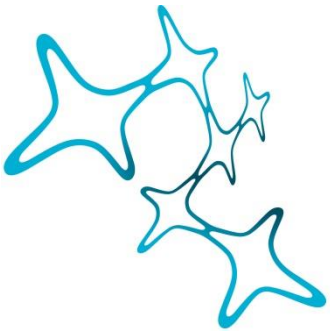
Gaze behaviour and brain activation patterns during real-space navigation in hippocampal dysfunction

Stephanie Irving

Dissertation der Graduate School of Systemic Neurosciences

der Ludwig-Maximilians-Universität München



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Abbreviations

AD	Alzheimer's disease
ANOVA	Analysis of variance
BDI	Beck´s Depression Inventory
BVP	Bilateral vestibulopathy
CA	Cornu Ammonis
CERAD plus	Consortium to Establish a Registry for Alzheimer's Disease plus
DG	Dentate gyrus
DWI	Diffusion-weighted imaging
EC	Entorhinal cortex
[^{18}F]-FDG	[^{18}F]-fluorodeoxyglucose
HF	Hippocampal formation
MCI	Mild cognitive impairment
MMSE	Mini mental state exam
MRI	Magnetic resonance imaging
MTC	Medial temporal cortex
OPA	Occipital place area
PET	Positron emission tomography
PPA	Parahippocampal place area
rCGM	regional cerebral glucose metabolism
RSC	Retrosplenial cortex
TD	Topographical disorientation
TGA	Transient global amnesia
TMT-B	Trail making test B

Summary

Spatial navigation is the innate ability to successfully orientate in naturally complex environments. It consists of a system for representation and storage of one's location in relation to the environment. It is guided by cues provided by the visual and vestibular systems, where visual landmarks and optic flow (visual image-motion) are processed in conjunction with vestibular path integration. Two navigational strategies emerge: allocentric spatial representations guide wayfinding to locations via central integrative abilities to form a cognitive map; egocentric spatial representations guide wayfinding to locations via visual information being relayed to the individual.

Neuroimaging studies in navigation indicate the presence of a complex cerebral navigation network involving the prefrontal cortex, the parietal cortex, and the hippocampal formation. Visual cues project to the dorsal regions of the hippocampal formation and vestibular information projects into the anterior hippocampal formation. Allocentric strategies are represented predominantly by place cells and grid cells throughout the hippocampal formation. Egocentric strategies, on the other hand, are represented in extrahippocampal regions, namely the parahippocampal and posterior parietal cortex. The retrosplenial cortex and precuneus assist with integration of both allocentric and egocentric reference frames. When there are lesions or degeneration in the cerebral navigation network, deficits in allocentric or egocentric navigation are present.

A more recent and less invasive technique for assessing navigation in humans is using gaze behaviour, which refers to visual exploration within an environment, where a number of parameters are determined and quantified. Calculation of the number of saccades, saccade frequency, fixations to landmarks, overall visual fixations during egocentric and allocentric

routes provides a description on individual reliance on visual cues, therefore providing detailed information on navigation strategy.

The aim of this thesis was to assess spatial navigation abilities in healthy subjects and in patients with hippocampal dysfunction with a novel experimental paradigm. We combined behavioural measurements of visual exploration and navigational performance with simultaneous measurements of brain activation. Navigation performance and gaze behaviour were measured with a head-mounted eye-tracking camera to record eye movements and analyse navigational performance and strategy in real-space. Brain activations were quantified by regional cerebral glucose metabolism (rCGM) with [^{18}F]-FDG-PET imaging. With this novel, real-space paradigm, I aimed to elucidate the relationship between spatial navigation performance, strategies, and their relation to regional brain activations, sensory feedback and motor control during locomotion.

This new method is a major departure from the typical approaches for assessing spatial navigation in humans with virtual environments as it utilises target-search in a real environment, allowing for multisensory feedback and motor control to be included in the overall analyses. This is of particular importance as this thesis also intends to extend understanding of the dynamics of the multisensory integration involved in spatial orientation and navigation, and how aging and strategic lesions contribute to impairment.

Participants performed a target-search task in a complex and unfamiliar real-space environment. The area had five items as target points; participants were shown each target, then, after tracer injection, participants were to navigate to the items autonomously. The sequence of target items was pseudorandomised and split to allow for both egocentric and allocentric strategies to be utilised within the 10 minute experimental session. Participants wore a gaze-monitoring head-mounted camera to record their visual exploration and head

position and were then placed in the PET scanner to record the metabolic activity of the brain during navigation.

Three studies are included to clarify the navigation control in the real world: firstly, in a study with healthy adults, we defined normal parameters for navigation performance, gaze behaviour, and regional brain activity, then analysed for age and gender effects on spatial navigation. Secondly, using a group of patients with transient global amnesia, presenting with focal hippocampal lesions, we performed the same experiment in the postacute stage (3 days) and during follow-up (3 months) and compared all parameters with healthy age-matched controls. Finally, we performed the paradigm with a single patient, who had a strategic right-sided hippocampal haemorrhage, and compared behavioural parameters with healthy age-matched controls. The patient was assessed a second time, 4 months after symptom onset. These patient samples were selected as examples of "pure" hippocampal dysfunction, therefore giving a clearer indication of the extent of the involvement of the hippocampus in navigation.

In this thesis I have demonstrated how the successful integration of behavioural, PET imaging and gaze data has led to a novel paradigm for measuring navigation impairment in real-space, sensitive to hippocampal dysfunction and aging. The paradigm could depict a change of navigational strategy with age, where older adults showed a deterioration in allocentric navigation, but compensate with egocentric strategies. This was accompanied by a reduced navigation-induced hippocampal activation in older relative to younger subjects.

Secondly, I present evidence that the paradigm is sensitive and reliable to detect prolonged navigational strategy deficits in transient global amnesia. Allocentric, but not egocentric, navigation remained impaired 3 months after initial symptom presentation; where patients remained dependent on visual cues. During the postacute stage, patients had greater brain activation in extrahippocampal hubs of the cerebral navigation network.

Finally, in a case report of a single subject, I argue that the paradigm is able to detect an almost complete loss of navigation abilities following a small, strategic right-sided hippocampal lesion, where the single symptom was topographical disorientation. Rapid functional compensation was complete over time, with re-establishment of allocentric and egocentric navigation strategies, as well as exploratory gaze behaviour, indicating reorganisation of the cerebral navigation network or functional substitution by the left hippocampus.

With these three studies, I argue that the paradigm has been shown to be a reliable, sensitive and valid method for measuring and discriminating spatial navigation deficits caused by hippocampal dysfunction and is a potential biomarker for other navigation pathologies, such as Alzheimer's disease and impending cognitive decline.

Introduction

1.1 Previous navigation research

Much of what we know about navigation, particularly the neural mechanisms, has emerged from animal studies. Indeed, the discovery of the cellular processes involved in navigation came from spatial navigation studies in the hippocampus of rodents (O'Keefe & Dostrovsky, 1971; O'Keefe, 1976; O'Keefe & Nadel, 1978; Moser et al., 2008; Chersi & Burgess, 2015; Moser et al., 2017). Further investigations over the decades revealed a series of distinct cells, located throughout the rodent brain, each responsible for specific navigational and orientation functions (Moser et al., 2015).

Place cells fire individually and in relation to where you are, rather than what you are doing, and discriminate between locations in an environment, i.e. different place cells fire at different positions, with no apparent topography (Derdikman & Moser, 2010; O'Mara, 2017). Grid cells, on the other hand, have multiple firing locations and form a hexagonal grid over the environmental space (Derdikman & Moser, 2010). Recent evidence has suggested that place cells are dependent upon grid cell input and emerge from grid cell output, thus strongly connecting the two cellular groups together in forming a neuronal network for rodent spatial orientation (Derdikman & Moser, 2010).

Head direction cells act as an inertial compass, providing relative orientation and spatial orientation from distance-travelled and direction from an arbitrary point of reference (Moser et al., 2017). They integrate head angular velocity and, with the hippocampal formation (HF), are involved in path integration. This acts as a basis for creating spatial coordinates for navigation, assisting to form a "cognitive map" of the environment; a mental representation of one's spatial environment (McNaughton et al., 2006; Moser et al., 2017).

The story of spatial navigation is one of discovery, initially directed by psychological theory, moving to animal physiology, and finally emerging with studies in humans (see figure 1) (Moser et al., 2017).

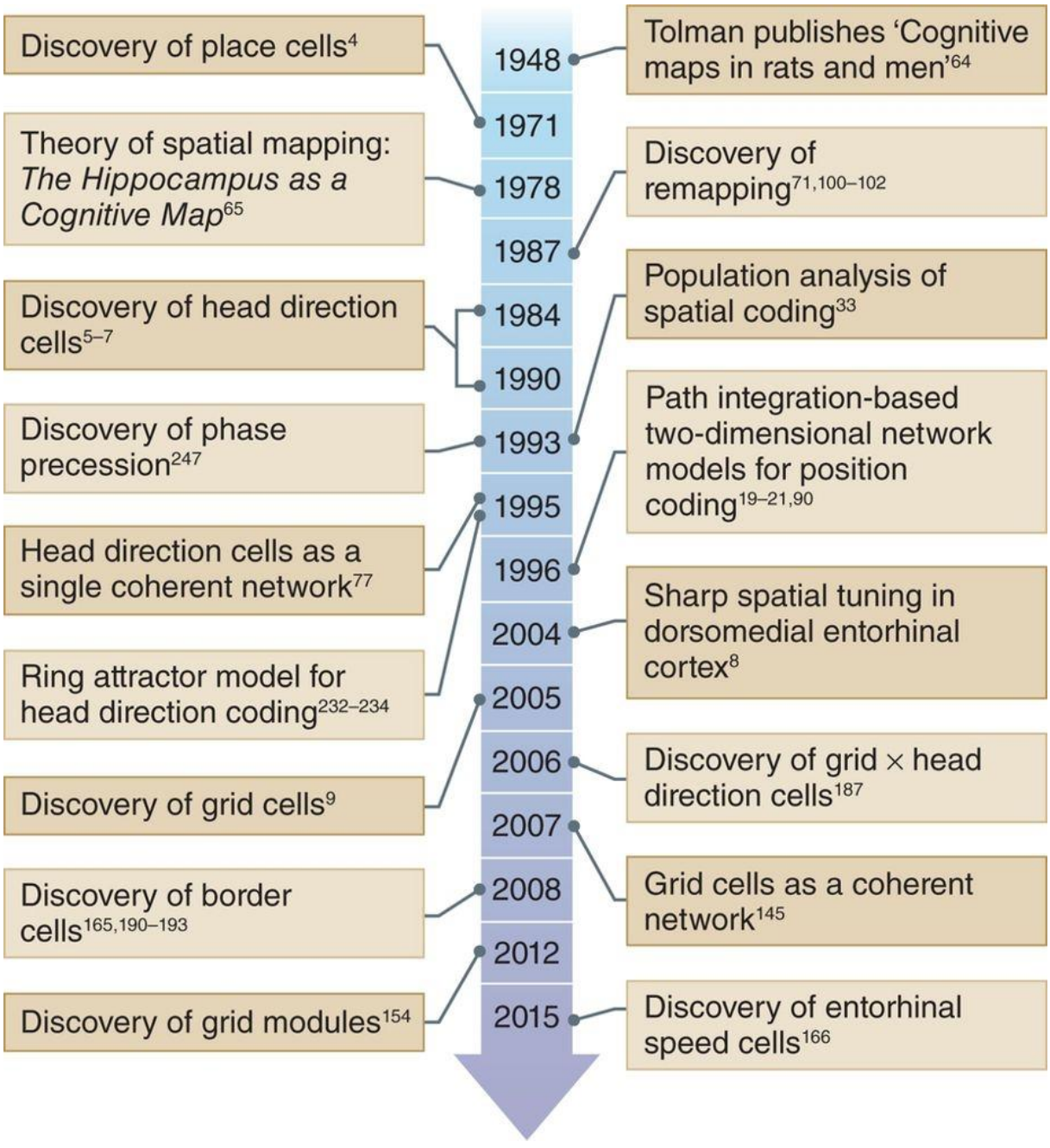

Figure 1: Discoveries over time in spatial orientation research. A selection of historical milestones in spatial orientation coding in the hippocampal formation. Adapted with permission from (Moser et al., 2017).

Human spatial navigation, however, is fundamentally different from that of rodents as humans are more visually dependent. Yet, like rodents, humans navigate through complex

environments by relying on differing forms of spatial memory to produce spatial representations; each of which utilises different frames of reference, learning strategies, and neuroanatomical structures (Arnold et al., 2015; Ekstrom & Isham, 2017; Lester et al., 2017; Wang 2017). Two navigational mechanisms are shared between rodents and humans: path-integration and landmark-guidance. The path-integration system is a sense of direction based on self-motion information and motor efference copy from the vestibular system. The landmark-guidance system is visually orientated in utilising landmarks and other environmental cues (Stackman et al., 2002; Zhao & Warren, 2015).

Locomotion during human navigation requires continuous position updating as we move between environmental objects and landmarks, and active decision-making regarding their relevance in reaching the target location (Ekstrom et al, 2014; Ekstrom et al, 2017; Wang 2017). The visual system is the favoured modality during navigation, however simultaneous processing of vestibular, motor, and proprioceptive information enables the path integration system to work alongside optic flow to optimise spatial orientation and navigation (Angelaki & Cullen, 2008; Hüfner et al., 2011).

Navigation is not only a complex multimodal task, but involvement of memory storage and recall of information, and the planning and execution of behaviour is key to our understanding. There are extensive experimental data on strategy-based behaviour, environmental manipulations, neurophysiological structures, and the cellular aspects of spatial navigation (Burgess, 2014; Chersi & Burgess, 2015).

The primary region for spatial orientation is a cluster of interconnected structures located within the medial temporal cortex (MTC): the HF, which includes the hippocampus proper, parahippocampus, entorhinal cortex (EC), subiculum, and the dentate gyrus (DG) (Hartley et al., 2013; Schultz & Engelhardt, 2014). This network of brain regions is a key part of the cerebral navigation network, a series of linked structures throughout the brain that

successfully generates representations of space during navigation. Structures include the HF, the retrosplenial cortex (RSC), and the neocortex, particularly the posterior parietal and prefrontal cortices. In unison, the functional cerebral navigation network enables successful navigation in space (Zwergal et al., 2016).

Vestibular-hippocampal interaction plays a significant role in hippocampal processing of spatial information, wherein the vestibular input to the hippocampus updates spatial representations during locomotion in order for the spatial representations to reflect the present body position in space (Stackman et al., 2002). Indeed, the vestibular system is involved in spatial navigation inasmuch as vestibular stimulation activates a number of regions throughout the cerebral navigation network, particularly the HF, RSC, and the parietal cortex (Stackman et al., 2002).

Integration of available sensory cues aids navigation by creating internal spatial representations responsible for generating relative distances, directions, and objects in our environment. The reference frames used in spatial coding is key for understanding spatial navigation as all spatial information is relative (Wang 2017). To specify the location of an object, a reference frame must be established to determine how the object's location can be measured. This reference could be another object, a direction, known point, the navigator itself, etc.

These spatial representation frames are divided into two: allocentric navigation, which is spatial information relative to the external world, and egocentric navigation, which is spatial information relative to the self (Bartsch & Deutschl, 2010; Ekstrom et al, 2017; Wang 2017). Due to the cue-rich nature of our environments, both allocentric and egocentric navigation strategies can be implemented simultaneously (Jacob et al., 2014).

1.1.2 Allocentric and egocentric navigation

Allocentric navigation is based on overall representations of the environment, utilising multiple landmarks and surrounding spatial geometry, external to oneself in space. As one navigates through an environment, in an allocentric frame, one's position in space relative to landmarks is used to determine location. This forms a stable coordinate-based system, known as a cognitive map (Bartsch & Deutschl, 2010; Ekstrom & Isham, 2017; Ekstrom et al., 2017; Lester et al., 2017; Wang 2017).

The cognitive map is essentially the representation of relative direction and distance of objects and landmarks to each other within the environment. This internal representation of space is located in the HF and supported by place cells and grid cells (O'Keefe, 1991, Moser et al., 2008). As a flexible function, it allows the navigator to use novel shortcuts in the environment, where a unified representation is created based on combined information of other spatial references to support spatial memory and to guide future action (Epstein et al., 2017; Wang, 2017).

Egocentric navigation is viewpoint-dependent. It is based on representations formed from reference to one's body position, calculating the distance an object is from oneself, for example, and is predominantly used to avoid collisions in space and to navigate in the immediate surrounding space (Epstein 2008; Ekstrom & Isham, 2017; Lester et al., 2017). Target locations are coded in relation to the navigator and each target is updated based on an estimation of self-motion.

Simply, this dynamic spatial representation frame feeds information about object location relative to the navigator from wherever in the environment the navigator is, allowing the navigator to directly use the information to reach a target goal without further spatial processing (Lester et al., 2017; Wang, 2017).

1.1.3 Navigation in different spaces

How we structure our spatial knowledge can be divided into two functional spatial scales; the 'vista space' is small-scale and room-sized environments, where all relevant spatial knowledge can be acquired from one viewpoint. The 'environmental space' is large-scale and requires integration of multisensory information across viewpoints and trajectories, experienced at different points in time during locomotion (Meilinger et al., 2014, 2016; Ekstrom & Isham, 2017).

Vista space allows for the rapid formation of spatial representations, whereas environmental space requires more time for dynamic representations to become internalised. Therefore, environmental space requires conversion of egocentric coordinates into allocentric coordinates through the integration of multiple egocentric reference frames. Egocentric navigation is optimal for vista spaces and allocentric navigation is optimal for environmental spaces (Meilinger et al., 2016; Ekstrom & Isham, 2017).

In sum, successful navigation is a multitude of complex behaviours involving perceptual, executive, and memory processes, requiring the integration of allocentric and egocentric navigation strategies, and utilising a coordination of different tasks and processes (Lester et al., 2017).

Specific anatomical regions are involved in spatial navigation, where the hub of information processing is the hippocampus, which coordinates widespread cortical regions that map different forms of space and is the neural basis of cognitive mapping (Ekstrom et al., 2003; Bartsch & Deutschl, 2010; Eichenbaum, 2015).

Indeed, this can be seen with spatial reference frames: both egocentric and allocentric navigation strategies utilise overlapping parieto-frontal networks, but egocentric navigation dominates the right superior parietal and superior frontal cortex, particularly in the right

hemisphere. Allocentric navigation additionally activates more temporal lobe structures and occipital regions, alongside the core of the HF. Damage to these brain regions can severely disrupt navigation (Chen et al., 2014; Arnold et al., 2015; Filimon, 2015; Lester et al., 2017).

1.2 The role of the hippocampal formation in spatial navigation

The HF refers to a group of anatomical structures, centred on the hippocampus, which feed information into each other. It is located in the MTC, formed around the temporal horn of the lateral ventricle, and includes the hippocampus proper, the DG, the subiculum, and the EC (see figure 2).

Extensive connectivity allows for large-scale and highly processed multimodal sensory integration and projection to numerous cortical and subcortical areas (see figure 3) (Martin, 2012; Hartley et al., 2013; Schultz & Engelhardt, 2014).

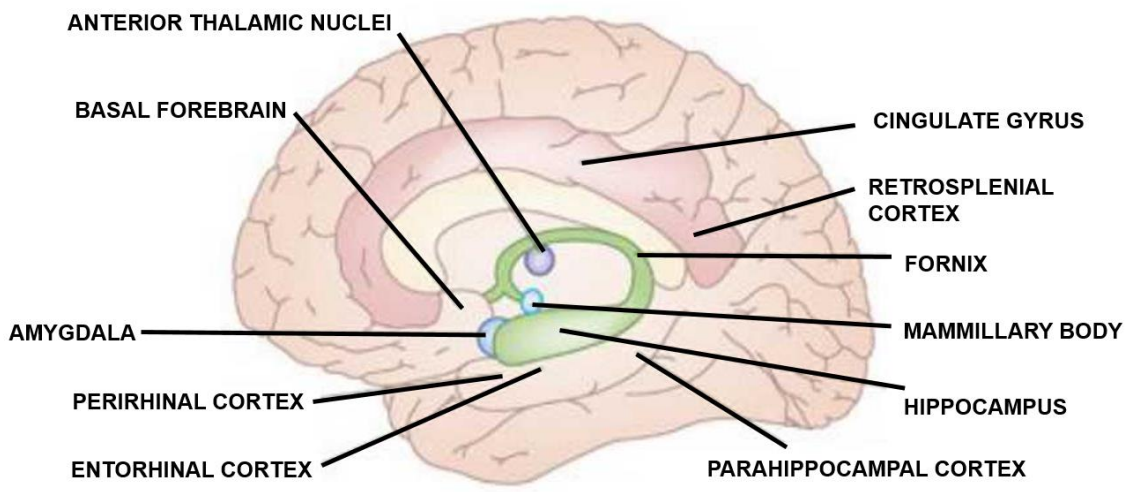

Figure 2: The human hippocampal formation. Located within the medial temporal cortex and showing the locations of the substructures of the hippocampal formation. Adapted with permission from (Nadel & Hardt, 2011).

In its entirety, the HF measures at approximately 5cm. It can be divided into precommissural, supracommissural, and retrocommissural sections, with the retrocommissural hippocampus as the main portion of the HF (Insausti & Amaral, 2012; Schultz & Engelhardt, 2014).

Caudally, the HF merges into the retrosplenial cortex (RSC) going upward around the splenium of the corpus callosum (Martin, 2012; Insausti & Amaral, 2012; Schultz & Engelhardt, 2014), projecting into the precuneus (Cavanna & Trimble, 2006) and the neocortex (Kessels & Kopelman, 2012).

Each anatomical structure is interconnected and largely unidirectional in communication, giving the appearance of a single functional entity (Insausti & Amaral, 2012).

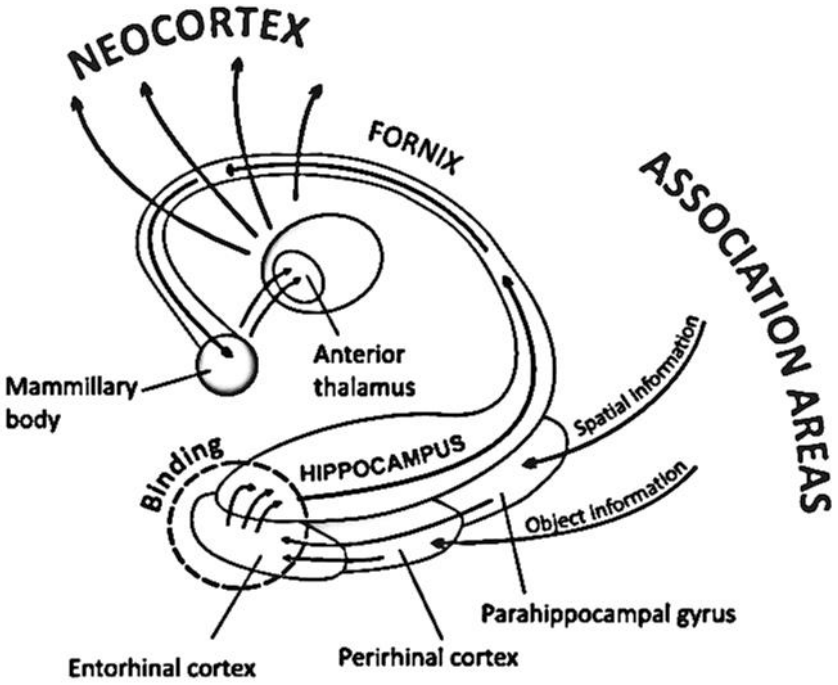

Figure 3: The human hippocampal formation and its connections. Showing extensive connectivity between structures, where information is processed in the HF and projected to the neocortex. Adapted with permission from (Kessels & Kopelman, 2012).

