{t \in [t.start, t.end]} \{d(f_1(t), f_2(t))\}, \quad (4.1)$$

where T_1 and T_2 are represented by two continuous functions f_1 and f_2 over time period t, and *t.start*/*t.end* represent the starting and end times of t. For each participant, we calculated the Fréchet distances for all combinations of their outing trajectories, and computed the mean of these values.

An overview of the GPS trajectory data pre-processing procedure and summary of all the outdoor mobility variables are illustrated in Fig. 4.1.

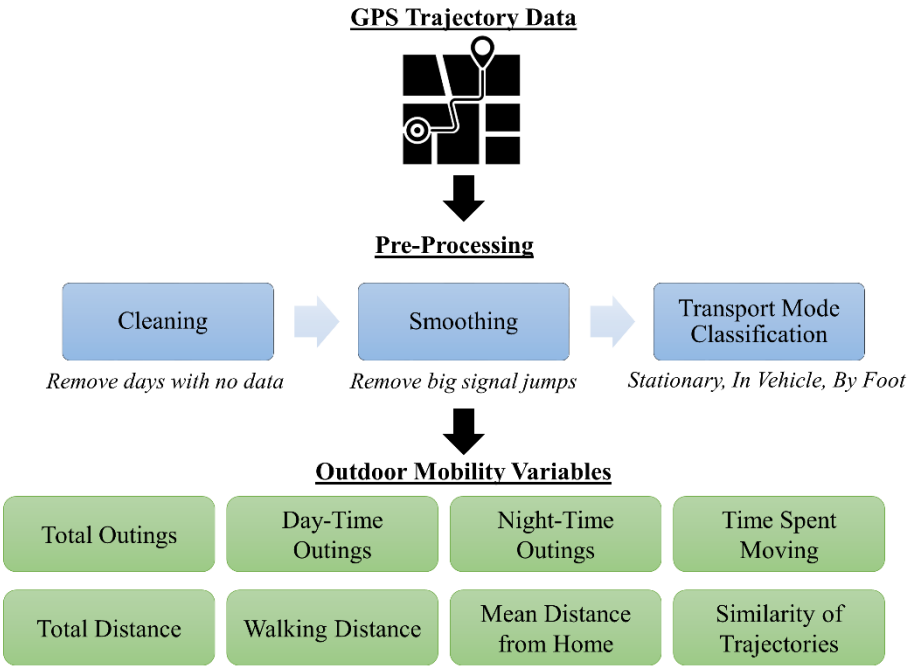

Figure 4.1: Overview of GPS trajectory data pre-processing procedure and summary of outdoor mobility variables used in this study. The collected GPS trajectory data from all participants undergo a data cleaning and smoothing procedure, followed by transport mode classification. Eight outdoor mobility variables are then generated from the pre-processed data[4].

4.2.3.2.5 Analysis Steps

After generating all the outdoor mobility variables, we conducted our analysis in three different steps using R software package version 3.4.2 [105]. In the first step, we compared differences of all variables between the controls and patients using t-tests and if the variables had a non-normal distribution, Wilcoxon Rank Sum tests.

Then in the second step, using information from the navigation diaries, we split the outings of each patient into outings made alone and outings made accompanied. The rationale for this is because due to their impairments in navigation, we expect patients' outdoor mobility patterns to be influenced by whether they are alone or accompanied. When accompanied they can rely on other individuals (i.e., the carer) to navigate whereas this is not possible when they are alone, hence the latter situation is more likely to highlight mobility patterns which are more

[4] Icon used in this figure – "GPS tracking" by Visual World, from thenounproject.com

reflective of their navigation impairments. Meanwhile, for controls we do not expect their outdoor mobility patterns to be influenced by whether they are alone or accompanied, owing to their lack of navigation impairments, and hence did not split the data of this group further. Hence in the second analysis step, we compare differences in all of the outdoor mobility variables across three groups – controls (all outings), patients (outings alone), and patients (outings accompanied). Linear mixed models were used to assess these differences using the nlme package in R (https://cran.r-project.org/web/packages/nlme/nlme.pdf), with group chosen as the fixed effect/between-subjects factor and participant as the random effect/within-subjects factor in the model. This statistical model was chosen as it accounts for participants in two of the groups (i.e., patients when alone/patients when accompanied) being the same, and the resulting interdependence that arises in the collected data of these individuals under both conditions. After running a separate mixed model for each variable, ANOVAs that were in-built in the R package were run to assess overall group significance, followed by post-hoc pairwise tests (also in-built in the R package) that were corrected for multiple comparisons using the FDR method.

For the third and final step, using the information on disorientation during the tracking period that we obtained retrospectively from the carers of the patients, we divided the patients into 2 groups (disoriented vs. not disoriented during tracking period). We then investigated group differences in all the outdoor mobility variables across controls, patients with disorientation, and patients without disorientation using one-way ANOVAs and if the variables had a non-normal distribution, Kruskal-Wallis tests.

4.2.3.3 Geospatial Analysis of GPS Trajectories

We conducted a geospatial analysis of our participants' trajectories to test our findings that increased outdoor landmark density and complex road network structure may contribute to spatial disorientation in patients. For this, we imported and plotted each participant's walking

trajectories (i.e., data points classified as by foot) into ArcGIS software, using the WGS 1984 geographic co-ordinate system. We chose to focus on only the participants' walking trajectories as we assume that spatial disorientation is unlikely to occur for the AD patients when they are not walking (i.e., passively sitting in vehicle); disorientation can still occur if the patients were actively driving a vehicle, however we assume that none of the patients in our sample are active drivers given that they have cognitive impairments.

We first tested whether patients that had disorientation during the tracking period had walking trajectories that passed through areas with an increased outdoor landmark density. Here, we used the same outdoor landmark dataset and spatial buffer methodology as in Chapter 2 to measure the outdoor landmark density in the areas that all participants visited. Here, we selected a relatively stringent radius of 50 metres (as opposed to the more liberal 1 kilometre used in Chapters 2 and 3) for the buffer zones generated around the participants' walking trajectories. A more stringent threshold was chosen here as due to the availability of the trajectory data, we know exactly which routes were taken by the participants whereas in Chapter 2, we had to account for all potential areas that were within a reasonable walking distance from the last known location of the missing patients. Furthermore, 50 metres was chosen as the threshold as previous studies have suggested this distance as being appropriate to capture all environmental features, such as outdoor landmarks, which are directly accessible along a travelled route [142,143]. It must be mentioned here that to account for the measurement error in the GPS device (10 metres), we add another 30 metres to the buffer zones (i.e., 3 times the standard deviation of the measurement error to ensure 97% confidence for determining position) in addition to the initial 50 metres, following guidelines in the literature [136]. Hence for each participant, geodesic buffer zones of 80 metres were generated around their walking trajectories, and the number of outdoor landmarks falling within these buffer zones (normalised for total walking distance) were then computed. Group

comparisons on this variable were then made across the controls, patients with disorientation, and patients without disorientation using a Kruskal Wallis test.

We next tested whether patients that had disorientation during the tracking period had walking trajectories that passed through areas with a high road intersection density and complexity. For this, we used the same road network dataset and spatial buffer methodology as in Chapter 3. Here, a buffer zone radius of 30 metres, to account for measurement error in the GPS device, was chosen and generated around the participants' walking trajectories. The number and average complexity of the road intersections (normalising the former for total walking distance) falling within the buffer zones of all participants were computed, and group comparisons were made using a Kruskal Wallis and one-way ANOVA tests respectively.

We then tested the impact of road orientation entropy in contributing to patients experiencing spatial disorientation during the tracking period. As we found a buffer radius of 2 kilometres to be sensitive to identify changes in road orientation entropy between different locations in Chapter 3, we continue to use this distance (plus a 30 metres error buffer) for our buffer zones here. Subsequently, buffer zones of 2.03 kilometres were generated around the participants' trajectories, and the orientation entropy of the roads falling within these buffer zones were computed using Shannon's entropy (introduced in Chapter 3). Group comparisons were then made using a one-way ANOVA.

4.3 Results

4.3.1 Participant Demographics

The controls and AD patients in this study did not differ statistically in their age or gender, however a statistical difference was seen for number of years of education, with controls having higher number of years of education than the patients. The AD patients performed significantly worse than controls on the Mini-ACE; the scores of all patients met the upper

cut-off of ≤ 25/30, indicating the likely presence of dementia. Majority of the patients were reported to have had a past history of at least one missing incident (Table 4.1).

Table 4.1: Participant Demographics

	Controls (Mean; SD)	**AD Patients (Mean; SD)**	**Significance**
Total Sample	18	15	-
Age	68.33 (7.53)	70.33 (6.86)	ns
Education (Years)	15.44 (3.11)	12.80 (1.78)	*
Males	9	8	ns
Females	9	7	
Mini-ACE Score	28.52 (1.50)	18.13 (5.64)	***
Had Missing Incident History	-	12	-

ns = not significant, *p < 0.05, ***p<0.001

4.3.2 Outdoor Mobility Variables Analysis

The results of our first analysis of the outdoor mobility variables (controls vs. patients) showed that overall, there were no significant group differences for any variable. However, statistical trends were seen for patients making fewer night-time outings and having a lower distance travelled by foot when compared to the controls (Table 4.2).

Table 4.2: Comparison of Outdoor Mobility Variables (Controls vs. Patients)

Variable	**Controls (Mean; SD)**	**Patients (Mean; SD)**	**Significance (p-value)**
Outings Per Day	2.28 (0.79)	1.95 (0.85)	ns
Day Outings Per Day	1.90 (0.63)	1.73 (0.74)	ns
Night Outings Per Day	0.39 (0.32)	0.22 (0.24)	p = 0.098
Time Spent Moving Per Outing (Hours)	1.17 (0.59)	0.95 (0.59)	ns
Total Distance Per Outing (Miles)	14.54 (14.08)	11.15 (9.13)	ns
Total Walking Distance Per Outing (Miles)	1.22 (0.64)	0.90 (0.69)	p = 0.079
Mean Distance From Home Per Outing (Miles)	2.92 (2.56)	2.08 (1.85)	ns
Similarity of Trajectories Across Outings (Mean Fréchet Distances)	0.14 (0.13)	0.10 (0.09)	ns

ns = not significant

The results of our second analysis (i.e., after splitting the data of the patients into outings made alone and accompanied) showed significant group effects for 7 of the 8 variables (Table 4.3).

