Hippocampal-dependent episodic memory and its relation to visual-perceptual processing

Doctoral thesis

to obtain a doctorate (PhD)

from the Faculty of Medicine

of the University of Bonn

Pitshaporn Leelaarporn

from Bangkok, Thailand

2024

Written with authorization of

the Faculty of Medicine of the University of Bonn

First reviewer: Dr. med. Dr. phil. Cornelia McCormick

Second reviewer: Prof. Dr. phil. Christoph Helmstaedter

Day of oral examination: 03 December 2024

From Klinik für Alterspsychiatrie und Kognitive Störungen / Department for Cognitive Disorders and Geriatric Psychiatry

Director: Prof. Dr. med. Anja Schneider

Table of Contents

List of abbreviations

AD	Alzheimer's Disease
AE	Autoimmune Encephalitis
AI	Autobiographical Interview
AM	Autobiographical Memory
AMI	Autobiographical Memory Interview
BOLD	Blood Oxygenation Level Dependent
bvFTD	Behavioural-variant Frontotemporal Dementia
CA	Cornu Ammonis
CSF	Cerebrospinal Fluid
CVLT	California Verbal Learning Tests
DCS-R	Diagnostikum für Zerebralschäden
DG	Dentate Gyrus
FACS	Fluorescence Activated Cell Sorting
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
HS	Hippocampal Sclerosis
LE	Limbic Encephalitis
MA	Mental Arithmetic
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
PB	Peripheral Blood
PFC	Prefrontal Cortex
RAVLT	Rey Auditory Verbal Learning Test
T	7 Tesla
TLE	Temporal Lobe Epilepsy
VLMT	Verbal Learning and Memory Test
vmPFC	Ventromedial Prefrontal Cortex
VVIQ	Vividness of Visual Imagery Questionnaire
WMS	Wechsler memory scale

1. Abstract

Our understanding of the mechanisms by which the human hippocampus mediates the relationship between episodic autobiographical memory and visual imagery remains limited. There is growing interest and further evidence on how the hippocampus supports the recollection of past personal experiences and influences the vividness of the images we visualize in our mind's eye.

In this thesis, the first study (Leelaarporn et al., 2024) investigates the neural processes involved in retrieving episodic autobiographical memory in healthy individuals. It utilizes a novel ultra-high field 7 Tesla fMRI sequence at submillimeter voxel size to capture the functional differentiation of the hippocampal subfields and their interactions with neocortical structures during memory retrieval. The second study (Monzel, Leelaarporn et al., 2024) investigates neural correlates of autobiographical memory in individuals with Aphantasia, who are characterized by absent or dim visual mental imagery. Furthermore, the third study (Hansen et al., 2022) explores the lymphocyte population as possible biomarkers for limbic encephalitis patients with memory dysfunction.

Taken together, the results suggest a complex relationship between autobiographical memory, visual-perceptual scene processing, and its dependence on the hippocampus. We propose specifically that the pre-/parasubiculum in the anterior body of the hippocampus may interact with the visual-perceptual cortex to orchestrate the recall of autobiographical memory retrieval. Damage to the hippocampal structure may be conducive to the deficits in episodic memory functions, highlighting the critical role of the hippocampus in maintaining the integrity of visual-perceptual processing. Future studies in individuals with hippocampal pathology are necessary to relate and map the functional and structural connectivity of this specific hippocampus-dependent processing.

2. Introduction and aims

Visual-perceptual processing enables most of us to perceive the visual-spatial world around us and episodic autobiographical memory (E-AM) enables us to later retrieve this information. This thesis focuses on the dependence of E-AM on visual-perceptual processing with a specific focus on the integrity of the hippocampus, a key brain region supporting both cognitive abilities. In the following paragraphs, a short overview of the neuroanatomy and functions of the hippocampus, as well as the theoretical framework of the current status quo of the relationship between E-AM and visual-perceptual processing are described.

2.1 Neuroanatomy of the hippocampus

The hippocampus is positioned deep within the mesial temporal lobe (MTL), adjacent to the amygdala and surrounded by the parahippocampal cortex, the perirhinal cortex, and the entorhinal cortex (Moscovitch et al., 2005). Its main body also borders the fimbria, in which its projection expands towards the cortical regions via the fornix. Along the longitudinal axis, the hippocampus has been divided into four portions: anterior, anterior body, posterior body, and tail (Berron et al., 2017). In addition, the crosssection of the hippocampus encompasses the uncus, dentate gyrus (DG), Cornu Ammonis (CA) 1-4, the subicular cortices (prosubiculum, subiculum, presubiculum, parasubiculum, and postsubiculum), and the entorhinal cortex. Efforts have been made to translate the individual sub-regions within the hippocampus from histologically stained slices to non-invasive imaging techniques (Ding, 2013; Lerma-Usabiaga et al., 2016; Zeidman und Maguire, 2016). This translation has led to the development of different protocols for manual hippocampal subfields segmentation and the introduction of automated software for this purpose (Berron et al., 2017; Dalton et al., 2017; Poiret et al., 2023; Winterburn et al., 2013; Wisse et al., 2017). However, despite these advancements, inconsistencies still exist regarding the presence of different regions within the hippocampus. These discrepancies are important because much scientific endeavor has been done to relate the precise subregions of the hippocampus to specific cognitive functions, with episodic memory and visual-perceptual processing amongst them.

2.2 The link between E-AM and visual-perceptual processing

The hippocampus is traditionally strongly associated with episodic memory (Addis et al., 2004; Scoville und Milner, 1957; Tulving und Markowitsch, 1998). Episodic memory retains the detailed information of events that are specific in spatial and temporal features (Conway, 2009; Moscovitch et al., 2016). Episodic autobiographical memory (E-AM), refers to our ability to retrieve vivid episodes from our personal past which are specific in time and place (Svoboda et al., 2006). Some researches separate E-AM recall in two distinct phases, the construction and elaboration phase. During the construction, the original event is reconstructed, and during the elaboration phase, episodic event details are recollected (Addis et al., 2007; Holland et al., 2011; Peters et al., 2019).

During the elaboration phase, the vividness of E-AM retrieval appears to be influenced by our ability to construct visual mental imagery (Sheldon und Levine, 2013). Visual mental imagery refers to our ability to reconstruct visual representations even when the actual visual stimuli are not present (Ganis und Schendan, 2011). This vivid visual imagery is typically thought of as containing mental models of three-dimensional scenes, populated by specific entities, such as people and/or objects (Maguire et al., 2016; Zeidman et al., 2015). In relation to E-AM, studies have demonstrated that mental scenes naturally arise in our mind’s eye when recalling specific E-AMs (Robin und Moscovitch, 2014). Furthermore, visual cues are found to prompt faster E-AM retrieval times and more detailed memories in comparison to other sensory cues (Anderson et al., 2017). Therefore, there is a clear connection between E-AM retrieval and visual-perceptual scene processing with high face validity. However, due to the inherent complexity and intertwined nature of these two cognitive processes, hardly any experimental research has been conducted to examine whether E-AM required vivid visual imagery.

One way to address this knowledge gap is to turn to inter-individual differences. In fact, the cognitive tendency to create vivid images in our mind’s eye is varied amongst individuals (Greenberg und Knowlton, 2014; Palombo et al., 2018). Of note, as visual imagery leads to the feeling of memory re-experiencing, weak or reduced visual imagery has been associated with lessened E-AM retrieval (Butler et al., 2016; Palombo et al.,

2018). This feature is especially pronounced in a population of individuals with Aphantasia. Aphantasia refers to a phenomenon in which people report to have no or only very dim voluntary visual mental imagery (Zeman et al., 2015). As expected, Aphantasics report far less detailed E-AMs than those without Aphantasia (Dawes et al., 2022). Furthermore, the hippocampus has also been shown to support the ability to conjure up mental models of visual-spatial scene imagery (Aly et al., 2013; De Luca et al., 2019; McCormick et al., 2017). Thus, whereas there is a hint of a strong connection between E-AM and visual-perceptual processing, potentially mediated by the hippocampus, further research is necessary to thoroughly test this connection. This includes investigating the specific hippocampal subregions.

2.3 The role of the hippocampal subregions in E-AM and visual-perceptual processing

There is an ongoing debate about the functional differentiation between hippocampal subregions, with regards to its long-axis as well as its subfields. Evidence from neuroimaging studies suggest the involvement of different portions preferentially in the anterior medial portion of the hippocampus during scene-based imagination and reconstruction, while the posterior portion has been shown to be active during scene perception, modulating fine and detailed information (Hodgetts et al., 2017; Tang et al., 2020; Zeidman und Maguire, 2016; Zeidman et al., 2015).

Potential functions of individual hippocampal subfields have been previously proposed. For instances, CA regions have been shown to be responsible for integration of information and details, including episodic memory by CA1 (Bartsch et al., 2011), recall precision and pattern completion by CA3 (Chadwick et al., 2014; Miller et al., 2020), and pattern separation by DG/CA4 (Berron et al., 2016). CA1, CA2, DG, and subiculum in the anterior hippocampus are thought to hold information from both remote and recent E-AM, while anterior CA3 and DG only concern details from remote E-AM (Bonnici et al., 2013). Of special interest in the light of the current thesis are efforts to pinpoint scene-based cognition to hippocampal subregions. As shown in non-human studies, large population of grid cells together with place cells, boundary vector cells, and head-direction cells are

localized within the presubiculum and the parasubiculum (pre-/parasubiculum), suggesting an involvement in constructing spatial representations (Boccara et al., 2010). In humans, these subregions have been shown to preferentially respond to scene-based distinctions (Hodgetts et al., 2017). Moreover, the anterior medial portion of the hippocampus, where the pre-/parasubiculum are anatomically located, has been coherently linked to scene construction as well as scene perception (Dalton und Maguire, 2017). Interestingly, it is precisely the anterior body of pre-/parasubiculum in which structural connectivity from the visual-perceptual cortex enters the hippocampus. Therefore, the pre-/parasubiculum may represent a pre-destined spot for scene-based cognition which may be crucial for vivid E-AM retrieval.

2.4 Functional hippocampal-neocortical connectivity during E-AM

During E-AM, multiple regions have been identified to be functionally engaged alongside the hippocampus. Typical regions consist of the bilateral prefrontal cortex (PFC), including the superior and inferior frontal gyri as well as the ventromedial prefrontal cortex (vmPFC), parahippocampal gyri, lateral parietal cortices, lateral temporal cortices, PCC/retrosplenial cortex, calcarine sulcus, and occipito-parietal regions (Bauer et al., 2016; Cîrneci et al., 2022; McCormick et al., 2018; Monk et al., 2021; Setton et al., 2022; Tang et al., 2020). Specifically, during the elaboration of E-AM, in contrast to the construction phase, the connections between the hippocampus and the visual-perceptual cortex seem to be crucial (McCormick et al., 2015). In this study, effective connectivity measures illustrated strong connections from both posterior hippocampi to the visual-perceptual cortices only during the vivid and detail-rich elaboration of E-AM. Moreover, the visual-perceptual processing routes have been shown to involve both dorsal and ventral parieto-medial temporal pathways and occipito-temporal processing pathway targeting the hippocampus directly (Kravitz et al., 2013). Together, there is evidence for a strong functional connection between the hippocampus and the visual-perceptual cortex which may facilitate the construction of mental models of spatially-coherent scenes used for vivid E-AM recall.

2.5 Clinical conditions associated with episodic memory deficits

The ability to recall vivid, detail-rich E-AMs is diminished in various clinical populations which are associated with hippocampal damage, such as Alzheimer's disease (AD), temporal lobe epilepsy (TLE), and limbic encephalitis (LE) (Hutchinson und Mathias, 2007; Irish, 2022; Irish et al., 2011; Johnen und Bertoux, 2019; Miró et al., 2019). In TLE, damages in the MTL regions are linked to the deficits in verbal (language) and figural (visual) aspects of E-AM (Helmstaedter, 2002; Helmstaedter et al., 1997). Functional lateralization has been previously described, designating the right hippocampus to visual and non-verbal, and the left hippocampus to language-dominated verbal memory (Gleiβner et al., 1998; Witt et al., 2014). These diseases underscore the role of the hippocampus in E-AM depending on the extent of the damage within the involved regions.

Rare autoimmune LE is characterized by the presence of autoimmune antibodies that target either surface or intracellular antigens and which are linked to inflammatory processes in the limbic system (Bien, 2022; Loane et al., 2019). These pathological changes potentially lead to the impairment of hippocampal-dependent episodic memory, behavioral changes, and emotional disturbances (Witt und Helmstaedter, 2021). The deficits typically involve impairments of anterograde and retrograde episodic memories both in the visual and verbal domain (Hansen, 2019; Lad et al., 2019). The extent of cell loss in the hippocampus differs among individuals (Witt et al., 2019; Witt und Helmstaedter, 2021).

Although not a clinical population, Aphantasia is associated with episodic memory impairment, potentially through a diminished ability to experience visual imagery (Monzel et al., 2021). In fact, aphantasics commonly produce less episodic details, such as event, place, and time details during E-AM recall than their controls (Arcangeli, 2023; Bainbridge et al., 2021; Dawes et al., 2022). Thus, the investigation of the neural correlates during E-AM retrieval in aphantasia offers the unique opportunity to study the link between E-AM and visual-perceptual processing in a non-clinical population.

2.6 Methodology

Understanding the hippocampus, its intricate sub-structures and its associated brain networks, is crucial for unraveling the mechanism of episodic memory and visual-perceptual processing. This endeavor necessitates the application of multifaceted methodological approaches. In the following paragraphs, I will briefly describe the methods which are relevant for the current thesis.

2.6.1 Magnetic Resonance Imaging

Advancements in newer non-invasive functional magnetic resonance imaging (fMRI) devices with the strength of 3 and 7 Tesla (T) have offered unparalleled opportunities to evaluate brain function and network connectivity during cognitive processing. Particularly, fMRI at 7 Tesla is a major step forward in neuroimaging technology that can shed light on the relationship between E-AM and visual-perceptual processing. In fact, the improved functional data achieve signal stability at much smaller voxel size (T. Vu et al., 2017; van der Zwaag et al., 2009; Yoo et al., 2018). Using 7 T MRI, it becomes possible to develop tailored fMRI sequences that enables data collection at a submillimeter voxel size across the entire brain. This, for the first time, allows the simultaneous assessment of hippocampal subfield activation in a whole-brain context, enabling connectivity analysis of individual hippocampal subregions and the neocortical interactions at an unprecedented spatial resolution.

2.6.2 Neuropsychological assessments

Standard neuropsychological assessments, designed to evaluate the level of cognitive performance, are useful for clinical assessments, diagnosis, and the monitoring of disease progression (Helmstaedter und Witt, 2012; McAndrews und Cohn, 2012). These assessments are crucial for understanding episodic memory impairments, as they provide observable information into cognitive functions linked to the hippocampus, enabling the identification and analysis of specific deficits that arise from hippocampal damage. Various tests and interviews exist to assess different aspects of neuropsychological

conditions, quantifying attention, executive functions, verbal, and figurative memory, aiding the examination of conditions with memory dysfunction (Witt und Helmstaedter, 2022). To evaluate E-AM, the Autobiographical Memory Interview (AMI), followed by Autobiographical Interview (AI), was developed to assess spatial and temporal richness from the interviewee's own events from different periods of life (Kopelman, 1994; Kopelman et al., 2008; Levine et al., 2002). The semi-structured AI uses a scoring approach to assess the episodic richness of visual-perception details (time, place, emotion, and perception). Moreover, the Vividness of Visual Imagery Questionnaire (VVIQ) has been used to assess the vividness of visual imagery (Marks, 1973). The result from this 16-item scale estimates the person's ability to visualize mental images and scenes. The VVIQ score ranges from 16 (low vividness) to 80 (high vividness). The cut-off score for an individual with low vivid imagery, hence aphantasia varies slightly amongst studies (25-32) (Bainbridge et al., 2021). Thus, the AI and the VVIQ are the gold-standard methods which can be used to evaluate E-AM and visual-perceptual processing.

Other test batteries such as the Wechsler memory scale (WMS) for verbal episodic memory, the Verbal Learning and Memory Test (VLMT) and the German counterpart of the Rey Auditory Verbal Learning Test (RAVLT) for verbal memory, the revised version of the Diagnostikum für Zerebralschäden (DCS-R) for figural memory, and the California Verbal Learning Tests (CVLT) for semantic vocabulary learning, are available in numerous clinics and centers for memory and cognitive evaluations (Helmstaedter et al., 2001; Helmstaedter et al., 2009). Attention and executive functions, which are known to be impaired in dementia and epilepsy patients, can also be assessed using EpiTrack® (Lutz und Helmstaedter, 2005). The higher the sensitivity of these tests, the higher the accuracy clinicians can identify the dysfunctions in specific cortical regions.

2.6.3 Flow Cytometry

Hippocampal deterioration may occur due to the localized deposition of inflammatory cells, which has been linked with episodic memory impairment (Heine et al., 2015). Flow cytometry is an innovative technology for precise identification and quantification of different cell types within complex tissues such as the hippocampus. Peripheral blood (PB) or cerebrospinal fluid (CSF) can be collected to determine the correlation between

immunological attributes and the cognitive performance. For clinical applications, flow cytometry is an innovative technology utilized for rapidly examining PB or CSF by separating different components including immune cells and antibodies which can be sorted for biomarkers for various diseases by Fluorescence Activated Cell Sorting (FACS) (Ryan et al., 1988). The detection of different antigen isotypes on T lymphocytes (T-cells) and B lymphocytes (B-cells) as well as the testing for neural antibodies are suitable methods for determining any suspected immune cell-mediated disease such as LE and Hippocampal Sclerosis (HS) (Hansen et al., 2020a; Hansen et al., 2020b; Helmstaedter et al., 2020). This analysis can offer additional information of the nature of inflammation affecting the hippocampus and potentially E-AM.

2.7 Aims

The overall aim of this thesis is to examine the relationship between E-AM, visual-perceptual scene processing and its reliance on the hippocampus. The aims of three publications are described with this larger goal in mind.