The hippocampus proper is a phylogenetically ancient cortical structure that forms a comma-shaped prominence and is embedded within the parahippocampal gyrus of the MTC (Tatu & Vuillier, 2014).

As one of the most-studied anatomical regions, the hippocampus is implicated in a number of memory processes, spatial navigation, emotion processing, scene construction, and perception. Due to its extensive structural and functional connectivity to a wide range of other brain regions (Henson et al., 2016), it enables multisensory integration of information throughout the HF (Fogwe & Mesfin, 2018).

Structurally, the hippocampus is unique in its neuronal architecture (Henson et al., 2016) and is made of two interlocking structures, the DG and the cornu ammonis (CA). According to Lorente de Nó's (1934) nomenclature, the CA is a horn-like structure of different layers divided into four fields of differing functions: CA1, CA2, CA3, and CA4, based on cellular morphology of the cortical neurons (Tatu & Vuillier, 2014) (see figure 4.).

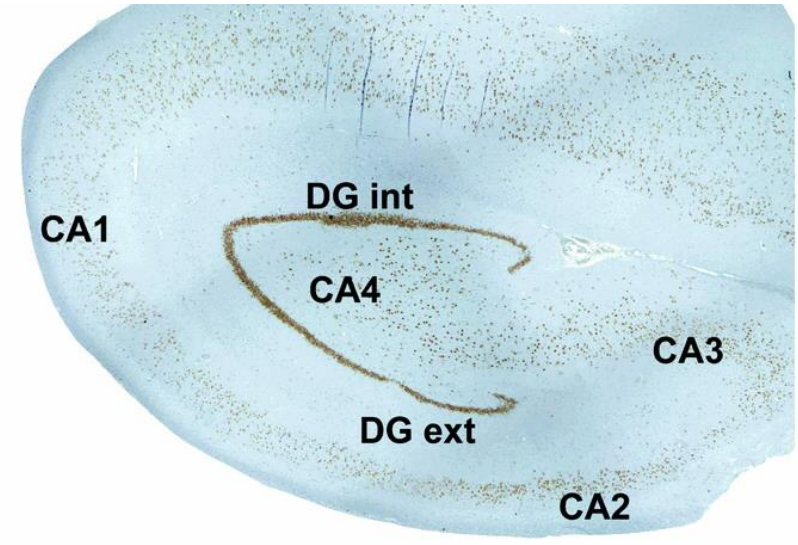

Figure 4. Surgical specimen of a human hippocampal formation, showing the different anatomic sub-regions, including cornu ammonis sectors CA1, CA2, CA3, and CA4. The CA regions are morphologically distinct fields. Adapted with permission from (Pauli et al., 2006).

CA2 and CA3 are located in the EC and border the DG. CA3 is the largest in the hippocampus and CA2 has widespread anatomical connectivity and unique signalling properties. CA4 receives signals from CA3 and projects into the DG (Lorente de Nó, 1934; Tatu & Vuillier, 2014; Pang et al., 2018; Fogwe & Mesfin, 2018).

CA1 has strong connections to the EC and subiculum, and is strongly implicated in successful spatial navigation, alongside CA3 neurons. When there is focal damage to CA1 neurons, deficits in allocentric spatial navigation are present (Lorente de Nó, 1934; Guillery-Girard et al., 2006; Moser et al., 2008; Bartsch et al., 2010; Bartsch & Deutschl, 2010).

The DG is a region of the hippocampus implicated in pattern separation and pattern completion, the formation of episodic memories in space, and spontaneous exploration. Pattern separation, which transforms similar-looking spatial representations into separate representations, is a key component of spatial cognition (Bakker et al., 2008; Baker et al., 2016). Input from the EC to the DG creates sparse orthogonalised representations of the environment, important for exploration (Bakker et al., 2008).

The outer layers of the EC are a major pathway for information from the neocortex to enter the hippocampus and DG, while the deeper layers of the EC and the subiculum supply output from the HF to the rest of the brain (Hartley et al., 2013). Together with the hippocampus, the EC creates a detailed cognitive map through visually-guided navigation and is involved in the planning of routes during navigation (Epstein, 2008; Epstein et al., 2017).

Located around the hippocampus, and a key structure for of the HF, the parahippocampus is implicated in scene processing in spatial navigation (Schultz & Engelhardt, 2014; Spiers & Barry, 2015), The parahippocampus processes contextual spatial information, and during navigational tasks, the parahippocampal place area (PPA) works alongside the hippocampus and RSC to encode distance and landmark recognition (Taube et al., 2013; Spiers & Barry,

2015). Damage to the parahippocampal cortex can lead to topographic disorientation (TD), whereas because the PPA responds to pictures of places and complex visual scenes, perception or encoding of the local scene in an environment becomes impaired with PPA damage (Epstein, 2008; Hartley et al., 2013). The parahippocampus and RSC have distinct yet complementary roles in spatial navigation; the PPA creates a representation of the local visual scene and the RSC places the scene within the broader spatial environment (Epstein, 2008).

Although not part of the HF itself, the RSC forms part of the posterior cingulate region and has complimentary connections with notable regions of the HF: the subicular complex (subiculum, presubiculum and parasubiculum), the parahippocampal region, and the EC (Epstein, 2008; Vann et al., 2009).

Likewise, the RSC is directly involved in spatial navigation and memory, particularly in scene construction, mental navigation, and interactive navigation in virtual-reality environments (Epstein, 2008; Auger & Maguire, 2013). By translating different perspectives of the environment, i.e. body-centred spatial representations into internal spatial representations and vice versa, the RSC acts as a form of short-term buffer for these spatial representations whilst they are processed by the hippocampus proper (Wolbers & Büchel, 2005; Epstein, 2008; Burgess, 2008).

The hippocampus and EC receive inputs from the PPA and RSC, which broadly support the cognitive map, encode spatial memory and encode different scene representations. Similarly, at the cellular level, throughout the HF there are different cells working together as specialised neuronal substrates of navigation: place cells, grid cells, and head direction cells (Hüfner et al., 2011). Altogether, these structural and cellular interactions are vital in making the HF entire a key composition for successful spatial navigation and orientation (Burgess, 2008; Epstein, 2008; Vann et al., 2009; Hüfner et al., 2011; Spiers & Barry, 2015).

1.2.1 Place cells

In 1971, the discovery of place cells in the hippocampus by O'Keefe and Dostrovsky marked the beginning of our understanding of spatial representation in the brain. Spatial receptive fields were recorded in complex-spiking neurons in the rat hippocampus, which fired whenever the rat was in a certain place in an environment. Similarly, neighbouring cells fired in different locations in such a manner that throughout the hippocampus, the entire environment was represented by the firing activity patterns of the local cell population (O'Keefe & Dostrovsky, 1971).

Different place cells have different firing locations, known as place fields, which are mapped non-topographically throughout the hippocampus (see figure 5) (O'Keefe, 1976). The combination of active cells per location within an environment is unique, suggesting the hippocampus is central to creating an internal representation of the spatial environment, as external features and events get mapped internally (O'Keefe & Nadel, 1978; Moser et al., 2008; Moser et al., 2017).

Early indications suggested place cells were part of an immediate and direct representation of location and to be independent of memory; however, they are now known to express previous, current and future locations and feed directly into a much broader network of different spatially modulated cells for spatial representation (Moser et al., 2015).

Place cells respond to a wide range of spatial inputs, such as extrinsic landmarks and translational and directional movement signals. Coupled with strong involvement in hippocampal spatial learning, the expression of both positional and directional information in place cells strongly argues for a central role of the hippocampus in spatial representation and information processing (Hafting et al., 2005; Moser et al., 2015).

Further, a number of studies have revealed that CA1 place cell activity increases in relation to proximity to goal locations. Such proximity coding is suggestive of a stored cognitive map of the environment, directly linked to place cell activity (Spiers et al., 2017).

Place cells have also been directly recorded in the human hippocampus and parahippocampal region: intracranial electrodes in the medial temporal lobes of patients with temporal lobe epilepsy, navigating in a virtual reality environment, revealed cellular firing for location in the environment, desired destination in the environment, and specific landmarks in the environment (Ekstrom at el., 2003).

This is a growing field of study and is likely to yield exciting results of the involvement of human place cells in spatial navigation.

1.2.2 Grid cells

Grid cells, located primarily in the MEC and subiculum, display multiple place fields firing in multiple locations in the environment to create a hexagonal grid pattern (Moser et al., 2008). Entorhinal cortical grid cells provide a metric for extended space, which when coupled with place cells, their relative firing rate at population level can represent the entire spatial layout of an environment (see figure 5) (O'Mara, 2017).

These environmental cues serve as a corrector of path integration errors and create an internal representation of an allocentric reference frame (McNaughton et al., 2006; Moser et al., 2008, 2017).

This integration, which also includes speed, velocity, and orientation information, shows grid cells and the EC itself are central to the cerebral navigation network; they form the basis of path integration, cognitive maps, and enable successful navigation through complex environments (McNaughton et al., 2006; Moser et al., 2008, 2017; Lester et al., 2017; Strangl et al., 2018).

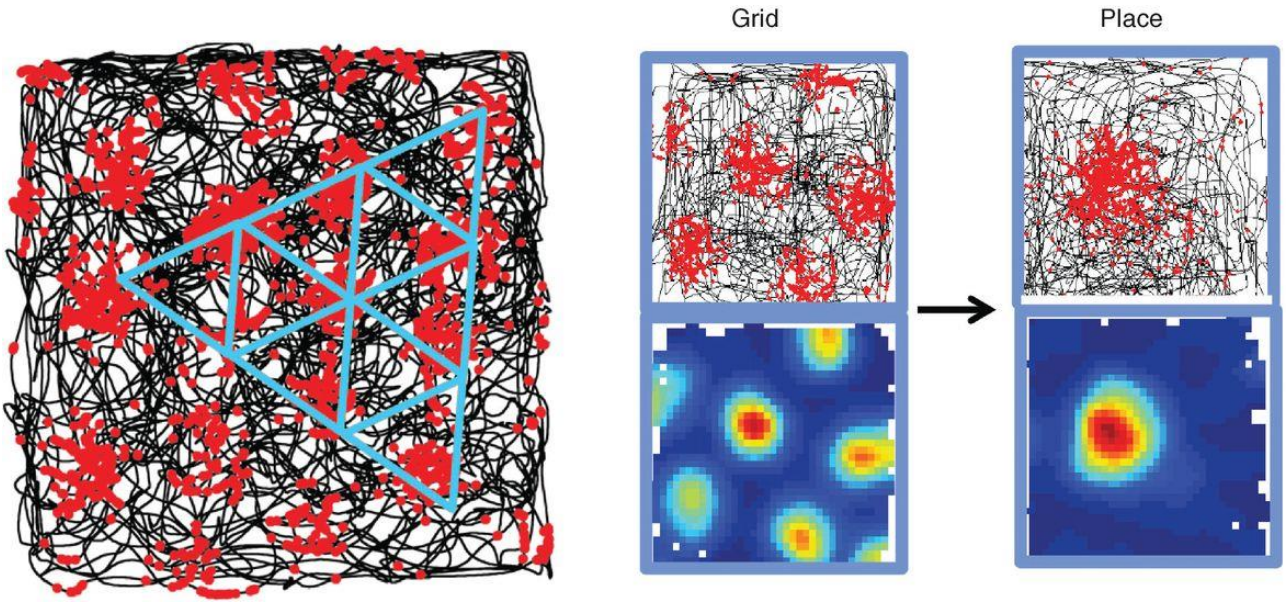

Figure 5. Grid cells and place cells. (*Left*) A grid cell from the rat EC. The black trace shows trajectory in part of a square enclosure. Spike locations of the grid cell are superimposed in red, each red dot corresponds to one spike. Blue triangles illustrate the hexagonal structure of the grid pattern. (*Right*) Grid cell and place cell. (*Top*) Trajectory with spike locations. (*Bottom*) Colour-coded rate map with red showing high activity and blue showing low activity. Adapted with permission from (Moser et al., 2015).

The grid field has three properties: scale, orientation, and spatial phase. Space is determined by the distance between adjacent firing rate peaks, orientation via grid axes relative to a reference direction, and spatial phase by the two-dimensional offset of the grid in relation to an external reference point (Hartley et al., 2013).

In humans, grid cells have been shown to support a flexible neuronal code for space that is dynamic to thoughts and mental simulations (Horner et al., 2016; Jacobs & Lee, 2016). They are, however, susceptible to damage and age-related decay, where grid-cell representations in the EC are compromised in normal adult aging. Impairment in grid cell functioning is arguably key in the decline in higher cognitive functions, such as spatial navigation (Strangl et al., 2018).

1.2.3 Head direction cells

The discovery of head direction cells revealed a neural coding for heading direction in a compass-like fashion. Located in the presubiculum, EC, RSC, thalamus, and beyond, they fire rapidly when the individual is faced in a preferred direction (Hartley et al., 2013; O'Mara, 2017). They record angular and linear accelerations in the head and provide a representation of allocentric heading that is independent of location, detected by the vestibular system (Hartley et al., 2013; Jacob et al., 2014).

A substantial population of head direction cells in the thalamus project to the CA1 area. This input from the head-direction system is required by place cells to discriminate between identical-looking environments of differing orientations. When this directional input is removed, place cells cannot discriminate between locations, indicating directional information provided is a key input for allowing place cells to resolve differences in visually ambiguous environments (O'Mara, 2017).

In humans, research into head direction cells is relatively new: fMRI studies examining coding in virtual reality have reported changes in activation in the RSC and subiculum, with coding apparently insensitive to global landmarks (Marchette et al., 2014; Shine et al., 2016). This is possibly due to the experimental setup being visually-based and lacking vestibular input to differentiate orientation (Shine et al., 2016).

However, when the option to make physical rotations to steer orientation in a virtual environment is included, results are consistent with rodent research: signal detection in the RSC, thalamus, and precuneus, with head direction cells in the thalamus likely integrating visual and vestibular orientation cues (Shine et al., 2016). These findings bolster the idea of vestibular-to-HF connectivity in spatial orientation and provides a viable way to investigate the neural basis of navigation in humans.

1.3 **Imaging of cerebral navigational networks**

Neuroimaging gives insight into the functional role of anatomical structures in cognitive and motor actions, for example HF activation during vestibular stimulation has been shown (Hüfner et al., 2011). Positron emission tomography (PET) is a powerful imaging tool which enables in vivo examination of brain functionality, a non-invasive quantification of cerebral blood flow, metabolism, and receptor binding in relation to a given task or action (Tai & Piccini, 2004).

Imaging with fluorine 18 fluorodeoxyglucose ([^{18}F]-FDG) PET is commonly used for studying brain glucose metabolism as it is sensitive to the progressive neurodegeneration associated with AD (Karow et al., 2010; Laforce et al., 2010; Omami et al., 2014). This effect is seen even in prodromal AD pathologies, such as mild cognitive impairment (MCI), and in comparison of several neurodegenerative pathologies to normal aging. [^{18}F]-FDG-PET has been extensively used in research and in clinical investigations due to its diagnostic sensitivity and accuracy (Berti et al., 2014).

Glucose is the major metabolic substrate of the brain and its oxidation produces the amount of energy that is necessary for cerebral activity. Injection of the tracer [^{18}F]-FDG, which has a cerebral uptake in the first 10 minutes after injection, allows for the study of cerebral glucose metabolism, reflecting neuronal and synaptic activity in the brain (Berti et al., 2014; Zwergal et al., 2016).

As the [^{18}F]-FDG cerebral uptake correlates strictly with local neuronal activity, wherein it proportionally increases with stimulus intensity or frequency, and decreases in conditions of sensory deprivation, it therefore provides an estimation of neuronal activation specific for the action or task performed (Berti et al., 2014; Zwergal et al., 2016).

In a seminal study on London taxi drivers, Maguire et al. (1998) demonstrated the plasticity of the hippocampus in relation to spatial navigation. Using MRI and PET, it was possible to show that not only is the hippocampus activated in the processing of topographical memory, but in London taxi drivers, there is an increase in grey matter volume in the posterior hippocampus when compared with healthy controls.

It is argued that as London taxi drivers must retrieve complex routes throughout the city; the plasticity of the hippocampus is reflected in relation to the complex nature of the task. Further, the right hippocampus was particularly activated during large-scale environmental navigation (Maguire et al., 1998).

To enhance our understanding of the functional role of the hippocampus in spatial processing and navigation, imaging has also been applied to a number of studies of amnesic deficits in patients with lesions to the hippocampus (Guillery-Girard et al., 2006; Bartsch et al., 2010). Diffusion-weighted imaging (DWI) has shown that small lesions to CA1 neurons profoundly impacts spatial learning and navigation (Bartsch et al., 2006, 2007, 2011).

However, recent studies have placed less importance on the hippocampus proper and have extended into the RSC. In virtual reality environments, neuroimaging showed increased hippocampal activity during the learning phase of an environment, where there was subsequent activation decay, and increased bilateral RSC activation in parallel to navigational performance. The hippocampus was concluded to incorporate new information into memory representations (Wolbers & Büchel, 2005; Epstein, 2008) and the RSC is associated with navigation in familiar environments (Epstein, 2008; Auger & Maguire, 2013).

Damage to the RSC can cause a selective deficit in spatial navigation, particularly in successful navigation in familiar environments, indicating failure to derive directional information from landmark cues (Epstein, 2008).

Like hippocampal lesions, patients with RSC lesions can present with impairments in learning to navigate new environments, however retention of sense of direction and navigation in familiar environments remains intact (Epstein, 2008; Auger & Maguire, 2013).

Such specific spatial deficits in patients with RSC pathology bolsters the theory that the RSC has a translational function for the hippocampus and serves to support stimulus conversion through integrating egocentric spatial information with allocentric spatial information (Wolbers & Büchel, 2005; Epstein, 2008).

Over the years a number of studies revealed a network of brain regions that were more active during navigation than in perceptual control conditions. Key regions of this network include the HF, RSC, and the occipital place area (OPA), all of which perceive and use landmarks and generate an internal cognitive map for successful navigation in a dynamic environment (Epstein et al., 2017) (see figure 6).

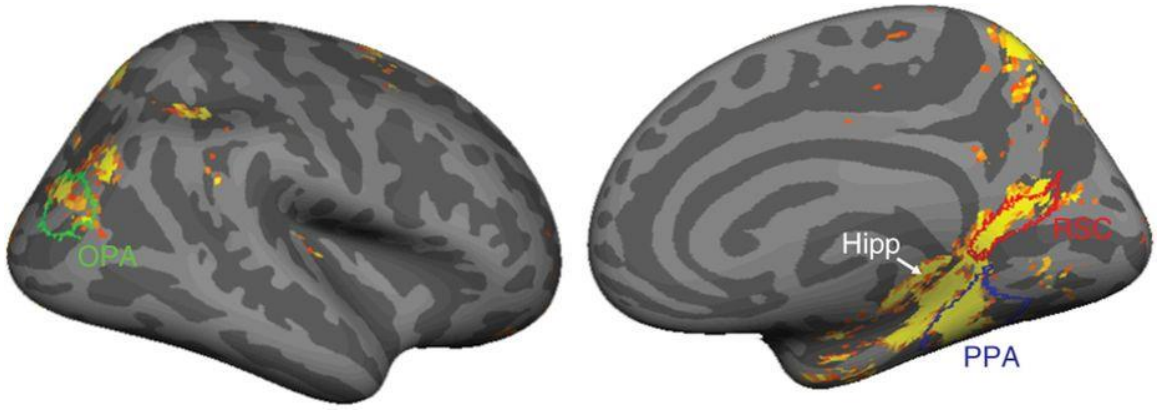

Figure 6. A network of brain regions involved in spatial navigation showing the hippocampus (Hipp), retrosplenial cortex (RSC), entorhinal cortex, parahippocampal cortex and place area (PPA), and occipital place area (OPA). Adapted with permission from (Epstein et al., 2017).

Here we see more than a foundation for the concept of hippocampal involvement in a wider HF and neocortical network in spatial navigation; hippocampus, RSC, parahippocampal

cortex, and the medial prefrontal cortex were activated during successful path integration (Epstein et al., 2017).

In sum, to create internal spatial representations, findings from neuroimaging suggest that spatial navigation is a dynamic process recruiting a number of anatomical structures to support path integration, self-motion, spatial reference frame integration, and spatial learning. All of this resulting in the cerebral navigation network, a collaborative network for successful navigation (Wolbers & Büchel, 2005; Epstein 2008; Bartsch & Deutschl, 2010; Chrastil et al., 2015; Epstein et al., 2017).

1.4 Quantification of navigation performance and strategy

Regarding navigation and spatial orientation, eye-tracking studies have mainly focused on investigating the relationship between gaze and locomotion. Navigation, however, as a higher cognitive function, requires encoding of spatial information, retrieval from spatial memory, path planning, and executive functioning for decision making (de Condappa & Wiener, 2014; Wiener et al., 2011).

So how does gaze behaviour relate to navigation? When studying human spatial navigation, a key issue is discerning navigation strategies used during tasks. To accommodate this, eye tracking has been used to quantify gaze behaviour and thus to discriminate egocentric and allocentric strategies. This is possible by analysing the differences in gaze position within an environment (Livingstone-Lee et al., 2011; de Condappa & Wiener, 2014).

In virtual reality environments, it is possible to identify dominant gaze positions, i.e. towards the distal features or proximal features in strategy-biased mazes. Eye movements and targets of focus, such as landmarks and unique objects, provide an indication whether an egocentric or an allocentric strategy is utilised (Livingstone-Lee et al., 2011; de Condappa & Wiener, 2014). Furthermore, heat maps of gaze position during navigation and orientation in an

allocentrically or egocentrically biased environment reveal different strategies during route learning and navigation (Livingstone-Lee et al., 2011; de Condappa & Wiener, 2014).

As gaze behaviour during navigation tasks can be predicted by environmental features, there can be a gaze bias directed towards environmental landmarks that are decisive for spatial learning and decision making (Wiener et al., 2011). Spatial attention connects and integrates environmental landmarks and unique features to spatial decision making. This in turn indicates cognitive strategies underlying navigation (Wiener et al., 2011).

Despite a wealth of knowledge gained from gaze behaviour studies, the vast majority are lab-based and in virtual realities. They demonstrate the relevance of gaze behaviour for navigation, yet they are limited due to simple visual stimuli and a lack of vestibular input (Wenczel et al., 2017).

Humans navigating real-world environments must process complex multisensory input, which cannot be replicated in virtual environments or lab settings, which may result in differences compared with real-world gaze behaviour (Wenczel et al., 2017).

1.5 Navigation control during healthy aging, sensory and cognitive decline

The decline in spatial navigation was shown to be apparent after 60 years of age and further accelerated after 70 years of age. Studies performed in virtual reality showed a specific pattern of spatial navigation deficits in older adults, where allocentric navigation is reduced, and showed an increase in a compensatory egocentric strategy. This indicates the use of extrahippocampal hubs instead of the hippocampus proper (Barrash, 1994; Wiener et al., 2013; Bates et al., 2014; Lester et al., 2017; Strangl et al., 2018).