Table 4.3: Comparison of Outdoor Mobility Variables
(Controls vs. Patients Accompanied vs. Patients Alone)

Variable	Controls (Mean; SD)	Patients Accompanied (Mean; SD)	Patients Alone (Mean; SD)	Group Significance (p-value)	P-Hoc (Controls – Patients Accompanied)	P-Hoc (Controls – Patients Alone)	P-Hoc (Patients Accompanied – Patients Alone)
Outings Per Day	2.28 (0.79)	1.57 (0.85)	1.04 (0.78)	***	*	***	p = 0.090
Day Outings Per Day	1.89 (0.62)	1.36 (0.77)	1.02 (0.76)	**	p = 0.058	**	ns
Night Outings Per Day	0.38 (0.31)	0.21 (0.24)	0.01 (0.04)	***	*	***	*
Time Spent Moving Per Outing (Hours)	1.17 (0.58)	0.92 (0.57)	0.41 (0.55)	**	ns	**	*
Total Distance Per Outing (Miles)	14.53 (14.08)	10.96 (9.27)	2.86 (6.47)	*	ns	**	p = 0.080
Walking Distance Per Outing (Miles)	1.21 (0.64)	0.83 (0.57)	0.59 (0.71)	*	ns	*	ns
Mean Distance From Home Per Outing (Miles)	2.92 (2.55)	2.04 (1.96)	0.50 (1.16)	**	ns	**	p = 0.079
Similarity of Trajectories Across Outings (Mean Fréchet Distances)	0.14 (0.13)	0.09 (0.08)	0.04 (0.09)	ns	ns	ns	ns

ns = not significant, *p < 0.05, **p< 0.01, *** p<0.001

Post-hoc pairwise comparisons between the groups showed that compared to controls, patients when alone had significantly fewer outings per day (total outings, $p < 0.001$; day outings, $p = 0.003$; night outings, $p < 0.001$), lower time spent moving per outing ($p = 0.001$), lower total distance covered per outing ($p = 0.009$), lower walking distance per outing ($p = 0.027$) and lower mean distance from home per outing ($p = 0.004$) (Fig. 4.2). For the last variable (i.e., similarity of trajectories across all outings), no significant differences were seen between these two groups. Meanwhile, when comparing the controls to patients when accompanied, no significant differences were seen in any of the variables except for total and night outings made per day, whereby patients when accompanied made significantly fewer total and night outings per day than the controls ($p = 0.024$ and $p = 0.044$) (Fig. 4.2). A statistical trend was also seen for patients when accompanied making fewer day outings per day than the controls ($p = 0.058$).

When comparing patients when they were alone to when they were accompanied, significant differences were seen with patients when alone making fewer night outings per day and having less time spent moving per outing compared to when they were accompanied ($p = 0.044$ and $p = 0.040$ respectively) (Fig. 4.2). No significant differences were seen in any of the remaining variables, although statistical trends were seen for patients when alone having fewer total outings per day ($p = 0.090$), lower total distance per outing ($p = 0.080$), and lower mean distance from home per outing ($p = 0.079$) compared to when they were accompanied.

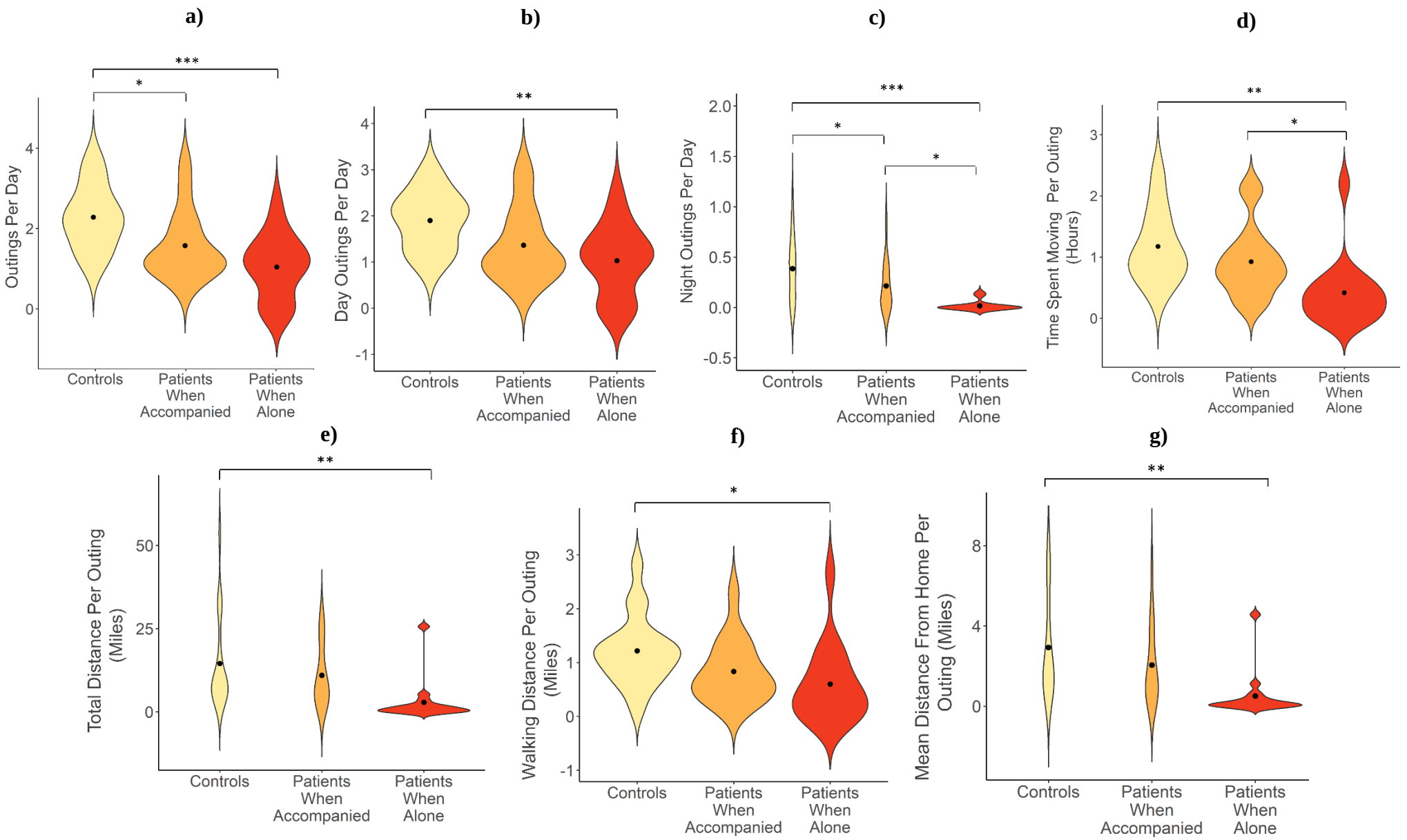

Figure 4.2: Violin plots of post-hoc pairwise comparisons of the outdoor mobility variables (waves indicate probability distribution of variables; black dots indicate group means) – **a)** outings per day, **b)** day outings per day, **c)** night outings per day, **d)** time spent moving per outing, **e)** total distance per outing, **f)** walking distance per outing, **g)** mean distance from home per outing. Note that ranges of violin plots extend slightly above/below actual range of data as plots show smoothed out distribution

To explore whether inter-individual differences in the outdoor mobility variables for patients when alone was related to their subjective perception of spatial ability, we correlated their output on all variables (on outings alone) with their respective scores on the SBSOD scale. We were also interested to explore whether the patients' output on the outdoor mobility variables on outings alone were related to their navigation impairments as reported by their carers, and hence correlated these variables with their scores on the SOS. Pearson's correlations and if the variables had a non-normal distribution, Spearman's correlations, were run. The results showed no significant correlations between patient scores on either the SBSOD or SOS and their output on any of the outdoor mobility variables.

For the purpose of our third analysis, we found that none of the patients were reported to have had missing incidents during the tracking period by their carers. However, six patients were reported as having experienced more subtle moments of spatial disorientation. The results of our third analysis did not show any significant group differences for any of the outdoor mobility variables (Table 4.4).

Table 4.4: Comparison of Outdoor Mobility Variables
(Controls vs. Patients with Disorientation vs. Patients without Disorientation)

Variable	Controls (Mean; SD)	Patients with Disorientation (Mean; SD)	Patients without Disorientation (Mean; SD)	Group Significance (p-value)
Outings Per Day	2.28 (0.79)	1.70 (0.71)	2.11 (0.92)	ns
Day Outings Per Day	1.89 (0.62)	1.49 (0.62)	1.87 (0.80)	ns
Night Outings Per Day	0.38 (0.31)	0.20 (0.19)	0.23 (0.27)	ns
Time Spent Moving Per Outing (Hours)	1.17 (0.58)	1.13 (0.75)	0.82 (0.44)	ns
Total Distance Per Outing (Miles)	14.53 (14.08)	13.44 (10.20)	9.62 (8.61)	ns
Walking Distance Per Outing (Miles)	1.21 (0.64)	1.21 (0.93)	0.68 (0.38)	p = 0.067
Mean Distance From Home Per Outing (Miles)	2.92 (2.55)	2.57 (1.95)	1.75 (1.80)	ns
Similarity of Trajectories Across Outings (Mean Fréchet Distances)	0.14 (0.13)	0.11 (0.09)	0.09 (0.08)	ns

ns = not significant

4.3.3 Geospatial Analysis of GPS Trajectories

Our first set of results for the geospatial analysis showed that there was a significant group difference in the outdoor landmark density surrounding the walking trajectories ($p < 0.001$). Post-hoc pairwise Wilcoxon Rank Sum tests showed that the walking trajectory buffer zones of the controls had a significantly higher outdoor landmark density than that of the patients with and without disorientation respectively ($p = 0.002$ and $p < 0.001$). However, there were no significant differences when comparing the outdoor landmark density falling within the walking trajectory buffer zones of the patients with disorientation to those without ($p = 0.606$).

Our second set of results showed that there were no significant group differences in the density or complexity of the road intersections that were encountered by the participants' walking trajectories ($p = 0.436$ and $p = 0.457$). Our final set of results showed that there was a significant group difference in the road orientation entropy surrounding the participants' walking trajectories ($p = 0.010$). Post-hoc pairwise t-tests showed that the road orientation entropy surrounding the walking trajectories of controls was significantly higher than that of patients with and without disorientation respectively ($p = 0.037$ for both). However, there were no significant differences seen in the road orientation entropy surrounding the walking trajectories of the patients with disorientation to those without ($p = 0.894$).

4.4 Discussion

In this chapter, using 2 weeks GPS tracking data, we aimed to understand the outdoor mobility patterns of AD patients in the community and how this relates to spatial disorientation. Moreover, we also aimed to explore if we could validate our findings from Chapters 2 and 3 that increased outdoor landmark density and complex road network structure may contribute to spatial disorientation in AD patients.

Although previous studies have investigated the outdoor mobility patterns of AD patients, they did not investigate these patterns as a factor of whether they were alone or accompanied. Addressing this for the first time here, our first set of findings extend the findings from these studies. In line with our hypothesis, we found that AD patients when alone exhibited lesser and more restricted outdoor mobility in the community compared to the controls, whereas when they were accompanied, most of their mobility patterns were similar to the controls. Specifically, on outings alone, AD patients cover lower distances (total and walking), spend less time moving outside and stay closer to home, the latter two of which are in line with findings from previous studies [125,127]. Expanding on the finding from one of these studies that the timing of outings made by AD patients are less varied than controls [125], we show here that AD patients make less day-time and night-time outings when alone. Furthermore, it has previously been reported qualitatively (i.e., on the basis of interview accounts) that AD patients stick to using familiar routes in their neighbourhood [103]. Our findings disagree with this, as we found no significant differences in the similarity of routes taken by controls and patients, regardless of whether the latter were on outings alone or accompanied.

Overall, it is apparent that these patterns of restricted outdoor mobility seen in patients on outings made alone is associated with spatial disorientation, with carers of most patients (n = 11) indicating on the SOS questionnaire that their loved one refrains from travelling/participating in activities alone due to being worried about finding their way. Hence, it can be seen that patients try to reduce their risk of experiencing spatial disorientation by restricting their outdoor mobility in the community. To the best of our knowledge, this is the first study to relate the outdoor mobility patterns of AD patients in the community to spatial disorientation, with previous studies having only related these patterns to caregiving burden and patients' own wellbeing [126,128].

Our findings from this study showed that we were not able to identify significant outdoor mobility risk factors for spatial disorientation in patients. Moreover, we also found that the areas visited by patients with disorientation had a similar outdoor landmark density and complexity of road network structure when compared to the patients without disorientation, and this null result suggests that we are not able to validate our findings from Chapters 2 and 3 at this stage.