2.7.1 Differential activation and functional connectivity of hippocampal subfields during E-AM retrieval

The main aim of this study was to investigate the neural correlates of E-AM in the healthy brain using a highly customized, novel whole-brain 7T fMRI with submillimeter voxel size. This fMRI sequence allowed us, for the first time, to zoom into the functional differentiation of hippocampal subfields and their neocortical interactions. Following the aforementioned line of thoughts, we had the very specific hypothesis based on structural connectivity and previous neuroimaging work that the anterior body of the pre/parasubiculum would be more engaged during E-AM than the other hippocampal subregions (along the longitudinal axis and other subfields). A second aim was to examine the functional connectivity of individual hippocampal subregions during E-AM retrieval. This endeavor sought to enhance our understanding of hippocampal involvement during E-AM and start to disentangle episodic E-AM and visual-perceptual processes.

2.7.2 Neural correlates of E-AM deficits in Aphantasia

Since individuals with Aphantasia have no or weak visual mental imagery as a defining feature, they provide a natural model to test whether vivid E-AM relies on visual imagery. Whereas previous studies have shown an E-AM deficit associated with Aphantasia, the main goal of this study was to examine the neural correlates associated with this E-AM deficit. As described above, the hippocampus and its functional connectivity to the visual-perceptual cortex had been of particular importance during the vivid elaboration phase of E-AM. We therefore hypothesized that this connection should be altered in those with Aphantasia, who have presumably difficulties to elaborate on specific E-AMs.

2.7.3 Distinct biomarkers in LE patients with memory dysfunction

Memory impairment has been linked to the presence of autoantibodies in the hippocampus of patients with LE (Gibson et al., 2020). The altered levels of various immune cells and antibodies in the peripheral blood serum and CSF of LE patients have been speculated to correspond to different neuropsychological characteristics (Hansen et al., 2020a; Hansen et al., 2020b; Helmstaedter et al., 2020). These features, including verbal and/or figural memory, attention-executive functions, and mood, are frequently overlapped in patients. This alone often leads to the difficulty in distinguishing types of patients. Thus, we aimed to examine the lymphocytes and autoantibodies using flow cytometry and identify their respective cognitive parameters. Matching the cellular profiles to the neuropsychological phenotypes could assist classifying LE patients and understanding their impairments.

3. Publications

3.1 Publication 1: Hippocampal subfields and their neocortical interactions during autobiographical memory

Imaging Neuroscience
an open access journal

Research Article

Hippocampal subfields and their neocortical interactions during autobiographical memory

Pitshaporn Leelaarporn[a,b], Marshall A. Dalton[c], Rüdiger Stirnberg[b], Tony Stöcker[b,d], Annika Spottke[b], Anja Schneider[a,b], Cornelia McCormick[a,b]

[a]Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn Medical Center, Bonn, Germany
[b]German Center for Neurodegenerative Diseases, Bonn, Germany
[c]School of Psychology, The University of Sydney, Sydney, Australia
[d]Department of Physics and Astronomy, University of Bonn, Bonn, Germany

Author: Pitshaporn Leelaarporn (pitshaporn.leelaarporn@ukbonn.de)

ABSTRACT

Advances in ultra-high field 7 Tesla functional magnetic resonance imaging (7 T fMRI) have provided unprecedented opportunities to gain insights into the neural underpinnings supporting human memory. The hippocampus, a heterogeneous brain structure comprising several subfields, plays a central role during vivid re-experiencing of autobiographical memories (AM). However, due to technical limitations, how hippocampal subfields differentially support AM, whether this contribution is specific to one portion along the hippocampal long-axis, and how subfields are functionally connected with other brain regions typically associated with AM retrieval remains elusive. Here, we leveraged technical advances of parallel imaging and employed a submillimeter Echo Planar Imaging sequence over the whole brain while participants re-experienced vivid, detail-rich AM. We found that all hippocampal subfields along the long-axis were engaged during AM retrieval. Nonetheless, only the pre/parasubiculum within the anterior body of the hippocampus contributed over and above to AM retrieval. Moreover, whole-brain functional connectivity analyses of the same data revealed that this part of the hippocampus was the only one that was strongly connected to other brain regions typically associated with AM, such as the ventromedial prefrontal cortex (vmPFC) and medial/lateral parietal regions. In the context of the broader literature, our results support recent proposals that the anterior body of the pre/parasubiculum may play an important role in scene-based cognition, such as its engagement during the re-experiencing of personal past events.

Keywords: autobiographical retrieval, episodic memory, neural networks, functional connectivity, 7 Tesla functional MRI, hippocampal subfields

1. INTRODUCTION

Neuropsychological and functional magnetic resonance imaging (fMRI) studies have firmly established the hippocampus as a central structure underpinning vivid autobiographical memory (AM, i.e., memories of personal past events). The hippocampus is a heterogeneous brain structure comprising several subfields, including the dentate gyrus (DG), cornu ammonis (CA) 1-4, subiculum, presubiculum, and parasubiculum (hereafter referred to collectively as the pre/parasubiculum). The hippocampus interacts with a broader set of brain areas that together comprise the AM network. This network includes areas in the ventromedial prefrontal cortex (vmPFC) and medial/lateral parietal cortices (Addis et al., 2007; McCormick

Received: 10 August 2023 Revision: 15 February 2024 Accepted: 15 February 2024 Available Online: 22 February 2024

et al., 2015, 2020; Moscovitch et al., 2005; Rosenbaum et al., 2008; Scoville & Milner, 1957). While we have a broad understanding that the hippocampus works within this network to support AM retrieval, we lack a detailed understanding of how hippocampal subfields interact with cortical areas of the AM network during AM retrieval. To address this gap, we leveraged recent advances in ultra-high field 7-Tesla functional magnetic resonance imaging (fMRI), to: (i) examine the contributions of hippocampal subfields to AM; (ii) assess how this differs along the anterior-posterior axis of hippocampal subfields; and (iii) characterize their associated functional connectivity with the neocortex.

AM retrieval is a complex cognitive process supported by a dynamic interplay between brain areas within the AM network (Conway, 2009; Conway & Pleydell-Pearce, 2000; McCormick et al., 2015; Sekeres et al., 2018). It is widely acknowledged that the hippocampus plays a central role in this network and is consistently and reliably activated during AM retrieval, including at the single-subject level. Several studies have investigated the relationship between hippocampal subfields and AM, albeit with mixed results (Barry et al., 2021; Bartsch et al., 2011; Bonnici et al., 2013; Chadwick et al., 2014; Miller et al., 2020; Palombo et al., 2018). For example, Bonnici et al. (2013), Chadwick et al. (2014), and Miller et al. (2020) reported evidence that the CA3 region may be particularly involved in AM retrieval while Bartsch et al. (2011) speculated a key role of the CA1 region. Furthermore, Palombo et al. (2018) and Barry et al. (2021) found support for a central position of the subiculum and pre/parasubiculum in AM retrieval. However, these mixed observations may result from methodological differences across these studies which used different subfield segmentation protocols (e.g., Bonnici et al. (2013) did not segment the pre/parasubiculum), different imaging modalities/analysis (i.e., structural versus functional MRI), and different measures of AM retrieval success (i.e., interview-based markers versus task-based fMRI, etc). Taking this into consideration, our understanding of how hippocampal subfields preferentially engage during AM retrieval remains limited.

In addition to its subfields, functional differentiation has also been observed along the longitudinal axis of the hippocampus (Poppenk et al., 2013, Strange et al., 2014, Zeidman et al., 2016). Interestingly, an increasing number of 3 T fMRI studies have observed that a specific region in the anterior medial hippocampus is consistently engaged during AM tasks (see Zeidman et al., 2016 for review). While the majority of these studies did not have the spatial resolution to explicitly examine hippocampal subfields, activation patterns consistently align with the medial most portion of the anterior body of the hippocampus, aligning with the location of the pre/parasubiculum and distal subiculum. Indeed, the pre/parasubiculum has recently been proposed as crucial hub for scene-based cognition (Dalton & Maguire, 2017) and subsequent experimental work has provided empirical support that this specific region preferentially engages during scene-based cognition (Dalton et al., 2018; Grande et al., 2022). In addition, previous research has shown that this region of the anterior medial body of the hippocampus (aligning with the location of the pre/parasubiculum) was functionally connected with parts of the AM network, including the vmPFC and medial/lateral parietal cortices during the vivid re-experiencing of autobiographical memories (McCormick et al., 2015). Despite these preliminary insights, we do not know how different portions of hippocampal subfields along their anterior-posterior axis engage during AM retrieval.

As noted above, traditional 3 T fMRI sequences at a whole-brain level and a reasonable repetition time are usually limited to a voxel size of approximately 3 mm isotropic, thus prohibiting accurate functional imaging of small brain structures like hippocampal subfields in a whole-brain setting (Willems & Henke, 2021). Technical advances in high-resolution 3 T fMRI have facilitated an increase in spatial resolution that can be used to capture dissociable activity of small adjacent brain structures of the medial temporal lobes, including hippocampal subfields (Bonnici, Chadwick, Lutti, et al., 2012; Dalton, McCormick, & Maguire, 2019; Dalton, McCormick, De Luca, et al., 2019). However, these sequences require a reduced field-of-view for a reasonable spatiotemporal resolution, thus precluding detailed examination of hippocampal subfield interactions with the broader AM network. Recent innovations in ultra-high field 7 Tesla (7 T) fMRI sequence development including 2D high parallel imaging acceleration capabilities now permit submillimeter voxel sizes at a whole-brain level while keeping temporal resolution high (Stirnberg & Stöcker, 2021; Stirnberg et al., 2017). In the current study, we leveraged these technological advances to conduct a fine-grained examination of functional connectivity between hippocampal subfields along their longitudinal axis and the neocortex during AM retrieval.

To date, a few studies have investigated memory signals using 7 T fMRI (Berron et al., 2016; Grande et al., 2019; Risius et al., 2013). For example, recent reduced field-of-view 7 T fMRI studies examined hippocampal subfield contributions to distinguish between or combine similar experiences (Berron et al., 2016; Grande et al., 2019). Other neuroimaging studies have exploited advances of 7 T fMRI to study targeted layer-specific effects of mnemonic processes (Finn et al., 2019; Maass et al., 2014; Norris & Polimeni, 2019). However, to our

knowledge, no study has hitherto leveraged both increased speed and spatial resolution of 7 T fMRI to examine differential hippocampal subfield–neocortical interactions during AM retrieval.

Here, we deployed ultra-high field 7 T fMRI with a dedicated AM retrieval task to achieve two primary goals: (1) to investigate the differential activation of hippocampal subfields along their longitudinal axis during AM retrieval, and (2) to examine hippocampal subfield functional connectivity with neocortical brain regions associated with the AM network.

2. MATERIALS AND METHODS

2.1. Participants

Twenty-four healthy young individuals (right-handed, age: 26.66 ± 4.15 years old, Males: 12, Females: 12) with no history of neurological or psychiatric disorders and normal or corrected-to-normal vision were recruited. All participants completed secondary level of education (at least 12 years of education). All participants provided oral and written informed consent in accordance with the local ethics board.

2.2. Autobiographical memory and visual imagery assessment

In order to examine vivid, detail-rich AM retrieval, we only included participants who reported being able to recall detail-rich personal memories and construct mental images with ease. Each participant was first asked to assess their ability to recall vivid AMs on a Likert scale from 1 to 6 (1 = able to recall detail-rich memories; 6 = unable to recall any personal events). Participants were also asked to assess their ability to construct vivid mental images on a Likert scale from 1 to 6 (1 = able to create detail-rich mental images; 6 = lack of visual imagery). This procedure was adapted from Clark and Maguire (2020) in which the authors demonstrated that these questions effectively captured the ability to engage in AM retrieval.

2.3. Experimental fMRI task

The experimental task was adapted from a previous protocol by McCormick et al. (2015). The experimental procedure was clarified to the participants prior to the scanning. Participants were presented with a set of 40 randomized trials consisting of an AM retrieval task and a simple mental arithmetic (MA) task. As MA task generally does not involve the activation of hippocampus or memory, it was chosen to serve as a baseline. Each trial lasted a maximum of 17 s with a jittered inter-stimulus interval (ISI) between 1 and 4 s. The AM trials consisted of word cues of various general events, for example, birthday celebration. Once the stimulus appeared on the screen, participants were instructed to search covertly for a relevant personal event which was specific in time and place and more than 1 year ago and press a response button once a memory had been chosen without verbally describing it. Participants were then asked to re-experience the memory in their mind by re-living the event with as many perceptual details as possible. In comparison, the MA trials consisted of simple addition or subtraction problems, for example, 13 + 53. After the MA problem was solved, participants were instructed to press a response button and add 3 to the solution iteratively, for example, (13 + 53) + 3 + 3n. Following all AM trials, participants were asked to indicate with a button press whether the AM had been re-experienced in a detailed manner or whether the retrieval was faint. Following all MA trials, participants were asked to indicate with a button press whether the MA problem had been easy or difficult.

2.4. MRI data acquisition

MRI data were acquired using a MAGNETOM 7 T Plus ultra-high field scanner (Siemens Healthineers, Erlangen, Germany). Participants viewed the stimulus screen placed at the back end of the scanner bore through a mirror mounted between the inner 32 channel receiver head coil and the outer circular polarized transmit coil. The MRI protocol consisted of the following scans:

2.4.1. Whole-brain T1-weighted structural image

A 0.6 mm isotropic whole-brain T1-weighted multi-echo MP-RAGE scan was acquired using a custom sequence optimized for scanning efficiency (Brenner et al., 2013) and minimal geometric distortions (van der Kouwe et al., 2008) (TI = 1.1 s, TR = 2.5 s, TEs = 1.84/3.55/5.26/6.92 ms, FA = 7°, TA = 7:12, readout pixel bandwidth: 970 Hz, matrix size: 428 x 364 x 256, elliptical sampling, sagittal slice orientation, CAIPIRINHA (Breuer et al., 2006) 1 x 2_{z1} parallel imaging undersampling with on-line 2D GRAPPA reconstruction, turbofactor: 218). Finally, the four echo time images were collapsed into a single high-SNR image using root-mean-squares combination.

2.4.2. Reduced hippocampus field-of-view T2-weighted structural image

For motion-robust hippocampal subfield-segmentation, three rapid, 0.4 mm x 0.4 mm x 1.0 mm T2-weighted, slice-selective TSE scans were acquired consecutively on a reduced hippocampus field-of-view (TE = 76 ms, TR = 8090 ms, FA = 60° using Hyperecho (Hennig &

Scheffler, 2001), TA = 2:59, readout pixel bandwidth: 150 Hz, matrix size: 512 x 512, 55 oblique-coronal slices of 1 mm thickness orthogonal to the long hippocampus axis, 3-fold parallel imaging undersampling with online 1D GRAPPA reconstruction, turbofactor: 9). The RF transmit power reference voltage was varied across the scans (200 V, 240 V, 280 V) such that the nominal refocusing flip angles of the protocol were approximately reached in all brain regions in at least one of the scans. Finally, the three images from each participant were coregistered, denoised following the Rician noise estimation (Coupé et al., 2010), and averaged.

2.4.3. *Rapid whole-brain submillimeter fMRI*

A custom interleaved multishot 3D echo planar imaging (EPI) sequence was used (Stirnberg & Stöcker, 2021) with the following paramaters: TE = 21.6 ms, TR_{vol} = 3.4 s, FA = 15°, 6/8 partial Fourier sampling along the primary phase encode direction, oblique-axial slice orientation along the anterior-posterior commissure line, readout pixel bandwidth: 1136 Hz, matrix size: 220 x 220 x 140. To obtain both a high nominal spatial resolution of 0.9 mm isotropic at TR_{vol} = 3.4 s while imaging the whole brain at sufficient signal-to-noise-ratio (SNR) with a BOLD-optimal TE, several unique sequence features were combined for this work at 7 T. (A) Skipped-CAIPI 3.1 x 7_{z2} sampling (SNR-optimized 7-fold CAIPIRINHA undersampling combined with interleaved 3-shot segmentation) (Stirnberg & Stöcker, 2021) with on-line 2D GRAPPA reconstruction. (B) One externally acquired phase correction scan per volume instead of typically integrated phase correction scans per shot (Stirnberg & Stöcker, 2021). (C) Variable echo train lengths, skipping only the latest EPI echoes outside of a semi-elliptical k-space mask that defines 0.9 mm isotropic voxel resolution (Stirnberg et al., 2017). (D) Rapid slab-selective binomial-121 water excitation instead of time-consuming fat saturation (Stirnberg et al., 2016). A 3-min fMRI practice-run was performed before the two main functional sessions, which lasted approximately 15 min each. The MRI session was concluded by a standard 3 mm isotropic two-echo gradient-echo field-mapping scan acquired within 35 s. A maximum number of 264 imaging volumes were acquired from each functional session. The first five images consisting of the waiting period of 17 s prior to the beginning of the first trial were excluded to rule out non-steady-state signals.

2.5. MRI data processing

2.5.1. *Segmentation of hippocampal subfields*

Manual segmentation of hippocampal subfields was performed on the averaged and denoised native space T2-weighted structural scans according to the protocol described by Dalton et al. (2017). ROI masks were created for six hippocampal subfields, including DG/CA4, CA3/2, CA1, subiculum, pre/parasubiculum, and uncus using the software application ITK-SNAP 3.8 (Yushkevich et al., 2006). We excluded the uncus from our analyses because this region contains a mix of different hippocampal subfields (Ding & Van Hoesen, 2015) that are difficult to differentiate on structural MRI scans (Dalton et al., 2017) even with the high-resolution achieved in the current study. To assess intra- and inter-rater reliability, five hippocampi were segmented by two independent raters (P.L. and M.A.D) and again 6 months after initial segmentation. The inter-rater reliability as measured by the DICE overlap metric (Dice, 1945) was in accordance with those reported in the existent literature (Bonnici, Chadwick, Kumaran, et al., 2012; Palombo et al., 2013): DG/CA4 = 0.87 (aim 0.86-0.80), CA3/2 = 0.73 (aim of 0.74-0.67), CA1 = 0.80 (aim of 0.81-0.67), subiculum = 0.80 (aim of 0.79-0.57), and pre/parasubiculum = 0.64 (aim of 0.67-0.57). Intra-rater reliability was measured 8 months apart and also showed high concordance between segmentations at the two different time points (0.92 for DG/CA4, 0.79 for CA3/2, 0.84 for CA1, 0.84 for subiculum, and 0.86 for pre/parasubiculum).