Younger navigators tend to adopt an allocentric navigation strategy, whilst older participants, even with successful recollection of the route, show preference for an egocentric strategy, resulting in a poorer navigational performance. As allocentric spatial navigation is dependent

on hippocampal processes, age-related hippocampal degeneration is proposed to force a change in navigation strategy (Gazova et al., 2013; Konishi & Bohbot, 2013; Wiener et al., 2013; Bates et al., 2014;).

Mild cognitive impairment (MCI) refers to a cognitive impairment present in older adults where there is a functional impairment and an increased likelihood of developing Alzheimer's disease (AD) (Cushman et al., 2008; Laczó et al., 2010; Rusconi et al., 2015). MCI and AD patients show impairment in allocentric and egocentric navigation strategies, visuo-spatial perception, and the selection of relevant information for successful navigation.

Specifically, navigational impairment is associated more with impaired allocentric than egocentric processing (Vlcek & Laczó, 2014; Wood et al, 2016), and it is more prominent in early-stage AD patients (Hort et al., 2007).

Functional disability early in AD often involves navigational deficits, such as wandering and getting lost. Further, there is evidence of decreased tissue volume in the right posterior hippocampal and parietal areas, key regions for allocentric navigation (Cushman et al., 2008).

The hippocampus is a core structure for learning and memory, receiving both visual and vestibular input. Visual information is projected to the posterior hippocampus and vestibular information is projected to the anterior hippocampus (Hüfner et al., 2011; Göttlich et al., 2016).

The vestibular system has both a central and peripheral component, each presenting with different symptoms and syndromes. Peripheral vestibular disorders affect the vestibular nerve or ear labyrinths. Central vestibular disorders, on the other hand, are caused by lesions to the central vestibular system; an extensive network of regions that includes the vestibular nuclei in the brain stem up to the multisensory vestibular cortex regions (Brandt & Dieterich, 2017).

Changes to vestibular function and the knock-on effects to the hippocampus are seen in two ways: in cellular morphology and in hippocampal functionality. This morphological change is complex, is dependent upon how the vestibular system is dysfunctional (i.e. bilateral, unilateral), and for how long it has been dysfunctional. For example, rodents with bilateral vestibulopathy (BVP) show irregular place cell response and theta rhythm in the hippocampus (Smith, 2017).

Similarly, with humans, bilateral vestibular loss is linked to bilateral anterior hippocampal atrophy of 16.9% volume reduction, correlated with decreased spatial memory and navigation abilities (Brandt et al., 2005). These patients also show decreased grey matter in the CA3 region of the hippocampus, which correlated with the length of clinical vestibular impairment (Göttlich et al., 2016).

In hippocampal functionality, navigation impairments are persistent and a likely consequence of disruption to hippocampal coding of spatial information in BVP patients (Stackman et al., 2002). BVP directly impairs the vestibular system and therefore path integration abilities (Angelaki & Cullen, 2008; Kremmyda et al., 2016; Popp et al., 2017; Fogwe & Mesfin, 2018), where atrophy-associated volume loss in the anterior hippocampus has been implicated (Brandt et al., 2005; Brandt et al., 2014).

As navigation requires constant integration of self-motion and external cues to track one's location in space, disturbance to the vestibular-hippocampal network affects navigation accuracy via impaired internal monitoring of both external landmark cues and internal self-motion cues (Stackman et al., 2002).

Recent unpublished data, utilising a head-mounted and gaze-controlled camera combined with [^{18}F]-FDG PET imaging, demonstrated decreased activation of the right anterior hippocampus and a route-based, landmark-reliant navigation strategy. An impaired ability to

generate a cognitive map has been linked to degeneration of the anterior hippocampus. Increased activation in the bilateral posterior hippocampus, on the other hand, indicates a visual system compensation for lack of vestibular input (Zwergal et al., unpublished).

The vestibular system responds to angular and linear accelerations in the head, which project to the central vestibular nuclei to create a neuronal representation of angular and linear head velocity. It is hypothesised that there are at least four pathways that transmit vestibular information to the hippocampus (Hitier et al., 2014). Damage to these pathways have wide-ranging consequences regarding spatial cognition and memory, but imply heavily the presence of not only vestibular input into the hippocampus, but of a functional interaction between the vestibular system and the cerebral navigation network (Jacob et al., 2014; Zwergal et al., 2016).

1.6 Navigation control in focal hippocampal damage

Patients with focal hippocampal damage tend to show decreased connectivity to the posterior cingulate cortex and a number of other regions in the cerebral navigation network, including the medial prefrontal cortex, parietal cortex, and thalamus (Henson et al., 2016).

Disruption of connectivity caused by damage to the HF can have far-reaching consequences, where not only is navigation affected, but also episodic memory storage and retrieval (Gratton et al., 2012; Schedlbauer et al., 2014).

Hippocampal lesions in animals have sufficiently shown disruption to spatial memory and the ability to acquire and use mapping strategies (O'Keefe, 1991; Moser et al., 2017). In humans, however, it is difficult to assess hippocampal subfield contributions to spatial navigation. In exceptional circumstances, it is feasible to directly record cells from the hippocampus in humans: place cells have been directly recorded in the human hippocampus in patients with temporal lobe epilepsy, where 24% of cells were responsive to spatial location. Using

intracranial electrodes in the medial temporal lobes of these patients navigating in a virtual reality environment, cell firings were isolated for location in the environment, specific landmarks in the environment, and the desired destination (Ekstrom et al., 2003).

It is with these exceptional circumstances we can add weight to the argument that the human hippocampus is directly involved in spatial navigation in a similar manner to rodents.

The majority of our knowledge on the relationship between the HF and spatial navigation has been acquired from animal studies and patients. Therefore, patients with damage to the hippocampus, and focal lesions to the hippocampus in particular, provide insight into spatial memory and navigation abilities (Bartsch & Deutschl, 2010).

Aims of this thesis

Much of previous research into spatial navigation and orientation deficits in patients with hippocampal dysfunction has consisted of virtual reality paradigms, with few and sparse real-space paradigms. Virtual reality paradigms lack essential sensory feedback and motor control. Here, we measure spatial navigation abilities in a real-space environment, using combined sequential quantitative spatial navigation, brain activation patterns from PET, and visual exploration from gaze behaviour patterns as a sensitive and reliable marker of hippocampal function and dysfunction.

Here, we have documented and quantified potential pathological signs of spatial memory deficits and correlated with functional cerebral activation and differences in gaze behaviour. We have further elucidated the contribution of landmark-based/egocentric and cognitive-map-based/allocentric navigational strategies and analysed changes in patients with hippocampal dysfunction.

This cumulative thesis consists of three manuscripts, of which the first one has been **published** in the peer-reviewed journal *Journal of Neurology*®. The second has been **published** in the peer-reviewed journal *Neurology*®. The third has been **published** in the peer-reviewed journal *Brain and Behaviour*®.

The aims of this cumulative thesis are: first, to determine the effects of gender and aging on spatial navigation, gaze behaviour, and navigation strategies in healthy adults, in a real-space and novel environment. Secondly, to understand the basis of behavioural neurophysiology, i.e. navigation strategies, gaze behaviour, and brain activation patterns in patients with strategic brain lesions. Thirdly, to improve our understanding of how the visual and vestibular systems interconnect for successful spatial navigation, and conversely, to what extent specific deficits within these systems contribute to spatial disorientation.

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ORIGINAL COMMUNICATION

A novel real-space navigation paradigm reveals age- and gender-dependent changes of navigational strategies and hippocampal activation

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Abstract

Objective To establish a novel multimodal real-space navigation paradigm and define age- and gender-related normative values for navigation performance and visual exploration strategies in space.

Methods A group of 30 healthy subjects (mean age 45.9 ± 16.5 years, 16 men) performed a real-space navigation paradigm, requiring allo- and egocentric spatial orientation abilities. Visual exploration behaviour and navigation strategy were documented by a gaze-controlled, head-fixed camera. Allo- and egocentric spatial orientation performance were compared in younger and older subjects (age threshold 50 years) as well as men and women. Navigation-induced changes of regional cerebral glucose metabolism (rCGM) were measured by [^{18}F]-fluorodeoxyglucose-positron emission tomography in a subgroup of 15 subjects (8 men) and compared across age and gender.

Results The majority of healthy subjects (73.3%) completed the navigation task without errors. There was no gender difference in navigation performance. Normalized total error rates increased slightly, but significantly with age ($r=0.36$, $p=0.05$). Analysis of navigation path indicated a significantly reduced use of short cuts in older age ($r=0.44$, $p=0.015$). Visual exploration analysis revealed that older subjects made significantly more total saccades ($r=0.49$, $p=0.006$) and search saccades ($r=0.54$, $p=0.002$) during navigation. All visual exploration parameters were similar in men and women. Navigation-induced rCGM decreased with age in the hippocampus and precuneus and increased in the frontal cortex, basal ganglia and cerebellum. Women showed an increase of rCGM in the left hippocampus and right middle temporal gyrus, men in the superior vermis.

Conclusion Real-space navigation testing was a feasible and sensitive method to depict age-related changes in navigation performance and strategy. Normalized error rates, total mean durations per item and total number of saccades were the most sensitive and practical parameters to indicate deterioration of allocentric navigation strategies and right hippocampal function in age irrespective of gender.

Keywords Spatial navigation · Aging · Eye movements · Hippocampal dysfunction

Introduction

Navigation in space is one of the most fundamental cognitive abilities of humans, which involves multiple strategies and levels of processing [1–3]. It can be based on static environmental and dynamic self-motion clues. Egocentric navigation strategies rely on a self-centred reference frame, in which route trajectories are planned along landmarks in space [4]. Allocentric strategies comprise of cognitive representations of the environment [5, 6]. Here the position in space is predominantly updated by self-motion clues. The preferred navigation strategy varies considerably between subjects. Age and gender are

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within the most important influencing factors. Young subjects tend to shift between ego- and allocentric strategies. In the healthy elderly, allocentric navigation abilities decline because key structures of the cerebral navigational network deteriorate as a consequence of aging [7, 8]. Men often report using cognitive map-like strategies, whereas women apply route-based strategies along known landmarks more likely [9].

In the last years, age- and gender-related changes of spatial navigation abilities and corresponding brain activations have been examined mainly in virtual environments [7, 10, 11]. The major advantage of such an approach is that the setting can be well controlled and exactly manipulated. However, navigation in virtual space predominantly relies on visual information and neglects vestibular and proprioceptive stimuli as well as motor efference copy signals, which are essential body-based self-motion clues [12]. Therefore, in the current study we investigated spatial navigation in a real-space environment in healthy male and female subjects across the age spectrum by combining behavioural measurements of visual exploration and navigational performance with simultaneous measurements of cerebral glucose metabolism by positron emission tomography (PET).

The major aims were (1) to investigate age- and gender-dependent changes in real-space navigation strategy and visual exploration, (2) to relate those to alterations of navigation-induced cerebral glucose metabolism and (3) to define concrete behavioural parameters, which are easy to record and robust across subjects of different age and gender to quantify real space navigation performance. It was hypothesized that navigation efficiency and accuracy would deteriorate mildly and navigation behaviour would shift towards a more egocentric strategy in the elderly. For gender it was assumed that women would use preferentially landmark-based strategies while navigation performance would be gender-independent. As concerns robust markers for navigation performance and strategy, we hypothesized that the number of saccades during visual exploration would reflect a visually-guided navigation strategy and would increase in older subjects and women. For navigation-induced brain activation patterns, it was expected that glucose uptake during navigation would decrease in the hippocampus and increase in extrahippocampal hubs of the navigation network (e.g. frontal cortex, basal ganglia) with age and that women would recruit additional brain areas, which are dedicated to landmark processing (e.g. parietal cortex).

Methods

Subjects

Thirty healthy, right-handed subjects (mean age 45.9 ± 16.5 years, 16 men) with normal neurological and physical status were included in the study. All participating subjects had intact vestibular function, as measured by the head-impulse test, no signs for a polyneuropathy, and no relevant deficits in visual function. Cognitive function was tested in all subjects by the CERAD plus test.

Standard protocol approvals and patient consent

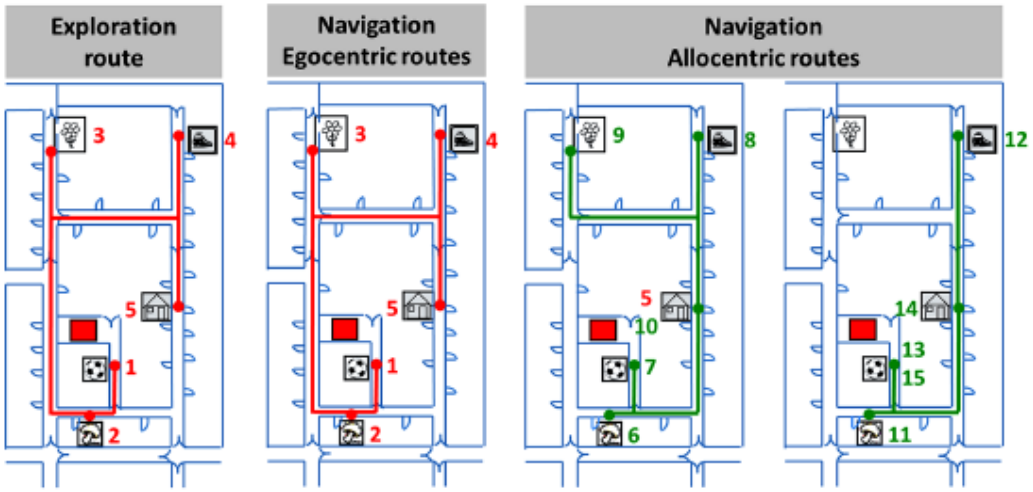
All subjects gave their informed, written consent to participate in the study. The protocol was approved by the Ethics Committee of the Ludwig-Maximilians University of Munich and by the German Federal Office for Radiation Protection.

Spatial orientation paradigms

All participants performed a navigation paradigm in a complex and unfamiliar spatial environment to test their spatial orientation performance. The 700 m^2 area, in which five items had been placed as target points, was shown first on an investigator-guided walk (exploration). The exploration route followed a defined sequence of target items (Fig. 1). Afterwards, over the next 10 min, participants were requested to navigate autonomously and by a self-determined strategy to items given by the investigator respectively (navigation). In the first part of the navigation paradigm, the sequence of target items requested was identical to the previous exploration route, thus requiring no spatial cognitive map (an egocentric strategy); in the second part, the order of target items was pseudo-randomised, which required the planning of novel routes, potentially including short cuts (an allocentric strategy) (Fig. 1).

Recording of navigational path and visual exploration behaviour

Participants wore a gaze-monitoring head camera to document their visual exploration and head position [13]. Error rates for items approached during the navigation phase were calculated for the total paradigm (normalized to 15 target items) and separated by egocentric and allocentric routes based on post-hoc analysis of the recorded videos. The search path during the navigation task was mapped by accumulating time at a specific place and analysed quantitatively. Viewing the video recordings allowed all fixation targets to be categorised into fixed objects in space, mobile objects, and non-object fixations. The total number of objects and unique objects viewed were quantified. Analysis was carried out by MATLAB® 2012a based on established algorithms [14]. Raw eye movements were converted into degrees in the x and y axes. The overall distance traversed by gaze was determined as:



	Navigation target items	Routes	Short cuts
1	ball	egocentric	
2	mushroom	egocentric	
3	flower	egocentric	
4	train	egocentric	
5	house	egocentric	5 -> 6
6	mushroom	allocentric	
7	ball	allocentric	7 -> 8
8	train	allocentric	
9	flower	allocentric	
10	house	allocentric	10 -> 11
11	mushroom	allocentric	11 -> 12
12	train	allocentric	12 -> 13
13	ball	allocentric	13 -> 14
14	house	allocentric	14 -> 15
15	ball	allocentric	

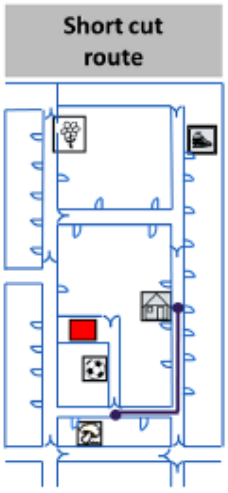


Fig. 1 Navigation paradigm in real space. All subjects performed a navigation paradigm in a complex and unfamiliar spatial environment to test their spatial orientation performance. The 700 m^2 area (20× 35 m), in which five items had been placed as target points, was shown to the subjects first on an investigator-guided walk (exploration, upper panel, left side). Afterwards subjects had to find the items in a pseudo-randomised order over the next 10 min (navigation, lower panel, left side). In the first part of the navigation paradigm, routes were tested, which were identical to the previous exploration route (the so-called egocentric routes, upper panel, middle); in the second part, the order of target items was changed in a way that required the planning of new routes (the so-called allocentric routes, upper panel, right side). Potential short cuts on the allocentric route-planning were registered (lower panel, right side). The sequence of items during exploration and navigation is depicted in a table and appears as numbers beside the target items in the figures. If subjects managed to find all 15 targets items betimes, the sequence started again with item number 1 and was continued as shown in the table until 10 min were over

$$\text{Distance} = \sqrt{(x_{t1} - x_{t2})^2 + (y_{t1} - y_{t2})^2},$$

where t_1 and t_2 refer to adjacent time points. Velocity was computed as distance/time, acceleration as (velocity_{t1}–velocity_{t2})/time. Saccades were classified above a velocity threshold of 240 °/s. The total number of saccades and the saccade frequency was computed. Saccades directed to objects that were feasible landmarks were defined as search saccades. Fixations were defined as events lasting longer than 100 ms at a velocity and acceleration cut-off of less than 240 °/s and 3000 °/s^2, respectively. The total number of fixations, fixation frequency, and duration were analysed quantitatively. Fixation on a potential landmark was termed a search fixation. x and y gaze magnitudes and direction corresponding to the peak saccadic velocities and median fixation periods were grouped into classes at 20° intervals and displayed as wind rose plots (direction and frequency of each class). The 20° direction intervals were coded in colour bands resembling the number of events in that particular direction and position combination. Search saccades and search fixations were defined as those directed ± 20° from the horizontal.

Positron emission tomography imaging

To investigate the age- and gender-related changes of navigation-induced cerebral glucose metabolism, 15 subjects (8 men) above 50 years of age were examined by [^{18}F]-fluorodeoxyglucose-PET ([^{18}F]-FDG-PET) during navigation following an established protocol [15]. Each subject was scanned while in a fasting state > 6 h (validated by means of blood glucose concentration). [^{18}F]-FDG was injected at the start of the 10 min navigation phase. This paradigm was chosen because the cerebral glucose utilisation is known to be weighted to the first 10 min following [^{18}F]-FDG injection and is integrative due to intracellular trapping of the tracer [16] (Supplementary Figure 1). Image acquisition started 30 min after tracer administration and emission was recorded in an ECAT EXACT HR$^+$ PET scanner (Siemens/CTI, Knoxville, TN, USA) from 30 to 60 min post injection. A transmission scan was obtained using a rotating [^{68}Ge] point-source. For further evaluation, images were reconstructed as 128 × 128 matrices of 2 × 2 mm voxels by filtered back-projection using a Hann filter with a cut-off frequency of 0.5 Nyquist and corrected for random, dead time, scatter, and attenuation. The reconstructed [^{18}F]-FDG images were then transformed to NIfTI format for further processing.

PET image analysis

Data processing and statistical analysis were performed using statistical parametric mapping software SPM8 implemented in MATLAB® 2012a as described previously [15]. All the reconstructed [^{18}F]-FDG brain PET images were linearly co-registered to the corresponding magnetic resonance image (MRI) using automated algorithms implemented in SPM8. Anatomical brain MRIs were spatially normalised into the Montreal Neurological Institute (MNI) standard template using an affine transformation, whose parameters were applied to the co-registered [^{18}F]-FDG-PET images. Then the spatially normalised images were blurred with a Gaussian filter (FWHM 12 mm) to adjust for anatomical inter-subject differences. The normalisation prior to voxel-based statistics was done with an anatomical mask (centrum semiovale) to remove the effects of the differences in the overall counts. Correlation analyses of regional cerebral glucose metabolism (rCGM) with the covariate age and subgroup comparison of rCGM in male versus female subjects were done in SPM8. Both glucose-metabolism increases and decreases were calculated and considered significant for a $p < 0.005$ uncorrected for multiple comparisons.

Statistical analysis

Behavioural and navigational measurements were analysed using SPSS® 24. Correlation analysis between age, navigation performance (error rates) and eye movement was conducted using Pearson's correlation, with a $p < 0.05$ considered significant. Furthermore, behavioural parameters during the navigation phase were compared in a group of younger (< 50 years) and older subjects (> 50 years) as well as male and female subjects using independent t-test or Kruskal–Wallis Chi-square test, respectively ($p < 0.05$ considered significant).