In conclusion, our results showed that AD patients when alone restrict their outdoor mobility to reduce their risk for experiencing spatial disorientation in the community. As such restrictions can have a negative impact on their autonomy and overall quality of life [144], this may not be the most appropriate response to the problem as not all these patients may actually be at a high risk for experiencing spatial disorientation in the community. In order to strike a balance between their right to autonomy and right to safety, an important step is to identify which patients are indeed at a high risk for spatial disorientation. In the next chapter, we aim to investigate whether we can identify AD patients in our sample that are at a high risk for spatial disorientation using RW navigation tests, and examine whether this can be predicted from their performance on VR tests of spatial navigation.

Chapter 5

Prediction of AD Patients at a High Risk for Spatial Disorientation in the Community Using Virtual Reality Spatial Navigation Tests

Paper under Preparation

Puthusseryppady V, Patel M, Hornberger M. (2021). Predicting Alzheimer's disease patients' risk for spatial disorientation in the community using virtual reality navigation tests. In preparation, to be submitted to *JMIR Serious Games* (tentative).

5.1 Introduction

In the previous chapter, we found that the AD patients exhibit reduced and restricted outdoor mobility patterns when they make outings alone, as a strategy to reduce their perceived risk of experiencing spatial disorientation in the community. Since not all these patients may actually be at a high risk for spatial disorientation, and as restricting outdoor mobility can have a negative impact on their quality of life, there is a clear need to identify which patients are at a high risk for spatial disorientation. This is of clear importance due to not only its implications in safeguarding this subgroup of individuals from going missing in the future but also due to ethical implications, with regards to encouraging those not at a high risk to maintain their autonomy in the community for as long as possible.

Our results in Chapters 2 and 3 suggest that we can identify patients at a high risk for spatial disorientation in terms of the environment that they navigate through (i.e., increased outdoor landmark density and complex road network structure). However, at a behavioural level, very little is known about the extent to which fundamental impairments to patients' spatial navigation abilities predict their risk for experiencing spatial disorientation in the community. In this study, we aim to address this question by first systematically investigating how our sample of AD patients navigate in VR settings followed by how they navigate in a familiar

RW community setting, in a situation where spatial disorientation is likely to occur. We then relate findings from both tests to explore whether we can predict which patients are at a high risk for spatial disorientation in the community based on their performance in the VR navigation tests.

We hypothesise that patients will exhibit impaired performance on both the VR and RW navigation tests, as AD patients are widely reported to be impaired in navigating through both VR and RW environments (reviewed in Chapter 1). We also hypothesise that patients who perform relatively worse on the egocentric orientation components of the VR tests will in turn be the ones that exhibit more spatial disorientation in the RW test. This is because findings from previous studies have suggested that AD patients rely and use more of an egocentric strategy to navigate in the RW, potentially as a means to compensate for early impairments to their allocentric navigation abilities [74,94,95]. Hence, we hypothesise that those with relatively weaker egocentric orientation abilities will be less able to use this strategy to aid their navigation, and hence be at higher risk for experiencing spatial disorientation. It is envisioned that such a finding would enhance the RW applications of the VR navigation tests that we use, towards risk stratification of a patients' propensity for spatial disorientation in the community.

5.2 Methods

5.2.1 Participants

The same cohort of controls and AD patients from the previous study were used here. An additional 5 controls were added, who were individuals that opted out of the GPS tracking component of the previous study, resulting in a total sample size of 23 controls and 16 AD patients. Signed informed consent was obtained from all participants prior to undergoing the experimental protocol. Ethical approval for this study was provided by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia

(FMH2017/18 – 123) as well as the National Health Service Health Research Authority (project ID 205788; 16/LO/1366).

5.2.2 Protocol

All participants underwent an experimental protocol which consisted of a VR spatial navigation testing session, 2 weeks GPS tracking, and a RW spatial navigation testing session. Of relevance to this chapter, we will be focusing only on the VR and RW navigation testing sessions.

The VR navigation testing session was held in a quiet testing room in the university campus for the controls, whilst for patients this was held at a quiet room in their own home. In this session, participants were tested on their spatial navigation abilities using two non-immersive VR navigation tests on an iPad – the Virtual Supermarket Test and Sea Hero Quest [57,145]. Following the VR testing, the RW navigation testing session was held on a separate day for all participants, where they completed an outdoor Detour Navigation Test in their own neighbourhood. Both VR and RW navigation tests are detailed below.

5.2.2.1 VR Navigation - Virtual Supermarket Test

The Virtual Supermarket Test (VST) is a spatial navigation test that looks at egocentric orientation, allocentric orientation, and heading direction. We chose this test as since it has been used by previous studies to highlight navigation impairments in AD patients, we wanted to explore if patient performance on this test relates to their spatial disorientation in the RW [57,67,68]. In this test, an iPad is used to show participants 14 different videos (trials) lasting 20-40 seconds in duration, of a shopping trolley moving around a virtual supermarket, from a first person perspective (Fig. 5.1a). The virtual environment did not contain any salient landmarks or features, and is designed to test spatial navigation abilities without tapping into episodic memory, as any spatial representation acquired during testing is as a result of

incidental encoding. In each video, participants begin at a fixed starting location and follow a different route, whilst making a series of 90º turns, to reach a specific destination in the supermarket (first 7 trials = 20 seconds, 3 turns; remaining 7 trials= 40 seconds; 5 turns). At the end of each trial, participants are asked three sets of questions to assess their egocentric orientation, allocentric orientation, and heading direction, respectively.

To assess egocentric orientation, participants are asked to indicate the direction of the starting location in relation to their current location (i.e., destination). Here, participants are instructed to give two directional components for their response (i.e., *front left, back right, front right, etc.*) (Fig. 5.1b). For each trial, a response was scored as being correct only if both directional components were given correctly, and the outcome measure was total percentage of correct answers across all trials. Participants are next assessed on their allocentric orientation, where they are shown a blank map of the supermarket with only the starting location labelled, and are instructed to mark on the map where they think the destination is (Fig. 5.1c). Here, the outcome measure is the distance error (i.e., displacement) between the participant's response and correct location, and this was measured and expressed as percentage of map size. Lastly, on the map of the supermarket the participants are asked to indicate their heading direction (i.e., the direction that they were facing when the trial finished). They could give their response in terms of the four cardinal directions (*north, east, south, and west*) (Fig. 5.1d). Similar to egocentric orientation, the outcome measure here was the total percentage of correct answers across all trials.

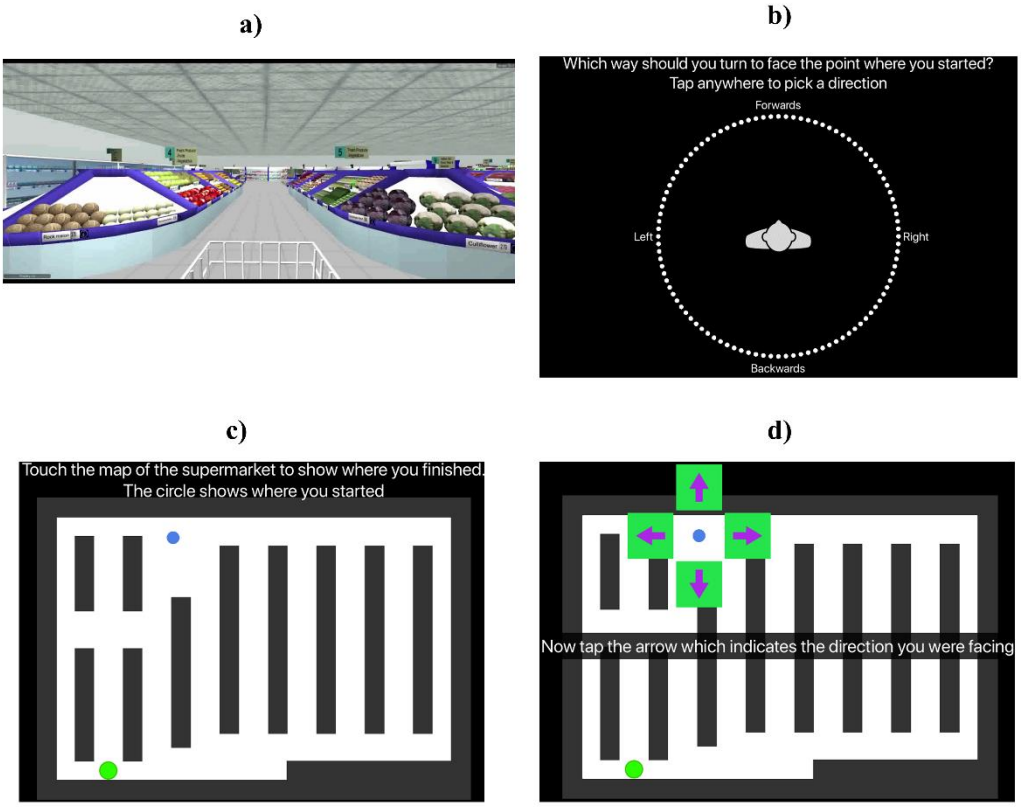

Figure 5.1: Illustration of the VST – **a)** Participants are shown videos of a shopping trolley, from a first person perspective, moving along fixed routes in a supermarket, **b)** Egocentric orientation component of task, where the direction of the starting location in relation to destination location must be indicated, **c)** Allocentric orientation component of task, where the destination location must be indicated (blue circle represents example response) on a blank map of the supermarket with only the starting location labelled (green circle), **d)** Heading direction component of task, where the direction faced when the trial finished must be indicated.

5.2.2.2 VR Navigation – Sea Hero Quest

Sea Hero Quest (SHQ) is a mobile game that measures the spatial navigation abilities of individuals in laboratory and non-laboratory settings. We chose this test as previous studies have shown its utility to assess navigation abilities in healthy individuals [53,145], and we wanted to investigate whether the test can also identify navigation impairments in AD patients. Furthermore, navigation performance on this test has also been shown to relate to navigation performance in naturalistic RW environments [145]. The game involves players navigating a boat to various locations in a VR ocean environment on an iPad, and is composed of two types of levels – wayfinding and flare levels.

In the wayfinding levels, players are first shown a map containing the start location and location of 3 numbered checkpoints. They are instructed to study the map for as long as they need, and once they are ready, they tap on the screen and the map disappears. Their task is to then navigate the boat (from a first person perspective) to the checkpoints in order using their memory of the map (Fig. 5.2a). These levels necessitate participants to form and utilise a cognitive map for their wayfinding, and requires them to use more of an allocentric as opposed to an egocentric navigation strategy. Participants are timed as they complete the level; if they exceed a set time threshold, an arrow appears that points in the Euclidean direction of the goal location in order to aid their wayfinding. The two outcome variables for the wayfinding levels are total distance travelled to visit all the checkpoints and total duration to complete the level. Here, higher distance travelled and duration to complete the level are considered to reflect less efficient navigation and hence, worse wayfinding performance. Here, a caveat for increased wayfinding duration is that it can also reflect participant's use (or lack of) of the boat's acceleration (i.e., swiping up on the iPad screen temporarily increases the boat's speed) and hence can be indicative of more non-navigational factors like navigation confidence or personal preference of boat's speed. Hence, we consider wayfinding distance as representing more the participants' navigation ability compared to duration, and use this as our primary measure for these levels.