2.5.2. *Segmentation of hippocampal subfields in anterior, anterior body, posterior body, and tail*

Each hippocampal subfield ROI mask was divided into four portions along the longitudinal axis of the hippocampus (anterior, anterior body, posterior body, and tail) using the software application ITK-SNAP 3.8, according to the protocol described by Dalton et al. (2017, 2019). The anterior masks encompassed the first slice on which the hippocampus was visible up to the slice preceding the first slice of the DG. The mean number of slices in the anterior mask was 7.67 (SD = 2.01). The remaining slices, beginning with the first slice of the DG until the last slice of the hippocampus, were summed and divided into three parts to create equivalent slices in the anterior body, posterior body, and tail, resulting in a mean of 11.04 (SD = 1.01), 10.73 (SD = 0.98), and 10.54 (SD = 0.94) slices respectively. The average total number of slices covering the hippocampus was 39.98 (SD = 2.57).

2.5.3. *Functional MRI preprocessing*

To address both research aims, two steps of MRI preprocessing were performed using SPM12 (Statistical Parametric Mapping 12) software package (www.fil.ion.ucl.ac.uk/spm/) on MATLAB v17a (MathWorks) computing platform (https://matlab.mathworks.com/). For both steps,

the anatomical and the functional scans obtained from each subject were reoriented to be in line with the anterior-posterior commissure axis. The field maps, including the phase and magnitude images, were used to calculate the voxel displacement maps (VDM) to geometrically correct the distorted EPI images. The VDMs were then applied to the functional scans during realignment and unwarping. The averaged anatomical scans (and hippocampal subfield masks) were co-registered with the functional scans (see Fig. S1). After motion correction and co-registration, the preprocessing pipelines for the two research aims diverged: For the first aim (to examine differential activation of hippocampal subfields), fMRI data were kept in native space to allow maximum spatial precision. Only a sparse Gaussian smoothing kernel of 1 mm full-width half-maximum (FWHM) to reduce excess noise (Yoo et al., 2018) and a temporal high-pass filter of 128 s was applied to the function data. Then, one-sample T-Test contrasts (T-contrasts) were calculated to test the effects of AM retrieval versus baseline (MA). For the second aim (to examine functional connectivity of hippocampal subfields to other neocortical regions), motion-corrected and co-registered fMRI data were normalized to the Montreal Neurological Institute (MNI) space and smoothed with a slightly smaller than standard 6 mm FWHM to examine activation and functional connectivity at the group level.

Additionally, in order to mitigate the artifacts produced by unsolicited movements during the functional tasks for further exclusion criteria, we screened for motion artifact outliers in the time series using the ARtifact detection Tools (ART) software package (v2015). The standard threshold of outlier detection if motion exceeds the 97th percentile of the global mean intensity (relating to under 1 mm motion) for more than 10% of the number of the scans. No excessive motion was detected; hence, no participant was excluded from the study.

2.6. Statistical analyses

2.6.1. Hippocampal subfield activation extraction

For the native space fMRI analyses, we followed the standard GLM procedure in SPM12 with trials designated as mini blocks and covering the elaboration period fixed at the last 8 s of the stimulus time and prior to the display of the vividness rating. Since only a few trials were rated as faint/difficult, we included all trials in our analyses. Furthermore, motion correction parameters were included in the GLM as covariate of no interest. The contrasts of interest of the first level were specified as (1) AM versus Baseline and (2) MA versus Baseline. Signal intensity values were extracted for both contrasts for the five right and five left hippocampal subfield ROIs covering the entire length of the hippocampus. We then subtracted the signal intensities for MA from the signal intensities for AM for each of the ROIs for each participant. In a second step, we extracted signal intensities for AM and MA of the five right and five left hippocampal subfields for the anterior body, posterior body, and tail portions separately. Signal intensities were extracted for each participant in native space using MATLAB-based Response Exploration (REX) toolbox (https://www.nitrc.org/projects/rex) by applying the segmented ROI masks. Since we found no evidence of laterality effects ($t = 1.04$, $df = 23$, $p = 0.3568$, see Table S1), signal intensities for bilateral subfields were collapsed. Differential signal intensity values were subjected to a 1-way-RM-ANOVA with Tukey's multiple-comparison test. A significance threshold of $p < 0.05$ was applied. Furthermore, the temporal signal-to-noise ratios (tSNR) across the fMRI time series along the longitudinal axis of the hippocampal subfields were examined and the 1-way-RM-ANOVA with Dunnett's multiple-comparison tests were applied (see Fig. S2).

2.6.2. Group analyses of whole-brain activation and hippocampal subfield functional connectivity

First, to assess differences between AM and MA, a multivariate mean-centered partial least squares (PLS) group analysis was performed. Detailed descriptions of PLS can be found elsewhere (Krishnan et al., 2011; McIntosh & Lobaugh, 2004). In brief, PLS uses singular value decomposition to extract ranked latent variables (LVs) from the covariance matrix of brain activity and conditions in a data-driven manner. These LVs express patterns of brain activity associated with each condition. Statistical significance of the LVs was assessed using permutation testing. In this procedure, each participant's data were randomly reassigned (without replacement) to different experimental conditions, and a null distribution was derived from 500 permutated solutions. We considered LVs as significant at $p < 0.05$. Furthermore, we assessed the reliability of each voxel that contributed to a specific LV's activity pattern using a bootstrapped estimation of the standard error (bootstrap ratio, BSR). For each bootstrapped solution (100 in total), participants were sampled randomly with replacement and a new analysis was performed. In the current study, we considered clusters of 50 or more voxels with BSRs greater than 3 (approximately equal to a $p < 0.001$) to represent reliable patterns of activation. Of note, PLS uses two re-sampling techniques that (1) scramble the data of each participant's conditions so that small but reliable differences between true experimental conditions can be detected, and (2) exclude whole datasets of participants, so that outliers who may drive significant effects can be detected.

To assess functional connectivity between hippocampal subfields and the rest of the brain, seed PLS, an extension of the mean-centered PLS was used (McIntosh & Lobaugh, 2004). Seed PLS examines the relationship between a target region (seed region) and signal intensities in all other brain voxels as a function of the experimental conditions (Krishnan et al., 2011). The main difference to the mean-centered PLS is that, in seed PLS, the covariance matrix used in the single value decomposition stems from correlation values between the seed region and all other voxels for each experimental condition. Thus, seed PLS offered us to examine the multivoxel patterns which correlate with fMRI signal extracted from individual hippocampal subfields. Signal intensities of individual subfields (extracted in native space) were used as seeds for the group analyses (performed in MNI space). We conducted three seed PLS analyses (1. anterior body, 2. posterior body, and 3. tail) containing all five hippocampal subfields and contrasting AM versus MA trials. A significance threshold for the LV's (500 permutations) was $p < 0.05$. After establishing whether the functional connectivity pattern differed between AM and MA across all five subfields for a specific portion of the hippocampal long-axis, we then examined this portion more closely with follow-up PLS analyses. In these post hoc analyses, functional connectivity of each of the five hippocampal subfields was assessed separately and a Bonferroni multiple-comparison correction was applied so that we considered statistical significance for the LV's at $p < 0.01$ (see for a similar approach (McCormick et al., 2021)). Boot strap ratios (100 bootstraps) of <3 and >3 (corresponding approximately to a $p < 0.01$) were considered significant.

3. RESULTS

3.1. Behavioral results

All 24 participants reported being able to recall detail-rich autobiographical memories (average of 1.92 ± 0.67, 1 = able to recall detail-rich memories; 6 = unable to recall any personal events) and construct vivid mental images (average of 1.83 ± 0.69, 1 = able to create detail-rich mental images; 6 = lack of visual imagery). During scanning, the participants spent 3.53 s (±0.98) on average to select a memory and around 3.66 s (±0.97) to solve the MA problem. Whereas some trials were excluded from the analyses due to missing button presses, no significant difference was found between the speed of AM retrieval and MA solving ($t = 0.8601$, $p = 0.3958$). Participants indicated in 35.67 (±4.67) trials out of 40 trials that their memories were vivid ($t = 19.36$, $df = 23$, $p < 0.0001$) and 28.13 (±6.15) trials out of 40 MA problems were reported as easy ($t = 8.553$, $df = 23$, $p < 0.0001$).

3.2. Hippocampal subfield activation during AM

Greater bilateral hippocampal activation during AM retrieval than MA solving was found in all participants (see Fig. 1). Furthermore, all hippocampal subfields showed greater activation during AM retrieval than solving an MA problem (DG/CA4: $t = 6.140$, $df = 23$, $p < 0.001$, CA2/3: $t = 5.217$, $df = 23$, $p < 0.001$, CA1: $t = 3.768$, $df = 23$, $p = 0.001$, subiculum: $t = 3.068$, $df = 23$, $p = 0.005$, pre/parasubiculum: $t = 4.637$, $df = 23$, $p < 0.001$, Bonferroni corrected). Further analyses revealed differences in hippocampal subfield activity associated with AM retrieval ($F = 5.887$, $df = 5$, $p = 0.017$, Fig. 1 and Table S1 for an overview of % signal changes). In line with our hypothesis (Fig. 1E), we found that activation during AM was much stronger in the pre/parasubiculum compared with CA1 ($df = 23$, $p = 0.001$), the subiculum ($df = 23$, $p = 0.001$), CA2/3 ($df = 23$, $p = 0.049$), and at a non-significant trend level in DG/CA4 ($df = 23$, $p = 0.075$). There were no other significant differences between subfield activation associated with AM retrieval.

3.3. Hippocampal subfield activation along its longitudinal axis during AM

Next, we assessed differential subfield engagement of the anterior body, posterior body, and tail portions separately. Strikingly, the RM-ANOVA found a main effect of subfield activation levels in the anterior body of the hippocampus ($F = 4.440$, $df = 4$, $p = 0.024$, see Fig. 1G) but not in the posterior body ($F = 1.650$, $df = 4$, $p = 0.1895$) or tail ($F = 1.157$, $df = 4$, $p = 0.3286$) of the hippocampus (Fig. 1H and 1I, respectively). The anterior (the first 7.67 slices on average) was omitted from these analyses due to (1) significantly less number of slices and voxel count compared to the other portions and (2) not all subfields being present in this portion of the hippocampus (e.g., the DG). No signal intensity was detected in the anterior portion in one participant, possibly due to signal drop out. Post hoc analyses revealed that, in the anterior body portion of the hippocampus, activation relating to AM versus MA was much stronger in the pre/parasubiculum than in CA1 ($df = 23$, $p < 0.001$), CA2/3 ($df = 23$, $p = 0.019$), subiculum ($df = 23$, $p = 0.034$), and DG/CA4 ($df = 23$, $p = 0.034$). There were no other significant differences between anterior body subfields in activation associated with AM retrieval (see Table S2 for signal change during AM versus MA tasks). Further comparison ($F(2, 23) = 9.878$, $p < 0.001$) revealed that the activation difference (AM versus MA) of the pre/parasubiculum in

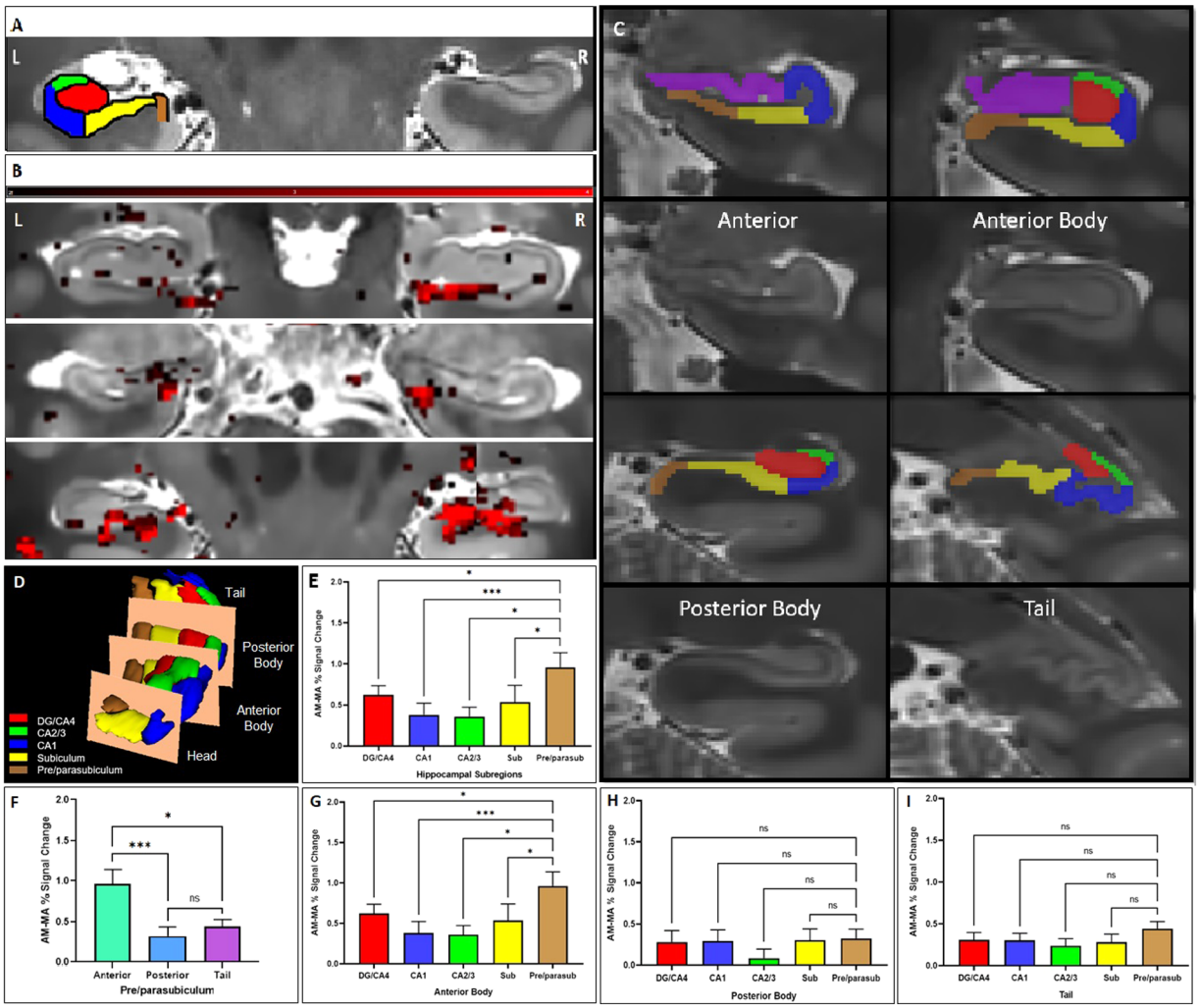

Fig. 1 (Color). Differential hippocampal subfield engagement during AM retrieval. (A) Overlaid segmentation of labeled hippocampal subfields, including the DG, CA1-4, subiculum, and pre/parasubiculum on high-resolution structural T2-weighted scan. (B) Examples of AM versus MA activation along the longitudinal axis of the hippocampus (shown in red) from three participants (Y coordinates from upper to lower panels of 20, 17, and 27, beginning from rostral to caudal of 55 slices, respectively). (C) Examples of manual hippocampal subfields segmentation for signals extraction. The subfields along the longitudinal axis are divided into four portions of anterior, anterior body, posterior body, and tail (Y coordinates of 16, 21, 38, and 46, respectively). (D) Hippocampus subfields along the longitudinal axis. (E) The comparison between the % signal change during AM and MA in hippocampal subfields (DG/CA4, CA1, CA2/3, subiculum, and pre/parasubiculum). The pre/parasubiculum showed stronger differentiation between AM and MA than most other subfields. (F) This effect was driven by the anterior body part of the hippocampus. (G) The anterior body of the pre/parasubiculum shows greater differentiation between AM and MA than all other subfields, whereas no significant difference was found in the posterior body (H) nor the tail (I). *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$, and + $p < 0.1$ (non-significant trend level).

the anterior body was stronger than the pre/parasubiculum in the posterior body ($df = 23$, $p < 0.001$) and the tail ($df = 23$, $p = 0.020$).

3.4. Hippocampal subfield-neocortical interactions during AM

On a whole-brain, whole-group basis, we found greater activation during AM retrieval than MA in all regions typically associated with AM retrieval, including bilateral hippocampal activation as well as vmPFC and medial/lateral parietal activation (LV1, $p < 0.0001$, see Fig. 2 and Table S3 for peak MNI coordinates).