RESULTS

Spatial navigation performance and strategy of subjects across age and gender

The majority of participants performed considerably well in the real-space navigation task with 22 of 30 subjects having found all target items. Men trended to have lower total error rates (2.10 ± 6.89) compared to age-matched women (5.94 ± 7.76) ($t = 3.30$, $p = 0.069$). The percentage of short cuts taken was higher in men compared to women (62.96 ± 43.33 versus 36.90 ± 41.95; $t = 2.52$, $p = 0.112$) (Fig. 2a, b). Error rates increased only slightly with age: in the group of younger subjects below 50 years of age ($n = 16$) the total error rate was 3.02 ± 5.91 versus 4.88 ± 9.02 in the group of older subjects above this age ($n = 14$) ($t = 0.14$, $p = 0.708$). The same tendency was found during planning of egocentric routes (younger group 4.38 ± 13.15; older

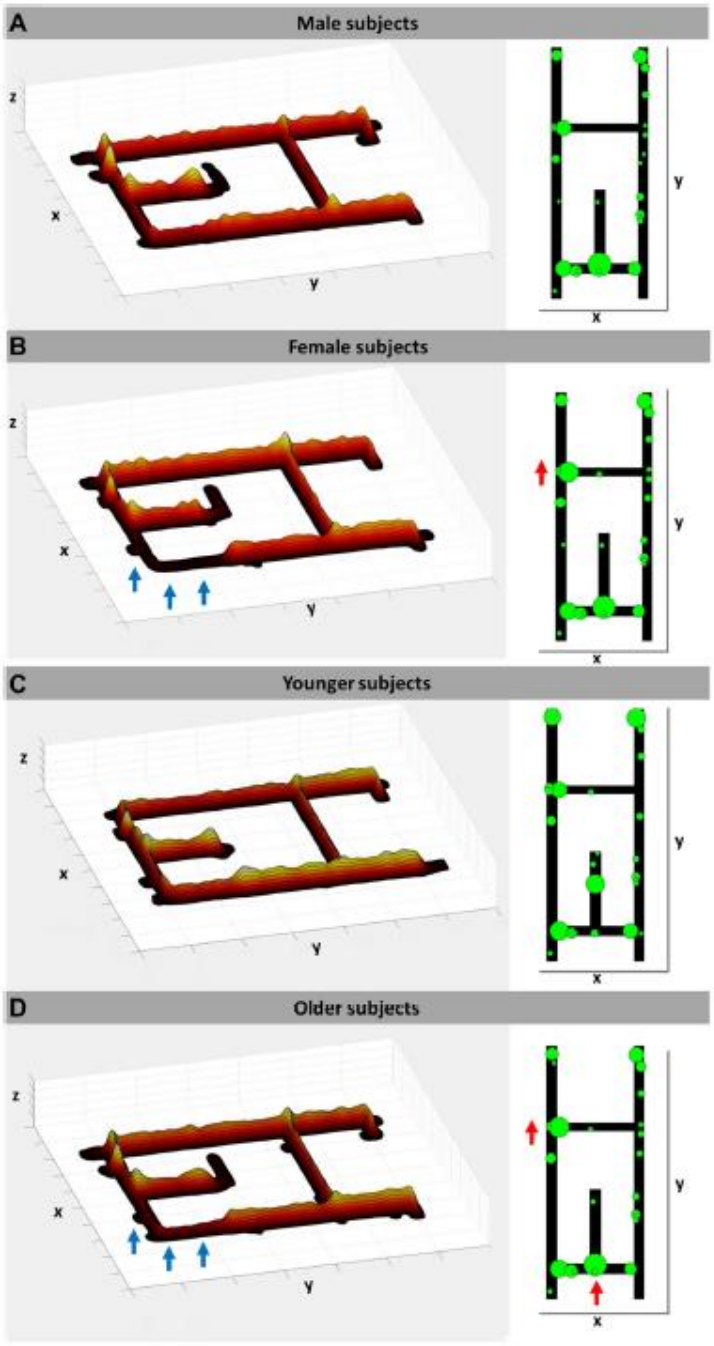


Fig. 2 Navigation strategy and visual exploration patterns in younger and older as well as male and female subjects. **a** Male subjects had a more allocentric navigation strategy and used short cuts more regularly. **b** Female subjects embedded short cuts less often in their navigation route (blue arrows) and had a tendency to explore strategic landmarks at way crossings more frequently (red arrow). **c** Younger controls showed a navigation strategy that included the use of short cuts, indicating the presence of a spatial cognitive map. Visual exploration was mainly directed to strategic landmarks (e.g. at crossings). **d** In contrast, older subjects used significantly less short cuts (blue arrows) and showed more frequent fixations of strategic landmarks (red arrows), indicating a more visually-guided navigation strategy. Search paths during navigation were colour-coded on a ground map (x, y) as cumulative time at location (z). Most frequent visual fixation targets were indicated as green circles on the ground map with diameter proportional to the cumulative time of fixation

group 8.21 ± 13.95; t = 1.15, p = 0.284) and allocentric routes (younger group 2.57 ± 7.60; older group 3.10 ± 6.22; t = 0.37, p = 0.543). A logistic regression analysis showed a significant increase of the normalized total error rate with age (r = 0.36, p = 0.05) (Fig. 3a), especially if only the eight subjects with errors were taken into account (r = 0.74, p = 0.006). Older subjects had a lower navigation efficiency: the mean total duration per item was significantly higher (46.8 ± 10.2 s) compared to younger subjects (40.4 ± 6.9 s) (t = 2.0, p = 0.05). Linear regression analysis showed a significant increase of total duration per item during aging (r = 0.46, p = 0.01) (Fig. 3b). This difference resulted from longer search duration during allocentric route planning (older subjects 47.52 ± 11.78; younger subjects 38.28 ± 6.19; t = 2.74, p = 0.11; r = 0.56, p = 0.001), whereas older subjects on average reached targets slightly faster on egocentric routes (40.89 ± 12.72 s) compared to younger participants (46.69 ± 51.38) (t = 0.41, p = 0.684). Younger subjects used short cuts more frequently (64.06 ± 39.17) compared to older subjects (35.65 ± 45.63) (t = 2.49, p = 0.114) (Fig. 2c, d). Linear regression analysis revealed a decrease of short cut use with age (r = 0.44, p = 0.015).

Visual exploration behaviour during navigation in younger and older subjects as well as male and female subjects

The visual exploration behaviour of older subjects profoundly differed from that of the younger controls. Quantitative analyses revealed a significantly higher total number of saccades during navigation (older group 2673.57 ± 1323.15; younger group 1906.06 ± 626.68;

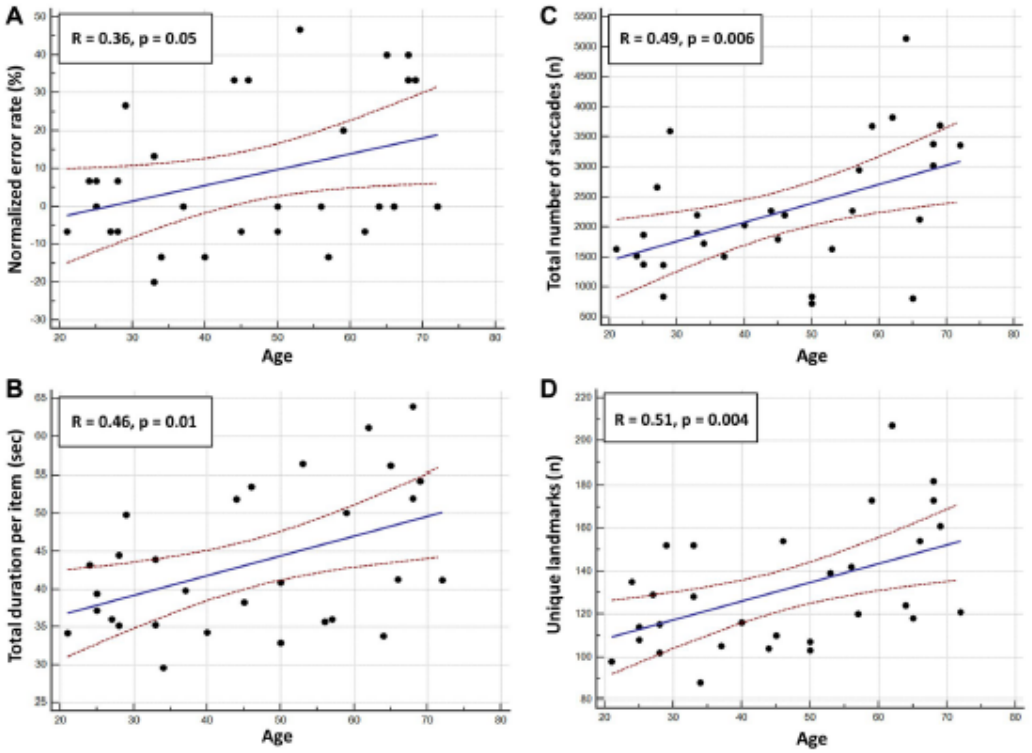


Fig. 3 Correlations of navigation performance and visual exploration patterns with age. **a** Normalized error rates increased slightly, but significantly ($r = 0.36$, $p < 0.05$) with age. **b** Older subjects needed a longer mean time to find an item ($r = 0.46$, $p = 0.01$). **c** The total number of saccades during navigation was higher in the elderly ($r = 0.49$, $p = 0.006$), indicating a more visually-guided strategy. **d** Use of unique landmarks was significantly more frequent in older subjects ($r = 0.51$, $p = 0.004$). The linear regression lines of the Pearson's correlation are depicted in blue and the 95% confidence intervals of the fit as red dashed lines. Error rates were normalized to 15 items. If more than 15 items were approached successfully, the additional number of items was calculated as negative values (outperformer). If less than 15 items were reached within 10 min, the outstanding targets were calculated as errors

t = 2.07, p = 0.047) and a higher total number of saccades per approached item (older group 197.70 ± 96.48; younger group 132.07 ± 56.80; t = 2.31, p = 0.029). Similarly, logistic regression analysis of the total number of saccades and saccades per item with age revealed significant correlations (r = 0.49, p = 0.006; r = 0.54, p = 0.002, respectively) (Table 1; Fig. 3c). Number of saccades per item significantly increased with age both during navigation on egocentric and allocentric routes (r = 0.51, p = 0.004 versus r = 0.61, p < 0.001). The total number of saccades increased during allocentric as compared to egocentric routes, both in younger subjects (allocentric routes 1196.25 ± 363.72; egocentric routes 536.88 ± 378.22; t = 5.03, p < 0.001) and older subjects (allocentric routes 1961.86 ± 1074.58; egocentric routes 703.36 ± 321.87; t = 4.2, p < 0.001). Older subjects used significantly more unique landmarks in total (older subjects 144.57 ± 31.30; younger subjects 119.38 ± 20.33; t = 2.61, p = 0.013; r = 0.51, p = 0.004) and per item (older subjects 11.08 ± 3.77; younger subjects 8.21 ± 2.13; t = 2.61, p = 0.014; r = 0.53, p = 0.003) (Fig. 3d). Use of unique landmarks was especially increased on allocentric routes (older subjects 126.36 ± 25.00; younger subjects 106.81 ± 22.15; t = 2.27, p = 0.031, r = 0.46, p = 0.01). Accordingly, the total number of search saccades increased with age (r = 0.36, p = 0.05) (Table 1). Position of eyes in space was focussed to the straight-ahead position in younger subjects, whereas older subjects had more diffuse eye movements along the horizontal (Fig. 4). Comparison of male versus female subjects revealed no significant difference in any of the recorded visual exploration parameters (Table 2).

Age- and gender-dependent cerebral glucose metabolism during navigation

Correlation analysis of rCGM with age in the older subjects indicated the following relative increases and decreases: rCGM decreased with age in the hippocampal formation bilaterally (right parahippocampal gyrus, BA 35; left

Table 1 Statistical comparison of visual exploration behaviour in younger and older subjects during navigation

	Younger subjects (n = 16)	Older subjects (n = 14)	Independent t test (p)
Total number of saccades	1906.06 ± 626.68	2673.57 ± 1323.15	**0.047**
Total number of fixations	1349.69 ± 150.79	1328.36 ± 272.02	0.789
Total number of search saccades	1039.25 ± 408.92	1288.64 ± 628.89	0.203
Total number of search fixations	693.56 ± 164.80	647.57 ± 239.34	0.541
Total saccades per item	132.07 ± 56.80	197.70 ± 96.48	**0.029**
Total fixations per item	92.23 ± 16.40	100.90 ± 29.97	0.326
Total egocentric saccades	536.88 ± 378.22	703.36 ± 321.87	0.208
Total egocentric fixations	380.25 ± 143.62	362.43 ± 135.95	0.731
Egocentric saccades per item	109.34 ± 75.55	174.73 ± 77.39	**0.027**
Egocentric fixations per item	77.06 ± 25.76	91.65 ± 34.97	0.200
Total allocentric saccades	1196.25 ± 363.72	1961.86 ± 1074.58	**0.012**
Total allocentric fixations	894.13 ± 143.33	960.07 ± 215.61	0.327
Allocentric saccades per item	124.15 ± 48.79	207.79 ± 111.07	**0.018**
Allocentric fixations per item	91.29 ± 16.40	104.84 ± 32.68	0.154
Total duration per item	40.39 ± 6.89	46.84 ± 10.2	**0.05**
Egocentric duration per item	46.69 ± 51.38	40.89 ± 12.72	0.684
Allocentric duration per item	38.28 ± 6.19	47.52 ± 11.78	**0.011**
Percentage duration at crossroads	20.50 ± 3.18	21.42 ± 3.08	0.428
Total landmarks	1644.44 ± 270.36	1657.93 ± 330.84	0.903
Unique landmarks	119.38 ± 20.33	144.57 ± 31.30	**0.013**
Total landmarks per item	113.48 ± 30.47	125.40 ± 34.73	0.325
Unique landmarks per item	8.21 ± 2.13	11.08 ± 3.77	**0.014**
Total allocentric landmarks	1210.88 ± 222.80	1227.00 ± 237.26	0.849
Unique allocentric landmarks	106.81 ± 22.15	126.36 ± 25.00	**0.031**

Visual exploration behaviour significantly changed with age. A higher number of total saccades, search saccades, saccades per item and unique landmarks indicated more visual dependency in the elderly. This was especially the case on allocentric navigation routes. Significant values in the independent t test are indicated in bold

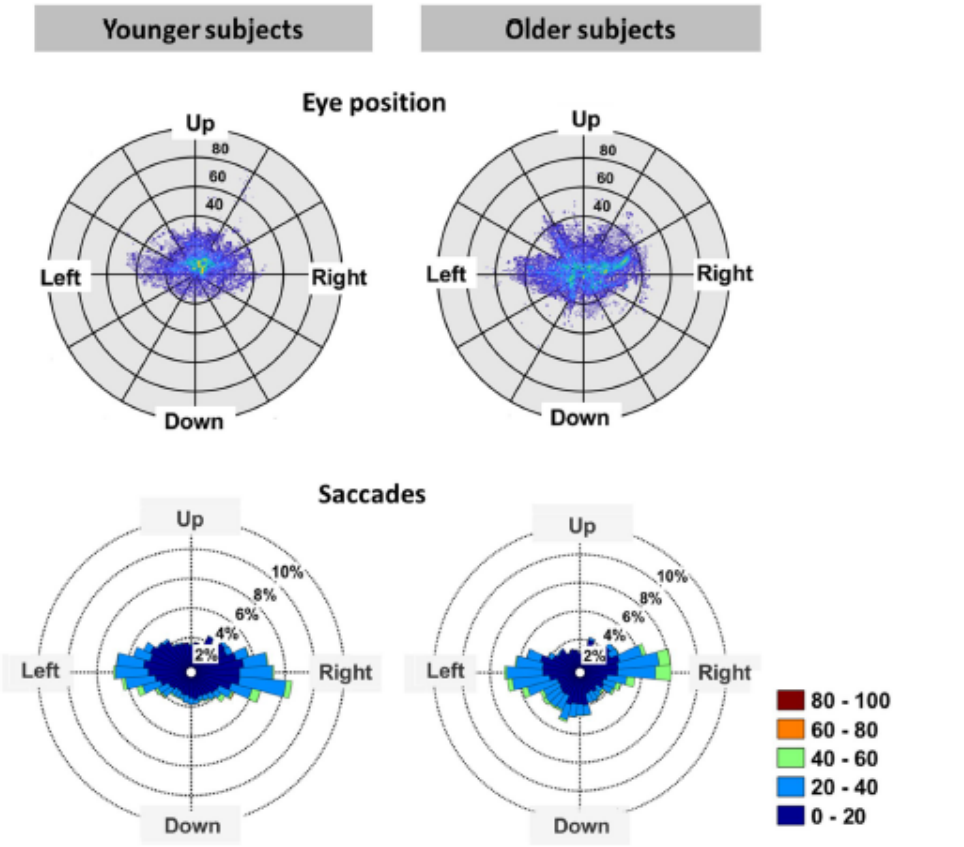


Fig. 4 Eye movements of younger and older subjects during navigation. **a** Younger subjects (left side) showed eye movements focused in the straight-ahead position, whereas older subjects (right side) had more diffuse eye movements, with the maxima aligned along the horizontal. **b** Saccadic eye movements in the younger group were mainly directed to a lateral position (left). Older subjects guided saccades alternately to the ground ahead and the lateral position (right). Exploratory saccades to the sides (>40°) were more frequent than in younger controls. Direction and frequency of saccades is presented as wind rose plots with the angle of respective saccades categorised by 20° intervals and coded in colours (see legend)

hippocampus), in the right precuneus (BA 31), in the left postcentral gyrus (BA 40) and in the left pontomedullary tegmentum ($p < 0.005$) (Fig. 5a). In contrast, rCGM increased during aging in the cerebellum (left posterior lobe, right anterior lobe), right putamen, left superior frontal gyrus (BA 10) and right medial frontal gyrus (BA 10) ($p < 0.005$) (Fig. 5b). Comparison of male versus female subjects revealed the following differences in rCGM patterns: women had more rCGM in the left hippocampal formation and in the right middle temporal gyrus (BA 21), men a higher rCGM in the superior cerebellar vermis during navigation ($p < 0.005$) (Fig. 5c, d).

Discussion

The major findings of this study were the following: (1) allocentric navigation strategies in real space deteriorated with age, but were successfully substituted by more egocentric navigation strategies. (2) Age-related behavioural changes were accompanied by a reduced rCGM in the hippocampus and the precuneus and an increased rCGM in the frontal lobe, basal ganglia and cerebellum. (3) Male subjects tended to prefer allocentric, female subjects egocentric navigation strategies. Variability of navigation strategy between subjects was considerable. (4) Women recruited more left hippocampal and right temporal areas

Table 2 Statistical comparison of visual exploration behaviour in male and female subjects during navigation

	Male subjects ($n=16$)	Female subjects ($n=14$)	Independent t test (p)
Total number of saccades	2149.19 ± 1187.76	2395.71 ± 937.82	0.537
Total number of fixations	1352.31 ± 258.97	1325.36 ± 150.63	0.735
Total number of search saccades	1044.25 ± 506.44	1282.93 ± 543.61	0.224
Total number of search fixations	657.31 ± 233.03	689.00 ± 163.10	0.674
Total saccades per item	143.20 ± 74.41	184.98 ± 90.07	0.175
Total fixations per item	93.07 ± 24.28	99.94 ± 23.32	0.438
Total egocentric saccades	534.00 ± 280.62	706.64 ± 420.23	0.191
Total egocentric fixations	358.06 ± 125.95	387.79 ± 153.79	0.565
Egocentric saccades per item	123.53 ± 68.77	158.52 ± 94.18	0.251
Egocentric fixations per item	83.52 ± 32.98	84.27 ± 29.24	0.948
Total allocentric saccades	1518.81 ± 981.28	1593.21 ± 727.88	0.818
Total allocentric fixations	949.44 ± 197.96	896.86 ± 160.89	0.436
Allocentric saccades per item	142.57 ± 83.06	186.73 ± 100.11	0.197
Allocentric fixations per item	93.09 ± 23.83	102.78 ± 27.84	0.313
Total duration per item	41.37 ± 9.64	45.73 ± 8.58	0.205
Egocentric duration per item	36.03 ± 12.60	53.08 ± 53.63	0.227
Allocentric duration per item	40.09 ± 9.66	45.45 ± 10.38	0.154
Percentage duration at crossroads	21.11 ± 2.58	20.72 ± 3.72	0.739
Total landmarks	1653.75 ± 323.75	1647.29 ± 270.06	0.953
Unique landmarks	129.31 ± 29.81	133.21 ± 28.06	0.716
Total landmarks per item	113.36 ± 27.94	125.54 ± 37.06	0.314
Unique landmarks per item	8.96 ± 2.87	10.23 ± 3.70	0.303
Total allocentric landmarks	1237.69 ± 236.87	1196.36 ± 219.08	0.625
Unique allocentric landmarks	116.25 ± 25.97	115.57 ± 25.14	0.943

There was no statistically significant difference in any of the recorded visual exploration parameter between male and female subjects

of the cerebral navigation network compared to men. (5) Visual exploration parameters like total number of saccades or search saccades were gender-independent and thus most feasible to reflect changes of navigation performance and strategy across age. Taken together, real-space navigation paradigms are practical to investigate physiology of cerebral navigation control and promising to discriminate age-related changes against spatial orientation pathologies, e.g. in patients with impending cognitive decline.

Age-dependent differences of real-space navigation performance and strategy

Aging has considerable impact on computation, consolidation and retrieval of spatial information [8]. Previous studies reported that spatial navigation abilities significantly declined with increasing age in the absence of neurodegenerative processes [7, 17–19]. Older subjects were less efficient in using cognitive map-like knowledge for route planning and showed a spontaneous preference for egocentric response strategies, which were well preserved [10, 20–23]. Switching navigational strategies was significantly impaired in the elderly, which might be a main issue for everyday navigational challenges [17, 22, 23]. The current study was in good accordance with these findings. Our real-space navigation paradigm combined egocentric routes, where the sequence of items was identical to the routes learned during the exploration phase, and allocentric routes, which required the planning of new routes, including the use of hitherto unknown short cuts. Older subjects showed a mild deterioration of overall navigation performance, reduced navigation efficiency and impaired allocentric navigation strategies. This was indicated by a reduced use of path optimization strategies via short cuts and an increase in dependence on visual landmarks. The total amount of saccades, as well as search saccades was a robust marker to quantify the age-related shift towards a more egocentric reference frame. These findings agreed with previous navigation experiments in virtual environments, which have provided convincing evidence that eye tracking datasets can give valuable information about

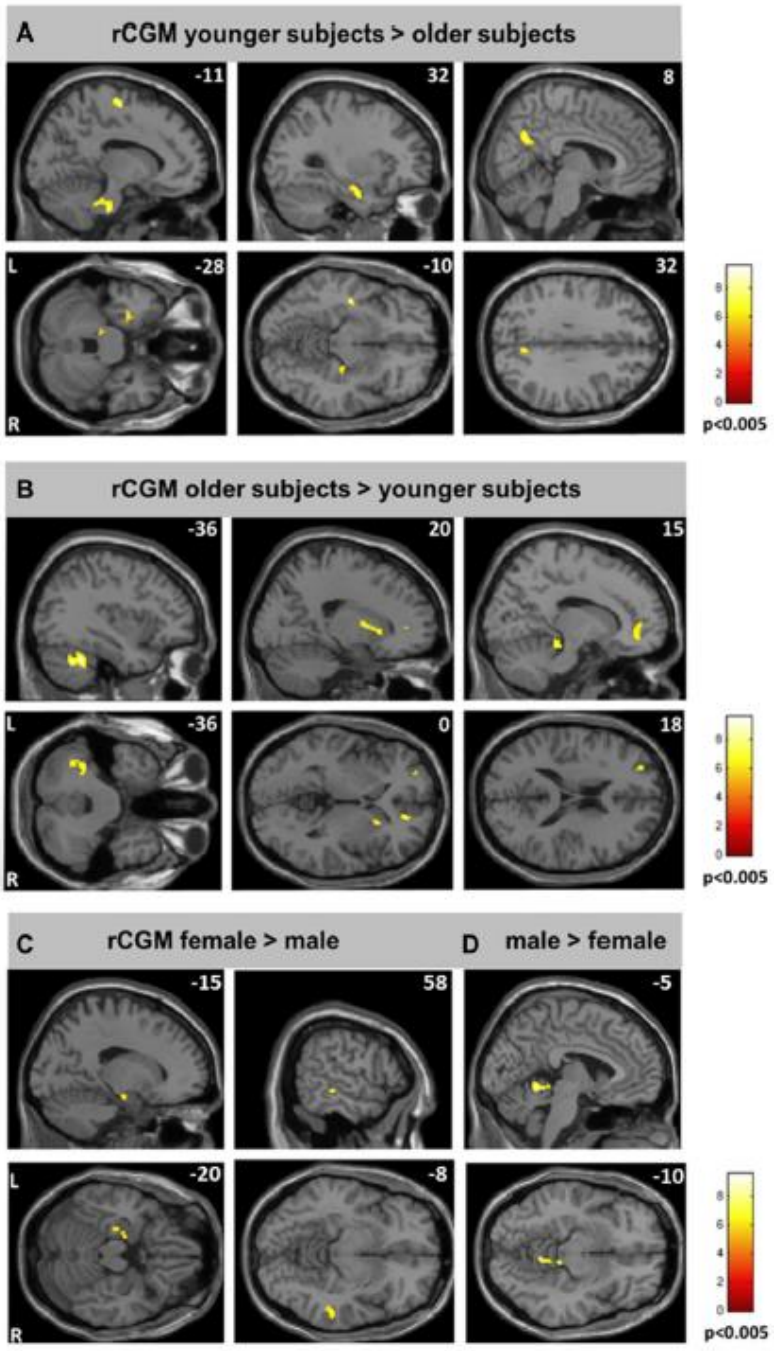


Fig. 5 Regional cerebral glucose metabolism (rCGM) during navigation in younger and older subjects as well as male and female subjects. **a** In younger subjects, rCGM during navigation was relatively increased in the left pontine tegmentum, bilateral anterior hippocampus and right precuneus as compared to older subjects. **b** Older subjects had relatively more navigation-induced activations in the left lateral cerebellum, right striatum, right mesial frontal and left superior frontal gyrus. **c** Female subjects had an increased navigation-induced rCGM in the left hippocampus and right middle temporal gyrus, male subjects in the superior vermis (**d**). Significance level $p < 0.005$, levels of sections in x- and z-direction are given by MNI coordinates

underlying navigational strategies and major deficits. Livingston-Lee et al. showed that heat maps of gaze position in normal subjects are strong indicators of orientation in allocentric environments, demonstrating that gaze is predominantly straight ahead and above the horizon [24].