Importantly, to account for inter-individual differences in gaming proficiency, two practice levels are administered at the start of the game, where participants memorise and navigate to the location of a single checkpoint. In these levels the checkpoint is simply located at the end of a straight path, and hence these levels do not require much spatial navigation ability and instead measure gaming proficiency. Each participant's score on the wayfinding levels were then normalised for the sum of their scores on the practice levels, to account for their gaming proficiency. In this study, the wayfinding levels 6, 8, and 11 (which increases in complexity)

were used, as these levels have been shown to challenge the navigation abilities of participants by a previous study [145]. However, with many of the AD patients finding level 6 (i.e., the relatively easiest level) quite challenging, the remaining levels were not administered for them; hence for the entire participant cohort, we used only wayfinding performance on level 6 for our analysis.

In the flare levels, participants are not provided with a map and are simply asked to navigate the boat from their starting location along various bend/turns on a river, until they find a flare gun. Once the flare gun is found, the boat rotates by 180º clockwise and the participants are asked to shoot the gun in the direction of where they think the starting location is, and are given 3 directions to choose from (*right, front, left*) (Fig. 5.2b). Based on their response, participants are awarded 1, 2, or 3 stars for their flare accuracy, with higher stars indicating higher accuracy. Similar to the VST, this level requires participants to encode the starting location in relation to their current position, and hence measures their egocentric orientation. In line with a previous study [145], the flare levels 9 and 14 were used and in addition, level 19 was also used. These three levels had only one 90º turn along the route. In order to challenge the participants further, and to really identify those with better egocentric orientation, a final challenging level (i.e., level 49) was administered which had four 90º turns along the route. Flare accuracy for each level was weighted for the total number of turns in that level, and mean flare accuracy across all levels was the outcome measure.

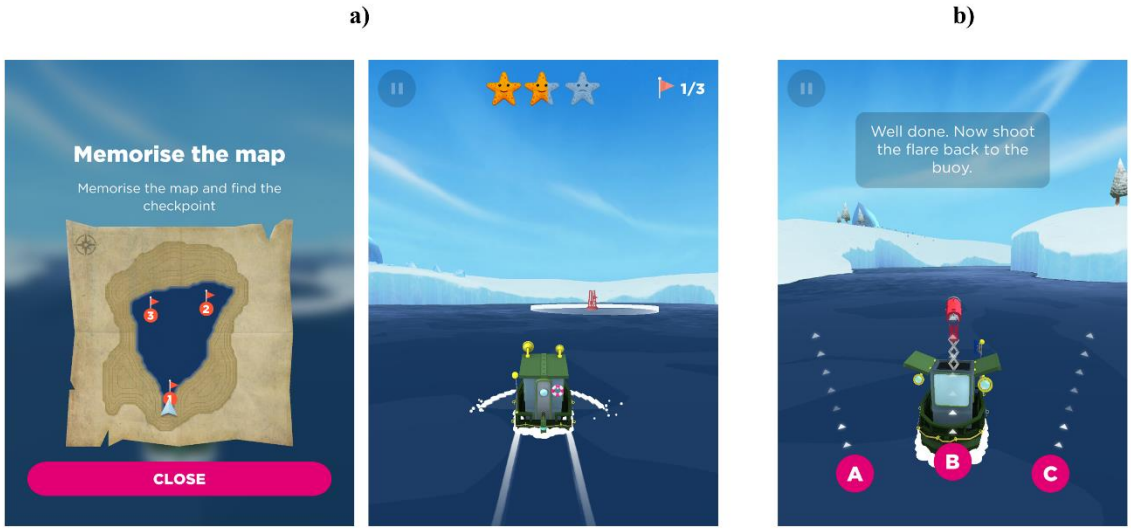

Figure 5.2: Illustration of SHQ – **a)** Wayfinding level 6, where locations of 3 numbered checkpoints are first shown on a map. After the map disappears, participants have to navigate the boat to the numbered checkpoints in order, **b)** Flare level 9, where participants navigate the boat from a starting location along the river, until they find a flare gun. Once found, the boat rotates by 180º clockwise and the participants are asked to shoot the gun in the direction of the starting location.

5.2.2.3 RW Navigation – Detour Navigation Test

The Detour Navigation Test (DNT) is a novel RW test that we are using for the first time, which tests the spatial navigation abilities of participants on an accompanied walk in a naturalistic community setting, that is also a highly familiar environment (i.e., their own neighbourhoods). We chose to use participants' own neighbourhoods as the test setting to accurately simulate the most common RW situation where AD patients go missing in the community (i.e., during routine neighbourhood walks). An additional advantage of using a neighbourhood setting is that it enables us to overcome confounds of differences in spatial learning between controls and patients that would impact test performance if navigation was assessed in an unfamiliar environment [146].

At the end of the VR navigation testing session, the participants are asked to choose and describe a familiar route (Route A) from their house to a landmark/location in their neighbourhood that they often visit by foot, and this route is then marked by the experimenter

on Google Maps. On a separate day, the participants are visited at home and accompanied by the experimenter on Route A. As taking familiar routes often lends itself more towards the use of egocentric navigation [147], this route enables us to assess the use of this strategy in a RW situation. Once at the end of Route A, the participants are instructed to navigate back to their house using the same route. Unknown to the participant, at the first intersection on the way back, they are asked to stop and find an alternative, detour route (Route B) back home that does not overlap at all (or if this is not possible, a route that overlaps as minimal as possible) with Route A. This task requires participants to use the cognitive maps of their neighbourhoods, and lends itself more towards the use of an allocentric navigation strategy. An overview of the DNT is illustrated in Fig. 5.3.

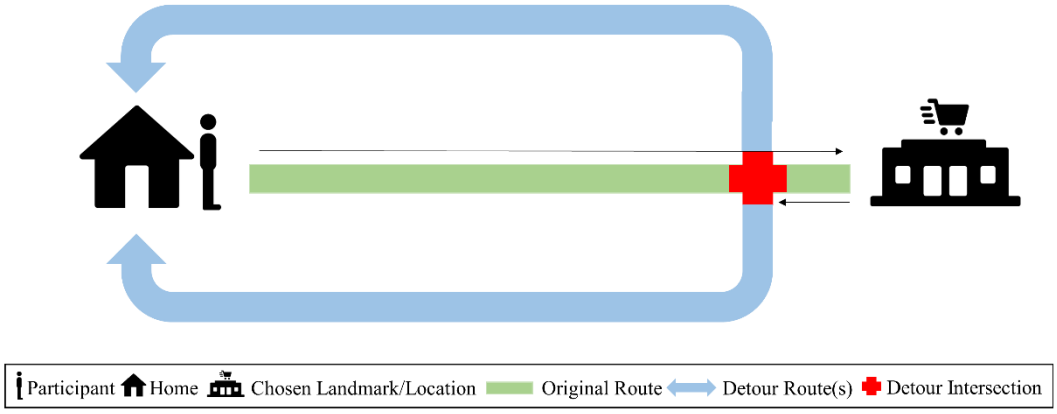

Figure 5.3: Illustration of the DNT. Participants navigate to a chosen landmark/location in their neighbourhood that they commonly visit using their usual route (i.e., original route). At the first intersection on the way back, they are asked to find an alternative route back home which does not overlap with the original route (i.e., detour route)[5].

In this task, we measured spatial disorientation exhibited by the participants along these routes. Specifically, spatial disorientation is measured as the number of – a) wrong turns made and b) moments of hesitation. A wrong turn is defined as movement at an intersection (either straight or right/left turns) onto a path that is not marked as a viable alternative route

[5] Icons used in the figure – "Person" by Irene Hoffman, "Home" by Tauficon, "Supermarket" by Adrien Coquet, all from thenounproject.com

on the map or onto part of the original route. For the latter, exceptions are made where the participant has no other alternative but to use part of the original route to get back home, in which case this is considered as an acceptable overlap and hence not marked as a wrong turn (eg. home located at end of a cul-de-sac). Participants could make a total of two consecutive wrong turns, at which point they would be brought back to the location before the first wrong turn was made and encouraged to try again.

For the second variable, a moment of hesitation was defined as the participant either slowing down/stopping and looking around to aid orientation or verbally admitting that they are unsure about their whereabouts, in line with a previous study [94]. Initially, in addition to the experimenter visually identifying and recording the frequency of these behaviours, we also planned to measure this variable more objectively using accelerometer data. For this, we used a motion sensor app on an iPad, which measures an individual's linear acceleration in the three axes (x, y, z) every 10 milliseconds. As they performed the DNT, the participants carried the iPad by grasping it like a steering wheel in their hands, and their linear acceleration values were recorded. Using the values in the x axis of the iPad (i.e., denoting forward/backward movement), our objective was to examine the step intervals (i.e., time interval between two consecutive steps) of the participants to identify moments of hesitation. The idea here was that when participants exhibit hesitant walking, more variation would be seen in their step intervals as compared to when they are more confident, where more uniform intervals would be seen. However, after data collection we noticed that due to a bug in the app, only the first and last 2 minutes of the DNT trials were recorded for each participant. Since this data was insufficient for our purpose, we discarded this data and only used measures of moments of hesitation as identified visually by the experimenter.

Overall, for each participant the total number of wrong turns made and moments of hesitation were calculated for both original/detour routes, and normalised for the respective total route

distance and total route intersection number. Furthermore, for patients, a total disorientation score was calculated using the formula below:

$$\text{Total Disorientation Score} = \frac{\text{Detour Route Disorientation Score} + 1}{\text{Original Route Disorientation Score} + 1}. \qquad (5.1)$$

Here, a coefficient of 1 was added to both original/detour route disorientation scores to overcome the division by zero problem, in cases where a patient exhibited no original route disorientation (i.e., score = 0). Hence, a total disorientation score of 1 indicates that the patient had no disorientation in either the original or detour routes, a score greater than 1 indicates more disorientation on the detour than the original route, and a score less than 1 indicates more disorientation on the original than detour route.

5.2.3 Data Analysis

The data analysis was conducted in 4 different steps using R software package version 3.4.2 [105]. In the first step, we investigated group differences in VR navigation by comparing patient performance on the VST (egocentric orientation, allocentric orientation, and heading direction) and SHQ (wayfinding and flare levels) to that of controls. In the second step, we assessed group differences in RW navigation by comparing patient performance on the DNT (original & detour route disorientation scores) to that of controls. To assess group differences in the VR and RW navigation variables, t-tests and/or Wilcoxon Rank Sum tests were used depending upon whether the variables had a normal/non-normal distribution.

In the third analysis step, we related patient performance on the VR navigation tasks to that of their RW navigation. Here, we investigated whether any of the VR navigation variables (i.e., VST and SHQ variables) predict patients' total disorientation score on the DNT using linear regression models. In the fourth and final analysis step, we explored whether patient performance on any of the VR navigation variables predict whether they are at a high risk for RW spatial disorientation. For this, we first divide the patients into high/low risk groups

based on their total disorientation score on the DNT. We then select the VR navigation variables that significantly predicted DNT total disorientation score from step three, and assess how well these variables predict risk classification using binomial logistic regression models.

5.3 Results

5.3.1 Participant Demographics

After adding 5 controls to our participant cohort from the previous study, an updated demographics analysis was run (Table 5.1). There were no significant group differences in age ($p = 0.440$), gender ($p = 0.939$), or duration that the participants lived at their address ($p = 0.699$). Controls were significantly more educated ($p = 0.002$) and had a higher Mini-ACE score than the patients ($p < 0.001$).