Next, we evaluated patterns of functional connectivity along the long-axis of the hippocampus. We found that only functional connectivity patterns of the anterior body of the hippocampus differed between AM and MA (anterior body: LV 1, $p = 0.027$, posterior body: LV 1, $p = 0.51$, tail: LV 1, $p = 0.64$). In Bonferroni corrected post hoc analyses (thus applying a threshold of $p < 0.01$), we found that

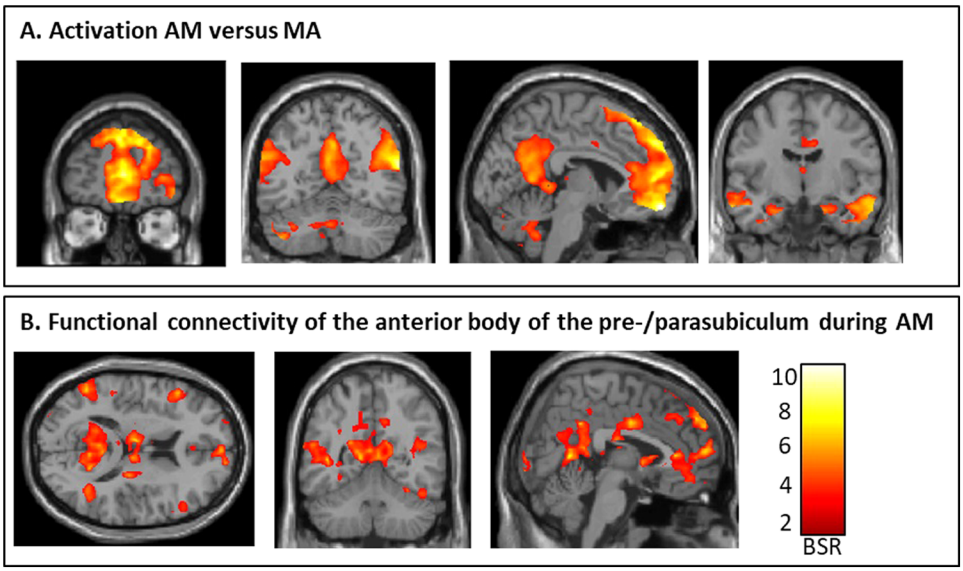

Fig. 2. Hippocampal subfield functional connectivity during AM. (A) Greater activation for AM versus MA is shown in bootstraps ratios (BSR). All regions typically associated with AM show greater activation of bilateral hippocampi, vmPFC, and medial/lateral parietal cortex for AM. The whole-brain fMRI activation is overlaid on a standard T1-weighted MRI image. (B) Greater functional connectivity of the anterior body of the pre/parasubiculum during AM than MA is shown. All regions typically associated with AM retrieval show strong functional connectivity, including vmPFC and medial/lateral parietal cortices.

only the functional connectivity of the pre/parasubiculum differed between both conditions (pre/parasubiculum: $p < 0.001$), whereas the other subfields did not (DG/CA4: $p = 0.53$, CA2/3: $p = 0.16$, CA1: $p = 0.36$, subiculum: $p = 0.28$). Figure 2 illustrates the brain pattern associated with functional connectivity of the anterior body of the pre/parasubiculum during AM, including all canonical regions typically associated with AM, including the vmPFC and medial/lateral parietal cortices (see Table S4 for peak MNI coordinates and Table S5 for peak MNI coordinates of MA). In addition to these areas that are traditionally associated with the AM network, the anterior body of the pre/parasubiculum also showed significant functional connectivity with posterior visual-perceptual cortices (i.e., right lingual gyrus and bilateral fusiform gyrus) during AM than MA.

4. DISCUSSION

By exploiting a novel whole-brain 7 T fMRI sequence with submillimeter voxel size, this study provides two novel insights into hippocampal memory processes. First, we found evidence that the anterior body of the pre/parasubiculum was significantly more engaged during the vivid re-experience of AMs than other hippocampal subfields. Second, during AM, only the anterior body of the pre/parasubiculum showed stronger functional connectivity to neocortical brain regions typically engaged during AM retrieval over and above other hippocampal subfields. We discuss these findings in turn.

We observed that all hippocampal subfields differentiated between AM and MA with the pre/parasubiculum differentiating between cognitive tasks to a greater extent than the neighboring subiculum and CA fields. While our AM task was not designed to specifically target different cognitive states (i.e., scene-specific content), our finding indicates that overall AM retrieval preferentially engages the pre/parasubiculum. Examining our study design closer, we only included participants who reported to be able to retrieve visually detail-rich AMs easily and we focused our analyses on the last 8 s of the AM trials. This served to highlight the period in which participants were most likely engaged in re-experiencing visual-perceptual imagery. One explanation for our findings, therefore, is that the pre/parasubiculum is preferentially engaged in tasks which rely on vivid scene-based cognition (Dalton & Maguire, 2017). For example, previous work suggests that the pre/parasubiculum is more strongly activated during scene-imagery than object-imagery (Dalton et al., 2018; Zeidman et al., 2015), and scene/object discrimination (Hodgetts et al., 2017). Furthermore, we know from rodents and nonhuman primates that the pre/parasubiculum contains an abundance of head, grid, and border cells (Boccara et al., 2010; Lever et al., 2009; Robertson et al., 1999), which has recently been extended to human goal direction cells (Shine et al., 2019). Arguably, AM retrieval relies heavily on scene-based cognition since AMs tend to unfold on a visuo-spatial stage (Greenberg & Knowlton, 2014). In fact, when participants

are asked to imagine personal events, they tend to place the event onto a spatial stage (Robin et al., 2018), indicating that visuo-spatial imagery plays a fundamental role in episodic memory retrieval. Further strengthening the tight link between the ability to recall AMs and visual imagery, people with little or no ability to experience visual imagery, commonly referred to as aphantasics, also tend to have difficulties recalling AM (Dawes et al., 2020; Milton et al., 2021; Zeman et al., 2015, 2020). Interestingly, aphantasics not only have difficulties to recall visual-perceptual details to their AMs, but they seem to have a worse ability to retrieve personal memories in general (Dawes et al., 2020) and show poorer verbal and non-verbal memory function (Monzel et al., 2021). In fact, a recent phenomenon called severe deficient autobiographical memory or SDAM (Palombo, Sheldon, et al., 2018; Watkins, 2018) has also been associated with aphantasia (Pearson, 2019). This line of thought meshes well with the scene construction theory positing that a dominant function of the hippocampus is to construct spatially coherent internal models of the environment (Dalton & Maguire, 2017; Maguire & Mullally, 2013; McCormick, Ciaramelli, et al., 2018; Zeidman & Maguire, 2016), and the pre/parasubiculum may be of special significance to this process (Dalton & Maguire, 2017; Dalton et al., 2018). In line with the scene construction theory, patients with hippocampal damage have been shown to use less scene-based cognition in their mind-wandering episodes (McCormick, Rosenthal, et al., 2018), moral decision-making (McCormick et al., 2016), and scene-based judgements (McCormick et al., 2017). Therefore, our results point towards a potential role of the pre/parasubiculum in tasks relying heavily on vivid visuo-spatial imagery, such as vivid AM retrieval.

Having highlighted the role of the pre/parasubiculum in vivid AM retrieval, we further found that all other hippocampal subfields also showed stronger activation during AM retrieval than MA. This result is not surprising since there might be many factors differentiating the cognitive process of recalling AMs from solving MA problems. Especially, since AM retrieval is a complex cognitive task with a magnitude of different operations (such as detail integration, and discrimination), it is likely that the other hippocampal subfields contribute to different processes which we could not dissociate in the current study. In fact, recent investigations show different contributions of hippocampal subfields to mnemonic processes. Although there is somewhat mixed evidence in the current literature, CA fields have been implicated in the integration or associations of memory details, such as external and internal (Chadwick et al., 2014; Grande et al., 2019; Miller et al., 2020; Newman & Hasselmo, 2014), whereas the DG/CA4 region (Baker et al., 2016; Berron et al., 2016; Newman & Hasselmo, 2014; van Dijk & Fenton, 2018) may support the separation or discrimination of mnemonic information. The aim of the current study was to evaluate a submillimeter 7 T fMRI sequence during a robust, reliable, and established AM paradigm. Future studies will now have to experimentally target specific subfield functions, such as examining AMs with and without visual imagery. Our newly developed 7 T fMRI sequence will allow the innovative investigation of differential hippocampal subfield contributions to cognition.

The second major goal of the current study was to examine functional connectivity of hippocampal subfields to the neocortex during AM retrieval. We found that the anterior body of the pre/parasubiculum, over and above other subfields, has strong functional connectivity to neocortical regions known to support AM retrieval. In addition, this effect was specific to the anterior body and not evident in the posterior body or tail portions of the hippocampus. This finding adds new detail to several lines of research. For example, both 3 T and 7 T fMRI resting-state studies have identified the subiculum (in which the pre/parasubiculum was included) as a functional connectivity hub correlating with activity in the default mode network which has overlapping brain regions to the AM network (Ezama et al., 2021; Shah et al., 2018). In addition, previous task-based 3 T fMRI revealed that hippocampal functional connectivity during AM of a seed region in the vicinity of the pre/parasubiculum (McCormick et al., 2015) was strongly connected to a brain-wide network comprising the vmPFC and medial/lateral parietal cortices, as well as visual-perceptual regions of the occipital cortex. Furthermore, the same region of the anterior medial hippocampus was more strongly connected to frontal and parietal cortices during scene construction than object construction (Zeidman et al., 2015). Additionally, from a neuroanatomical perspective, the pre/parasubiculum is a primary target of the parieto-medial temporal visual pathway carrying information about visuo-spatial representations of the environment (Dalton & Maguire, 2017). The parieto-medial temporal pathway directly links the pre/parasubiculum with the inferior parietal lobule, posterior cingulate cortex, retrosplenial cortex, and parahippocampal gyrus (Ding, 2013; Ding & Van Hoesen, 2015; Kravitz et al., 2011). Each of these regions has been heavily associated with visuo-spatial cognition (Auger & Floresco, 2014; Epstein et al., 2007) and AM (Svoboda et al., 2006) and connect directly with the pre/parasubiculum, giving it privileged access to visuo-spatial information. While most of this evidence stems from anatomical connectivity studies in rodent and nonhuman primates, a recent diffusion-weighted imaging study supports this framework by showing, for the first time in the human brain,

that circumscribed regions along the anterior-posterior axis of the pre/parasubiculum, including a specific portion in the anterior body of the hippocampus, have dense patterns of anatomical connectivity with distributed cortical brain areas implicated in AM (Dalton et al., 2022). The anterior portion was shown to exhibit greater connectivity with temporal, medial parietal, and occipital regions. The posterior hippocampus, more intense in the tail, was partially found to be connected with medial parietal and occipital cortices. Our results dovetail nicely with this collection of structural and functional data and provide new evidence that the pre/parasubiculum in the anterior body of the hippocampus may be an important hippocampal hub for scene-based cognition.

In summary, here we utilized a novel submillimeter 7 T fMRI sequence which enabled us to examine functional connectivity between hippocampal subfields and neocortical regions during vivid AM retrieval. We enhanced our knowledge of hippocampal subfield contributions to cognition by showing that the anterior body of the pre/parasubiculum was more engaged during AM than other neighboring hippocampal subfields and that this part of the hippocampus was strongly functionally connected to regions typically recruited during AM. In context of the broader literature, these observations correspond well with multiple lines of evidence, suggesting that the anterior body of the pre/parasubiculum may be a central component of the networks underpinning AM retrieval.

DATA AND CODE AVAILABILITY

The data are available upon request by contacting the Lead Contact, Cornelia McCormick (cornelia.mccormick@ukbonn.de).

AUTHOR CONTRIBUTIONS

P.L.: Data curation, formal analysis, and original draft writing. M.A.D.: Methodology, visualization, writing, reviewing, and editing. R.S.: Methodology. T.S.: Methodology. A.Sp.: Reviewing, editing. A.Sc.: Reviewing, editing. C.M.: Conceptualization, methodology, data curation, visualization, supervision, writing, reviewing, and editing.

DECLARATION OF COMPETING INTEREST

The authors have no competing interests to declare.

ACKNOWLEDGMENTS

C.M. and P.L. are supported by a BONFOR fellowship (2019-2-06, 2021-2A-01) and the German Research Foundation (MC-244/3-1). We thank Sascha Brunheim, Anke Rühling, and Jennifer Schlee for their technical support during scanning and all participants for their time.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available with the online version here: https://doi.org/10.1162/imag_a_00105.

REFERENCES

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, *45*, 1363–1377. https://doi.org/10.1016/j.neuropsychologia.2006.10.016

Auger, M. L., & Floresco, S. B. (2014). Prefrontal cortical GABA modulation of spatial reference and working memory. *Int J Neuropsychopharmacol*, *18*, pyu013. https://doi.org/10.1093/ijnp/pyu013

Baker, S., Vieweg, P., Gao, F., Gilboa, A., Wolbers, T., Black, S. E., & Rosenbaum, R. S. (2016). The human dentate gyrus plays a necessary role in discriminating new memories. *Curr Biol*, *26*, 2629–2634. https://doi.org/10.1016/j.cub.2016.07.081

Barry, D. N., Clark, I. A., & Maguire, E. A. (2021). The relationship between hippocampal subfield volumes and autobiographical memory persistence. *Hippocampus*, *31*, 362–374. https://doi.org/10.1002/hipo.23293

Bartsch, T., Döhring, J., Rohr, A., Jansen, O., & Deuschl, G. (2011). CA1 neurons in the human hippocampus are critical for autobiographical memory, mental time travel, and autonoetic consciousness. *Proc Natl Acad Sci U S A*, *108*(42), 17562–17567. https://doi.org/10.1073/pnas.1110266108

Berron, D., Schütze, H., Maass, A., Cardenas-Blanco, A., Kuijf, H. J., Kumaran, D., & Düzel, E. (2016). Strong evidence for pattern separation in human dentate gyrus. *J Neurosci*, *36*, 7569–7579. https://doi.org/10.1523/jneurosci.0518-16.2016

Boccara, C. N., Sargolini, F., Thoresen, V. H., Solstad, T., Witter, M. P., Moser, E. I., & Moser, M. B. (2010). Grid cells in pre- and parasubiculum. *Nat Neurosci*, *13*, 987–994. https://doi.org/10.1038/nn.2602

Bonnici, H. M., Chadwick, M. J., Kumaran, D., Hassabis, D., Weiskopf, N., & Maguire, E. A. (2012). Multi-voxel pattern analysis in human hippocampal subfields. *Front Hum Neurosci*, *6*, 290. https://doi.org/10.3389/fnhum.2012.00290

Bonnici, H. M., Chadwick, M. J., Lutti, A., Hassabis, D., Weiskopf, N., & Maguire, E. A. (2012). Detecting representations of recent and remote autobiographical memories in vmPFC and hippocampus. *J Neurosci*, *32*, 16982–16991. https://doi.org/10.1523/jneurosci.2475-12.2012

Bonnici, H. M., Chadwick, M. J., & Maguire, E. A. (2013). Representations of recent and remote autobiographical memories in hippocampal subfields. *Hippocampus*, *23*(10), 849–854. https://doi.org/10.1002/hipo.22155

Brenner, D., Stirnberg, R., Pracht, E. D., & Stöcker, T. (2013). ESMRMB 2013, 30th Annual Scientific Meeting, Toulouse, France, 3–5 October: Abstracts, Friday. *Magn Reson Mater Phy*, *26*, 151–301. https://doi.org/10.1007/s10334-013-0383-6

Breuer, F. A., Blaimer, M., Mueller, M. F., Seiberlich, N., Heidemann, R. M., Griswold, M. A., & Jakob, P. M. (2006). Controlled aliasing in volumetric parallel imaging (2D CAIPIRINHA). *Magn Reson Med*, *55*, 549–556. https://doi.org/10.1002/mrm.20787

Chadwick, M. J., Bonnici, H. M., & Maguire, E. A. (2014). CA3 size predicts the precision of memory recall. *Proc Natl Acad Sci U S A*, *111*, 10720–10725. https://doi.org/10.1073/pnas.1319641111

Clark, I. A., & Maguire, E. A. (2020). Do questionnaires reflect their purported cognitive functions? *Cognition*, *195*, 104114. https://doi.org/10.1016/j.cognition.2019.104114

Conway, M. A. (2009). Episodic memories. *Neuropsychologia*, *47*, 2305–2313. https://doi.org/10.1016/j.neuropsychologia.2009.02.003

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychol Rev*, *107*, 261–288. https://doi.org/10.1037//0033-295x.107.2.261

Coupé, P., Manjón, J. V., Gedamu, E., Arnold, D., Robles, M., & Collins, D. L. (2010). Robust Rician noise estimation for MR images. *Med Image Anal*, *14*, 483–493. https://doi.org/10.1016/j.media.2010.03.001

Dalton, M. A., D'Souza, A., Lv, J., & Calamante, F. (2022). New insights into anatomical connectivity along the anterior–posterior axis of the human hippocampus using in vivo quantitative fibre tracking. *Elife*, *11*, e76143. https://doi.org/10.7554/elife.76143

Dalton, M. A., & Maguire, E. A. (2017). The pre/parasubiculum: A hippocampal hub for scene-based cognition? *Curr Opin Behav Sci*, *17*, 34–40. https://doi.org/10.1016/j.cobeha.2017.06.001

Dalton, M. A., McCormick, C., De Luca, F., Clark, I. A., & Maguire, E. A. (2019). Functional connectivity along the anterior-posterior axis of hippocampal subfields in the ageing human brain. *Hippocampus*, *29*, 1049–1062. https://doi.org/10.1002/hipo.23097

Dalton, M. A., McCormick, C., & Maguire, E. A. (2019). Differences in functional connectivity along the anterior-posterior axis of human hippocampal subfields. *Neuroimage*, *192*, 38–51. https://doi.org/10.1016/j.neuroimage.2019.02.066

Dalton, M. A., Zeidman, P., Barry, D. N., Williams, E., & Maguire, E. A. (2017). Segmenting subregions of the human hippocampus on structural magnetic resonance image scans: An illustrated tutorial. *Brain Neurosci Adv*, *1*, 2398212817701448. https://doi.org/10.1177/2398212817701448

Dalton, M. A., Zeidman, P., McCormick, C., & Maguire, E. A. (2018). Differentiable processing of objects, associations, and scenes within the hippocampus. *J Neurosci*, *38*, 8146–8159. https://doi.org/10.1523/jneurosci.0263-18.2018

Dawes, A. J., Keogh, R., Andrillon, T., & Pearson, J. (2020). A cognitive profile of multi-sensory imagery, memory and dreaming in aphantasia. *Sci Rep*, *10*, 10022. https://doi.org/10.1038/s41598-020-65705-7

Dice, L. R. (1945). Measures of the amount of ecologic association between species. *Ecology*, *26*, 297. https://doi.org/10.2307/1932409

Ding, S.-L. (2013). Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum in human, monkey, and rodent. *J Comp Neurol*, *521*, 4145–4162. https://doi.org/10.1002/cne.23416

Ding, S.-L., & Van Hoesen, G. W. (2015). Organization and detailed parcellation of human hippocampal head and body regions based on a combined analysis of cyto- and chemoarchitecture. *J Comp Neurol*, *523*, 2233–2253. https://doi.org/10.1002/cne.23786