Age-dependent patterns of cerebral glucose metabolism during real-space navigation

Previous imaging studies have shown that spatial navigation relies on a large network of brain regions involving the medial temporal lobe (hippocampus, parahippocampal, entorhinal cortex), parietal lobe (retrospinal cortex, precuneus), frontal lobe, as well as subcortical regions (basal ganglia, cerebellum) [2–4] Allocentric navigation strategies are represented predominantly by cell ensembles (place cells, grid cells) in the hippocampal formation [5, 25], whereas egocentric navigation control relies on visual landmark processing found in the parahippocampal and posterior parietal cortex [4]. The retrosplenial cortex and precuneus play a role for the integration of allo- and egocentric reference frames [26]. Age-related neural changes in critical hubs of the cerebral navigation network have been reported, including a decrease in hippocampal volume, change in hippocampal long-term potentiation, and instability of grid-cell representation in the entorhinal cortex [27–29]. Accordingly, older subjects in our study had relatively less navigation-induced rCGM in the hippocampal formation bilaterally and the precuneus. These patterns explain, why allocentric navigation strategies, which ultimately depend on a hippocampal cognitive map, decline with age and flexible shifting between allo- and egocentric navigation strategies, which relies on the integrity of retrosplenial cortex and particularly precuneus functions, are impeded in the elderly. Furthermore, older subjects had a reduced rCGM in the left pontine tegmentum in the area of the vestibular nucleus during navigation. Given that vestibular signals convey information about translation and rotation of the body, age-related changes of vestibular functioning could impair self-motion perception during navigation [8]. Reduced rCGM in the left postcentral gyrus may also reflect reduced somatosensory feedback during navigation in the elderly. On the other hand, older subjects showed a relative navigation-induced rCGM increase in the frontal cortex, basal ganglia and cerebellum. Frontal cortex involvement could reflect efforts being made for path planning, as this area is involved in anticipating novel routes and direction decisions at way crossings [30]. Basal ganglia have been linked to stimulus–response strategies of navigation [31]. Navigation-induced cerebellar activations could reflect sequence-based, non-allocentric navigation such as route learning [32, 33].

Real-space navigation in male and female subjects

Gender-dependent navigation strategies have been investigated mostly in virtual environments. A male advantage was reported for navigation tasks which require spatial cognitive map knowledge, like pointing to an unseen location in a known environment or orientating along compass directions in an unknown surrounding [9, 34]. In paradigms, which could be accomplished with route or landmark knowledge no significant sex difference were reported [35]. Visual exploration strategies in real space have not been systematically investigated in men and women. In the current study, overall navigation performance and navigation efficiency were not statistically different between male and female subjects. This finding could be explained by the fact that the navigation paradigm could be sufficiently solved by either ego- or allocentric navigation strategies. Indeed, analysis of navigation strategies revealed a more allocentric navigation strategy in male subjects. Men by trend used more short cuts, while women fixated strategic landmarks at way crossing longer (Fig. 2). However, none of the analysed visual exploration parameters like total saccades, search saccades, saccades per item, total fixations or total search fixations differed statistically between men and women (Table 2). Furthermore, the number of landmarks and their localisation in space were irrespective of gender (Fig. 2a, b). Sex-related differences in spatial navigation seem to be not triggered by landmark recognition per se but rather by alternative internal strategies of embedding landmarks into route planning.

Gender-dependent cerebral glucose metabolism patterns during real-space navigation

Previous studies in virtual environments have reported partially contradictive results about gender differences in navigation-induced brain activations: Grön and colleagues found an increased activation of the left hippocampus in men and the right parietal and prefrontal cortex in women during mental navigation in a complex three-dimensional virtual-reality maze [36]. Another group showed a relatively increased activation of the right hippocampus during navigation in a virtual maze in men and of the left hippocampus during a direction pointing task in space in women [37]. These differences were explained by alternative demands of the respective navigation paradigms. In our study, women had an increased glucose metabolism in the left hippocampal formation and right middle temporal gyrus compared to men during navigation (Fig. 5). This finding could be interpreted as a recruitment of additional hubs of the cerebral navigation network in women during navigation in a large-scale real environment, which required planning of previously unfamiliar routes. The relatively increased rCGM of the

superior vermis in men is likely a correlate of a slightly higher locomotion velocity of male versus female subjects, as this region is known as a cerebellar pacemaker during locomotion [38].

Navigation testing in real space: which parameters are suitable and which problematic to reflect performance differences across subjects?

Testing of navigation performance and strategy has not yet reached clinical practice, although there is a consensus that it may have great potential, e.g. for the early detection of impending cognitive decline. One major challenge is to define parameters, which can be recorded easily and are sensitive to indicate relevant changes of navigation performance and strategy despite a high physiological variability of navigation strategies across healthy men and women. In the current study, the following parameters fulfilled these criteria: (1) normalized error rate for finding items (number of items found/number of items approached). While there was no difference between men and women, age-related decline of navigation performance could be documented based on this parameter. (2) Total mean duration per item. This parameter was sensitive to age-related deterioration of navigation efficiency, but sex-independent. (3) Total number of saccades and saccades per item. These parameters are easy to detect with modern eye tracking technology, independent of gender and robust to document overall changes of visual exploration behaviour during navigation across age. Other parameters, like the number of short cuts or the number of landmarks, may suffer from either a high variability across subjects of both gender or from the major disadvantages, that their recording is quite difficult and less standardised thus making them less appropriate to test navigation performance.

Limitations of the current study

A limitation of the current study is the relatively small number of subjects tested, which allows depicting statistically significant differences of navigation performance only as a function of age. Possibly gender differences would be more pronounced in a larger sample. In the PET study, subgroups were even smaller due to regulations for radiation protection. Significant results could only be found for uncorrected data. The minimum age limit for inclusion allowed comparing PET data only across an age range of 50–78 years.

Navigation testing in real space versus virtual environments: future perspectives

There is no consensus about a mode of testing navigation performance and strategies in a clinical context. The major challenges for any experimental approaches are (1) to deal with the high natural variability of navigation strategies across subjects, (2) to be applicable to clinical conditions by use of a widely available technique, and (3) to result in distinct parameters which can be measured quantitatively and can reliably reflect navigation performance. Basically, test paradigms can either be designed in virtual environments or performed in real space. Navigation tests in virtual reality allow a high degree of standardization and modification and are more practical with the spread of commercially available hard- and software setups. However, concerns have been raised that virtual reality paradigms may test only specific aspects of navigation (e.g. visually-guided navigation) and neglect others (e.g. navigation by path integration due to multisensory processing and continuous updating). Furthermore, easily measureable readout parameters for navigation performance are not yet defined.

On the other hand, navigation paradigms in real space are more comparable to everyday conditions and include processes of motor planning, sensory feedback and central multisensory integration. Larger environmental spaces are needed and it remains unclear how navigation performance and strategy can be quantified across different environments. Based on the current study, we suggest that recording of visual exploration behaviour (especially saccades) is a feasible method to quantify navigation abilities. This approach can take advantage of commercially available eye tracking systems and can be adapted to different spatial environments. In our experience, testing can be reliably done in spaces like outpatient units or hospital hallways, even in parallel to clinical routine business. Further studies are urgently needed, which compare real versus virtual space paradigms directly as concerns practical clinical use.

Conclusions

Taken together, our study established real-space navigation as an alternative approach to test navigation and defined normative values for navigation abilities and strategies in healthy subjects across age and gender. Analysis of exploratory saccadic eye movements during navigation was shown to be a gender-independent, accurate and robust measure of the individual navigation strategy. The current data confirmed an age-related shift towards egocentric navigation strategies with significantly more total saccades and search saccades during navigation. Recording of regional cerebral glucose metabolism during real space navigation indicated a decline of right hippocampal function in the elderly and an additional recruitment of the left hippocampal formation in women. Together, these findings lay the foundation for future studies, aiming to further explore pathological

changes of navigational functions in real space and identify distinctive biomarkers, e.g. in the early diagnosis of impending cognitive decline.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All experiments were done in accordance with ethical standards of the Declaration of Helsinki.

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ARTICLE

Prolonged allocentric navigation deficits indicate hippocampal damage in TGA

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Abstract

Objective

To investigate long-term recovery of allocentric and egocentric spatial orientation as a sensitive marker for hippocampal and extrahippocampal network function in transient global amnesia (TGA).

Methods

A group of 18 patients with TGA performed an established real-space navigation paradigm, requiring allo- and egocentric spatial orientation abilities, 3 days (postacute stage) and 3 months (follow-up) after symptom onset. Visual exploration behavior and navigation strategy were documented by a gaze-controlled, head-fixed camera. Allo- and egocentric spatial orientation performance was compared to that of 12 age-matched healthy controls. Navigation-induced brain activations were measured using [^{18}F]-fluorodeoxyglucose-PET in a subgroup of 8 patients in the postacute stage and compared to those of the controls.

Results

In the postacute stage, the patients navigated worse and had higher error rates than controls in allocentric ($p = 0.002$), but not in egocentric, route planning ($p = 0.30$), despite complete recovery of verbal ($p = 0.58$) and figural memory ($p = 0.11$). Until follow-up, allocentric navigation deficits improved, but higher error rates and reduced use of shortcuts persisted ($p < 0.0001$). Patients still exhibited relatively more fixations of unique landmarks during follow-up ($p = 0.05$). PET measurements during the postacute stage showed increased navigation-induced brain activations in the right hippocampus, bilateral retrosplenial, parietal, and mesiofrontal cortices, and cerebellar dentate nucleus in patients compared to controls ($p < 0.005$).

Conclusions

Patients with TGA show selective and prolonged deficits of allocentric spatial orientation. Activations in right hippocampal and extrahippocampal hubs of the cerebral navigation network functionally substitute for the deficit in creating and updating the internal cognitive map in TGA.

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Glossary

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; **DWI** = diffusion-weighted imaging; **[^{18}F]-FDG** = [^{18}F]-fluorodeoxyglucose; **HC** = healthy control; **TGA** = transient global amnesia.

Transient global amnesia (TGA) is typically characterized by temporary antero- and retrograde amnesia and spatial disorientation of sudden onset, without any other neurologic signs or symptoms.[1–6] While verbal and figural memory functions resolve completely, more detailed assessments detect subtle long-term, persistent deficits in episodic memory.[7] Neuropsychological and imaging studies suggest that the hippocampus, especially the CA1 region, is predominantly involved in the pathophysiology of TGA.[5,8] Recently, detailed analyses of fractional anisotropy and diffusivity indicated long-term microstructural hippocampal damage in TGA.[9] Functional imaging studies have yielded contradictory results with some reporting hyper- and other hypofunction in the hippocampal formation.[10,11] Given these controversies, in the current study, we aimed to analyze spatial orientation performance as a marker of hippocampal function in patients with TGA over time. A new multimodal quantitative analysis of search path, visual exploration behavior, and navigation-induced brain activation was used during a real-space navigation paradigm. The major questions were as follows:

1. Do spatial orientation and memory deficits in patients with TGA persist over time? Which clinical cofactors influence the extent and time course of these deficits?
2. Is there a dissociation of allocentric (i.e., hippocampus-mediated) and egocentric (i.e., extrahippocampal) navigation performance?
3. Which cerebral circuits and hubs are recruited in the postacute stage of TGA during a real-space navigation paradigm?

Overall, we aimed to further harden the view that TGA is a disorder with long-term hippocampal dysfunction, which can be detected only by specific and demanding hippocampal testing, for example, with orientation in real space.

Methods

Participants

Eighteen patients (aged 64.7 ± 8.3 years, 11 men), who fulfilled the diagnostic criteria for TGA proposed by Hodges and Warlow,[12] and 12 age-matched healthy controls (HCs) (aged 63.7 ± 5.2 years, 6 men) were included in the study. Relevant neurologic comorbidities affecting sensory or cognitive functions (i.e., dementia and psychiatric disease, use of sedative medication) were ruled out by neurologic and neuropsychological assessment (data available from Dryad, table e-1, doi.org/10.5061/dryad.s07ch56). All patients with TGA underwent a standardized diagnostic workup including MRI and EEG.

Standard protocol approvals and patient consents

All participants gave their informed written consent to participate in the study. The protocol was approved by the ethics committee of the Ludwig Maximilians University, Munich, in accordance with the Declaration of Helsinki and by the German Federal Office for Radiation Protection.

Study protocol

The patients with TGA performed a real-space navigation task on 2 occasions: first, within 2 to 3 days (median 54 hours, range 48–72 hours) after symptom onset (postacute stage), and second, 3 to 4 months later (median 98 days, range 82–132 days) (follow-up). The postacute stage (>24 hours from symptom onset) was chosen for the following reasons: working and short-term memory problems had resolved by that time, allowing detection of selective impairments of spatial memory and navigation without overlay. Furthermore, the complex testing paradigm (including PET imaging on fasting conditions) could not be performed ad hoc. At the postacute stage, all patients underwent a standardized neuropsychological assessment. A subgroup of 8 patients were subjected to PET imaging at the postacute stage to depict navigation-induced brain activations and compared to a sample of 12 age-matched HCs.

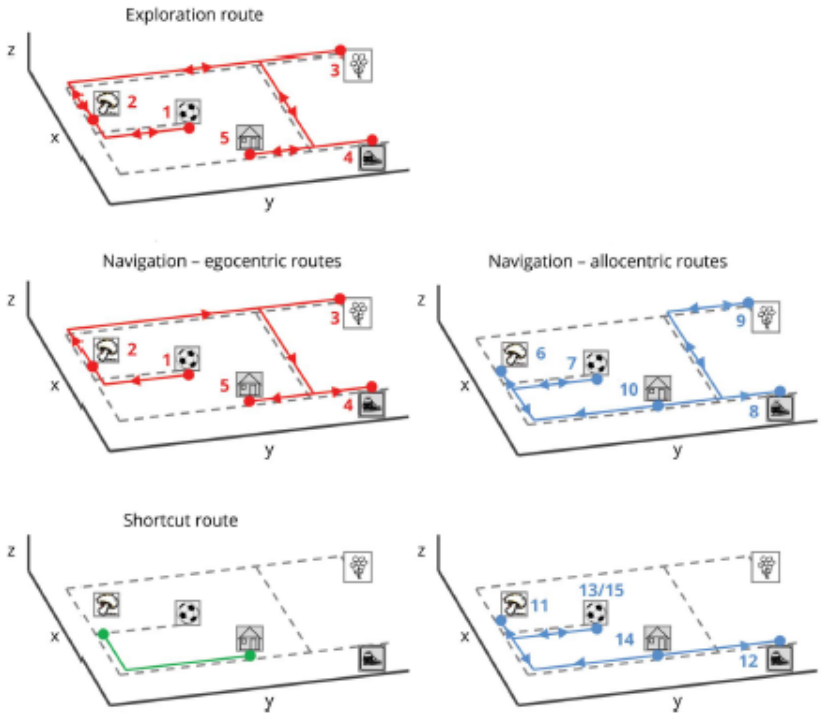
Neuropsychological testing

Cognitive function was tested in all participants in the postacute stage by using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-Plus test, including subtests for attention, psychomotor speed and flexibility, executive functioning, and memory.[13] The absolute values for the following subtests were included on a group level: word-list learning (immediate, delayed recall and discrimination), figural learning (delayed recall), and the Trail Making Test Part B; they were considered parameters for verbal learning, nonverbal learning, and executive functions. Depression was excluded by the Beck's Depression Inventory in both groups.

Spatial orientation paradigms

All participants performed a well-established navigation paradigm in a complex unfamiliar spatial environment to test their spatial orientation performance.[14] The area, in which 5 target items had been placed, was shown to the participants first during an investigator-guided walk (exploration). Afterward, participants had to find 15 target items in a pseudorandomized order (navigation).[15] In the first part of the navigation paradigm, routes that were similar to the previous exploration route were tested; in the second part, the order of target items was changed (figure 1). Clear spatial clues were covered. Based on current concepts from the literature, routes

Figure 1 Navigation paradigm in real space



First row: exploration route with a defined sequence of items. Second row, left: in the first part of the navigation paradigm, routes were tested, which were identical to the previous exploration route (egocentric routes). Second and third row, right: in the second part, the order of target items was changed in a way that required the planning of novel routes (allocentric routes). Third row, left: potential shortcuts within the allocentric route were recorded. The sequence of the target items during exploration and navigation appears as corresponding numbers beside the target items in the figures.

were categorized as "egocentric" and "allocentric" according to 2 criteria[16]: (1) whether the exact sequence of 2 consecutive target items had been explored before and (2) whether route planning to a target item allowed novel path optimization strategies. Specifically, the routes to the first 5 target items were termed egocentric because the sequence resembled exploration and way optimization was not applicable (figure 1). In contrast, the remaining routes were classified as allocentric because participants had to plan novel routes potentially including shortcuts. For this purpose, a cognitive map of the environment was required to improve the optimality of the search path (figure 1). Each participant had to recall the 5 target items after the exploration and navigation phases in order to exclude the possibility of verbal memory dysfunction.

Recording of navigational path and visual exploration behavior

To document their visual exploration and head position, participants wore a gaze-monitoring head camera throughout the experiment (for the method in detail, see references 14, 15, and 17). Post hoc analysis of the recorded videos revealed the error rate for finding items during navigation. Error rates were further separated for ego- and allocentric route planning to depict specific deficits of both navigational strategies. The search path during the navigation task was mapped by cumulating time at a specific place and analyzed quantitatively (e.g., usage of shortcuts and time spent at way crossings). Video recordings were used to categorize all fixation targets as fixed objects in space, mobile objects, or unspecific fixations (e.g., the ground, wall).

The orientation of eye-in-head and head during the navigation task was plotted as cumulative "heat maps." Analysis based on a previously reported algorithm was performed with MATLAB 2012a software (MathWorks, Natick, MA).[18] Eye movements were displayed as heat maps on the x and y axes. The cumulative distance of eye movement was calculated by

$$\text{Distance} = \sqrt{(x_{t1} - x_{t2})^2 + (y_{t1} - y_{t2})^2}$$

where t1 and t2 represent consecutive time points. Eye velocity (distance/time) and acceleration ($[\text{velocity}_{t1} - \text{velocity}_{t2}]$/time) were computed. Saccades were automatically

detected on the basis of thresholds for velocity (>240°/s), acceleration (>3,000°/s^2), and duration (<100 milliseconds). Fixations were considered to last longer than 100 milliseconds (velocity and acceleration below above-named thresholds).[14,15] To analyze the basic visual exploration behavior, the following parameters were determined: first, the total number of saccades, saccade frequency, and the overall visual fixations were investigated; second, saccades and visual fixations during egocentric and allocentric routes (i.e., egocentric saccades and fixations as well as allocentric saccades and fixations) were calculated. Based on previous literature, fixations directed to objects feasible as visual cues were defined as landmarks, and the visual objects that were fixated more than once were defined as unique landmarks.[19] Finally, the ratio of unique allocentric landmarks to overall allocentric saccades was calculated in order to estimate the reliance on visual cues as exactly as possible.

The total number of fixations, fixation frequency, and duration were analyzed quantitatively. The x and y magnitudes and directions of gaze shifts were depicted as wind rose plots.[14] The 20° direction intervals were color-coded with the length/thickness of the color bands resembling the number of events in that particular combination of direction and position.

The traveled routes during the navigation paradigm were visualized for both the TGA group in the postacute and follow-up stages and the control group by 3-dimensional plots (so-called navigograms). The landmark fixations during the navigation task were plotted to the ground map of the environment, in which the navigation paradigm took place.

Magnetic resonance imaging

All patients with TGA underwent an MRI in the postacute stage within 24 to 72 hours after the TGA episode. The following sequences were included: whole-brain T1, T2, fluid-attenuated inversion recovery, T2*, diffusion-weighted imaging (DWI), 3-dimensional fluid-attenuated inversion recovery, and DWI temporal lobe fine-slice sequences (3 mm). DWI lesions were plotted on a 3-dimensional hippocampal template to indicate the exact localization of the lesions within the hippocampus. Furthermore, the lesion size was calculated on the axial and coronal DWI slices in square millimeters. The anterior-posterior distribution of lesions was indicated as distance from the anterior commissure.

PET imaging

To investigate the navigation-induced cerebral activation patterns, a subgroup of 8 patients with TGA were examined by using [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG)-PET in the postacute stage (for method, see references 14 and 15). [^{18}F]-FDG was injected at the beginning of the 10-minute navigation phase and images were acquired 30 minutes later. Because more than 90% of [^{18}F]-FDG is trapped in neurons within 10 minutes after injection, this protocol is suitable to depict navigation-induced cerebral activations.[14,20,21] Emission recording was done from 30 to 60 minutes postinjection in 3 frames, followed by a transmission scan using a rotating [^{68}Ge] point source. Images were reconstructed (128 × 128 matrices, 2 × 2 mm voxels) and transformed to NIfTI (Neuroimaging Informatics Technology Initiative) format for further processing.[22]

PET image analysis

The reconstructed [^{18}F]-FDG-PET data were linearly coregistered to the corresponding MRI using automated algorithms in SPM8. As described earlier, brain MRIs were spatially normalized into the MNI standard template (McGill University, Montreal, Canada) using an affine transformation, whose parameters were applied to the coregistered [^{18}F]-FDG-PET images.[22] Signal to noise ratio was increased by blurring the normalized images with a gaussian filter (full width at half maximum >12 mm).[14] Images of the patients with TGA were compared with those of a group of 12 age-matched HCs in a voxel-wise manner. Increases and decreases of glucose metabolism were considered significant for a p value <0.005.

Statistical analysis

The statistical analysis of patient data was performed with SPSS version 20 (IBM Corp., Armonk, NY). As appropriate, an unpaired t test was applied for parametric data, the X^2 test for nonparametric data, and analysis of variance for repeated measures. Bonferroni and Šidák methods were used for post hoc corrections. Significance was set at $p < 0.05$. Nonparametric testing with Spearman ρ was used for correlation analysis and interpreted as significant if more than ±0.5 and $p < 0.05$, respectively.

Data availability

Data reported in this article will be shared with any appropriately qualified investigator on request after pseudonymization.