Table 5.1: Participant Demographics

Variable	Controls (Mean; SD)	AD Patients (Mean; SD)	Significance (p- value)
Sample Size	23	16	-
Mini-ACE Score	28.59 (1.43)	18.25 (5.47)	***
Age	68.36 (7.57)	70.25 (6.63)	ns
Gender (Males, Females)	10M, 13F	8M, 8F	ns
Education (Years)	15.65 (2.96)	12.81 (1.72)	**
Duration Lived at Address (Years)	15.04 (11.27)	15.85 (16.33)	ns

ns = not significant, **p < 0.01, *** p<0.001

5.3.2 Differences in VR Navigation

Our results for the VST showed that patients had significantly worse performance on the egocentric orientation ($p < 0.001$), allocentric orientation ($p = 0.004$), and allocentric heading direction ($p < 0.001$) components when compared to the controls.

Our results for the egocentric flare levels on SHQ showed that patients had no significant differences in their weighted flare accuracy scores when compared to controls ($p = 0.297$). However, patients had worse performance than controls on the allocentric wayfinding level 6

as they had a significantly higher distance travelled ($p = 0.0015$) and duration taken to complete the level ($p = 0.011$). As map view duration can influence performance on the wayfinding levels, we ran one way ANCOVAs to see whether these effects remained even after controlling for this covariate. As the distance travelled and duration variables had a non-normal distribution, we inverse transformed these variables to alleviate the positive skewness, which enabled us to run this parametric test. Our results for the ANCOVAs show that these effects remained even after controlling for map view duration ($p = 0.021$ for distance travelled and $p= 0.014$ for duration to complete level).

Results of group differences for all VR navigation variables are summarised in Table 5.2.

5.3.3 Differences in RW Navigation

Our results for the DNT showed that there were no significant differences between patients and controls for their original route disorientation scores ($p = 0.259$), however patients had a significantly higher disorientation score when compared to controls for the detour route ($p = 0.007$) (Table 5.2).

Table 5.2: Overview of Group Differences in VR/RW Navigation Variables

Navigation Environment	Navigation Test	Variable	Controls (Mean; SD)	Patients (Mean; SD)	Significance (p-value)	Effect Size (Cohen's d)
VR	VST	Egocentric Orientation (% Correct)	81.49 (21.67)	30.35 (19.25)	***	2.47
		Allocentric Map Orientation (Displacement; % of Map Size)	18.57 (7.16)	26.44 (8.07)	**	1.04
		Heading Direction (% Correct)	83.76 (16.37)	34.37 (22.46)	***	2.57
	SHQ	Wayfinding Distance Score	0.71 (0.27)	1.21 (0.55)	**	1.24
		Wayfinding Duration Score	0.73 (0.27)	1.25 (0.63)	*	1.13
		Flare Accuracy Score	2.30 (0.54)	2.12 (0.54)	ns	-
RW	DNT	Original Route Disorientation Score	0.00 (0.00)	0.01 (0.07)	ns	-
		Detour Route Disorientation Score	0.001 (0.008)	0.25 (0.50)	**	0.76

ns = not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

5.3.4 Prediction of RW Navigation from VR Navigation – Linear Regression

The results of our linear regression models showed that for the VST, neither patient performance on egocentric orientation, allocentric orientation, nor heading direction predicted their total disorientation score on the DNT.

For SHQ, we found that 2 patients struggled quite extensively on the practice wayfinding levels, and hence level 6 was not administered for them. Based on this, we assume that if this level had been administered, both patients would have had performed more poorly on the wayfinding variables when compared to the other patients. Hence to include these patients in our regression models and increase its statistical power, we assign them both predicted scores for wayfinding distance and duration, which were the scores of the patients who performed most poorly on these variables on this level. Subsequently, our results showed that both wayfinding distance and duration on level 6 significantly predicted increased total disorientation score on the DNT ($p = 0.034$, $r^2 = 0.29$ and $p = 0.046$, $r^2 = 0.27$ respectively). Importantly, both models had normally distributed residuals. With distance travelled being our primary measure of the navigation ability on the wayfinding levels, we consider the model with this variable as the predictor as our main model (Fig. 5.4).

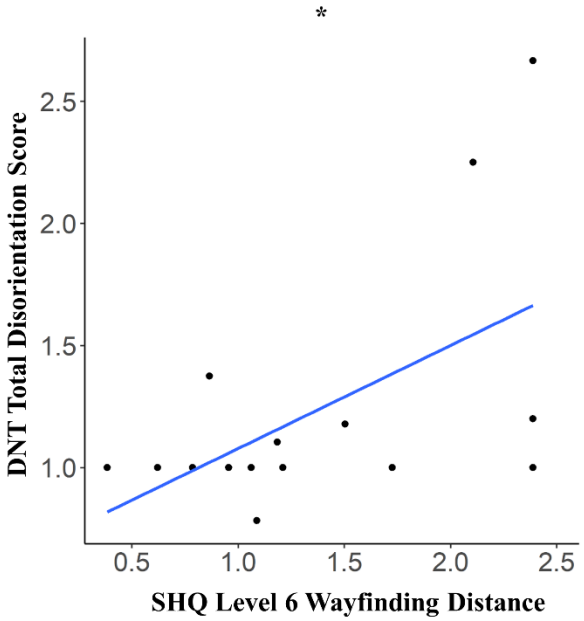

Figure 5.4: Linear regression model. Patient performance on SHQ level 6 wayfinding distance significantly predicted their DNT total disorientation score.

5.3.5 Prediction of RW Navigation from VR Navigation – Logistic Regression

To identify whether SHQ wayfinding distance performance of the patients can predict risk for RW spatial disorientation, we divided the patients into 2 risk groups. Patients who exhibited disorientation on the DNT (i.e., total disorientation score not = 1) were classified as high risk for RW spatial disorientation, whilst the rest (i.e., total disorientation score =1) were classified as low risk. A binomial logistic regression was then run to see how well SHQ wayfinding distance performance predicts patients' group membership. The results of this regression showed that SHQ wayfinding distance performance could not significantly predict patients at a high risk for RW spatial disorientation ($p = 0.155$).

In our previous study reported in Chapter 4, we found that there were 4 AD patients in our sample who only made outings accompanied (i.e., had no outings alone) during the 2 weeks tracking period. From conversations with the carers, we gathered that these patients made no outings alone due to their carers lacking confidence in their ability to independently navigate outdoors without getting lost, and as such we can consider these individuals as being at high

risk for RW spatial disorientation. Based on this factor, the remaining AD patients who did make outings alone during the tracking period were classified to be at low risk for RW spatial disorientation. As an exploratory analysis, we ran logistic regression models, this time to see if any of the VR navigation variables predicted the patient risk classification. The results here showed that none of the VST variables were significant predictors, however a statistical trend was seen for increased SHQ wayfinding distance as being a predictor for being at high risk for RW spatial disorientation ($p = 0.056$).

5.4 Discussion

In this chapter, we aimed to investigate whether we can predict AD patients at a high risk for spatial disorientation in the community based on their spatial navigation abilities measured using VR tests.

From a VR perspective, in line with our hypothesis, the results showed that AD patients exhibit impairments in all aspects of the VST when compared to controls, which is in agreement with previous studies [57,67]. Meanwhile on SHQ, which was used for the first time to test navigation in AD patients, our results showed that patients only exhibited impairments on the wayfinding levels and not the flare levels. Overall, these results add to the existing literature on AD patients experiencing spatial disorientation in VR environments.

From a RW perspective, our novel DNT showed that contradictory to the hypothesis, patients' performance on their original route (i.e., where they predominantly use an egocentric strategy) was comparable to controls. In line with the hypothesis however, our results showed that the patients performed significantly worse than controls on their detour route (i.e., where they predominantly use an allocentric strategy). Findings from previous RW navigation studies in AD suggest that patients are impaired in using both egocentric and allocentric navigation strategies in controlled, unfamiliar environments [89–93]. We extend

these findings by showing that in a naturalistic, familiar environment, patients exhibit impairments only in the latter as opposed to the former. To the best of our knowledge, this is the first study to systematically assess the ability of AD patients to use egocentric and allocentric strategies for navigation in a familiar community setting.

When relating the VR and RW navigation variables for the patients, we found that only performance on SHQ level 6 wayfinding distance related to performance on the DNT. Specifically, worse wayfinding performance on SHQ predicted increased DNT total disorientation score. Results from a previous study showed that SHQ wayfinding performance correlated with wayfinding performance in naturalistic, RW city environments for healthy participants [53]. Our finding extends this result by also suggesting associations between SHQ wayfinding performance and navigation impairments in a neighbourhood setting for AD patients. Despite this, SHQ level 6 wayfinding distance performance did not predict patients at a high risk for RW spatial disorientation, when risk was classified based on DNT performance. However, when risk was classified based on whether patients made any outings alone during the 2 weeks tracking period, a trend was seen with increased wayfinding distance predicting increased risk for RW spatial disorientation. Although we found associations between performance on the SHQ wayfinding level and the DNT, it was quite surprising that patient performance on any of the VST variables, despite indicating impairments in navigation, did not relate at all to the DNT. As far as we are aware, this is the first study to relate patient navigation performance in VR environments to their risk for spatial disorientation in the community.

In conclusion, our results showed that spatial navigation impairments can be detected in AD patients using VR navigation tests as well as when performing goal-oriented navigation tasks in a familiar, RW environment. However, the VR navigation tests in general were not able to predict which patients are at a high risk for RW spatial disorientation in the community.

Chapter 6

General Discussion

6.1 Summary

The aim of this thesis was to study the role of spatial navigation impairments and the outdoor environment in contributing to spatial disorientation in AD. Our specific objectives were to identify environmental risk factors for spatial disorientation as well as explore whether the outdoor mobility patterns of AD patients in the community offer further insight into this symptom. Our final objective was to investigate whether we can predict AD patients at a high risk for spatial disorientation in the community based on their performance on VR spatial navigation tests. Our work in Chapters 2 and 3, which investigated spatial disorientation in the context of dementia-related missing incidents, showed that these incidents are a widespread problem geographically and identified increased outdoor landmark density as well as complex road network structure as being potential environmental risk factors for their occurrence. Our work in Chapter 4 showed that AD patients have restricted outdoor mobility patterns in the community when alone, which instead of revealing risk factors for spatial disorientation reflects more a risk reduction response to previous episodes of going missing in the community. Lastly, our work in Chapter 5 showed that although AD patients exhibit spatial navigation impairments in both VR and RW community settings, the VR navigation tests could not predict which patients were at a high risk for spatial disorientation in the community. The remainder of this chapter will discuss the results of each experimental study in detail.

6.2 Chapters 2 and 3 - Discussion

6.2.1 Demographic and Geographic Patterns of Missing Incidents

In Chapter 2, we identified certain demographic patterns for patients going missing in the community. Our first finding was that missing incidents were prevalent year-round, with similar numbers of patients having went missing across all four seasons. We also found that the majority of patients went missing from domestic residences as opposed to care facilities, which could potentially be explained by the relatively lower levels of safeguarding available in home settings and the fact that patients living at home have greater opportunities to get outdoors compared to those in care facilities. Hence, our findings suggest that missing incidents are a significantly greater problem for patients still living at home as opposed to those in care facilities, even after accounting for the ratio of dementia patients living in these residences in the UK (home - 61%; care facilities - 39%) [148]. However, it is also important to normalise the number of missing incidents reported in each residence setting for the number of times the patients leave the premises, in order to truly determine whether missing incidents are more prevalent in one setting over the other. Lastly, our results also suggested gender as being a potential demographic risk factor for missing incidents, with gender differences seen in 3 of the missing incident variables (i.e., locality missing from, whether they went missing multiple times, time spent missing).