Epstein, R. A., Parker, W. E., & Feiler, A. M. (2007). Where am I now? Distinct roles for parahippocampal and retrosplenial cortices in place recognition. *J Neurosci*, *27*, 6141–6149. https://doi.org/10.1523/jneurosci.0799-07.2007

Ezama, L., Hernández-Cabrera, J. A., Seoane, S., Pereda, E., & Janssen, N. (2021). Functional connectivity of the hippocampus and its subfields in resting-state networks. *Eur J Neurosci*, *53*, 3378–3393. https://doi.org/10.1111/ejn.15213

Finn, E. S., Huber, L., Jangraw, D. C., Molfese, P. J., & Bandettini, P. A. (2019). Layer-dependent activity in human prefrontal cortex during working memory. *Nat Neurosci*, *22*, 1687–1695. https://doi.org/10.1038/s41593-019-0487-z

Grande, X., Berron, D., Horner, A. J., Bisby, J. A., Düzel, E., & Burgess, N. (2019). Holistic recollection via pattern completion involves hippocampal subfield CA3. *J Neurosci*, *39*, 8100–8111. https://doi.org/10.1523/jneurosci.0722-19.2019

Grande, X., Sauvage, M. M., Becke, A., Düzel, E., & Berron, D. (2022). Transversal functional connectivity and scene-specific processing in the human entorhinal-hippocampal circuitry. *Elife*, *11*, e76479. https://doi.org/10.7554/eLife.76479

Greenberg, D. L., & Knowlton, B. J. (2014). The role of visual imagery in autobiographical memory. *Mem Cognit*, *42*, 922–934. https://doi.org/10.3758/s13421-014-0402-5

Hennig, J., & Scheffler, K. (2001). Hyperechoes. *Magn Reson Med*, *46*, 6–12. https://doi.org/10.1002/mrm.1153

Hodgetts, C. J., Voets, N. L., Thomas, A. G., Clare, S., Lawrence, A. D., & Graham, K. S. (2017). Ultra-high-field fMRI reveals a role for the subiculum in scene perceptual discrimination. *J Neurosci*, *37*, 3150–3159. https://doi.org/10.1523/jneurosci.3225-16.2017

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nat Rev Neurosci*, *12*, 217–230. https://doi.org/10.1038/nrn3008

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial least squares (PLS) methods for neuroimaging: A tutorial and review. *Neuroimage*, *56*, 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Lever, C., Burton, S., Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci*, *29*, 9771–9777. https://doi.org/10.1523/jneurosci.1319-09.2009

Maass, A., Schütze, H., Speck, O., Yonelinas, A., Tempelmann, C., Heinze, H.-J., Berron, D., Cardenas-Blanco, A., Brodersen, K. H., Stephan, K. E., & Düzel, E. (2014). Laminar activity in the hippocampus and entorhinal cortex related to novelty and episodic encoding. *Nat Commun*, *5*, 5547. https://doi.org/10.1038/ncomms6547

Maguire, E. A., & Mullally, S. L. (2013). The hippocampus: A manifesto for change. *J Exp Psychol Gen*, *142*, 1180–1189. https://doi.org/10.1037/a0033650

McCormick, C., Barry, D.N, Jafarian, A., Barnes, G. R., & Maguire, E. A. (2020). vmPFC drives hippocampal processing during autobiographical memory recall regardless of remoteness. *Cereb Cortex*, *30*, 5972–5987. https://doi.org/10.1093/cercor/bhaa172

McCormick, C., Ciaramelli, E., De Luca, F., & Maguire, E. A. (2018). Comparing and contrasting the cognitive effects of hippocampal and ventromedial prefrontal cortex damage: A review of human lesion studies.

Neuroscience, *374*, 295–318. https://doi.org/10.1016/j.neuroscience.2017.07.066

McCormick, C., Dalton, M. A., Zeidman, P., & Maguire, E. A. (2021). Characterising the hippocampal response to perception, construction and complexity. *Cortex*, *137*, 1–17. https://doi.org/10.1016/j.cortex.2020.12.018

McCormick, C., Rosenthal, C. R., Miller, T. D., & Maguire, E. A. (2016). Hippocampal damage increases deontological responses during moral decision making. *J Neurosci*, *36*, 12157–12167. https://doi.org/10.1523/jneurosci.0707-16.2016

McCormick, C., Rosenthal, C. R., Miller, T. D., & Maguire, E. A. (2017). Deciding what is possible and impossible following hippocampal damage in humans. *Hippocampus*, *27*, 303–314. https://doi.org/10.1002/hipo.22694

McCormick, C., Rosenthal, C. R., Miller, T. D., & Maguire, E. A. (2018). Mind-Wandering in people with hippocampal damage. *J Neurosci*, *38*, 2745–2754. https://doi.org/10.1523/jneurosci.1812-17.2018

McCormick, C., St-Laurent, M., Ty, A., Valiante, T.A& ., McAndrews, M. P. (2015). Functional and effective hippocampal-neocortical connectivity during construction and elaboration of autobiographical memory retrieval. *Cereb Cortex*, *25*, 1297–1305. https://doi.org/10.1093/cercor/bht324

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: Applications and advances. *Neuroimage*, *23* Suppl 1, S250–S263. https://doi.org/10.1016/j.neuroimage.2004.07.020

Miller, T. D., Chong, T. T.-J., Aimola Davies, A. M., Johnson, M. R., Irani, S. R., Husain, M., Ng, T. W., Jacob, S., Maddison, P., Kennard, C., Gowland, P. A., & Rosenthal, C. R. (2020). Human hippocampal CA3 damage disrupts both recent and remote episodic memories. *Elife*, *9*, e41836. https://doi.org/10.7554/elife.41836

Milton, F., Fulford, J., Dance, C., Gaddum, J., Heuerman-Williamson, B., Jones, K., Knight, K. F., MacKisack, M., Winlove, C., & Zeman, A. (2021). Behavioral and neural signatures of visual imagery vividness extremes: Aphantasia versus hyperphantasia. *Cereb Cortex Commun*, *2*, tgab035. https://doi.org/10.1093/texcom/tgab035

Monzel, M., & Vetterlein, A., Reuter, M. (2021). Memory deficits in aphantasics are not restricted to autobiographical memory—Perspectives from the dual coding approach. *J Neuropsychol*, *16*(2), 444–461. https://doi.org/10.1111/jnp.12265

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., McAndrews, M. P., Levine, B., Black, S., Winocur, G., & Nadel, L. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: A unified account based on multiple trace theory. *J Anat*, *207*, 35–66. https://doi.org/10.1111/j.1469-7580.2005.00421.x

Newman, E. L., & Hasselmo, M. E. (2014). CA3 sees the big picture while dentate gyrus splits hairs. *Neuron*, *81*, 226–228. https://doi.org/10.1016/j.neuron.2014.01.004

Norris, D. G., & Polimeni, J. R. (2019). Laminar (f)MRI: A short history and future prospects. *Neuroimage*, *197*, 643–649. https://doi.org/10.1016/j.neuroimage.2019.04.082

Palombo, D. J., Amaral, R. S. C., Olsen, R. K., Müller, D. J., Todd, R. M., Anderson, A. K., & Levine, B. (2013). KIBRA polymorphism is associated with individual differences in hippocampal subregions: Evidence from anatomical segmentation using high-resolution MRI. *J Neurosci*, *33*, 13088–13093. https://doi.org/10.1523/jneurosci.1406-13.2013

Palombo, D. J., Bacopulos, A., Amaral, R. S. C., Olsen, R. K., Todd, R. M., Anderson, A. K., & Levine, B. (2018). Episodic autobiographical memory is associated with variation in the size of hippocampal subregions. *Hippocampus*, *28*, 69–75. https://doi.org/10.1002/hipo.22818

Palombo, D. J., Sheldon, S., & Levine, B. (2018). Individual differences in autobiographical memory. *Trends Cogn Sci (Regul Ed)*, *22*, 583–597. https://doi.org/10.1016/j.tics.2018.04.007

Pearson, J. (2019). The human imagination: The cognitive neuroscience of visual mental imagery. *Nat Rev Neurosci*, *20*, 624–634. https://doi.org/10.1038/s41583-019-0202-9

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends Cogn Sci*, *17*(5), 230-240. https://doi.org/10.1016/j.tics.2013.03.005

Risius, U.-M., Staniloiu, A., Piefke, M., Maderwald, S., Schulte, F. P., Brand, M., & Markowitsch, H. J. (2013). Retrieval, monitoring, and control processes: A 7 tesla FMRI approach to memory accuracy. *Front Behav Neurosci*, *7*, 24. https://doi.org/10.3389/fnbeh.2013.00024

Robertson, R. G., Rolls, E. T., Georges-François, P., & Panzeri, S. (1999). Head direction cells in the primate pre-subiculum. *Hippocampus*, *9*, 206–219. https://doi.org/10.1002/(sici)1098-1063(1999)9:3<206::aid-hipo2>3.3.co;2-8

Robin, J., Buchsbaum, B. R., & Moscovitch, M. (2018). The primacy of spatial context in the neural representation of events. *J Neurosci*, *38*, 2755–2765. https://doi.org/10.1523/jneurosci.1638-17.2018

Rosenbaum, R. S., Moscovitch, M., Foster, J. K., Schnyer, D. M., Gao, F., Kovacevic, N., Verfaellie, M., Black, S. E., & Levine, B. (2008). Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. *J Cogn Neurosci*, *20*, 1490–1506. https://doi.org/10.1162/jocn.2008.20105

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry*, *20*, 11–21. https://doi.org/10.1136/jnnp.20.1.11

Sekeres, M. J., Winocur, G., & Moscovitch, M. (2018). The hippocampus and related neocortical structures in memory transformation. *Neurosci Lett*, *680*, 39–53. https://doi.org/10.1016/j.neulet.2018.05.006

Shah, P., Bassett, D.S, Wisse, L. E. M., Detre, J. A., Stein, J. M., Yushkevich, P. A., Shinohara, R. T., Pluta, J. B., Valenciano, E., Daffner, M., Wolk, D. A., Elliott, M. A., Litt, B., Davis, K. A., & Das, S. R. (2018). Mapping the structural and functional network architecture of the medial temporal lobe using 7 T MRI. *Hum Brain Mapp*, *39*, 851–865. https://doi.org/10.1002/hbm.23887

Shine, J. P., Valdés-Herrera, J. P., Tempelmann, C., & Wolbers, T. (2019). Evidence for allocentric boundary and goal direction information in the human entorhinal cortex and subiculum. *Nat Commun*, *10*, 4004. https://doi.org/10.1038/s41467-019-11802-9

Stirnberg, R., Brenner, D., Stöcker, T., & Shah, N. J. (2016). Rapid fat suppression for three-dimensional echo planar imaging with minimized specific absorption rate. *Magn Reson Med*, *76*, 1517–1523. https://doi.org/10.1002/mrm.26063

Stirnberg, R., Huijbers, W., Brenner, D., Poser, B. A., Breteler, M., & Stöcker, T. (2017). Rapid whole-brain resting-state fMRI at 3 T: Efficiency-optimized three-dimensional EPI versus repetition time-matched simultaneous-multi-slice EPI. *Neuroimage*, *163*, 81–92. https://doi.org/10.1016/j.neuroimage.2017.08.031

Stirnberg, R., & Stöcker, T. (2021). Segmented K-space blipped-controlled aliasing in parallel imaging for high

spatiotemporal resolution EPI. *Magn Reson Med*, *85*, 1540–1551. https://doi.org/10.1002/mrm.28486

Strange, B. A., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci*, *15*(10), 655–669. https://doi.org/10.1038/nrn3785

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, *44*, 2189–2208. https://doi.org/10.1016/j.neuropsychologia.2006.05.023

van der Kouwe, A. J. W., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *Neuroimage*, *40*, 559–569. https://doi.org/10.1016/j.neuroimage.2007.12.025

van Dijk, M. T., & Fenton, A. A. (2018). On how the dentate gyrus contributes to memory discrimination. *Neuron*, *98*, 832.e5–845.e5. https://doi.org/10.1016/j.neuron.2018.04.018

Watkins, N. W. (2018). (A)phantasia and severely deficient autobiographical memory: Scientific and personal perspectives. *Cortex*, *105*, 41–52. https://doi.org/10.1016/j.cortex.2017.10.010

Willems, T., & Henke, K. (2021). Imaging human engrams using 7 Tesla magnetic resonance imaging. *Hippocampus*, *31*, 1257–1270. https://doi.org/10.1002/hipo.23391

Yoo, P. E., John, S. E., Farquharson, S., Cleary, J. O., Wong, Y. T., Ng, A., Mulcahy, C. B., Grayden, D. B., Ordidge, R. J., Opie, N. L., O'Brien, T. J., Oxley, T. J., & Moffat, B. A. (2018). 7 T-fMRI: Faster temporal resolution yields optimal BOLD sensitivity for functional network imaging specifically at high spatial resolution. *Neuroimage*, *164*, 214–229. https://doi.org/10.1016/j.neuroimage.2017.03.002

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R.G, Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage*, *31*, 1116–1128. https://doi.org/10.1016/j.neuroimage.2006.01.015

Zeidman, P., Lutti, A., & Maguire, E. A. (2015). Investigating the functions of subregions within anterior hippocampus. *Cortex*, *73*, 240–256. https://doi.org/10.1016/j.cortex.2015.09.002

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: The anatomy of perception, imagination and episodic memory. *Nat Rev Neurosci*, *17*, 173–182. https://doi.org/10.1038/nrn.2015.24

Zeman, A., Dewar, M., & Della Sala, S. (2015). Lives without imagery—Congenital aphantasia. *Cortex*, *73*, 378–380. https://doi.org/10.1016/j.cortex.2015.05.019

Zeman, A., Milton, F., Della Sala, S., Dewar, M., Frayling, T., Gaddum, J., Hattersley, A., Heuerman-Williamson, B., Jones, K., MacKisack, M., & Winlove, C. (2020). Phantasia—The psychological significance of lifelong visual imagery vividness extremes. *Cortex*, *130*, 426–440. https://doi.org/10.1016/j.cortex.2020.04.003

3.2 Publication 2: Hippocampal-occipital connectivity reflects autobiographical memory deficits in aphantasia

RESEARCH ARTICLE

Hippocampal-occipital connectivity reflects autobiographical memory deficits in aphantasia

Merlin Monzel[1,2*†], Pitshaporn Leelaarporn[2,3*†], Teresa Lutz[2], Johannes Schultz[4,5], Sascha Brunheim[2], Martin Reuter[1], Cornelia McCormick[2,3]

[1]Department of Psychology, University of Bonn, Bonn, Germany; [2]German Center for Neurodegenerative Diseases, Bonn, Germany; [3]Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, Bonn, Germany; [4]Center for Economics and Neuroscience, University of Bonn, Bonn, Germany; [5]Institute of Experimental Epileptology and Cognition Research, Medical Faculty, University of Bonn, Bonn, Germany

***For correspondence:** monzel@uni-bonn.de (MM); pitshaporn.leelaarporn@dzne.de (PL)

[†]These authors contributed equally to this work

Competing interest: The authors declare that no competing interests exist.

Funding: See page 17

Preprint posted 27 November 2023
Sent for Review 03 January 2024
Reviewed preprint posted 27 February 2024
Reviewed preprint revised 05 June 2024
Version of Record published 26 September 2024

Reviewing Editor: Marius V Peelen, Radboud University Nijmegen, Netherlands

Abstract Aphantasia refers to reduced or absent visual imagery. While most of us can readily recall decade-old personal experiences (autobiographical memories, AM) with vivid mental images, there is a dearth of information about whether the loss of visual imagery in aphantasics affects their AM retrieval. The hippocampus is thought to be a crucial hub in a brain-wide network underlying AM. One important question is whether this network, especially the connectivity of the hippocampus, is altered in aphantasia. In the current study, we tested 14 congenital aphantasics and 16 demographically matched controls in an AM fMRI task to investigate how key brain regions (i.e. hippocampus and visual-perceptual cortices) interact with each other during AM re-experiencing. All participants were interviewed regarding their autobiographical memory to examine their episodic and semantic recall of specific events. Aphantasics reported more difficulties in recalling AM, were less confident about their memories, and described less internal and emotional details than controls. Neurally, aphantasics displayed decreased hippocampal and increased visual-perceptual cortex activation during AM retrieval compared to controls. In addition, controls showed strong negative functional connectivity between the hippocampus and the visual cortex during AM and resting-state functional connectivity between these two brain structures predicted better visualization skills. Our results indicate that visual mental imagery plays an important role in detail-rich vivid AM, and that this type of cognitive function is supported by the functional connection between the hippocampus and the visual-perceptual cortex.

eLife assessment

This **important** work substantially advances our understanding of episodic memory in individuals with aphantasia, and sheds light on the neural underpinnings of episodic memory and mental imagery. The evidence supporting the conclusions is **convincing**, including evidence from a well-established interview paradigm complemented with fMRI to assess neural activation during memory recall. The work will be of broad interest to memory researchers and mental imagery researchers alike.

Introduction

Our unique and personal memories are stored in autobiographical memories (AM) providing stability and continuity of our self (***Svoboda et al., 2006***). For most of us, travelling mentally back in time and re-visiting such unique personal events is associated with vivid, detail-rich mental imagery (***D'Argembeau and Van der Linden, 2006***; ***Greenberg and Knowlton, 2014***). This vivid mental imagery during the re-experiencing of AMs has become a hallmark of autonoetic, episodic AM retrieval. However, up to date, it remains unclear to what extent episodic AM retrieval depends on visual mental imagery and what neural consequences a lack of mental imagery has on episodic AM retrieval. This knowledge gap exists because separating AM retrieval from mental imagery is a complex and challenging task.