Results

Neuropsychological assessment of patients with TGA in the postacute stage

In the acute stage, all patients had clinically severe problems in working and short-term memory. In the postacute stage (i.e., 2–3 days after symptom onset) patients with TGA performed equally well as HCs in the following subtests of the CERAD-Plus battery: the Mini-Mental State Examination ($p = 0.82$), the Trail Making Test Part B ($p = 0.33$), the immediate ($p = 0.52$) and delayed verbal memory recall ($p = 0.58$), the word recognition/discrimination ($p = 0.91$), and figural learning ($p = 0.11$) subtest (table 1). Normalization of verbal and nonverbal learning as well as executive function therefore was in accordance with the diagnostic criteria for TGA.

Spatial orientation performance of patients with TGA (postacute stage and follow-up) compared to HCs

Despite restoration of verbal memory, patients with TGA performed worse on the applied real-space navigation task,

Table 1 Clinical characteristics and neuropsychological test results for patients with TGA and HCs

Category	HCs	Patients with TGA, postacute	Unpaired *t* test, *p* values
Age, y	63.7 ± 5.2	64.7 ± 8.3	0.90
Sex, M/F, n	5/5	11/7	0.59
Years of education	11.5 ± 2.5	11.8 ± 3.0	0.68
BDI score	5.9 ± 0.7	5.8 ± 1.0	0.74
MMSE	29.3 ± 0.8	29.2 ± 0.9	0.82
TMT-B	103.9 ± 16.5	94.8 ± 26.0	0.33
Word list learning	5.9 ± 1.6	5.6 ± 1.2	0.52
Word list delayed recall	7.8 ± 1.2	7.4 ± 1.8	0.58
Word list discrimination	19.6 ± 0.7	19.6 ± 1.0	0.91
Figural learning	9.7 ± 2.6	11.2 ± 2.1	0.11

Abbreviations: BDI = Beck's Depression Inventory; HC = healthy control; MMSE = Mini-Mental State Examination; TGA = transient global amnesia; TMT-B = Trail Making Test Part B.
Data represent mean ± SD unless otherwise indicated. Both groups were matched for age, sex, and years of education. There were no significant differences between HCs and patients with TGA in the postacute stage in any subtest of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease)-Plus test battery.

both in the postacute stage and during follow-up 3 to 4 months later: total error rates on finding target items were higher than in HCs (postacute stage: 22.0% ± 19.9%; follow-up: 15.4% ± 18.3%; HCs: 2.4% ± 5.9%; $X^2 = 7.9$; $p = 0.02$) (figure 2). Post hoc analysis revealed a clear difference in error rates of patients with TGA and HCs in the postacute stage ($p = 0.005$) and a clear tendency toward a persistently inferior performance of the patients with TGA during follow-up ($p = 0.062$). The separate analysis of navigation performance on egocentric and allocentric routes (figure 1) showed an isolated allocentric spatial orientation deficit in the patients with TGA (egocentric routes: $X^2 = 2.4$, $p = 0.30$; allocentric routes: $X^2 = 10.5$, $p = 0.005$) (figure 2). Specifically, patients with TGA had higher error rates for allocentric route learning in the postacute stage compared to HCs (TGA: 24.8% ± 19.6%; HCs: 1.4% ± 4.5%; $p = 0.002$). Although it improved slightly in the follow-up (TGA: 15.4% ± 20.9%), it was still worse than that of HCs ($p = 0.074$) (figure 2). Ten of 18 patients with TGA reported subjective impairments in new spatial environments at follow-up. Some patients recognized a shift in their navigational strategy toward a more landmark-based approach. Considerable impairments in activities of daily life were not described.

Visual exploration behavior during spatial orientation of patients with TGA and HCs

Quantitative analyses of basic visual exploration parameters during the entire navigation paradigm such as total visual fixations ($F = 0.21$; $p = 0.81$), total saccades ($F = 1.49$; $p = 0.24$), and total fixations of possible landmarks ($F = 0.083$; $p = 0.92$) did not differ between the TGA group in the postacute and follow-up stages compared to HCs (table 2), although qualitatively, patients with TGA showed more lateral saccades (data available from Dryad, figure e-1, doi.org/10.5061/dryad.s07ch56). The amount of overall visual fixations and saccades during the egocentric and allocentric parts of the navigation paradigm was comparable between patients with TGA and HCs (table 2). However, more dedicated analyses revealed that patients with TGA had more fixations to unique landmarks during allocentric navigation routes compared to HCs ($F = 3.2$; $p = 0.05$), indicating visual cueing. The ratio of unique landmark fixations to the total number of saccades showed there was a difference between the TGA group in the postacute and follow-up stages and HCs ($F = 4.2$; $p = 0.023$) (table 2). Post hoc Šidák test showed an effect for TGA postacute vs HCs ($p = 0.022$) and a tendency for TGA during the follow-up vs HCs ($p = 0.08$).

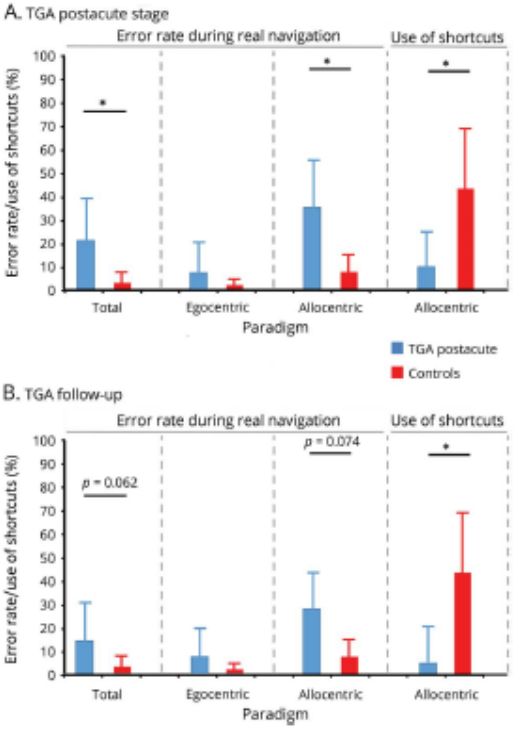
Search path during navigation of patients with TGA (postacute stage and follow-up) and HCs

The analyses of the search path during the real-space navigation paradigm showed remarkable differences between the TGA group and the HCs: the patients with TGA used shortcuts to a lesser extent in the postacute stage ($X^2 = 14.4$; $p = 0.0001$) as well as during follow-up ($X^2 = 17.3$; $p < 0.0001$) (table 2, figure 3). Furthermore, patients with TGA spent relatively more time at crossroads and unexplored routes. However, these effects were not significant (table 2).

DWI results for the patients with TGA

DWI lesions were found in 11 of 18 patients with TGA in the postacute stage. Altogether, 16 punctuate DWI lesions were found in the TGA group; 15 of these lay in the lateral parts of the hippocampus and only one lesion lay in the adjacent parahippocampal gyrus (figure 4). Seven patients with TGA had a single DWI lesion: 3 in the left and 3 in the right hippocampus, and one in the right parahippocampal gyrus. Three patients exhibited bilateral hippocampal lesions and one patient had 3

Figure 2 Performance during the real-space navigation task by patients with TGA (postacute stage, follow-up) and HCs



Error rates are depicted as % (number of target items not found/total number of target items). Shortcut rate is plotted as % (number of shortcuts used/number of potential shortcuts). Significant values ($p < 0.05$) are depicted with an asterisk. (A) The total error rate during the navigation paradigm was higher in patients with TGA during the postacute stage compared to HCs ($p < 0.005$). Error rates during egocentric routes did not differ between groups, while error rates during allocentric routes were increased for the patients with TGA in the postacute stage ($p = 0.002$). The patients with TGA used fewer shortcuts during allocentric routes ($p = 0.0001$). (B) Total error rates by tendency were still higher for patients with TGA during follow-up compared to HCs. Again during egocentric routes, error rate was similar to that of HCs; during allocentric routes, error rate showed a tendency to be higher for TGA. Patients with TGA used fewer shortcuts during follow-up ($p < 0.0001$). HC = healthy control; TGA = transient global amnesia.

distinct DWI lesions within the right hippocampus. The mean lesion size was 6.0 ± 2.1 mm^2 (range: 3.1–9.4 mm^2). Lesions were distributed within the hippocampus along an anterior-posterior axis (figure 4). An analysis of the hippocampal lesion localizations showed they selectively corresponded to the hippocampal cornu ammonis (CA1 sector).

Navigation-induced cerebral glucose metabolism in patients with TGA during the postacute stage compared to HCs

A subgroup of 8 patients with TGA underwent [^{18}F]-FDG-PET during the navigation task in the postacute stage. Direct comparison with an age-matched group of HCs (see reference 15) revealed the following differences in regional cerebral glucose metabolism during real-space navigation: patients with TGA showed an increased regional cerebral glucose metabolism in the right anterior hippocampus, bilateral retrosplenial, parietal, and mesiofrontal cortices, and cerebellar dentate nucleus compared to HCs ($p < 0.005$) (figure 5), while HCs only showed more activation in motion-sensitive visual areas ($p < 0.005$) (data not shown).

Correlation analyses of navigation performance with cofactors in the TGA group

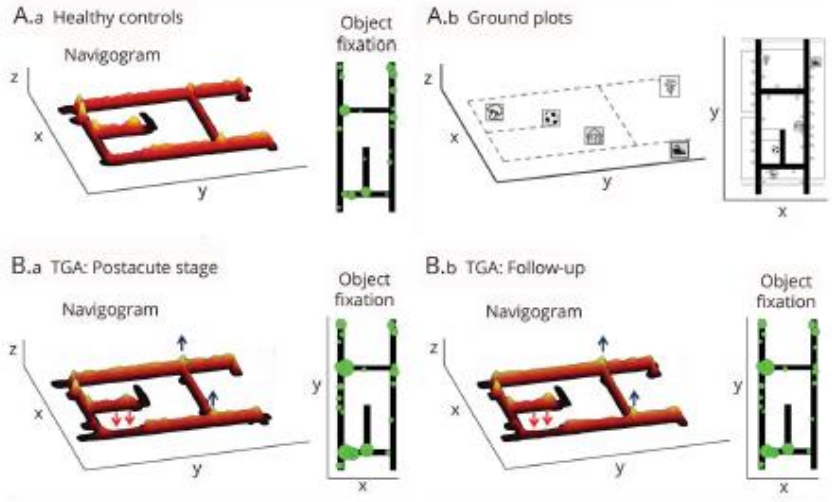
Lesion size and distance of the lesion from the anterior commissure did not correlate with navigation deficits (lesion size: $\rho = 0.16$, $p = 0.54$; lesion distribution: $\rho = 0.068$, $p = 0.84$). Duration of the TGA episode correlated with the navigation deficits ($\rho = 0.86$, $p < 0.0001$) (data available from Dryad, figure e-2, doi.org/10.5061/dryad.s07ch56). Correlation of navigation deficits with age was not significant, although there was a tendency for performance to worsen with increasing age.

Discussion

TGA is frequently thought to be a transient condition caused by hippocampal dysfunction. In the current study, we used sequential quantitative spatial orientation and visual exploration testing as a sensitive and reliable marker of hippocampal function, to document potentially more persistent spatial memory deficits in this disorder. The major findings were the following: (1) allocentric, i.e., hippocampus-dependent, but not egocentric real-space navigation abilities were critically impaired in patients with TGA in the postacute phase despite normalized verbal and figural memory; (2) allocentric navigation deficits persisted for months after the TGA episode; (3) patients with TGA remained more dependent on visual cues over time than HCs; (4) persistence of allocentric navigation deficits depended on the duration of the patient's TGA; and (5) brain activations during real-space navigation in the postacute stage showed recruitment of extrahippocampal hubs of the human spatial navigation network. Altogether, the current study clearly demonstrated persistent spatial orientation deficits as an indicator for hippocampal dysfunction in TGA.

Investigations of spatial orientation and memory in TGA over time are largely nonexistent. Only one previous study showed spatial navigation deficits in the virtual variant of the Morris water maze task during the very acute stage of TGA (<24 hours); these deficits recovered completely after 2 weeks.[5] In contrast, we found prolonged deficits of allocentric real-space orientation in the absence of verbal and figural memory problems. This discrepancy may be explained by different sensitivities of the experimental paradigms (virtual vs real navigation) to detect allocentric navigation impairment.[23] Deficits in allocentric navigation of our patients with TGA

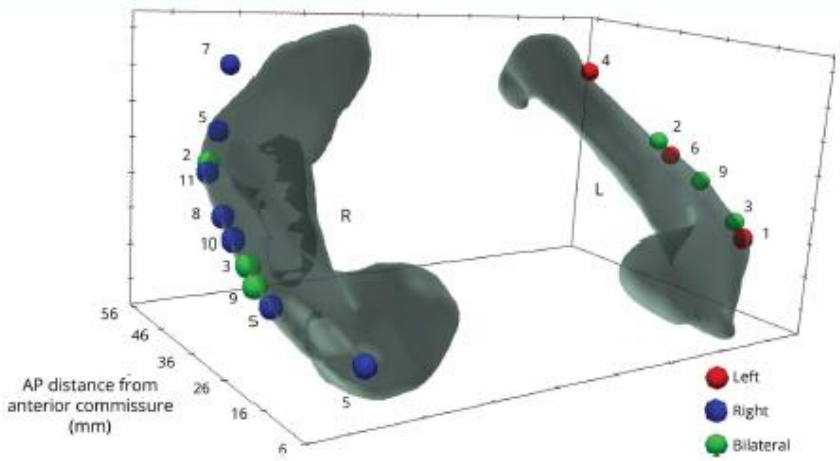
Figure 3 Navigation strategy and visual exploration patterns of patients with TGA (postacute stage, follow-up) and HCs



(A) HCs showed a navigation strategy that included the use of shortcuts (A.a), indicating the use of a spatial cognitive map of the environment (A.b). (B) Patients with TGA showed a reduced use of shortcuts during allocentric routes (red arrows) and spent more time at crossings (blue arrows) both in the postacute stage (B.a) and during follow-up (B.b). The visual exploration behavior of patients with TGA indicated a higher visual dependency than for HCs, both in the postacute stage and during follow-up. Search paths during navigation were color-coded on a ground map (x, y) as cumulative time at location (z). Visual exploration behavior was recorded by a head-fixed eye tracking system and analyzed post hoc. The position of the most frequently fixated objects in place was indicated on a ground map (x, y) as green circles (diameters representing the cumulative time of fixation to a respective object). HC = healthy control; TGA = transient global amnesia.

decision-making.[39] Furthermore, sequence-based, non-allocentric navigation such as route learning was shown to strongly depend on a hippocampal-cerebellar centered network.[40] Taken together, brain activations during real-space navigation in the present study underlined how hippocampal deficits in postacute TGA can intensely recruit, on the one

Figure 4 Localization of DWI lesions in patients with TGA relative to the hippocampal formation



All DWI lesions (a total of 16 lesions in 11 patients) were plotted on a hippocampus model. All lesions except one were in the lateral parts of the hippocampus, corresponding to the CA1 sector. The AP distribution was indicated as distance from the anterior commissure. The consecutive number of the respective TGA patient is indicated next to the lesion. Left-sided lesions are coded in red, right-sided in blue, and bilateral lesions in green. AP = anterior-posterior; DWI = diffusion-weighted imaging; L = left; R = right; TGA = transient global amnesia.

Table 2 Statistical comparison of visual exploration and spatial orientation parameters of patients with TGA (postacute stage, follow-up) and HCs during navigation

Parameter	HCs	Patients with TGA, postacute	Patients with TGA, follow-up	ANOVA *F*/*p* values, X^2/*p* values
Total fixations, n	1,394.1 ± 337.3	1,360.6 ± 374.9	1,440.9 ± 297.8	0.21/0.81
Total saccades, n	3,167 ± 1,181.6	2,586.2 ± 1,009.4	2,547.2 ± 629.8	1.49/0.24
Egocentric fixations, n	347.8 ± 127.5	407.4 ± 148.8	419.2 ± 133.8	0.89/0.44
Egocentric saccades, n	763.4 ± 287.6	702.1 ± 298.2	693.8 ± 298.7	0.19/0.83
Allocentric fixations, n	1,018.8 ± 206.7	899.5 ± 300.7	954.8 ± 261.1	0.64/0.53
Allocentric saccades, n	2,290.4 ± 925.2	1,726.7 ± 797.7	1,690.9 ± 538.6	2.2/0.13
Total landmarks, n	1,723.8 ± 347.6	1,782.4 ± 519.3	1,796.1 ± 387.9	0.083/0.92
Unique landmarks, n	151.4 ± 31.33	162.00 ± 37.63	172.54 ± 28.14	1.1/0.33
Unique allocentric landmarks, n	77.0 ± 42.2	117.8 ± 30.3	108.8 ± 44.4	3.2/0.05
Unique allocentric landmarks/saccades	0.036	0.075	0.069	4.2/0.023
Shortcuts used, %	45.0 ± 27	12.12 ± 17	4.8 ± 15	Postacute: 14.4/0.0001; follow-up: 17.3/<0.0001
Duration at crossroads, s	21.0 ± 2.4	24.3 ± 6.5	24.3 ± 6.4	Postacute: −1.6/0.10; follow-up: −1.2/0.24
Duration at unexplored roads, s	4.7 ± 6.0	7.2 ± 7.2	6.4 ± 8.3	Postacute: −0.84/0.40; follow-up: −0.39/0.69

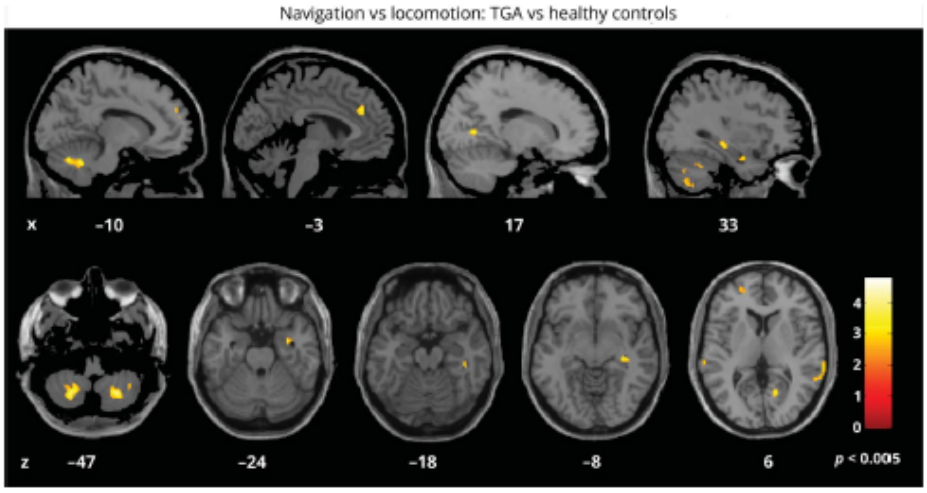
Abbreviations: ANOVA = analysis of variance; HC = healthy control; TGA = transient global amnesia.
Within all analyzed parameters, the number of unique objects and the ratio of unique objects vs total saccades viewed during allocentric routes were significantly higher in patients with TGA in the postacute stage and by tendency during follow-up. Patients with TGA used significantly fewer shortcut routes both in the postacute stage and during follow-up compared to HCs.

were reflected by a reduced use of shortcuts and increased time spent at way crossings, both in the postacute and follow-up stages (figure 3, table 2). A detailed analysis of visual fixations revealed that patients with TGA used more unique landmark fixations on their allocentric routes (table 2), indicating that they rely more on visual cues as a feature of egocentric navigation strategies. Altogether, the observed allocentric navigation problems and the associated behavioral differences in TGA reflect distinct deficits in constructing and updating an internal cognitive map of a novel environment, which is a key function of the hippocampal formation.

Brain activation patterns during navigation indicate reorganization processes following TGA. In the postacute stage, patients with TGA activated a cerebral network during spatial orientation, which was similar to previously reported patterns in HCs and included the hippocampus, retrosplenial, posterior parietal, and prefrontal cortices, as well as the cerebellum.[14,24–30] Remarkably, the right hippocampal formation was overactivated during navigation in patients as compared to controls. This finding could be explained by neuroplasticity and reorganization mechanisms in an attempt to compensate for the disease-specific hippocampal deficit.[5,31] It cannot be excluded definitely that the hippocampal hypermetabolism could be an unspecific phenomenon in the postacute stage of TGA. However, previous imaging studies in TGA report mostly a hippocampal hypometabolism/hypoperfusion in the acute and postacute stages.[11,32–34]

Extrahippocampal areas of navigation control (i.e., the posterior parietal, prefrontal, and retrosplenial cortices, and cerebellum) were recruited to a greater extent in patients with TGA than in HCs. Increased activation of the posterior parietal cortex could indicate the attempt to substitute the impaired ability to form hippocampal cognitive maps by a more egocentric navigation strategy, i.e., computation of distance and directions for successful route learning.[35] Greater activation of the prefrontal cortex could reflect efforts being made for path planning, as this area is involved in anticipating novel routes and direction decisions at way crossings.[3,6] Activation of the retrosplenial cortex might indicate an attempt to transfer egocentric coordinates to a more general allocentric cognitive map. It has been shown that the retrosplenial cortex can thereby partially assume hippocampal cognitive map functions despite a lack of detail-rich texture.[37,38] This would explain why patients with TGA did not fail completely on allocentric navigation routes but seemed to have problems incorporating certain spatial aspects such as shortcuts in the detail-rich texture of the navigational space (figure 3). The navigation-induced cerebellar activations in our study might be explained by a recruitment of prefrontal-cerebellar networks for executive functions, e.g., planning (of routes) and

Figure 5 rCGM during navigation in patients with TGA (postacute stage) and HCs



During navigation in the postacute stage, the rCGM in patients with TGA was increased in the right hippocampus, bilateral posterior parietal, retrosplenial, and mesiofrontal cortices, and the cerebellar dentate nucleus. Significance level $p < 0.005$; levels of sections in x and z directions are given by MNI (Montreal Neurological Institute) coordinates. HC = healthy control; rCGM = regional cerebral glucose metabolism; TGA = transient global amnesia.

hand, extrahippocampal hubs of the human spatial navigation network and, on the other, intrahippocampal plasticity and reorganization.

The experimental approach of the current study has certain methodological limitations. It is hardly possible to design navigation paradigms, which test only ego- or allocentric navigation abilities, for real space. A dichotomous classification of routes, as defined in the current study, can, therefore, only be an approximation based on theoretical concepts derived from previous navigational studies in virtual reality.[24,25] Detection and exact localization of hippocampal lesions on routine DWI sequences may be restricted by the spatial resolution of our 3-tesla MRI. Lesions were only found in about 60% of patients in lateral hippocampal areas including the CA1 sector, which is critically involved in allocentric navigation control.[24] These data are completely in line with results reported by key publications on MRI lesions in patients with TGA.[2,5,41,42] The statistical comparison of the TGA subgroups with and without lesions did not show any significant differences between these groups. Therefore, the presence or absence of a hippocampal lesion does not seem to be a relevant covariate in our study. There are no established scales for navigation performance that can reliably estimate the premorbid level in patients with TGA. None of the patients reported having had any subjective problem in spatial orientation before the onset of TGA.