In terms of geographic patterns, we did not find any hotspots (or coldspots) for the missing incidents in our study region, suggesting that missing incidents are not bound to particular locations but are rather, a widespread and prevalent problem. Furthermore, it strengthens the notion that spatial disorientation is endemic and therefore an integral part of the disease process, as opposed to being a direct factor of the environment [1].

6.2.2 Environmental Risk Factors – Outdoor Landmarks and Road Networks

We found that regardless of geographic location, increased outdoor landmark density and complex road network structure may represent environmental risk factors for missing incidents and more generally, for spatial disorientation in AD patients.

The exact mechanisms underlying how these factors contribute to spatial disorientation in AD patients is at present unclear. We know that landmarks play a key role in spatial navigation, functioning as building blocks for cognitive maps used in an allocentric navigation strategy and as external entities to orient ourselves to the surrounding environment when using an egocentric navigation strategy [75]. Studies have shown that when navigating in the community, patients are increasingly reliant on visible landmarks, especially when trying to reorient themselves once disoriented [94,95,103]. Moreover, it has also been previously reported that when landmarks are increased in a VR environment, healthy participants spend a longer amount of time looking at these landmarks [149]. Taken together, we speculate that when navigating through environments with a high outdoor landmark density, AD patients may have spent an increased amount of time fixating on the landmarks to aid their navigation. Moreover, with AD patients being widely reported to be impaired in landmark recognition [55,65], the increased number of landmarks might have made it more challenging for them to recognise and use relevant landmarks to aid their navigation, thus contributing to their disorientation. Indeed, it is possible that environments with higher outdoor landmark density have less distinct landmarks, often containing objects/locations that repeat regularly (eg. franchise supermarkets, street lamps, bus stops, etc.). The similarity of the repeating objects/locations to one another could have prevented them from being understandable landmarks for the patients, thereby challenging their navigation abilities in these areas and leading them to go missing.

The exact mechanisms underlying how complex road network structure contributes to spatial disorientation for patients is also at present unclear. As road intersections represent spatial decision points along a route, navigating through environments that have a high intersection density would more often place the patients in situations where important navigation decisions must be made (*"which way do I turn here?"*). This in conjunction with the presence of various route options at the intersections (i.e., high intersection complexity) has the potential to challenge the already impaired spatial navigation abilities of these individuals [1], increasing their chances of making navigation errors along a journey, and ultimately going missing. In support of this speculation is findings from a previous study, which reports that dementia patients find complex road intersections difficult to use and understand [103]. Indeed, the chances for AD patients to go missing may especially be high when navigation errors accumulate over multiple, sequential intersections – making it more difficult for them to reorient themselves and navigate to their intended location.

Our results also showed an effect for road layout, with patients going missing in environments with increased road orientation entropy (i.e., roads with less-defined patterns). It has previously been reported that people tend to remember roads with well-defined patterns (i.e., more grid-like) better than roads that have less-defined patterns (i.e., less grid-like) in their cognitive maps of local environments [150]. Considering this together with the impairments in using an allocentric navigation strategy seen in AD [1], we speculate that patients may lose earlier the parts of their cognitive maps containing roads with less-defined patterns, causing them to experience spatial disorientation when navigating through these environments.

One of the main limitations of our environmental risk factor findings from Chapters 2 and 3 is that we are unable to conclude exactly which outdoor landmarks or road intersections the patients were exposed to/used during the missing incident, due to the lack of available

trajectory data. Addressing this was our methodology in Chapter 4, where we found using trajectory data that outdoor landmark density and road network structure had no effect on AD patients experiencing spatial disorientation in the community. A potential reason for the discrepancy of this result with findings from Chapters 2 and 3 could be due to the differences in sample size, with our study in Chapter 4 having only 6 patients with spatial disorientation compared to the relatively larger sample of 210 patients in the previous studies. Another reason may be due to the lack of clarity on the specific locations where the patients felt disorientated in the study reported in Chapter 4. In Chapters 2 and 3, we conducted the spatial buffer analysis on locations from where patients were reported to have experienced spatial disorientation/went missing from whereas in Chapter 4, we did not have access to this information and hence conducted the buffer analysis on the entire trajectories of the patients who experienced disorientation in the tracking period. Considering these reasons, we give more weightage to our findings from Chapters 2 and 3 for the role that outdoor landmark density and road network structure may play in contributing to spatial disorientation in AD.

Lastly, despite our results suggesting contributory roles for landmark density and road network structure in spatial disorientation for AD patients, it is worth noting that these factors could represent proxies of other factors that may also be at play. In particular, locations in the community that have increased landmarks and complicated road networks also tend to be busier in terms of pedestrian/traffic flow. With a previous study reporting the effect that loud sounds can have in causing patients to lose their way [103], the enhanced auditory as well as visual stimuli in these locations could have been an additional factor that contributed to spatial disorientation in the AD patients. Future studies should examine the effect that increased outdoor landmark density and complex road network structure have with/without crowds on AD patients experiencing spatial disorientation, to determine which of these factors play a bigger role in doing so.

6.3 Chapter 4 – Discussion

6.3.1 Outdoor Mobility Patterns of AD Patients in the Community

In Chapter 4, we found that AD patients have distinct outdoor mobility patterns when alone, where the spatial and temporal extent of their outings in the community are restricted.

From the carers' responses on the SOS questionnaire, we can see that the reason underlying the restricted outdoor mobility patterns of AD patients when alone is due to the latter possessing a fear of having trouble when navigating in the community. With most patients in our sample having had a previous history of going missing in the community, our findings reflect a method adopted by patients (likely in response to these experiences) to reduce the risk of them experiencing spatial disorientation. Specifically, patients when alone seem to be limiting their night-time outings and restricting the spatial/temporal extent of any outings they do make in the community, which highlights an attempt to alleviate the occurrence of two common RW situations where a missing incident is likely to happen (i.e., during independent walks in the neighbourhood and at night-time). Indeed, this risk reduction strategy that we see in patients is in agreement with a previous study which reported that restricting outdoor mobility to very familiar locations acts as a protector against missing incidents for AD patients [81]. In addition to the patients themselves, we also consider the potential influence that their carers may have on the adoption of this risk reduction strategy, particularly with regards to them being hesitant to their loved ones making outings alone. Therefore, it is likely that it is the combination of external intervening behaviour from the carers and the internal curtailing of mobility behaviour by the patients themselves that causes their restricted mobility patterns when alone. Further to a fear of spatial disorientation, it must also be noted that other factors may also explain the restricted mobility patterns of AD patients when alone including physical mobility and visual acuity impairments, fear of accidents/falling, etc. which were not considered here.

The risk reduction strategy of restricting outdoor mobility suggests that patients are to an extent, aware of their impairments in navigating when in the community. Considering this, we would expect patients with a relatively lower perception of their spatial ability (i.e., lower scores on the SBSOD scale) to also exhibit lower output on the outdoor mobility variables compared to those with a higher perception of their spatial ability. However, interestingly we did not find any correlation between patients' scores on the SBSOD scale and their outdoor mobility behaviour when alone. Although the exact reason for this is unclear at present, with scores on the SBSOD scale having shown to correlate with scores on specific navigation tasks (learning new spatial layouts, making directional judgments in familiar environments, etc.) [130] , the lack of explicit measures of navigation ability in our outdoor mobility variables could explain this null result. Hence although patient responses on the SBSOD scale may relate to their performance on navigation tasks in RW environments, it may not be related more generally to measures of the spatial and temporal extent of their outdoor mobility in the community.

It is also worth noting that we did not find any relationship between patients' scores on the SOS questionnaires and their outdoor mobility behaviour when alone. With higher scores on this questionnaire indicating higher navigational impairments in the community (as reported by the carer), based on the risk reduction strategy for spatial disorientation seen in patients, we would expect those with higher scores to have less outdoor mobility when alone. One potential reason for our null result could be due to the SOS questionnaire being a new and yet to be validated instrument, hence the extent to which it relates to ecological measures of outdoor mobility in the community is unclear. More importantly however, it can be argued that the carers' responses on the second half of the SOS questionnaire (i.e., rating their loved one's current navigation abilities compared to how it was in the past – supplementary material 4.2) can potentially be influenced by their own anxiety levels about the condition of

their loved ones. As these responses can potentially factor into the overall questionnaire score, it may very well be that these scores may not be reflecting the true extent of patients' navigation impairments.

6.3.2 Outdoor Mobility Risk Factors for Spatial Disorientation

From our findings, we were unable to identify any outdoor mobility risk factors for spatial disorientation in the AD patients. Although this suggests that spatial disorientation cannot be explained by looking solely at how AD patients move in the community, we still think that the mobility patterns seen in AD patients on outings made alone can offer some insight into potential risk factors for spatial disorientation.

We saw that patients confine their outings made alone to a safety range near their home, which is done to reduce their risk of spatial disorientation. Here, the mobility variables that the patients are restricting could actually reflect risk factors for spatial disorientation. Along these lines, it may very well be that increased day-time and night-time outings, time spent moving outdoors, distance travelled (total and walking), and travelling further away from home increase the likelihood of patients experiencing spatial disorientation. However, further research is required to determine whether these variables truly represent outdoor mobility risk factors for spatial disorientation in the community.

6.4 Chapter 5 – Discussion

6.4.1 Spatial Navigation of AD Patients in VR and RW Settings

Our results in Chapter 5 showed that AD patients were impaired in all components of the VST and on the wayfinding, but not flare levels, of SHQ. It was quite surprising that the patients performed similar to controls on the flare levels of SHQ, considering that these levels measure egocentric orientation in a similar way to the VST. This null result could potentially be explained by the flare levels being relatively easier, having on average relatively fewer turns along the route and fewer multiple choice answer options when compared to the

egocentric component of the VST. This considered, our results suggest that the flare levels of SHQ, at least the ones used in this study, lack sensitivity to detect egocentric orientation impairments in AD patients.

Our results also highlight the utility of the DNT for studying spatial disorientation in AD patients in the community. We showed that AD patients exhibited impairments on the DNT, with deficits being seen on the detour route as opposed to the original route. It is interesting to note that despite these impairments, all patients (except one) were able to successfully complete the task (i.e., use an alternative route to find their way back home) without getting lost or external assistance. This may owe to the fact that they were navigating in a familiar environment and shortly after noon-time, where navigation conditions are more favourable. Nevertheless, our findings from the DNT suggest that although AD patients still have an intact cognitive map for their neighbourhood, they may be unable to apply these cognitive maps as effectively as controls when an allocentric strategy is required for navigation in these settings. This supports findings from a previous study which assessed AD patients' ability to use personal cognitive maps for familiar environments in a VR environment [63]. The differential impairment for patients on the detour route can also potentially be explained at a more cellular level by the concept of remapping in the hippocampal place cells that form cognitive maps. Specifically, previous animal model studies have shown that the firing patterns of place cells alter (i.e., remap) in response to changing task demands or goal locations, and that this ability is impaired in transgenic AD mice [151,152]. Applying these findings to our results, it is possible that the place cells in the AD patients failed to remap as effectively as in the controls when task demands where changed in the DNT, which could explain why AD patients had difficulties in using their cognitive maps for navigation on the detour route. However, future studies are required to further elucidate the relationship

between impairments in remapping and the use of cognitive maps for navigation in the community in AD patients.