One way to address this conundrum is to study people with aphantasia (***Zeman et al., 2015***). Recent research defines aphantasia as a neuropsychological difference in which people experience a marked reduction or complete lack of voluntary sensory imagery (***Monzel et al., 2022a***). This state is associated with psychophysiological alterations, such as reduced imagery-induced pupil contraction (***Kay et al., 2022***) and reduced imagery-induced priming effects (***Keogh and Pearson, 2018***; ***Monzel et al., 2021***). Thus, aphantasics offer the unique opportunity to examine the consequences for episodic AM retrieval in the absence or marked reduction of voluntary imagery. Indeed, a handful of previous studies report convergent evidence that aphantasics report less sensory AM details than controls (***Dawes et al., 2020***; ***Dawes et al., 2022***; ***Milton et al., 2021***; ***Zeman et al., 2020***), which may also be less emotional (***Monzel et al., 2023***; ***Wicken et al., 2021***). Spatial accuracy, on the other hand, was not found to be impaired (***Bainbridge et al., 2021***). Yet, task-based functional activity has not been fully explored.

Neurally, the hippocampus has been established as a central brain structure to support the detail-rich episodic AM retrieval in the healthy brain (***Bauer et al., 2017***; ***Brown et al., 2018***; ***Burianova et al., 2010***; ***McCormick et al., 2020***; ***Moscovitch et al., 2005***), albeit some studies differentiate between hippocampal support for remote and recent autobiographical memories (see ***Bayley et al., 2006***). In fact, hippocampal activity correlates with the vividness of AM recollection (***Addis et al., 2004***; ***Sheldon and Levine, 2013***) and patients with hippocampal damage show marked deficits in detailed episodic AM retrieval (***Miller et al., 2020***; ***Rosenbaum et al., 2008***). In addition, neuroimaging studies illuminate that the hippocampus is almost always co-activated with a wider set of brain regions, including the ventromedial prefrontal cortex (vmPFC), lateral and medial parietal cortices, as well as visual-perceptual cortices (***Svoboda et al., 2006***; ***Addis et al., 2007***). Interestingly, especially during the elaboration phase of AM retrieval, when people engage in the active retrieval of episodic details to a specific AM, the hippocampus exhibits a strong functional connection to the visual-perceptual cortices, suggesting a crucial role of this connection for the embedding of visual-perceptual details into AMs (***McCormick et al., 2015***; ***Leelaarporn et al., 2024***).

Yet, not many studies have examined the neural correlates of aphantasia, and none during AM retrieval. Of the little evidence there is, reports converge on a potential hyperactivity of the visual-perceptual cortices in aphantasia (***Fulford et al., 2018***; ***Keogh et al., 2020***). A prominent theory posits that because of this hyperactivity, small signals elicited during the construction of mental imagery may not be detected (***Pearson, 2019***; ***Keogh et al., 2020***). Pearson further speculates that since spatial abilities seem to be spared, the hippocampus may not be the underlying cause of aphantasia. In agreement, ***Bergmann and Ortiz-Tudela, 2023*** speculate that individuals with aphantasia might lack the ability to reinstate visually precise episodic elements from memory due to altered feedback from the visual cortex. In the same vein, ***Blomkvist, 2023*** proposes the extended constructive episodic simulation hypotheses (CESH+) that suggests that imagination and memory rely on similar neural structures, since both represent simulated recombinations of previous impressions. This hypothesis has been supported by shared representations for memory and mental imagery in early visual cortex (***Albers et al., 2013***; see also ***Zeidman and Maguire, 2016***). Within this framework, the hippocampus is supposed to initiate sensory retrieval processes (e.g. in the visual-perceptual cortices; ***Danker and Anderson, 2010***), comparable to its role in the hippocampal memory indexing theory (***Langille and Gallistel, 2020***). ***Blomkvist, 2023*** speculates that in aphantasics, either the hippocampal memory index or the retrieval processes may be impaired.

Thus, the main goal of our study was to examine the neural correlates of AM deficits associated with aphantasia. We hypothesized that the deficits in AM seen in aphantasia rely on altered involvement of the hippocampus, visual-perceptual cortices and their functional connectivity.

Results

VVIQ and binocular rivalry task

Aphantasics (*M*=16.57, SD = 1.02) scored significantly lower on the Vividness of Visual Imagery Questionnaire (VVIQ) than controls (*M*=62.94, SD = 8.71), *t*(15.47)=21.12, p<0.001, *d*=7.23. Furthermore, aphantasics and controls differed in the priming score of the binocular rivalry task, *t*(18.04)=2.41, p=0.027, *d*=0.87. While controls were primed by their own mental imagery in 61.3% (SD = 13.1 %) of the trials, aphantasics were only primed 52.6% (SD = 4.9 %) of the time. In fact, the performance of controls differed significantly from chance, *t*(14) = 3.34, p=0.005, *d*=0.86, whereas performance of aphantasics did not, *t*(13) = 1.96, p=0.072. Moreover, the VVIQ scores correlated positively with the performance on the binocular rivalry task, *r*(28) = 0.43, p=0.022. For the mock trials, no significant differences in priming scores were found between groups, *t*(28) = 0.86, p=0.396, or related to chance (aphantasics: *t*(13) = 0.74, p=0.475; controls: *t*(15) = 0.42, p=0.682). These findings validate our groups by indicating that visual imagery strength was diminished in aphantasics.

Autobiographical interview

Regarding the Autobiographical Interview (AI), we found significant main effects of memory period, *F*(1, 27)=11.88, p=0.002, η_p^2 = 0.31, type of memory details, *F*(1, 27)=189.03, p<0.001, η_p^2 = 0.88, and group, *F*(1, 27)=9.98, p=0.004, η_p^2 = 0.27. When the other conditions were collapsed, aphantasics (M=26.29, SD = 9.58) described less memory details than controls (M=38.36, SD = 10.99). For aphantasics and controls combined, more details were reported for recent (M=35.17, SD = 14.19) than remote memories (M=29.06, SD = 11.12), and internal details (M=43.59, SD = 17.91) were reported more often than external details (M=20.64, SD = 8.94). More importantly, a two-way interaction was found between type of memory details and group, *F*(1, 27)=54.09, p<0.001, η_p^2 = .67, indicating that aphantasics reported significantly less internal memory details, *t*(27) = 5.07, p<0.001, *d*=1.83, but not significantly less external memory details, *t*(27) = 0.13, p=0.898, compared to controls (see ***Figure 1b***). No two-way interaction between memory period and group, *F*(1, 27)=0.62, p=0.439, and no three-way interaction between memory period, group and type of memory details was found, *F*(1, 27)=3.87, p=0.060.

Based on the interaction effect between group and type of memory details, we compared specific categories of internal and external memory details between the groups. For internal details and in comparison to controls, aphantasics reported less internal events, *t*(27) = 3.22, p=0.016, *d*=1.17, less emotional details, *t*(27) = 4.40, p<0.001, *d*=1.59, less perceptual details, *t*(27) = 4.95, p<0.001, *d*=1.79, and less details regarding time, *t*(27) = 5.27, p<0.001, *d*=1.90, and place, *t*(27) = 3.31, p<0.013, *d*=1.20 (see ***Figure 1c***). On the other hand, no significant differences were found for external details, including external events, *t*(27) = 0.71, p>0.999, semantic details, *t*(27) = 0.02, p>0.999, repetition, *t*(27) = 0.46, p>0.999, and other details, *t*(27) = 0.45, p>0.999 (see ***Figure 1C***). Regarding the rating scales, we found that aphantasics showed less episodic richness, *t*(27) = 7.50, p<0.001, *d*=2.71, and less memory confidence, *t*(27) = 5.85, p<0.001, *d*=2.11 (see ***Figure 1a***) as well as lower self-reported visualization scores, *t*(27) = 11.92, p<0.001, *d*=4.30, than controls.

Debriefing questions

The debriefing questions were employed as a way for participants to reflect on their own cognitive abilities. Of note, these were not meant to represent or replace necessary future experiments. There were stark differences between the groups in how they answered our debriefing questions. While aphantasics reported that they typically have greater difficulty to recall autobiographical memories, *t*(27) = 6.20, p<0.001, *d*=2.31, and to use their imagination in daily life, *t*(24) = 10.18, p<0.001, *d*=3.93, they did not report difficulties in spatial orientation, *t*(27) = 0.62, p=0.541, *d*=0.23.

Behavioral results of the fMRI AM task

We found stark differences for the vividness response between groups, *t*(28) = 5.29, p<0.001. While controls reported in 86% (SD = 26 %) of trials that their AM retrieval had been vivid, aphantasics indicated only in 20% (SD = 20 %) of trials that their AM retrieval had been vivid. Moreover, aphantasics responded slower (*M*=1.34 s, SD = 0.38 s) than controls (*M*=1.00 s, SD = 0.29 s) when they were asked whether their retrieved memories were vivid or faint, *t*(28) = 2.78, p=0.009, possibly reflecting uncertainty in their response. In contrast, there were no significant differences between groups during the

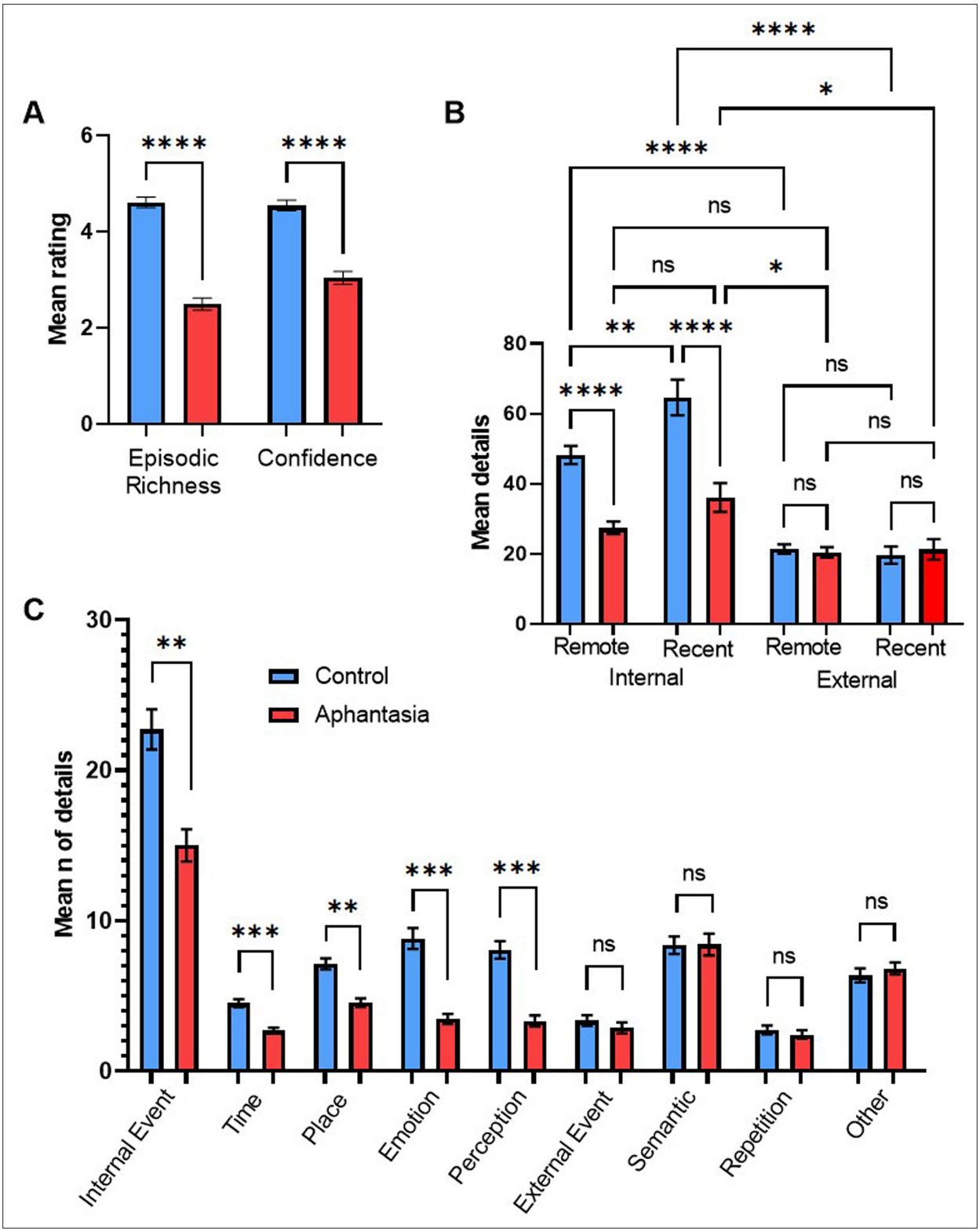

Figure 1. AM deficits associated with aphantasia. (**A**) Mean amount (± SEM) of episodic richness and confidence in the Autobiographical Interview for controls and aphantasics. (**B**) Mean amount (± SEM) of internal details and external details for recent and remote memories. (**C**) Mean amount (± SEM) of specific internal and external memory details for aphantasics and controls. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, n.s.=non-significant.

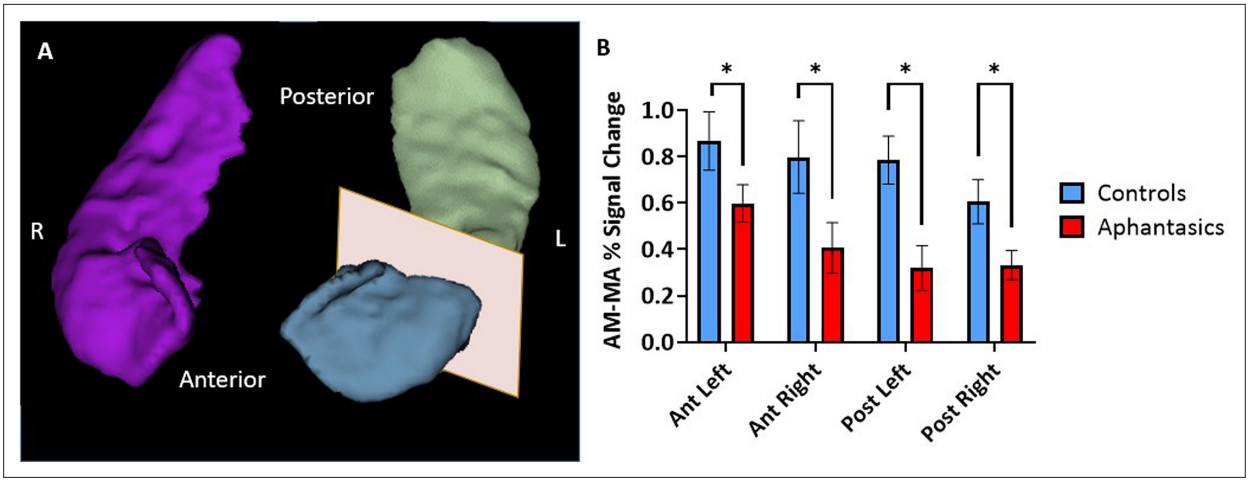

Figure 2. Reduced hippocampal activity during autobiographical memory retrieval associated with aphantasia. The signal intensities during autobiographical memory (AM) and mental arithmetic (MA) were extracted from anatomical hippocampal masks created from each individual participant. (**A**) An example of a 3D reconstruction of the hippocampus, separated into anterior and posterior portions for the left hippocampus. (**B**) The comparison between the percentage of signal change during the AM and MA tasks in the hippocampus of aphantasics and controls. Aphantasics show reduced differentiation between AM and MA than controls in all portions of the hippocampus. * p<0.05.

MA trials, neither on the easy/hard response, *t*(28) = 1.16, p=0.255, nor on the reaction times, *t*(28) = 0.58, p=0.567.

In addition, aphantasics and controls did not differ significantly in their time searching for a memory in AM trials, *t*(19) = 1.03, p=0.315. On average, aphantasics spent 3.42 s (SD = 0.74 s) and controls spent 3.15 s (SD = 0.48 s). Furthermore, both groups did not differ in their speed to solve the math problems, *t*(23) = 0.09, p=0.926. Aphantasics spent 3.87 s (SD = 0.97 s) to solve a math problem and controls spent 3.90 s (SD = 0.72 s). For the button press, there were 9% missing values in AM trials and 7% missing values in MA trials with no significant differences of missing values between groups, neither for AM trials, *t*(19.98)=1.11, p=0.281, nor for MA trials, *t*(18.13)=0.52, p=0.609.

Native space differences in hippocampal activation during AM retrieval

First, we sought to examine the hippocampal activation during an established AM-fMRI-task in aphantasics and controls (see ***Figure 2***). During fMRI scanning, participants saw either word cues (e.g. 'a party') and were asked to retrieve vivid, detail-rich AMs, or a number cue (e.g. 31+82) and were asked to solve the math problem. Using individual anatomical masks of the hippocampus, the extracted fMRI signals illustrated stark group differences in AM-associated activation, *F*(17, 252)=3.03, p<0.001. Aphantasics showed reduced activation of bilateral hippocampi, including the left anterior (p=0.033), left posterior (p=0.027), right anterior (p=0.047), and right posterior hippocampus (p=0.025). There was no laterality effect nor differences along the pattern of activation down the anterior-posterior axis between the groups (all p>0.05). These findings indicate that the behavioral AM deficit associated with aphantasia is reflected neurally by a reduced bilateral hippocampal activation.

Activation patterns associated with AM retrieval

Second, we examined whole-brain activation during AM retrieval of both groups and the results are displayed in ***Figure 3a and b***. Additionally, the peak coordinates of AM and MA activation for aphantasics and controls are shown in ***Tables 1 and 2***, respectively.