From a clinical perspective, the question remains whether prolonged navigation deficits affect activities of daily life of patients with TGA. Indeed, a majority of patients with TGA reported subtle deficits of orientation at follow-up, which, however, did not critically interfere with their functionality. Possible explanations may be the preservation of long-term spatial memory and knowledge in TGA, the reorganization of the cerebral navigation network, and the application of compensatory navigation strategies. In case of a reduced cognitive reserve or impaired compensatory neuroplasticity, e.g., due to age or structural cerebral damage, hippocampal dysfunction in TGA could become functionally relevant.

The current study provides evidence of prolonged deficits of allocentric spatial orientation and memory in patients with TGA. This finding contrasts with the previously described complete recovery of other memory domains, such as verbal, figural, or episodic memory.[4,3] Lesion localization in the lateral hippocampal CA1 area of patients with TGA may explain why hippocampal cell types, like place cells, are predominantly affected. These cells are involved in constructing an internal cognitive map of the environment. The time course of spatial orientation deficits suggests more persistent hippocampal dysfunction in TGA. PET data point toward a compensatory recruitment of right hippocampal neurons and a functional shift to extrahippocampal hubs of the cerebral navigational network. TGA provides a disease model for studying the particular role of hippocampal and extrahippocampal functions in spatial orientation and navigation.

Author contributions

Florian Schöberl: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis. Stephanie Irving:

drafting/revising the manuscript, acquisition of data, analysis and interpretation of data, statistical analysis. Cauchy Pradhan: drafting/revising the manuscript, acquisition of data, analysis and interpretation of data, statistical analysis. Stanislavs Bardins: revising the manuscript, acquisition of data, analysis and interpretation of data. Christoph Trapp: revising the manuscript, acquisition of data, analysis and interpretation of data. Erich Schneider: revising the manuscript, acquisition of data, analysis and interpretation of data. Günter Kugler: revising the manuscript, acquisition of data, analysis and interpretation of data. Peter Bartenstein: revising the manuscript, analysis and interpretation of data. Marianne Dieterich: revising the manuscript, study concept and design, analysis and interpretation of data. Thomas Brandt: revising the manuscript, study concept and design, analysis and interpretation of data. Andreas Zwergal: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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ORIGINAL RESEARCH

WILEY Brain and Behavior

Transient topographical disorientation due to right-sided hippocampal hemorrhage

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Abstract

Introduction: Topographical disorientation is defined as the inability to recognize familiar or unfamiliar environments. While its slowly progressive development is a common feature of neurodegenerative processes like Alzheimer's dementia, acute presentations are less frequent and mostly caused by strategic lesions within the cerebral navigation network. Depending on the lesion site, topographical disorientation can originate from deficits in landmark recognition and utilization for route planning (egocentric navigation deficit), or disturbance of an overarching cognitive map of the spatial environment (allocentric navigation deficit). However, objective measurements of spatial navigation performance over time are largely missing in patients with topographical disorientation.

Methods: We here report a 55-year-old patient with acute topographical disorientation as the single symptom of right-sided hippocampal hemorrhage and present quantitative gaze-monitoring head camera-based analyses of his path-finding strategy and visual exploration behavior in a real space navigation paradigm.

Results: The patient exhibited severe allocentric and also egocentric navigation deficits during the acute phase, shown by higher error rates at finding target items. In addition, he showed a more extensive use of search saccades toward, and fixations on, landmarks that could potentially serve as spatial cues. These deficits had been completely compensated for after four months, when the patient performed unremarkably in the real space navigation task, and used even more strongly allocentric path optimization strategies than age-matched controls.

Conclusions: This case report highlights the integral function and right-sided dominance of the hippocampal formation in the cerebral navigation network in humans. It shows that the cognitive map can be restored completely despite a residual hippocampal lesion, which illustrates the enormous plasticity of the cerebral navigation network in humans.

KEYWORDS
hemorrhage, hippocampus, navigation, stroke, topographical disorientation

*These authors contributed equally to the manuscript.

1 | INTRODUCTION

Previous studies show self-reported deficits of navigation abilities in about one-third of patients with mild stroke. However, isolated topographical disorientation is an uncommonly reported chief complaint of acute cerebral lesions characterized by sudden deficits in the recognition of familiar surroundings (Aguirre & D'Esposito, 1999; Van der Ham, Kant, Postma, & Visser-Meily, 2013). Lesions to various brain regions including critical hubs of the cerebral navigation network may result in this impairment (Claessen & van der Ham, 2017; Ekstrom, Arnold, & Iaria, 2014). Most often the right hippocampus or parahippocampus is involved. It has been proposed that topographical disorientation can originate from deficits in allocentric and/or egocentric spatial strategies (Claessen & van der Ham, 2017). The cognitive map theory posits that the right hippocampus mainly supports allocentric processing of space and is thus activated in more complex navigational situations (Burgess, Maguire, & O'Keefe, 2002; O'Keefe & Nadel, 1978). In contrast, egocentric navigation mainly relies on sequential distance and direction computations by means of landmark recognition and utilization, processed particularly in the parahippocampal and retrosplenial cortex (Epstein & Vass, 2013). In this case study, we report a spatially disoriented patient with an acute focal right-sided hippocampal/parahippocampal hemorrhage, and the long-term time-course of his deficits as documented by quantitative analyses of path-finding strategy and gaze behavior in a real space environment. We hypothesized that (a) allo- and egocentric navigation abilities would be impaired in the acute stage due to the anatomic localization of the lesion and (b) navigation deficits would compensate over time by plasticity mechanisms within the cerebral navigation network.

The 55-year-old patient H.W. presented to the emergency room after feeling a sudden loss of familiarity with the entire surrounding environment while he was driving home from work. He reported no further subjective deficits, and in particular no amnesia, aphasia, apraxia or visual deficits. The neurological status was unremarkable except for a severe spatial orientation deficit. In particular, we could not find any signs of visual field deficits, neglect/extinction phenomena or deficits of left/right recognition. MRI revealed an acute focal hemorrhage, affecting the medial-posterior hippocampus and adjacent parahippocampus (Figure 1). Detailed neuropsychological assessment was performed using the CERAD-plus test battery. Performance in the subtests word list learning total, word list trial 1, 2 and 3, word list delayed recall, word list recognition, figure drawing, figure drawing recall and trail making test B was compared to age-matched controls using *z*-scores. H.W. furthermore underwent CLOX1 and CLOX2 tests to identify potential executive or visuospatial/visuoconstructive deficits. To exclude (hemi)neglect the Line Bisection and Balloons Test were performed. Results were depicted as deviation from the true center of lines for the Line Bisection Test and total B Score and Laterality B Index for the Balloons Test. Upon informed written consent by the patient and approval by the Ethics Committee of the Ludwig-Maximilians-University, Munich, topographical orientation was further assessed by an item search task in an unfamiliar real space environment. The environment, in which five items were placed as target points, was shown to the patient first by an investigator-guided walk (exploration). Afterward, H.W. had to find the items in a pseudorandomized order within 10 min (navigation). The first part of the navigation paradigm was similar to the previous exploration route, which can be successfully solved by pure egocentric repetition of the route learned (i.e., sequential computations of distance and direction), thus requiring no cognitive map of the spatial environment. However, in the second part, the order of the target items was pseudorandomized, which consequently required detailed imagery of the environment as a whole and concrete planning of novel routes, potentially including short-cuts (i.e., a cognitive map-based or allocentric strategy) (Figure 2). Patient H.W. wore a gaze-monitoring head camera throughout the experiment to document his visual exploration and head position (Schneider et al., 2009). To quantify spatial navigation performance, the error rate for items approached during the navigation phase was calculated by offline analysis of the videos recorded by the gaze-monitoring head camera. Error rates were further separately analyzed for egocentric and allocentric routes to test for specific deficits of either navigation strategy. Error rates were compared to those of an age-matched cohort of 10 healthy men (age: 54.3 ± 6.2 years). The search path

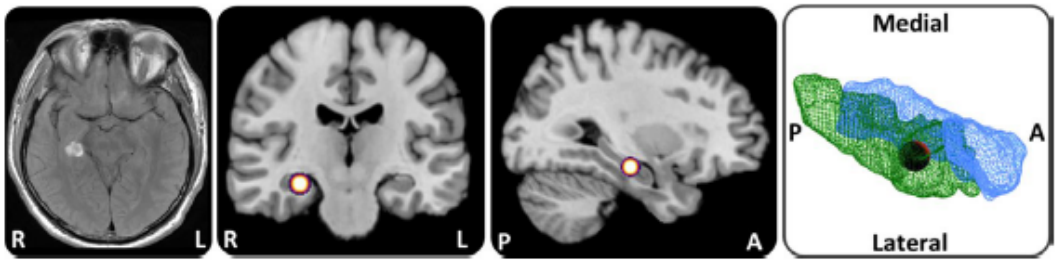
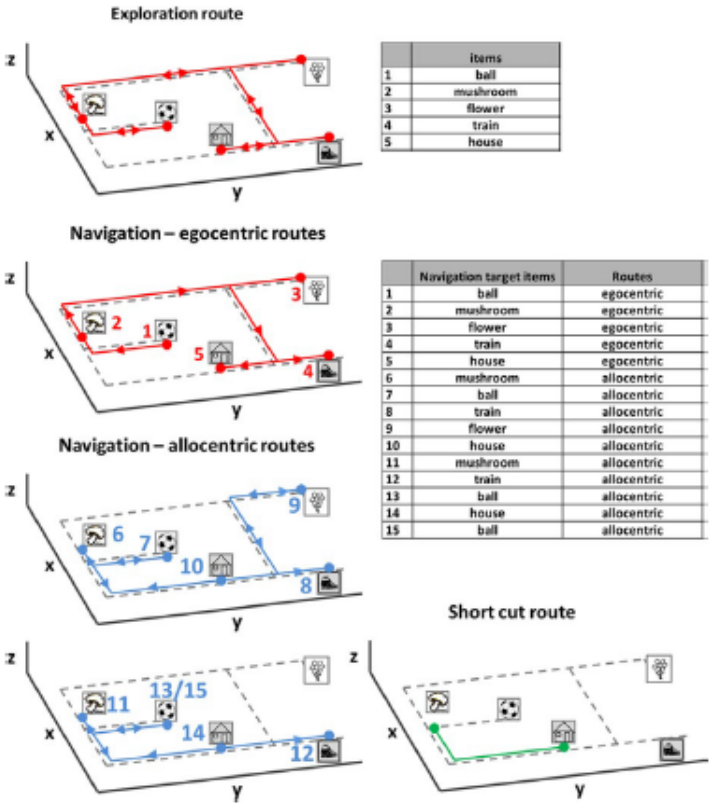


FIGURE 1 Lesion localization in a case of acute topographical disorientation. A T2 MRI sequence showed a focal hemorrhage in the right hippocampus and parahippocampus (left side). The lesion in full-scale (red sphere) was projected to a standard T1 brain template (middle) and a hippocampus (blue) and parahippocampus (green) 3D model (right side) to visualize the exact lesion localization. R: right, L: left, A: anterior, P: posterior



	items
1	ball
2	mushroom
3	flower
4	train
5	house

	Navigation target items	Routes
1	ball	egocentric
2	mushroom	egocentric
3	flower	egocentric
4	train	egocentric
5	house	egocentric
6	mushroom	allocentric
7	ball	allocentric
8	train	allocentric
9	flower	allocentric
10	house	allocentric
11	mushroom	allocentric
12	train	allocentric
13	ball	allocentric
14	house	allocentric
15	ball	allocentric

FIGURE 2 Navigation paradigm in real space. First row: exploration route with a defined sequence of items. Second row: In the first part of the navigation paradigm, routes were tested which were identical to the previous exploration route (so-called egocentric routes). Third and fourth row: in the second part, the order of target items was changed in a way that required the planning of novel routes (so-called allocentric routes). Potential short-cuts within the allocentric route were recorded (fourth row, right side). The sequence of the target items during exploration and navigation is depicted in a table and appears as corresponding numbers besides the target items in the figures

during the navigation task was mapped by accumulating time spent at a specific place and analyzed quantitatively (mean gait speed during exploration or navigation, use of short-cuts, and time spent at crossings). Video analysis allowed all fixation targets to be categorized into fixed objects in space, mobile objects, and unspecific, non-object fixations (e.g., the ground, wall, ceiling). The total number of objects viewed and the number of unique objects viewed were also recorded. The objects, which were fixated most frequently, were plotted on a ground map to indicate the visual exploration strategy and landmark use. Analysis was carried out as described previously (Stuart et al., 2014; Zwergal et al., 2016). The total number of saccades and the saccade frequency were computed. Saccades directed to objects that were feasible as landmarks were defined as search saccades. The total number of fixations, fixation frequency, and duration were analyzed quantitatively. Fixation on a potential landmark was termed a search fixation. X and y gaze magnitudes and direction corresponding to the peak saccadic velocities and median fixation periods were identified and displayed as wind rose plots (direction and frequency of each class). All eye movement parameters were compared to data from the healthy controls.

Detailed neuropsychological assessment with the CERAD-plus test battery indicated normal performance on all subtests. The respective z-scores of subtest performance compared to age-matched controls were as follows: word list learning total: 0.49; word list trial 1: 0.5, word list trial 2: 0.68; word list trial 3: −0.03; word list delayed recall: −0.09; word list recognition: 0.79; figure drawing: 0.7; figure drawing recall: −1.27; trail making test B: −0.76. The patient also showed a completely unremarkable performance on CLOX1/2 tests (15/15 points each). Neglect was ruled out by formally established tests such as the Line Bisection Test (deviation from true center of lines: 0.5 ± 1.1 mm) and Balloons Test (total B Score of 20 and Laterality B Index of 100%).

On Day 2 after symptom onset, H.W.'s spatial navigation performance was severely impaired compared to that of an age-matched control cohort: he had a higher error rate on both egocentric routes (patient: 100%, healthy controls: 5.0 ± 10.5%; $t(9) = -28.500$, $p < 0.001$) and allocentric routes (patient: 25%, healthy controls: 1.4 ± 4.5%; $t(9) = -15.500$, $p < 0.001$), stayed longer at crossroads ($t(9) = 4.118$, $p = 0.003$) and "neglected" half of the spatial environment (Figure 3a). Recognition of landmarks was impaired and fixations to objects were nonsystematic in the patient, while healthy controls had a high consistency in retrieval of strategically important landmarks (Figure 3b). The plot of H.W.'s visual fixations in space and the heat map of eye displacement from straight ahead position showed a pattern that was

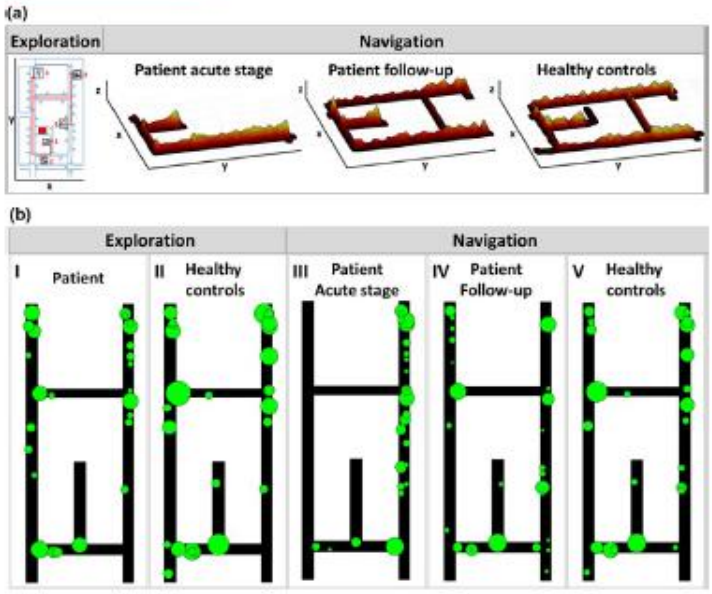


FIGURE 3 Navigational performance and visual exploration in the acute stage of topographical disorientation and during follow-up after 4 months. (a) Navigograms of the patient were constructed by plotting the search path onto the floor map, with x and y indicating position in space and z accumulated time at place. The spatial position of the five search items (ball, mushroom, flower, train, house) is indicated on the left. During the acute stage of topographical disorientation the navigogram showed a severely impaired navigational strategy with complete loss of an internal cognitive map of the spatial environment. In the follow-up examination 4 months later, the navigational performance was completely normal; the search path indicated an overall allocentric spatial strategy and was comparable to the group of healthy controls. (b) During guided exploration, the patient (I) and healthy controls (II) showed a similar pattern of object fixations. However, during navigation in the acute stage of topographical disorientation, the patient was not able to recognize these potential landmarks (III), whereas healthy controls showed a high consistency of retrieval of known objects (V). In follow-up testing, the visual fixation pattern of H.W. normalized (IV) and got more similar to the strategy of healthy controls. Green circles indicate the most frequently fixated objects with position in space indicated on a ground map and diameters being relative to the total duration of fixation

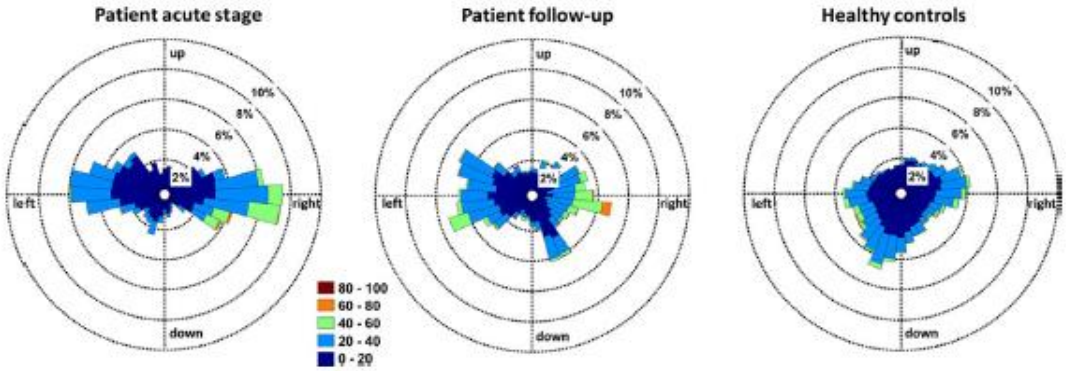


FIGURE 4 Visual exploration behavior in the acute stage of topographical disorientation and during follow-up after 4 months and in healthy controls. Visual exploration behavior during navigation showed that saccadic eye movements during the acute stage of topographical disorientation were mainly directed to the lateral position (left panel) and there were more exploratory saccades. During follow-up, saccadic eye movements were distributed more equally along the horizontal and vertical axes (middle panel). In healthy controls, saccades were directed mainly toward the ground and straight ahead (right panel)

symmetric with respect to the lateral gaze position. This indicates that there was no visual neglect or asymmetric visual exploration behavior, but instead, that visual awareness was comparable across both visual hemifields (Supporting information Figure S1). The apparent asymmetry of navigation path trajectory likely resulted from the lack of any internal cognitive map of the surrounding environment and the distribution of visual cues/landmarks within it. However, given the restrictions of neuropsychological testing in the acute stage, the possibility of basic spatial working memory problems could not definitely be excluded. The patient chose the wrong turn at the beginning of the paradigm and from then just strayed up and down one hallway, unaware that there was another hallway parallel which he could explore. During navigation, he used more search saccades ($t(9) = 3.613$, $p = 0.005$) and tended to make more fixations to possible landmarks ($t(9) = 2.085$, $p = 0.067$). His gaze behavior was predominantly oriented within the horizontal plane (Figure 4, left). After an intense work-up of possible bleeding etiologies, the patient was discharged and followed up four months later.

At that time, he reported no more problems with spatial orientation in his daily life. Therefore, H.W. performed the same real space navigation task like during the acute stage without any errors (egocentric routes $t(9) = 1.500$, $p = 0.168$ and allocentric routes $t(9) = 1.000$, $p = 0.343$), used even more short-cuts than age-matched controls (patient: 100%, healthy controls: 40.0 ± 46.07%; $t(9) = -3.417$, $p = 0.008$) and incorporated all possible paths into his navigational trajectory, thus highly indicative for the presence of an internal cognitive map of the spatial environment similar to healthy controls (Figure 3a). Landmark location and retrieval were similar to healthy controls (Figure 3b). Gaze behavior had also normalized, showing a more equal distribution of the vertical and horizontal planes (Figure 4, right). The numbers of search saccades ($t(9) = 0.813$, $p = 0.437$) and search fixations ($t(9) = 1.179$, $p = 0.269$) were comparable to that of age-matched controls.

Combining behavioral measurements of navigational and neuropsychological performance, we here present evidence that a small, but strategic right-sided hippocampal/parahippocampal lesion can cause acute topographical disorientation as a single symptom and can lead to severe deficits of both allo- and egocentric navigation strategies. This is remarkable as multiple brain areas form a distributed cerebral network for spatial navigation in humans (Ekstrom et al., 2014; Epstein & Vass, 2013; Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000). This case underlines the integral function of the right hippocampus and parahippocampus within this network (Aguirre, Detre, Alsop, & D'Esposito, 1996; Byrne, Becker, & Burgess, 2007; Hartley, Maguire, Spiers, & Burgess, 2003; Morgan, Macevoy, Aguirre, & Epstein, 2011; Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2009). Therefore, hippocampal dysfunction in patient H.W. was indicated by a nearly complete loss of his internal cognitive map for space during the acute stage of symptoms (Hartley et al., 2003; Howard et al., 2014). An increase in search saccades together with a pronounced deficit in the recognition and incorporation of landmarks were associated with parahippocampal dysfunction (Aguirre et al., 1996; Epstein & Kanwisher, 1998). The pathological changes in gaze behavior and spatial navigation abilities in our patient resembled the pattern of other hippocampal navigation disorders such as MCI-patients (unpublished data). Functional compensation of topographical disorientation in H.W. was rapid and complete, as reported in similar previous cases (Gil-Néciga et al., 2002; Rivest, Svoboda, McCarthy, & Moscovitch, 2018). The complete recovery of an allocentric navigation strategy despite a residual hippocampal lesion in follow-up MRI illustrates the great plasticity of the human navigation network (Byrne et al., 2007; Ekstrom et al., 2014). In the follow-up assessment, the patient utilized an allocentric strategy with successful use of short-cuts. Although it cannot be completely excluded that previous knowledge about the room representation alleviated the paradigm the second time, the most likely explanation may be a recruitment of extrahippocampal network structures as has been described earlier for hippocampal lesions (Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2018; Maguire, Nannery, & Spiers, 2006).

In conclusion, acute topographical disorientation should be recognized in clinical practice as a distinct and focal symptom indicating right-sided lesions of the hippocampal formation. The exceptional aspects of this case are the differentiation between egocentric and allocentric navigation strategies, the altered visual exploration behavior without any other signs for (hemi)neglect or any asymmetric visual exploration in general. Importantly, isolated and severe topographical disorientation due to a very strategic lesion as in our case can recover rapidly and completely without any sequelae. It can only be speculated how plasticity supported the recovery of topographical orientation—either through a functional substitution by the intact left hippocampus, or a fundamental reorganization within the broader human spatial navigation network including extrahippocampal hubs such as the retrosplenial and posterior parietal cortex.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Discussion

Navigation, being fundamental in both humans and animals, has been shown to involve multiple cognitive functions and processes: spatial reference frames are created by integrating dynamic self-motion cues with static environmental cues. Self-motion cues are derived from motor efference copy signals, vestibular information feedback, and proprioceptive processes, each integrated into a single process of establishing and maintaining one's position and orientation within an environment.