6.4.2 Predicting RW Spatial Disorientation from VR Navigation

When relating patient performance on the VR navigation tasks to that of the DNT, we found that only SHQ level 6 wayfinding performance significantly predicted total disorientation score on the DNT. This is not surprising as both tasks are quite similar in nature, with the wayfinding level on SHQ requiring participants to form/use a new cognitive map and the DNT requiring participants to use a pre-existing cognitive map, both to perform goal-oriented navigation. This finding highlights the real world application of the wayfinding levels on SHQ in predicting spatial disorientation for patients in situations where they have to explicitly use their cognitive maps for navigation in the community. However, with this finding being based on a limited sample of AD patients, validation using a relatively larger sample size is warranted.

In contrast to results from SHQ, we found that patients' impairments on the VST (i.e., egocentric, allocentric, and heading direction components) did not relate to their performance on the DNT. The reason for this null result is at present unclear, however it could potentially be due to differences in how the different aspects of navigation were measured in both tasks. Specifically, the DNT does not explicitly measure patients' heading direction or patients' allocentric knowledge of their destination's location on a blank map as the VST does, and hence it is no surprise that these variables did not relate to the DNT total disorientation score. Furthermore, although the use of an egocentric navigation strategy is measured in both tasks, differences exist in the way it is measured. In the VST, this is measured by looking at the ability of patients to correctly point to the starting location after passively navigating through a route. However in the DNT, egocentric navigation strategy use is measured mainly by looking at the ability of patients to correctly use a well familiar route to actively navigate to a

destination (i.e., original route); although not explicitly measured, patients are likely using this strategy on this task either by using visible landmarks or their sequential knowledge of left-right turns that need to be made to inform their navigation decisions [30]. Indeed, such differences in how egocentric navigation strategy use were measured in both tasks could explain why patient scores on the two tests did not relate to one another.

Considering that the VST does not assess egocentric navigation ability in relation to landmarks or sequential turns, it is at present unclear which patients in our sample are actually poor egocentric navigators (with respect to these two aspects) in the first place. Additionally, it is also unclear to what extent patients were using an egocentric strategy to compensate for their allocentric impairments on the detour route. As such, our current findings do not provide sufficient insight to validate our hypothesis that AD patients who are poor egocentric navigators are the ones that exhibit a high risk for spatial disorientation in the community. Future studies could test this hypothesis further by employing a route learning VR task, akin to those used by previous studies [64,65], that more closely simulate and measure how an egocentric strategy is used for navigation in the RW. Further, the extent to which patients are using an egocentric strategy to aid their navigation on the detour route should also be clarified by asking them to elaborate on the navigation strategies that they used for this route. It should then be explored whether those that experienced more disorientation on the DNT also happened to be the poor egocentric navigators as identified by the VR task.

6.5 Implications

6.5.1 Research Perspective

From a research perspective, our work in this thesis addresses current limitations and gaps in the literature. It was highlighted in Chapter 1 (Introduction) that very little is still known about what navigation-related factors associated with the outdoor environment may

contribute to spatial disorientation in AD. Our work in thesis contributes significant knowledge in this domain, by not only identifying two potential environmental risk factors for this symptom, but also in highlighting the utility for using geospatial analytical techniques to do so. Further, our work also shows how the outdoor mobility patterns of AD patients in the community are impacted by spatial disorientation. In addition to highlighting the potential for exploring these patterns before missing incidents occur for patients to identify mobility risk factors that may contribute to spatial disorientation, our results also underscore the utility of using GPS tracking to further elucidate the impact that environmental variables may have in causing spatial disorientation.

We also highlighted in Chapter 1 that the extent to which spatial navigation impairments of AD patients in VR environments relates to them experiencing spatial disorientation in the community is unclear. Our work here begins to address this gap, by suggesting that spatial navigation impairments of patients measured using current VR navigation tests, specifically the VST and SHQ, cannot yet fully explain who is at high risk for experiencing spatial disorientation in the community. Nevertheless, our methodology of administering a novel outdoor navigation task that captures the daily navigation challenges faced by AD patients whilst in the community, and relating their disorientation behaviour on this task to their navigation performance in VR environments, is indeed an approach that future studies can follow to help address this research gap.

6.5.2 Clinical Perspective

From a clinical perspective, the results of our work have implications in informing safeguarding guidelines to prevent AD patients from going missing in the community.

Our results suggest that patients living or navigating in regions with a high outdoor landmark density and complex road network structure are more likely to experience spatial

disorientation. For safeguarding, it may especially be beneficial for carers and healthcare professionals to encourage patients to plan and use routes with fewer intersections (where possible) on independent journeys or recommend the use of GPS tracking devices in areas dense with landmarks or exhibiting complex road network configurations.

Although we were unable to predict AD patients at a high risk for spatial disorientation based on their spatial navigation abilities, identifying this subgroup is of high importance due to the potential ethical implications it has for safeguarding. Ethically, it is essential for the level of any implemented safeguarding measure to be directly proportional to level of risk for spatial disorientation, in order to strike a balance between patients' right to safety and autonomy. For instance, for patients seen as being at high risk for spatial disorientation, more restrictions can be implemented in their safeguarding plan, thereby favouring their right to safety over autonomy. On the flipside, less restrictions can be implemented in the safeguarding plan for patients seen as being at low risk, hence favouring their right to autonomy over safety. Indeed, future research is required to develop tools, such as more sophisticated VR navigation tasks, that can accurately predict a patient's risk for experiencing spatial disorientation in the community before it occurs.

6.5.3 Beyond The Clinic Perspective

Beyond the clinic, our results have implications for the police, in terms of informing their awareness of and response to dementia-related missing incidents. Specifically, the findings that patients are more likely to go missing from locations with a high outdoor landmark density and complex road network structure can be used by the police and search & rescue services, with regards to ensuring more regular patrols in such areas. Moreover, the implications of not finding hotspots for missing incidents means that instead of focusing resources for these incidents more in certain regions, widespread information, training and support is required to reflect to the prevalent nature of the problem.

Our results also have implications in the planning/development of dementia friendly communities, of which a major part concerns with enhancing the navigability of physical environments to support patients to engage more with the community. In particular, our results support as well as add to current guidelines on landmark density and road network structure when planning or developing these communities. For landmark density, current guidelines for dementia friendly communities recommend having more distinct landmarks in areas with a high older population density [103,153], and our results add to this by suggesting that the number of landmarks should also be reduced. Indeed, having fewer landmarks may in turn enhance the distinctiveness of these landmarks, which may make it easier for AD patients to recognise and use these entities for their navigation. For road network structure, it should be noted that many residential areas currently have irregular road layout patterns that may not necessarily be designed accounting for the navigation difficulties seen in AD patients [154]. Our results reinforce current guidelines for dementia friendly communities recommending the road design of neighbourhoods in areas with a high older population density to be more straight/ordered (i.e., grid-like) and with more simple intersections [153]. In addition, our results add to these guidelines by suggesting that the number of road intersections should also be reduced. Overall, such a road design would make these environments easier to navigate for AD patients by offering more direct and continuous routes to local amenities [154,155]. This could in turn have potential advantages by not only helping to reduce the risk of AD patients experiencing spatial disorientation, but also helping carers to find them in the event that they go missing. Ultimately, these design factors could lead to AD patients making more independent outings into the community that are less restricted in nature, which would subsequently have a beneficial effect on their quality of life.

6.6 Limitations and Future Directions

Despite our novel and exciting findings, there are some methodological limitations to our work that need to be mentioned, in addition to those that have been already been discussed. As discussing these limitations highlight the potential for possible future directions of our work, both concepts are presented together.

6.6.1 Chapters 2 and 3 – Missing Patient Cases and Spatial Buffer Methodology

In these two chapters, the sample size only represents missing patients that were reported to the police, which mostly occurs only in the more severe cases (i.e., when the family or neighbours cannot locate the missing patient themselves). The true prevalence rates of missing incidents in the community are likely to be much higher and occur in far more locations across the county than reported. A second limitation pertain to the spatial buffer methodology used. Owing to its shape, the circular spatial buffers we used can potentially capture and measure environmental features in areas that are not directly accessible for patients by walking (i.e., areas with steep hills, poor road connectivity, etc.). An alternative approach that has been suggested is road-network buffers [142], which uses the road network as a base to more accurately capture areas that are directly accessible by individuals. Taken together, future studies should investigate whether our current findings can be replicated using more representative samples of missing incidents and the more ecological road-network buffers.

6.6.2 Chapter 4 – Additional Factors Influencing Outdoor Mobility Patterns

In Chapter 4, we did not consider the extent to which premorbid lifestyle patterns explain the restricted outdoor mobility patterns seen in the AD patients on outings alone. We also did not investigate further the effect of gender and different age groups, both of which have been suggested as factors influencing outdoor mobility patterns [125,156]. Future studies should focus on AD patients who have not yet gone missing before, and investigate longitudinally

the effect that the incidence of going missing has on changes in their outdoor mobility patterns, including how this varies by gender and age. This approach would not only help to gain a more holistic view of how outdoor mobility patterns are affected in AD patients due to spatial disorientation, but also potentially help identify mobility risk factors for spatial disorientation/missing incidents in these individuals.

6.6.3 Chapter 5 – Objective Measurements of Spatial Disorientation

In Chapter 5, one of the ways in which spatial disorientation of AD patients in the community was measured was by identifying whether they exhibited hesitation behaviour on the DNT. As hesitation behaviour was identified visually by a single experimenter, it is possible that more subtle moments of hesitation may have gone unnoticed. Moreover, although we used a set of behaviours that define hesitation from a previous study [94], there is a subjective bias that could have influenced the measurement of these behaviours in patients. Indeed, our planned (but ultimately unsuccessful) approach of objectively identifying hesitation behaviour in the patients using their recorded linear acceleration values during the DNT would have helped overcome these limitations. Indeed, a recent study has shown that hesitation behaviour of AD patients can be measured by looking at the spatio-temporal gait patterns (i.e., step patterns) of their walking paths in controlled RW environments using inertial measurement units [157]. This suggests that such an approach is indeed feasible, and future studies should explore the possibility of using sensor devices to identify spatial disorientation behaviour from patients' outdoor movement in the community. This also opens up the potential for applying machine learning approaches to this data for detecting and predicting how disorientation behaviour patterns may vary according to navigation strategy use as well as surrounding environmental features.

6.7 Conclusion

Taking together our findings from all the experimental chapters and previous research, we conclude this thesis by proposing a framework for studying spatial disorientation in AD that takes into account both RW factors (demographic, environmental, and outdoor mobility patterns) and brain-level cognitive factors (spatial navigation) (Fig. 6.1).