Overall, both groups showed greater activation in all areas typically associated with AM, including bilateral hippocampus, vmPFC, and medial/lateral parietal regions, during AM retrieval. When examining the group differences, aphantasics displayed greater activation in bilateral visual-perceptual regions (maximum in lingual gyrus) in the occipital lobe than controls, *t*(28) = 4.41, p<0.001 (MNI: right visual cortex: x=12, y = –79, z=5; left visual cortex: x = –9, y = –76, z=29, see ***Figure 3c, d and e***). In contrast, controls showed greater activation in the right hippocampus than aphantasics, *t*(28) = 3.77, p<0.001 (MNI: x=39, y = –31, z = –13). An additional correlational analysis revealed that those participants with higher visual-perceptual cortex activation had less hippocampal activation, *r*(28) = –0.39,

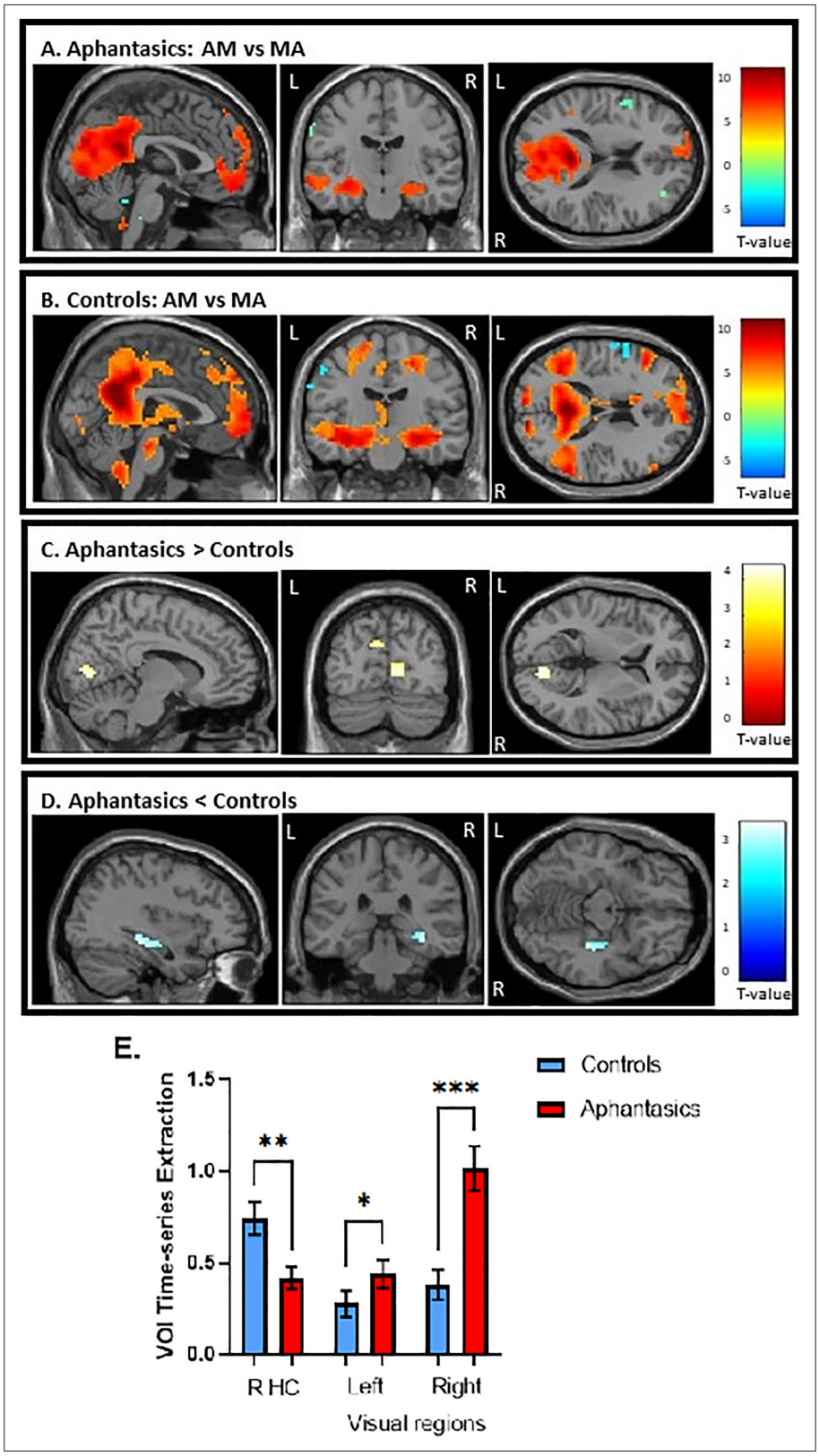

Figure 3. Activation during the autobiographical memory retrieval task. (**A**) Stronger activated cortical regions during AM retrieval (in warm colors) in comparison to mental arithmetic (in cool colors) in aphantasics and (**B**) controls. (**C**) Aphantasics showed greater activation in visual-perceptual cortices than controls, and (**D**) controls showed stronger activation in the right posterior hippocampus than aphantasics. Images are thresholded at

Figure 3 continued on next page

Figure 3 continued

p<0.001, cluster size 10, uncorrected, except (**D**) which is thresholded at p<0.01, cluster size 10, for display purposes only (i.e. the peak voxel and adjacent 10 voxels also survived p<0.001, uncorrected). (**E**) The percentage of signal change for the contrast AM versus MA were extracted from the peaks of activated voxels, each with 1 mm sphere for display purposes.

Table 1. Peak coordinates of the AM and MA activation for Aphantasia.

Region	Hemisphere	MNI Coordinates			Voxels	T-value
		X	Y	Z		
Activation AM >MA						
Posterior Cingulate Gyrus	Right	18	–57	11	4657	11.00
Parahippocampual Gyrus*	Left	–21	–31	–13		9.06
Hippocampus	Left	–27	–17	–19	205	8.40
Superior Frontal Gyrus	Left	–12	47	50	926	8.38
Angular Gyrus	Left	–42	–55	23	165	7.88
Lateral Orbitofrontal Cortex	Left	–42	38	–16	208	7.58
Hippocampus	Right	18	–37	-1	199	6.89
Cerebellum	Right	15	–79	–37	109	6.33
Brainstem	Right	3	–46	–52	43	6.03
Parahippocampual Gyrus*	Right	24	–31	–13		6.02
Middle Temporal Gyrus	Right	60	2	-–19	76	5.27
Supramarginal Gyrus	Right	54	–58	32	26	4.99
Middle Frontal Gyrus	Left	–39	20	50	12	4.52
Activation MA >AM						
Precuneus	Left	–18	–58	41	594	–3.85
Inferior Temporal Gyrus	Right	51	–46	–13	123	–3.85
Precuneus	Right	24	–49	53	718	–3.85
Insula	Left	–30	23	11	48	–3.85
Inferior Temporal Gyrus	Left	–51	–49	–13	67	–3.86
Cerebellum	Right	30	–67	–52	27	–3.87
Middle Frontal Gyrus	Right	33	41	17	34	–3.87
Superior Frontal Gyrus	Right	30	5	59	52	–3.87
Inferior Frontal Gyrus	Right	54	14	29	35	–3.88
Insula	Right	39	11	8	51	–3.88
Inferior Frontal Gyrus	Left	–57	11	26	182	–3.88
Lateral Globus Pallidus	Right	23	-7	14	14	–3.92
Cerebellum	Left	–24	–64	–46	16	–3.93

*Sub-cluster level, Cluster size = 10 voxels, p-value = 0.001.

Table 2. Peak coordinates of the AM and MA activation for healthy controls.

Region	Hemisphere	MNI Coordinates			Voxels	T-value
		X	Y	Z		
Activation AM >MA						
Parahippocampal Gyrus	Right	27	–28	–19	11319	12.41
Parahippocampal Gyrus*	Left	–24	–25	–16		9.01
Cerebellum	Left	–18	–76	–37	108	7.67
Anterior Cingulate	Right	9	35	11	13	7.01
Medial Frontal Gyrus	Right	18	32	29	233	6.93
Inferior Frontal Gyrus	Right	60	32	11	53	5.94
Hippocampus	Left	–36	–22	–16	252	5.64
Hippocampus	Right	27	–22	–16	233	5.28
Hypothalamus	Right	3	-4	–10	16	4.93
Activation MA >AM						
Post Central Gyrus	Left	–33	–43	62	643	–3.73
Precuneus	Right	21	–52	53	483	–3.74
Inferior Frontal Gyrus	Right	51	8	26	16	–3.74
Middle Occipital Gyrus	Right	33	–82	2	26	–3.75
Middle Temporal Gyrus	Left	–51	–58	-1	18	–3.76

*Sub-cluster level, Cluster size = 10 voxels, p-value = 0.001.

p=0.041, indicating that there was a trade-off between increased visual-perceptual cortex activation and decreased hippocampal activation.

Exploring functional connectivity of hippocampus and visual-perceptual cortices during AM

The whole-brain analyses strengthened our hypothesis that a core difference between aphantasics and controls lies in the interplay between the visual-perceptual cortex and the hippocampus. To test this interplay, in a third step, we examined functional connectivity between the peak differences of the hippocampus and the visual-perceptual cortex during AM retrieval (see ***Figure 4***). We found a group difference in functional connectivity between the right hippocampus and left visual-perceptual cortices, $t(28) = 2.65$, p=0.006. Interestingly, while aphantasics show almost no functional connectivity

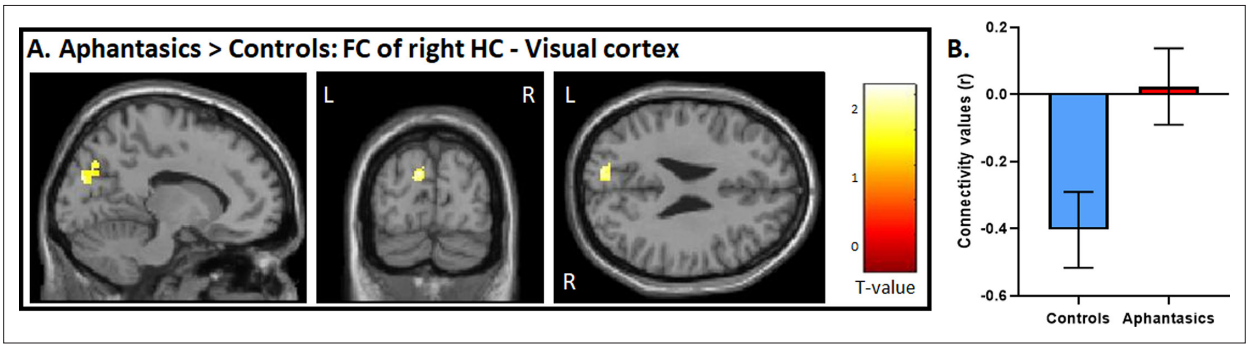

Figure 4. Functional connectivity between the visual-perceptual cortex and hippocampus during AM retrieval. (**A**) During AM retrieval, group differences in functional connectivity amongst the ROIs were only found between the right hippocampus, and left visual-perceptual cortices. (**B**) Controls displayed a stark negative correlation, whereas aphantasics did not. Image is displayed at p<0.05, small volume corrected, and a voxel cluster threshold of 10 adjacent voxels.

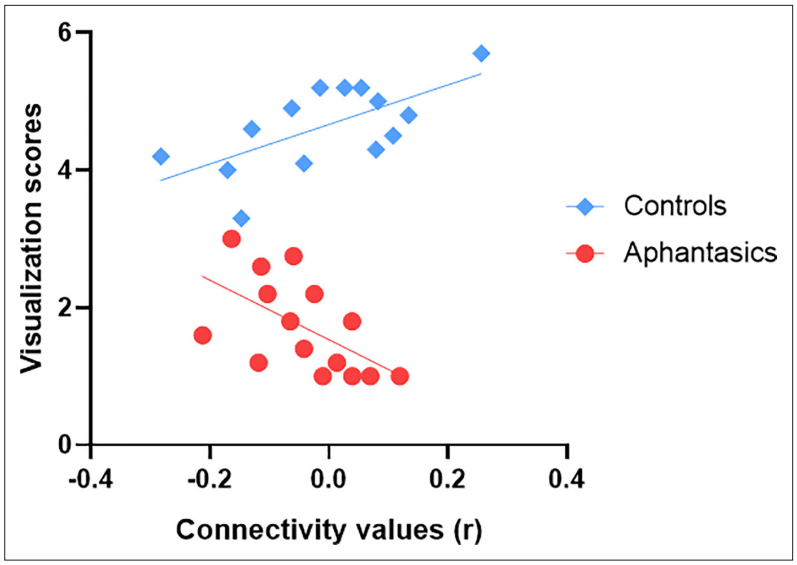

Figure 5. Functional connectivity between the visual-perceptual cortex and hippocampus during resting-state explains visualization abilities. Resting-state functional connectivity between the right hippocampus and the right visual-perceptual cortex correlates with visualization abilities. Fitted straight lines indicate a negative correlation for aphantasics (red) and a positive correlation for controls (blue).

between those two ROIs, controls displayed a strong negative connectivity between the two locations, p=0.013.

Exploring functional connectivity of hippocampus and visual-perceptual cortices during resting-state

Lastly, we examined resting-state connectivity between our identified ROIs in the right posterior hippocampus and left and right visual-perceptual cortex. There was no group difference during resting-state between these ROIs. In order to examine whether resting-state functional connectivity carried information about one's ability to visualize AMs, we added the visualization scores as a regressor of interest in our model. While connectivity alone did not predict the visualization scores in the interview, $F(14, 40)=1.651$, p=0.391, β = –0.06, we found a main effect of group, $F(3, 40)=353.2$, p<0.001, $\beta=0.92$, and an interaction between group and connectivity, $F(3, 54)=305.1$, p<0.001, $\beta=0.26$. Interestingly, for controls, we found a positive correlation between the resting-state connectivity of the right hippocampus and the visual cortex and the visualization scores from the interview, $r(13) = 0.65$, p=0.011 (see ***Figure 5***). On the other hand, for aphantasics, we found a negative correlation between the resting-state connectivity of the right hippocampus and the visual cortex and the visualization scores from the interview, $r(14) = –0.57$, p=0.027.

In sum, our fMRI results indicate that the impaired AM retrieval associated with aphantasia is reflected by functional alterations of the hippocampus and visual-perceptual cortex, as well as the interaction between them.

Discussion

In this study, we set out to examine the neural correlates of episodic AM retrieval in aphantasia as a way to examine the influence of visual imagery on episodic AM. In line with previous reports, we found that aphantasics reported less sensory details during AM retrieval regardless of the recency of memory (***Dawes et al., 2020***; ***Dawes et al., 2022***; ***Zeman et al., 2020***; ***Zeman et al., 2020***). Strikingly, the deficit in constructing visual imagery associated with aphantasia did not only lead to a reduced retrieval of visual-perceptual details but to a broader impairment in retrieving episodic AMs, including reduced emotions and confidence attached to the memories. Thus, in agreement with a recent account of aphantasia (***Blomkvist, 2023***), our results support the idea that a diminished construction of visual details during AM retrieval leads to a more general episodic memory deficit.

We expand the current knowledge by adding that this AM deficit is reflected neurally by an altered activation and connectivity pattern between the hippocampus and visual-perceptual cortices. Our findings provide novel insights into three current debates: (1) the mechanisms of aphantasia-related AM deficits, (2) the similarities and differences between aphantasics and individuals with hippocampal damage, and (3) the neural models of AM.

Potential mechanisms underlying aphantasia-related AM deficits

We report that aphantasics show increased activation of bilateral visual-perceptual cortices as well as decreased hippocampal activation during AM retrieval in comparison to controls. Increased activity in the visual-perceptual cortices in aphantasics has been reported previously, albeit not associated with AM (***Fulford et al., 2018***; ***Keogh et al., 2020***). In a prominent review, Pearson synthesizes evidence about the neural mechanism of imagery strength (***Pearson, 2019***). Indeed, activity metrics in the visual cortex predict imagery strength (***Cui et al., 2007***; ***Dijkstra et al., 2017***). Interestingly, lower resting activity and excitability result in stronger imagery, and reducing cortical activity in the visual cortex via transcranial direct current stimulation (tDCS) increases visual imagery strength (***Keogh et al., 2020***). Thus, one potential mechanism of aphantasia-related AM deficits is that the heightened activity of the visual-perceptual cortices observed in our and previous work hinders aphantasics to detect weaker imagery-related signals.

Further, we had the a priori hypothesis that hippocampal activation will be decreased in aphantasics; a hypothesis which we could confirm in our native space hippocampal analysis. On the whole-brain level, perhaps due to our small sample size, only the cluster of activation group differences in the right posterior hippocampus survived the statistical threshold. Given the low power, further studies are needed to confirm this effect; however, the right posterior hippocampus interacts in the healthy brain heavily with the visual-perceptual cortex only during the elaboration phase of AM retrieval (***McCormick et al., 2015***).

In addition, controls exhibited a strong functional connection between both brain structures during AM retrieval and this functional connectivity predicted better visualization skills. At first glance, it is surprising that this functional connectivity was negative. However, negative visual-perceptual cortex activation during perceiving and imagining scenes has been reported before (***McCormick et al., 2020***). One possible explanation might be that signals from the hippocampus selectively inhibit imagery-irrelevant activation in the visual-perceptual cortices (e.g. sensory noise) to carve out imagery-related signals (***Pace et al., 2023***). This would be in line with the hypothesis stated above, that a bad signal-to-noise ratio in the visual cortex hiders aphantasics to create mental imagery. Either way, the described functional connectivity between the hippocampus and the visual-perceptual cortex fits well to previous neuroimaging studies pointing towards a central role of the dynamic interplay between these brain structures during AM retrieval (***McCormick et al., 2015***). This interplay seems to be especially important during the elaboration stage of AM retrieval, a period when specific visual-perceptual details are being actively brought back into the mind's eye. At this point, however, it remains unclear whether the disruption of AM elaboration associated with aphantasia takes place during the encoding, storage, or retrieval process.