Visual landmarks and path integration, from the visual and vestibular systems respectively, interact to guide successful human navigation. However, disruption to the cerebral navigation network causes impairments in spatial orientation and navigation. Such disruption can come from trauma to the key structures of the network, such as the hippocampus, or through disease or age-related degeneration.

The major findings of this thesis are as follows:

Our first study aimed to validate a novel real-space navigation paradigm. We utilised behavioural data from navigation performance and gaze behaviour, where we measured visual fixations and saccades, and combined them with brain activation patterns obtained from [^{18}F]-FDG-PET imaging.

The main points of interest were that the paradigm successfully created normalised parameters for gaze behaviour and brain activation patterns during real-space navigation. This real-space navigation paradigm is a practical method for use in the clinical setting to investigate the cerebral navigation control of humans, with the sensitivity to detect age-related changes in navigation.

Comparisons within the healthy cohort revealed that allocentric navigation strategies in real-space deteriorated with age, but were successfully substituted by more egocentric navigation strategies. Increased saccades and visual fixations to environmental landmarks confirmed these findings. This was further accompanied by a reduced rCGM in the bilateral HF and increased rCGM in the frontal cortex in the older participants.

Regarding gender differences, males trended towards allocentric, females towards egocentric navigation strategies. Further, females were more likely to utilise left hippocampal and right temporal areas of the cerebral navigation network compared to males. Finally, visual exploration parameters, such as total number of saccades or search saccades were gender-independent; instead, they were more likely to reflect age-related changes of navigation performance.

Taken together, this novel real-space paradigm is a promising tool for the discrimination of age-related spatial orientation pathologies, such as impending cognitive decline.

Our second study focused on transient glabal amnesia (TGA), a “pure” hippocampal disorder, in order to assess if the paradigm was sensitive and reliable for hippocampal dysfunction. The main findings were supportive as we were able to discriminate that allocentric navigation, but not egocentric navigation was impaired, despite normalised neuropsychological testing.

We raise questions as to the transient nature of TGA, as the deficit in allocentric navigation was persistent 3 months after symptom onset, and the severity of the navigation deficit correlated with TGA duration.

The TGA patients were more reliant on visual cues. Furthermore, [^{18}F]-FDG-PET imaging showed increased recruitment of extrahippocampal regions of the cerebral navigation network. We present an enduring navigation deficit that is likely due to microstructural

damage in the hippocampus, following focal CA1 lesions, which is recognised for the first time with our real-space navigation paradigm.

Our third study was a case report of a small but strategic, right-sided hippocampal haemorrhage, where the singular symptom was topographical disorientation (TD). The paradigm showed itself to be sensitive and reliable in discriminating the nature of the acute TD: we recorded severe deficits in both allocentric and egocentric navigation, despite the vast majority of the HF remaining intact.

This highlights the importance of the right hippocampus for navigation and spatial orientation, as the patient showed a near complete loss of the ability to form a cognitive map.

Increased saccades and a lack of recognition of landmarks were linked to the parahippocampus, where there was oedema. Functional compensation was rapid and complete within 4 months, with complete navigation recovery and the utilisation of allocentric navigation, despite residual hippocampal damage. Gaze behaviour changed significantly over the course of 4 months and was comparable to healthy subjects.

We argue this case highlights the plasticity of the HF and cerebral navigation network, where either the left hippocampus or extrahippocampal regions were compensating for the right hippocampal lesion, and that changes in gaze behaviour reflect changes in navigation strategy.

The vast majority of previous research into human navigation has been conducted in laboratory settings, utilising virtual environments (Harris & Wolbers, 2012; Wiener et al., 2012). The standardisation of the setting is a major advantage as the environments can be controlled and manipulated as required, particularly for testing allocentric and egocentric abilities (Astur et al., 2002; Guderian et al., 2015).

However, navigation in virtual space relies on visual information; virtual environment paradigms neglect vestibular and proprioceptive input, as well as motor efference copy

signals. These body-based self-motion clues are a key component of vestibular-hippocampal communication, and studies lacking such input are at a major disadvantage when comparing results to human navigation in the real world (Taube et al., 2012).

Here we see the advantage of using our real-space navigation paradigm: we detect changes in navigational strategy by measuring saccades and fixations, and utilise [^{18}F]-FDG-PET imaging to discern the brain regions active during real-space navigation (Schöberl et al., 2018).

By combining navigation performance, measurements of visual exploration and simultaneous measurements of cerebral glucose metabolism by [^{18}F]-FDG-PET, a novel paradigm is created that presents itself as both a reliable and sensitive measure of spatial navigation in healthy adult aging and in hippocampal dysfunction.

Gaze behaviour discriminates allocentric and egocentric navigation strategies, and brain activation patterns show greater reliance on the visual system where the hippocampus has been compromised (Irving et al., 2018; Schöberl et al, 2018).

6.1 Navigation strategies in aging and cognitive decline

By analysing individual spatial navigation performance in healthy subjects and hippocampal dysfunction patients, it is possible to create reliable factors for the measurement of navigation strategy and to apply them in a broader clinical context. Markers that differentiate between normal adult aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD) has a specific diagnostic utility (Lester et al, 2017).

Navigational deficits in older adults is not a surprising finding as key structures of the cerebral navigation network (e.g. EC and HF) are vulnerable to the degenerative effects of aging (Lester et al, 2017). Indeed, the ability to form a cognitive map, a hippocampal-based

function, degenerates with normal adult aging (Harris & Wolbers, 2014). Younger participants can switch between egocentric and allocentric navigation strategies, yet older participants restrict themselves to egocentric strategies.

Moreover, as age increases, more time with allocentric route planning is required, but this effect is not present for egocentric route planning (Irving et al., 2018). This finding is also reflected in previous studies were older adults have been shown to outperform younger participants in egocentric navigation, but were significantly poorer in allocentric navigation (Lester et al., 2017; Strangl, 2018).

Our real-space paradigm combined egocentric and allocentric navigation routes. Reduced path optimisation, increased gaze behaviour directed towards visual landmarks, increased search saccades and total number of saccades recorded, implies dependence on visual input to the HF.

A switch to an egocentric navigation strategy, which is shown to utilise extrahippocampal regions and the more robust parietal cortex and striatal circuits of the cerebral navigation network, is a feasible compensatory method for age-related hippocampal decay (Burgess, 2008; Gazova et al., 2013; Wiener et al., 2013; Strangl et al., 2018; Irving et al., 2018).

Changes in gaze behaviour, wherein during navigation older participants accumulate more saccades, require more visual fixations, rely more on landmarks for navigation, and have more diffuse eye movements on the horizontal plane, also suggests a reliance on an egocentric navigation strategy (Irving et al., 2018). This reflects allocentric navigation deterioration with age.

The analysis of visual exploration behaviour in space firmly depicts alterations of navigation strategies and can be seen across various hippocampal pathologies (Burgess, 2008; Livingstone-Lee et al., 2011; Wiener et al., 2013; de Condappa & Wiener, 2014; Lester et al.,

2017). For example, comparing older healthy subjects with MCI patients, we see an even greater increase in saccades and visual fixations correlated with reduced hippocampal activation and increased pontine ocular motor centres, thus showing how pathological aging is distinguishable from healthy aging (Zwergal et al., unpublished).

Age-related changes to hippocampal volume and long-term potentiation can be detrimental to hippocampal place and grid cells – important for allocentric navigation (Strangl et al., 2018). Where we see a reduction in rCGM in the HF, decline in the ability to form a cognitive map, and poor flexibility in shifts in navigation strategy, the integrity of the RSC and hippocampus are compromised (Epstein, 2008; Fogwe & Mesfin, 2018). Similarly, the increased rCGM in the frontal regions indicate efforts being made for route-planning, as opposed to route-learning (Javadi et al., 2017).

This real-space navigation paradigm reflects the physiology of the cerebral navigation network and its functionality. It is a promising tool for the discrimination of healthy age-related changes in navigation against pathological changes, such as patients with MCI and prodromal dementia, and could be a potential marker for early detection and intervention in AD (Rusconi et al., 2015; Laczó et al., 2016; Lester et al., 2017; Irving et al., 2018).

Indeed, specific deficits in translating allocentric reference frames into egocentric reference frames has been found in early-stage AD, directly inferring degeneration of the RSC and hippocampus (Pai & Yang, 2013; Strangl et al., 2018). Early disruption to navigation circuitry as measured by both gaze behaviour and imaging is a potential diagnostic tool in the clinical setting (Rusconi et al., 2015; Lester et al., 2017).

6.1.1 Practical implications

Previous studies into spatial navigation and age-related pathologies utilised virtual realities to show their diagnostic capabilities. For example, with early stage AD, patients typically

present with impairments to both allocentric and egocentric navigation, as well as impaired translation between the two reference frames. This is likely caused by widespread neurodegeneration of temporal, medial, frontal, and frontal brain areas (Jheng & Pai, 2009; Coughlan et al., 2018).

On the other hand, with MCI patients, who have substantial hippocampal volume reduction compared to healthy age-matched controls, they also show impairment in spatial navigation and path integration. However, the difference between the two patient cohorts is the navigation impairment is severe in allocentric navigation. Egocentric navigation is also impaired, but to a lesser extent (Laczó et al., 2009). This important distinction is a key point in the diagnosis of MCI and early-stage AD.

By incorporating the use of gaze behaviour, clinical settings can quickly assess the nature of the navigational impairment and speed up a diagnosis of AD. For example, switching virtual reality to real-space allows for the inclusion of both vestibular and visual systems in navigating, and analysing the use of environmental landmarks and search saccades could distinguish normal aging from MCI and AD.

6.2 Navigation strategies in hippocampal lesions

TGA is a “pure” hippocampal dysfunction and is rapid in its presentation. It also has a rapid clinical recovery of approximately 24 hours. It is typically characterised by temporary and sudden onset of both anterograde and retrograde amnesia, as well as spatial disorientation. No other neurological signs or symptoms are present (Jäger et al., 2009; Bartsch & Deutschl, 2010).

Our data showed TGA patients in both pre- and post phases performed worse than healthy controls in overall navigation performance and presented with an isolated and persistent

allocentric navigation deficit: they had a greater dependency on visual cues to navigate the environment (Schöberl et al., 2018).

TGA is also characterised by focal lesions to the CA1 region of the hippocampus. However, the CA1 lesions are reversible; they are no longer present a few weeks after the episode (Bartsch et al. 2011). We report persistent navigation deficits 3 months following symptom onset. This persistent impairment in allocentric navigation from damage to CA1 neurons is likely due to a functional disconnection of the hippocampus, or residual microstructural damage (Döhring et al., 2017; Schöberl et al., 2018), thus resulting in compensatory navigation strategies from intact extrahippocampal structures (Chen et al., 2014).

TGA patients utilised more lateral saccades and used more fixations to unique landmarks during allocentric routes. They used less shortcuts, spent more time at crossroads and unexplored routes. This describes a route-based strategy, as opposed to creating a cognitive map of the environment (Schöberl et al., 2018).

The persistence in allocentric navigation impairment points to a longer-lasting deficit, indicating damage to place cells and the use of extrahippocampal regions for a compensatory navigation strategy (Wiener et al., 2013; Chen et al., 2014; Strangl et al., 2018).

There is not a large body of research on spatial navigation and memory in TGA beyond the days following symptom onset. We found just one previous study of navigation deficits in a virtual environment, with a repetition conducted 2 weeks after symptom onset. Interestingly, the recorded navigation deficits recovered completely after these 2 weeks (Jäger et al., 2009).

In contrast, we discovered prolonged deficits of allocentric navigation (Schöberl et al., 2018). This discrepancy is likely methodological: a different sensitivity in the virtual paradigms to the sensory systems could be an explanation as to why they were unable to detect allocentric navigation impairment, yet with our real-space paradigm, we were (Jung et al., 1996).

We report deficits in allocentric navigation of our TGA patients that were reflected by an increased use of fixations and saccadic behaviour, reduced use of shortcuts in the environment, and increased time spent at way crossings. These effects were present in both the post-acute and follow-up stages (Schöberl et al., 2018).

The allocentric navigation impairment and the associated behavioural differences reflect distinct deficits in constructing and updating an internal cognitive map of a novel environment, which is a key function of the hippocampal formation (Ekstrom et al., 2003; Angelaki & Cullen, 2008; Hüfner et al., 2011). The level of persistence of allocentric navigational deficits in TGA patients was dependent on the duration of the initial amnesia. Therefore, hippocampal plasticity, or adaptation from within the HF itself, is evident (Hartley et al., 2013).

In analogy to TGA navigation performance over time, the case report presented in this thesis indicates that strategic hippocampal haemorrhage can cause temporary but severe allocentric and egocentric navigation deficits. Patient H.W. showed a more extensive use of search saccades towards, and fixations on, landmarks serving as spatial cues. These deficits completely recovered after four months, when the patient navigated with strongly allocentric strategies (Irving et al., 2018).

It is likely that other structures within the HF had adapted: arguably, due to the great functional and structural connectivity of the HF, with the hippocampus as the hub, individual brain regions may not function as isolated for specific cognitive abilities, but instead are connected and integrated together (Hartley et al., 2013; Schultz & Engelhardt, 2014; Ekstrom et al., 2017).

When extrahippocampal structures are undisturbed by lesions or trauma, a number of spatial orientation and navigation functions remain intact. The parahippocampal regions encode local

scenes within an environment; i.e. egocentrically. Thus, egocentric navigation remains largely intact, despite hippocampal dysfunction (Epstein, 2008, Hartley et al., 2013). Similarly, patient H.W. shows that the cognitive map can be restored completely, in spite of residual hippocampal damage, demonstrating the extensive plasticity of the human cerebral navigation network (Wiener et al., 2013; Ekstrom et al., 2017).

Our paradigm has shown sensitivity to hippocampal dysfunction in TGA where other clinical assessments showed recovery. Similarly, with patient H.W., this paradigm accurately detected initial deficiencies in both allo- and egocentric navigation, with full recovery. Gaze behaviour, when combined with imaging data, was diagnostically useful for navigation deficits caused by hippocampal dysfunction, this is due to its sensitivity in detecting changes in visual exploration and therefore navigation strategies (Schöberl et al., 2018).

6.3 Imaging of the cerebral navigation network adaptation in hippocampal dysfunction

The cognitive map theory states the brain creates a unified representation of integrated spatial reference frames of the environment to support memory and guide future action. This takes the form of the cerebral navigation network, which extends beyond the HF (see figure 7). Deficits, either caused by aging or focal lesions, disrupt this network and spatial navigation impairments present (Chen et al., 2014; Wolbers & Büchel, 2005; Epstein et al., 2017).

The essential functions of the cerebral navigation network regard one’s location in space, what is in the environment, and how one got there. Specific neurons in the hippocampal formation, i.e. place cells and grid cells, process spatially-relevant information and both receive and project throughout the HF and beyond (Maguire et al., 1998, 1999; Ekstrom et al., 2003; Epstein et al., 2017).

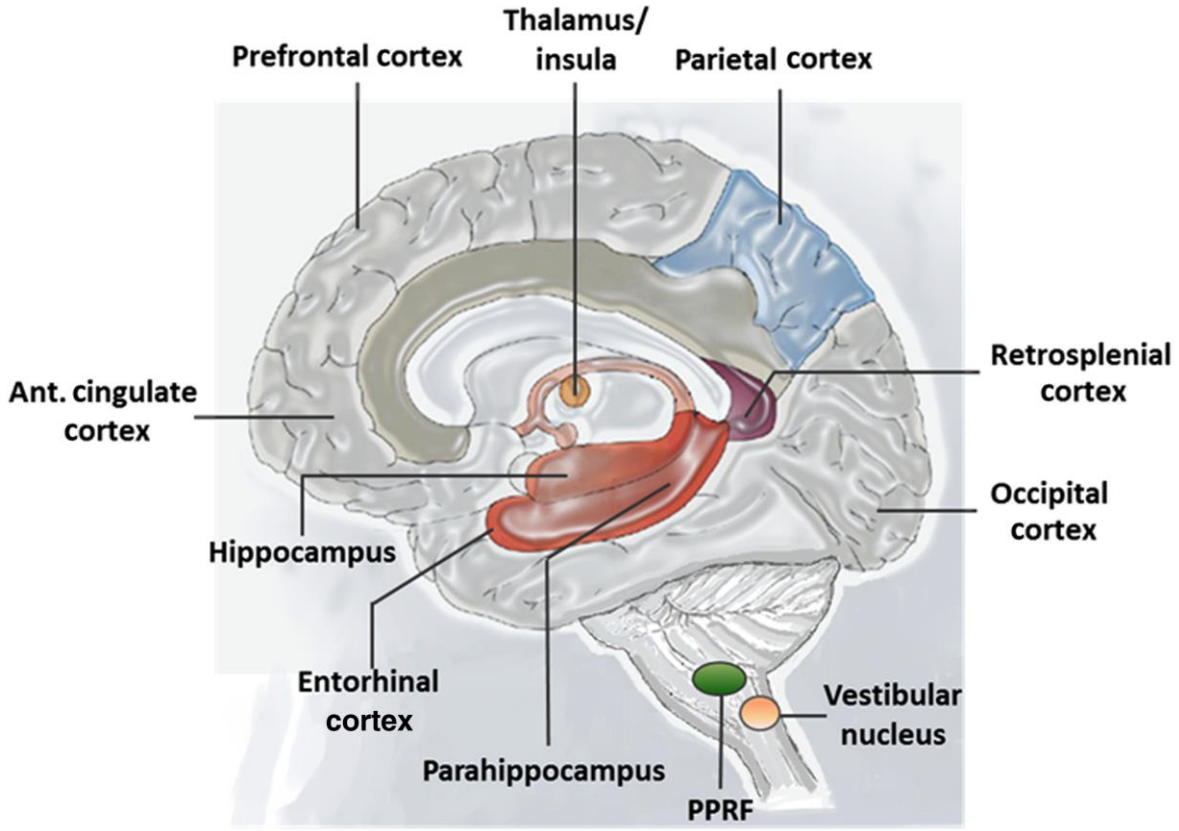

Figure 7. Schematic representation of the major anatomical structures of the cerebral navigational network. Adapted with permission from (Zwergal et al., 2016).

However, age-related decay and focal lesions to the HF result in increases in activations in some regions and decreases in activations in others. For example, the key anatomical structures in the cerebral navigation network of older adults decline with healthy adult aging (Lester et al., 2017).

In older adults, we reported decreased activation across the HF bilaterally, in the right precuneus in the parietal cortex, left postcentral gyrus, and the left pontomedullary tegmentum. However, there were increased activations in the cerebellum and the right medial frontal gyrus (Irving et al., 2018).

Similarly, other studies have reported decreases in activation in the hippocampus proper, parahippocampus and the RSC, respectively, when compared to younger participants (Chen et al., 2014; Lester et al., 2017).

These changes in activation patterns indicate changes in navigation strategies, as the key structures for allocentric navigation in the HF have decreased activation, yet extrahippocampal regions associated with egocentric navigation are more activated (Chen et al., 2014; Epstein et al., 2017).

This correlates with changes in gaze behaviour, where patients with impaired allocentric navigation have increased saccadic behaviour and more total overall fixations, particularly to landmarks (Irving et al., 2018, Schöberl et al., 2018).

Further, with strategic lesions in the hippocampus, spatial processing in functionally and structurally connected regions can be disrupted (Henson et al., 2016). In TGA patients, DWI regularly shows transient punctuate lesions in lateral CA1 region (Bartsch et al. 2011).

Our patients, however, showed fractual anisotropy and diffusivity, which indicated long-term microstructural hippocampal damage, indicating why allocentric navigation deficits persisted (Schöberl et al., 2018).

Activations in the post-acute phase were located in the parahippocampal hubs of the navigation network, pointing towards a compensatory mechanism for focal hippocampal damage, and the use of egocentric navigation strategies (Schöberl et al., 2018).

The use of imaging to detect age-related degradation of the cerebral navigation network is an expensive and time-consuming method for examination, however the use of gaze behaviour in a navigation task reveals intrinsic changes in navigation strategies, correlating with brain activation patterns, thus indicating the anatomical regions in use within the cerebral navigation network.

7. Conclusions

Navigation in virtual environments is easily controlled and manipulated but only rely on visual inputs. This thesis provides sufficient support that a real-space paradigm, combining visual, vestibular and proprioceptive inputs with motor efference copy signals (body-based self-motion cues), is a reliable and valid method of measuring spatial navigation and orientation abilities.

The analysis of visual exploration behaviour in space robustly depicts alterations of navigation strategies; where allocentric navigation is particularly vulnerable when the hippocampus is affected by age-related atrophy or strategic lesions within the cerebral navigation network. However, where allocentric navigation deteriorates with age, it is substituted with egocentric navigation strategies.

These findings correlate with decreased activation in the hippocampus and the precuneus, and increased activation of the frontal lobe, basal ganglia, and the cerebellum. Similarly, when unable to utilise allocentric strategies due to hippocampal damage, TGA patients used compensatory egocentric strategies, which correlates with increased activation in the extrahippocampal regions, such as the retrosplenial, parietal, and mesio-frontal cortices, respectively.

Multiple brain areas form a distributed cerebral network for spatial navigation in humans. Impairment can originate from deficits in landmark recognition and utilisation for route planning or disturbance of an overarching cognitive map of the spatial environment. We have shown that strategic lesions to multiple brain regions, including critical hubs of the cerebral navigation network, results in this impairment.

Gaze behaviour correlated with changes in navigation strategy, where increases in saccades, fixations on landmarks, and lateral or diffuse gaze patterns supports an egocentric navigation

strategy. In combination with brain activation patterns, our real-space paradigm is a sensitive and reliable tool for measuring discrete navigational changes in hippocampal dysfunction.

Overall, the combination of gaze behaviour and brain activation patterns with real-space navigation is a useful tool for investigating the physiology of cerebral navigation in patients. We have shown it can discriminate hippocampal-related changes in spatial orientation pathologies. For sequential quantitative spatial orientation and visual exploration testing, this paradigm is sensitive and reliable for hippocampal function in relation to spatial navigation and orientation, and can be considered as a diagnostic tool in a clinical setting for both hippocampal and age related pathologies, such as MCI and AD.

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Publications

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Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation:

"Gaze behaviour and brain activation patterns during real-space navigation in hippocampal dysfunction"

selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation:

"Gaze behaviour and brain activation patterns during real-space navigation in hippocampal dysfunction"

is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 29.01.2019

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Stephanie Irving

Author contributions

The authors contributed to the publications, as follows:

1. **Stephanie Irving**: drafting/revising the manuscript, acquisition of data, analysis and interpretation of data, statistical analysis. Florian Schöberl: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis. Cauchy Pradhan: drafting/revising the manuscript, acquisition of data, analysis and interpretation of data, statistical analysis. Matthias Brendel: revising the manuscript, analysis and interpretation of data. Peter Bartenstein: revising the manuscript, analysis and interpretation of data. Marianne Dieterich: revising the manuscript, study concept and design, interpretation of data. Thomas Brandt: revising the manuscript, study concept and design, interpretation of data. Andreas Zwergal: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis. Florian Schöberl: drafting/revising the manuscript, study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis.

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I thereby certify that the abovementioned statements in regard to the author contributions are correct.

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