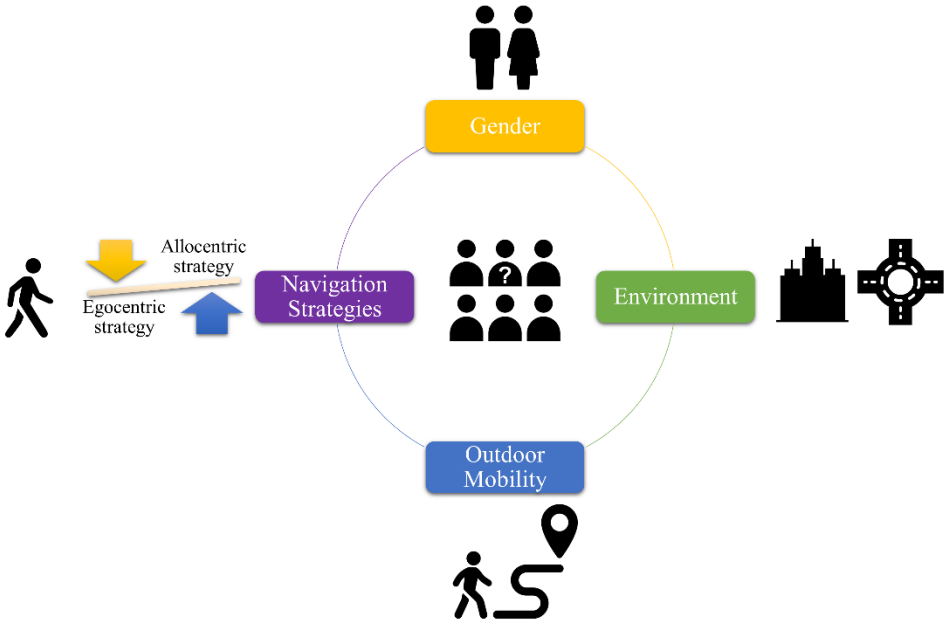

Figure 6.1: Framework for studying spatial disorientation in AD. Based on our results and the wider literature, we suggest that gender, navigation-related environmental factors, outdoor mobility patterns, and differences in the use of the navigation strategies should all be considered in future spatial disorientation studies in AD patients.[6]

As previous studies highlight gender differences in spatial navigation and with our results from Chapter 2 showing gender as a demographic risk factor associated with missing incidents, we suggest that gender should be considered when studying spatial disorientation in AD. Furthermore, our findings from Chapters 2, 3, and 4 highlight the importance of investigating the outdoor mobility patterns of AD patients in the community to identify the

[6] Icons used in this figure – "Missing" by Fahmi, "Gender" by Gregor Cresnar, "Building" by Iconcheese, "Road" by Ben Davis, "Path" by Adrien Coquet, "Person" by Yamini Ahluwalia, all from thenounproject.com

locations where spatial disorientation occurs as well as to explore potential environmental risk factors (i.e., outdoor landmark density and road network structure) in these locations that may be contributing to this. Lastly, we know from previous studies that AD patients increasingly prefer to use an egocentric strategy for navigation, potentially as a compensatory response to impairments in using an allocentric strategy [74]. Our hypothesis, as stated in Chapter 5, was that patients who are naturally (i.e., premorbid) relatively weaker at using an egocentric strategy for navigation would be less able to compensate and hence would be at higher risk for experiencing spatial disorientation in the community. Although we were not able to elucidate this from our findings in Chapter 5, premorbid differences in the ability to use different navigation strategies and the relationship of this to risk for spatial disorientation is indeed a factor that requires further investigation.

In conclusion, our findings from this thesis provide a platform for future studies to study how the different RW factors (demographic, environmental, and outdoor mobility patterns) interact with and affect impairments in spatial navigation to result in patients experiencing spatial disorientation in the community. The framework we suggest will provide further theoretical insight into this prevalent problem, and from a practical standpoint, will potentially help to build a cognitive and demographic profile of who is truly at high risk for experiencing spatial disorientation in the community.

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Appendix

Supplementary Information for Chapter 2

Supplementary Table 2.1: List of Landmark Categories and Tags

Category	Sub-Category	Tag
Amenity and Leisure	Food and Drink	Bakery, Bar, Biergarten, Café, Fast Food, Green Grocer, Pub, Restaurant, Supermarket
	Leisure	Arts Centre, Bank , Cinema, Clothes Store, Community Centre, Computer Store Convenience Stores, Department Stores, Do-It-Yourself Stores, Dog Park, Florist, Furniture Store, Gift Store, Garden Centre, Jeweler, Kiosk, Leisure Centers, Library, Mobile Phone Store, Newsagent, Nightclub, Outdoor Shop, Playground, Post Office, Other clubs and centers, Service Centre, Shoe Store, Shopping Mall, Stationery Store, Social Facility, Sports Centre, Stadium, Studio, Swimming Centers, Theatre Toy Store, Town Hall, Travel Agency, Video Store Village Hall
	Religious	Church, Hindu Temple, Synagogue, Mosque, Sikh Temple
	Health and Beauty	Beauty Shop, Chemist, Dentist, Doctors, Hairdresser, Hospital, Laundry, Nursing Home, Optician, Pharmacy, Veterinary
	Education	Kindergarten, Nursery, School, University
	Other	Graveyard, Prison
Tourism	Attractions	Local Attractions, Castle, Monument, Museum, Parks, Theme Parks, Viewpoints, Zoo
	Accommodation	Guesthouse, Hostel, Hotel, Other Overnight Accommodation, Motel
	Information Points	Tourist Information Points, Visitors Centers
Traffic and Transport	Transport Services	Bus station, Bus Stop, Car Dealership, Car Rental, Car Sharing, Car Wash, Crossing, Fire Station, Ferry Terminal, Fuel Station, Marina, Parking Lots (outdoor, multi-story, underground), Bicycle Parking, Police Station, Railway Platform, Railway Halt, Railway Station, Other Transport Services, Taxi Stand
	Road Signs	Mini Roundabout, Stop, Traffic Signals
Historic	-	Archaeological Sites, Memorials, Ruins
Urban and Rural Furniture	-	Artwork, Arch, Art Space, ATM Machines, Aviary, Bandstand, Barn, Belfry, Bench, Bunker, Canopy, Control Tower, Communications Tower, Cowshed, Dove Cote, Drainage Pump, Gatehouse, Glasshouse, Greenhouse, Fountain, Lighthouse, Hut, Hangar, Kennels, Lych Gate, Marquee, Mill, Pagoda, Pavilion, Power Station, Pump House, Pumping

	Station, Observation Tower, Post Box, Recycling Containers, Silo, Stable, Storage (containers, tank), Street Lamp, Telephone Box, Toilet, Tower, Vending (machine, parking) Waste Basket, Water Tower, Water Well, Warehouse, Wayside Cross, Windmill, Wind Pump

Supplementary Information for Chapter 4

4.1 Participant Recruitment

The patients were recruited from three main sources. The majority of patients were recruited from a research clinic run by our team; patients are in the first instance referred to this clinic from clinicians to participate in dementia research. Some patients were also recruited from the Join Dementia Research website, which is an online service allowing individuals with memory problems/dementia, carers of such individuals, and healthy individuals to self-register to participate in dementia research studies. Lastly, some patients were also recruited from memory and dementia cafes/fayres held by our study team.

Recruitment of the healthy controls included individuals who had attended the research clinic as well as individuals who had participated in other studies conducted by our team and who had also given consent to be contacted for future research. In addition, individuals who expressed their interest in the study as a result of word of mouth were also recruited as controls for the study.

4.2 Spatial Orientation Screening Questionnaire

Spatial Orientation Screening

The following questions are about the PARTICIPANT, to be completed by the STUDY PARTNER

1. Does your relative/friend have difficulties finding his/her way in familiar surroundings (such as when visiting the home of close friends, or when walking or driving in the neighbourhood)?
□ No, no difficulties
□ Yes, sometimes
□ Yes, often
2. Does your relative/friend have difficulties learning to find his/her way in new surroundings (such as when travelling or in new shopping centres)?
□ No, no difficulties
□ Yes, to some degree
□ Yes, pronounced difficulties
3. Does your relative/friend ever fail to recognise places where he/she has been before?
□ No, never
□ Yes, sometimes
□ Yes, often
4. Does your relative/friend ever refrain from travelling or from participating in activities alone because he/she is worried about finding his/her way?
□ No, never
□ No, but he/she spends a lot of time planning in advance
□ Yes

Changes

Please think now about what your relative or friend was like **10 years ago**, and compare this with what she or he is like **today**. Put a circle around the option which is best suited for the following situations.

Compared with 10 years ago, how is your relative or friend at:

Finding his/her way in familiar surroundings?	Much better	A bit better	Unchanged	Slightly worse	Much worse
Finding his/her way in unfamiliar surroundings?	Much better	A bit better	Unchanged	Slightly worse	Much worse

4.3 GPS Trajectory Data Pre-Processing

4.3.1 Data Smoothing

The data smoothing procedure involved identifying and removing big signal jumps between the data points. Big signal jumps represent random errors in the data collection process, and occur due to various reasons including issues with the satellite or receiver, troublesome weather or atmospheric disturbances, and the urban canyon effect (i.e., GPS signal being reflected by tall buildings and surfaces). One of the most straightforward methods that has been suggested in the literature to identify such big signal jumps is setting and using distance thresholds between data points. A distance threshold refers to the maximum distance that an individual could hypothetically cover in the time difference between two successively recorded data points, assuming that they are travelling at a certain speed. Since the GPS trajectories of all participants contains a mixture of transportation modes (i.e., they have not yet been classified according to transport modes), the maximum speed that our participants can travel, regardless of their transport mode, is 70mph; considering this maximum speed value and the GPS device's sampling frequencies of 3 seconds/5 seconds, we can assume that the distance between any two data points should not realistically exceed a threshold of 93.87/156.45 metres respectively. After setting these thresholds, for each participant we identified and removed data points which had distances to the point immediately before and immediately after that exceeded these thresholds (i.e., big signal jumps).

4.3.2 Transport Mode Classification

The GPS trajectory data points of each participant were classified into three main transport modes – stationary, by foot, and in vehicle. As a first step, we grouped all trajectory data points into time windows. For participants with data recorded every 3 seconds, every 3 data points were grouped into a single time window; hence a single time window had a duration of 9 seconds. Meanwhile, for participants with data recorded every 5 seconds, every 2 data points were grouped into a single time window; hence for these participants a single time

window had a duration of 10 seconds. Then, each time window was classified into one of the three transport modes based on the mean and maximum speed values of the data points in that time window. A time window is classified as:

- 'Stationary' if the mean speed was 0mph
- 'By foot' if the mean speed was greater than 0mph but less than or equal to 4mph and had a maximum speed value of less than or equal to 4mph. The rationale for choosing 4mph as the upper threshold is because in an outdoor navigation walking task that we got all participants to complete in another study (detailed in chapter 5), the maximum speed exhibited by any participant was 4mph.
- 'In vehicle' if the mean speed was greater than 4mph or if the mean speed was less than or equal to 4mph and had a maximum speed of greater than 4mph.

After the initial classification of all time windows into the different transport modes, a false positive check was conducted to refine this process. Regarding time windows classified as 'By foot', if such time windows were immediately preceded and proceeded by time windows classified as 'In vehicle' (eg. In vehicle, By foot, In vehicle), we can assume that these 'By foot' time windows are false positives. This is because such cases would realistically suggest instances when the vehicle (that the participants were in) was travelling really slowly, as opposed to suggesting instances where the participant got out of the vehicle, walked for 9-10 seconds, and got back in the vehicle. Here, these false positives were relabelled to 'In vehicle'. On the flipside, if time windows classified as 'In vehicle' were immediately preceded and proceeded by time windows classified as 'By foot' (eg. By foot, In vehicle, By foot), then these were also identified as false positives. This is because it is not realistic for a participant to have a 9-10 second period of being in a vehicle in the middle of a period of walking. Here, these false positives were relabelled to 'By foot'. After relabelling all false positives, all time windows labelled 'In vehicle' and 'Stationary' were filtered out, leaving

only portions of each participant's trajectory data where they were on foot (i.e., walking trajectories).

4.3.3 Walking Trajectories – Data Smoothing

Before calculating the distance travelled by foot, we first identified and removed big signal jumps in each participant's walking trajectory dataset by once again using the distance threshold method as used for the overall dataset. Here, considering a maximum speed of 4mph, the distance thresholds between any two data points were set to 5.36 metres and 8.94 metres for participants with data recorded every 3 and 5 seconds respectively. All data points in the walking trajectories which exceeded these thresholds (i.e., big signal jumps) were then identified and removed.