From a theoretical point of view, the extended constructive episodic simulation hypothesis proposes a top-down hierarchy during mental imagery (***Blomkvist, 2023***). In this model, the hippocampus initiates retrieval processes in primary sensory brain regions, such as the visual-perceptual cortex in order to retrieve visual-perceptual details associated with a specific AM. Evidence for such top-down hierarchies during mental imagery have been observed in fronto-parietal and occipital networks via effective connectivity analyses, such as Granger Causality and Dynamic Causal Modelling (***Dentico et al., 2014***; ***Dijkstra et al., 2017***; ***Mechelli et al., 2004***). For example, intracranial and high-density scalp electroencephalography (EEG) provided evidence of high-frequency hippocampal signaling during the recall of perceptual cues in patients with epilepsy, indicating that the hippocampus drives the switch from perception to memory recalling (***Treder et al., 2021***). In aphantasia, it is hypothesized that this top-down hierarchy is disrupted and therefore, the hippocampus can no longer initiate the retrieval and incorporation of visual-perceptual details in one coherent mental event. Because of the slow temporal resolution of our fMRI sequence, our data cannot directly speak to the question of temporal directionality between the hippocampus and visual-perceptual cortex. Nonetheless, our findings suggest that the bidirectional connectivity between both brain structures is crucial for the

re-experience of episodic AMs. As such, hippocampal processes may be needed to retrieve specific details and if these details are not provided by the visual-perceptual cortices, the entire episodic AM retrieval seems to fail.

Similarities and differences between aphantasics and individuals with hippocampal lesions

At face value, the episodic AM deficits in aphantasia in our data and reported previously (***Dawes et al., 2020***; ***Dawes et al., 2022***; ***Zeman et al., 2020***; ***Zeman et al., 2020***), as well as the decreased hippocampal activation during AM retrieval suggest that aphantasia is a selective episodic memory condition (see ***Blomkvist, 2023***), similar to AM amnesia known from individuals with hippocampal damage. In fact, previous and the current study show that aphantasics and individuals with hippocampal damage report less internal details across several memory detail subcategories, such as emotional details and temporal details (***Rosenbaum et al., 2008***; ***St Laurent et al., 2009***; ***Steinvorth et al., 2005***), and these deficits can be observed regardless of the recency of the memory (***Miller et al., 2020***). These similarities suggest that aphantasics are not merely missing the visual-perceptual details to specific AM, but they have a profound deficit associated with the retrieval of AM.

Nonetheless, there are also stark differences between aphantasics and individuals with hippocampal damage. Foremost, aphantasics seem not to have difficulties to retrieve spatial information (***Bainbridge et al., 2021***), which is another inherent function of the hippocampus (***Burgess et al., 2002***; ***O'Keefe, 1991***). In the current study, we did not set out to examine spatial cognition in aphantasics; however, parts of our data speak to this aspect. While in our study aphantasics reported less amount of spatial details during the AI, this standard scoring procedure only counts place details when the exact place is recalled and is not meant to assess the recall of spatial layout (***Levine et al., 2002***). Thus, this place score may not represent spatial cognition per se. In fact, when asking aphantasics about their experience, they point out difficulties in recalling AM and using imagination in daily life, however they report no difficulties in spatial orientation. Indeed, often during the interview, aphantasics would explain that they know how the space around them felt, they just cannot see it in front of their mind's eye. One aphantasic put her finger on it, describing it as: "I can put my consciousness in my kitchen at home and feel all around but there is no visual image attached to this feeling." These observations support the idea that some hippocampal processes, at least regarding spatial navigation, may be intact in people with aphantasia (***Bainbridge et al., 2021***). However, spatial cognition should be formally addressed in future studies. One way to assess this hippocampal function would be to examine tasks, which rely on scene construction. The scene construction theory states that the hippocampus is crucially needed for the construction of spatially coherent mental models of scenes (***Maguire and Mullally, 2013***). For example, patients with hippocampal damage cannot imagine the spatial layout of fictitious scenes (***Hassabis et al., 2007***), they detect less errors in spatially incoherent scenes than controls (***McCormick et al., 2017***), and they show less scene-dependent mind-wandering episodes (***McCormick et al., 2018b***). In contrast, we would predict that aphantasics have diminutive deficits in tasks that depend on hippocampal scene construction processes.

What could be impaired in aphantasics are all cognitive functions which rely on the population of the constructed scenes with visual-perceptual details, such as episodic AM retrieval, episodic future thinking, complex decision-making, and complex empathy tasks.

Towards a novel neural model of autobiographical memory

While more research is required exploring the cognitive landscape associated with aphantasia, such as spatial cognition and scene construction, our data contribute to an old debate of how AM retrieval and visual imagery are intertwined. We propose that the hippocampus is embedded in a brain-wide network, comprising the vmPFC and visual-perceptual cortices, in which each of these nodes contributes specific processes to the re-construction of extended detail-rich mental events (see also ***Ciaramelli et al., 2019***; ***McCormick et al., 2018a***). Within this model, the vmPFC initiates and oversees the scene construction process which takes place in the hippocampus. Further, the visual-perceptual cortex provides the visual details which are essential to populate the hippocampally constructed scenes. This model is backed up by a previous MEG study revealing that the vmPFC directs hippocampal activity during the initiation of AM retrieval (***McCormick et al., 2020***). This finding has been replicated and extended by ***Chen et al., 2021***, showing that the vmPFC leads hippocampal involvement during

scene construction and other scene-based processes (***Monk et al., 2021***). Moreover, the connection between the hippocampus and the visual-perceptual cortex seems equally crucial. There are a few case reports of damage to the occipital cortex causing AM amnesia (***Greenberg et al., 2005***), potentially by preventing the population of the hippocampally constructed scenes. Furthermore, our current study suggests that a reliable connectivity between the hippocampus and the visual-perceptual cortices is important to provide the visual details necessary for successful vivid, detail-rich AM retrieval.

Conclusion

Aphantasia provides a natural knock-out model for the influence of visual imagery on different cognitive functions. We here report a tight link between visual imagery and our ability to retrieve vivid and detail-rich personal past events, as aphantasics do not only report fewer visual-perceptual details during episodic AM retrieval but also show decreased confidence and emotionality associated with these memories. In this context, we highlight the central role of the functional connectivity between the hippocampus and occipital cortex to assemble visual-perceptual details into one coherent extended mental event. Exciting novel research avenues will be to examine hippocampal-dependent spatial cognition in aphantasics and to investigate whether neuroscientific interventions can be used to enhance AM retrieval by enhancing visual imagery.

Materials and methods

Participants

In total, 31 healthy individuals with no previous psychiatric or neurological condition participated in this study. Fifteen congenital aphantasics and 16 matched controls were recruited from the database of the *Aphantasia Research Project Bonn* (***Monzel et al., 2021***; ***Monzel et al., 2022b***). Due to technical issues during MRI scanning, one participant (with aphantasia) had to be excluded from the analyses. Groups were matched for basic demographic data, that is, sex, age, and education, as well as intelligence assessed with a short intelligence screening (***Baudson and Preckel, 2015***; see ***Table 3***). Oral and written informed consent was obtained from all participants prior to the commencement of

Table 3. Demographic data for aphantasics, controls and the total sample.

	Total (n=30)	Aphantasics (n=14)	Controls (n=16)	Test statistic	*p*	BF_{01}
Age				0.80*	.431	2.30
M	29.77	31.47	28.19			
SD	11.36	10.45	12.27			
IQ						
M	93.77	91.73	95.69	0.81*	.425	2.29
SD	13.53	16.61	10.02			
Sex				2.76†	.097	0.69
Male (%)	32.3	53.3	81.3			
Female (%)	67.7	46.7	18.8			
Education				1.59†	.662	7.90
Secondary school (%)	6.5	6.7	6.3			
A-levels (%)	35.5	40.0	31.3			
University degree (%)	54.8	46.7	62.5			
Doctoral degree (%)	3.2	6.7	0.0			

Note. BF_{01}=Bayes Factor, indicates how much more likely H0 is compared to H1.

*t-test.

† χ^2-test.

experimental procedure in accordance with the Declaration of Helsinki (***World Medical Association, 2013***) and the local ethics board of the University Hospital Bonn.

Vividness of visual imagery questionnaire

Aphantasia is typically assessed with the Vividness of Visual Imagery Questionnaire (VVIQ; ***Marks, 1973***; ***Marks, 1995***), a subjective self-report questionnaire that measures how vivid mental scenes can be constructed by an individual. For example, individuals are asked to visualize a sunset with as much details as possible and rate their mental scene based on a 5-point Likert scale (ranging from 'no image at all, you only "know" that you are thinking of the object' to 'perfectly clear and as vivid as normal vision'). Since there are 16 items, the highest score of the VVIQ is 80 indicating the ability to visualize mental images with such vividness as if the event were happening right there and then. The minimum number of points is 16 indicating that an individual reported no mental image for any of the items at all. Aphantasia is at the lower end of the spectrum of imagery-abilities and usually identified with a VVIQ-score between 16 and 32 (e.g. ***Dawes et al., 2020***; ***Dawes et al., 2022***).

Binocular rivalry task

Since self-report questionnaires such as the VVIQ are associated with several drawbacks, such as their reliance on introspection (***Schwitzgebel, 2002***), we administered a mental imagery priming-based binocular rivalry task to assess mental imagery more objectively (for more details, see ***Keogh and Pearson, 2018***; ***Pearson et al., 2008***). In short, after imagining either red-horizontal or blue-vertical Gabor patterns, participants were presented with a red-horizontal Gabor pattern to one eye and a blue-vertical Gabor pattern to the other eye. Subsequently, participants were asked to indicate which type of Gabor pattern they predominantly observed. Usually, successful mental imagery leads subjects to select the Gabor pattern which they had just visualized. This selection bias can be transferred into a priming score representing visual imagery strength. (Imagery strength is used to describe the results of the Binocular Rivalry Task, whereas vividness of mental imagery is used to describe the results of the VVIQ. Although both tasks are correlated, the VVIQ measures vividness, whereas the dimension of the Binocular Rivalry Task is not clearly defined.) Mock stimuli consisting of only red-horizontal or blue-vertical Gabor patterns were displayed in 12.5% of the trials to be able to detect decisional biases. Previous studies have shown that the binocular rivalry task validly correlated with mental imagery strength (***Pearson et al., 2011***; ***Wagner and Monzel, 2023***).

Autobiographical interview

Detailed behavioral AM measures were obtained in blinded semi-structured interviews either in-person or online via Zoom (Zoom Video Communications Inc, 2016) using the Autobiographical Interview (AI; ***Levine et al., 2002***). All interviews were conducted in German. During the AI, the interviewer asks the participant to recall five episodic AMs from different life periods: early childhood (up to age 11), adolescent years (ages 11–17), early adulthood (ages 18–35), middle age (35–55), and the previous year. In order to acquire five AMs in every participant, the middle age memory was replaced by another early adulthood memory for participants who were younger than 34 years old (see ***Levine et al., 2002***). Hence, all participants provided the last time period with memories from their previous year. Memories from the first four periods were considered remote, whereas the memory from the previous year was considered recent. The interview is structured so that each memory recollection consists of three parts: free recall, general probe, and specific probe. During free recall, the participants were asked to recall as many details as possible for a memory of their choice that is specific in time and place within the given time period. When the participant came to a natural ending, the free recall was followed by the general and specific probes. During the general probe, the interviewer asked the participant encouragingly to provide any additional details. During the specific probe, specific questions were asked for details about the time, place, perception, and emotion/thoughts of each memory. Then, participants were instructed to rate their recall in terms of their ability to visualize the event on a 6-point Likert scale (ranging from 'not at all' to 'very much'). The interview was audiotaped, and afterwards transcribed and then scored by two independent raters according to the standard protocol (***Levine et al., 2002***). The interviews were scored after all data had been collected, in random order, and scorers were blind to the group membership of the participant.

For scoring, the memory details were assigned to two broad categories, that is, internal and external details. There were the following subcategories of internal details: internal events (happenings, weather conditions, people present, actions), place (country, city, building, part of room), time (year, month, day, time of the day), perceptual details (visual, auditory, gustatory, tactile, smell, body position), and emotion/thought (emotional state, thoughts). The subcategories for external details were semantic details (factual or general knowledge), external events (other specific events in time and place but different to the main event), repetition (repeated identical information without request), and other details (metacognitive statements, editorializing). In addition, following the standard procedure, an episodic richness score was given for each memory by the rater on a 7-point Likert scale (ranging from 'not at all' to 'perfect'). Furthermore, we added a novel rating score of confidence to the protocol since many participants indicated very strong belief in the details they provided, while others were insecure about the correctness of their own memories. Confidence scores were again rated on a 7-point Likert scale (ranging from 'not at all' to 'perfect').

Debriefing questions

Following the AI, we asked participants three general questions. These were thought of as open questions to get people to talk about their personal perspective on AM, spatial cognition, and imagination.

1. Typically, how difficult is it for you to recall autobiographical memories?
2. Typically, how difficult is it for you to orient yourself spatially?
3. Typically, how difficult is it for you to use your imagination?

After a free report, participants were asked to rate the difficulty on a Likert-scale from 1 ('very easy') to 6 ('very difficult').

Autobiographical memory fMRI task

The experimental fMRI task was adapted from a previous protocol by ***McCormick et al., 2015***. Two conditions, an AM retrieval task and a simple math task (MA), each consisting of 20 randomized trials, were included in this experiment. During AM trials, cue words, such as 'a party', were presented on the screen for 12 s and participants were instructed to recall a personal event related to the word cue which was specific in time and place (e.g. their 20th birthday party). Participants were asked to press a response button once an AM was retrieved to indicate the time point by which they would start to engage in the AM elaboration phase. For the rest of the trial duration, participants were asked to re-experience the chosen AM and try to recall as many details as possible without speaking out loud. After each AM trial, participants were instructed to rate via button presses whether their retrieval had been vivid or faint. We chose a simple two-button response in order to keep the task as easy as possible. During MA trials, simple addition or subtraction problems, for example, 47+19, were presented on the screen for 12 s. Here, participants were instructed to press a response button once the problems were solved and asked to engage in adding 3 s to the solutions, for example, (47+19)+3 + ...+3, until the trial ended. The MA trials were followed by a rating whether the MA problems had been easy or difficult to solve. For both AM and MA, each trial lasted for 12 s, the maximum time for rating of 3 s, and a jittered inter-stimulus interval (ISI) between 1–4 s. Since we were especially interested in the elaboration phase of AM retrieval, for the fMRI analyses, we modelled the last 8 s of each AM and MA trial just before the rating screen appeared.

MRI data acquisition

Anatomical and functional data were acquired at the German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany, using a 3 Tesla MAGNETOM Skyra MRI scanner (Siemens Healthineers, Erlangen, Germany). A mirror was mounted on the 32 channel receiver head coil and was placed in the scanner for the participants to view the stimuli shown on an MRI conditional 30-inch TFT monitor (Medres medical research, Cologne, Germany) placed at the scanner's rear end. The MRI protocol consisted of anatomical, resting-state, and AM task-based fMRI scanning sessions. In addition, we acquired further experimental fMRI and DTI data which are not part of this manuscript. Of note, the resting-state scans were acquired before participants engaged in the AM task in order to prevent reminiscing about personal memories during the resting-state. For the anatomical scans, an in-house developed 0.8 mm isotropic whole-brain T1-weighted sagittal oriented multi-echo

magnetization prepared rapid acquisition gradient echo (MEMPRAGE; ***Brenner et al., 2014***) was employed with the following parameters: TR = 2.56 s, TEs = 1.72/3.44/5.16/6.88ms, TA = 6:48, matrix = 320 x 320 x 224, readout pixel bandwidth=680 Hz/Pixel, CAIPIRINHA mode. Resting-state (190 volumes, TA = 7 min) and AM task-based fMRI scans (460 volumes, TA = 15 min) were acquired using an interleaved multi-slice 3.5 mm isotropic echo planar imaging (EPI) sequence with TR = 2 s, TE = 30ms, matrix = 64 x 64 x 39, readout pixel bandwidth = 2112 Hz/Pixel (see ***Jessen et al., 2018***). The images were obtained in an oblique-axial slice orientation along the anterior-posterior commissure line. During resting-state, the participants were asked to close their eyes and to think about nothing at all. The first 5 frames of each functional session were excluded for the scanner to reach equilibrium. Before each functional session, an optimal B0 shim was determined and individually mapped by 2-echo gradient echo (GRE) with same voxel resolution and positioning for later post-processing.

Manual segmentation of the hippocampus

Since our main goal was to assess hippocampal involvement during AM retrieval in aphantasia, we sought to examine in depth whether there were any group differences in hippocampal activation in respect to the hemispheric laterality or along its long-axis. For this reason, we segmented the hippocampus based on the T1 structural images using ITKSnap (https://www.itksnap.org, Version 3.8). Although we did not segment specific hippocampal subfields, our masks included the dentate gyrus, CA1-4, subiculum and pre- and parasubiculum. Whole masks of the left and right hippocampus were segmented manually in their respective native space and were divided afterwards into anterior and posterior portions, using the location of the uncus as boundary.

fMRI preprocessing

SPM12 (Statistical Parametric Mapping 12) software package (https://www.fil.ion.ucl.ac.uk/spm/) on MATLAB v19a (MathWorks) computing platform (https://matlab.mathworks.com/) was used to perform resting-state and AM task-based fMRI data preprocessing. The anatomical T1w RMS of all MEMPRAGE's echoes and functional 2D-EPI images were reoriented along the anterior-posterior commissure axis. The phase and magnitude images within the field maps were applied to calculate the voxel displacement maps (VDM) for geometrical correction of the distorted EPI images. The echo times were set to 4.92ms (short) and 7.38ms (long). The total EPI readout time was 34.56ms. The calculated EPI and VDMs were applied to the functional scans for realignment and unwarping. The functional scans were then co-registered to the segmented bias corrected T1 scans.

Whole-brain differences between groups were evaluated. Thus, co-registered scans were normalized to the Montreal Neurological Institute (MNI) space and a Gaussian smoothing kernel of 8 mm FWHM was applied. In addition, for functional connectivity analyses, denoising was applied using a linear regression model of potential confounding effects (global white matter signal, CSF signal, and ART scrubbing parameters) in the BOLD signal using CONN software package v20.b (https://www.nitric.org/projects/conn/). Temporal band pass filter was set from 0.01 to infinite to further minimize artifacts.

Statistical analyses

Behavioral analyses

Two samples t-tests were calculated to assess differences in the priming scores of aphantasics and controls in the binocular rivalry task. One sample t-tests were used to distinguish the performances of both groups from chance. To assess differences of Autobiographical Interview scores between aphantasics and controls, a 2x2 × 2 ANOVA with post-hoc t-tests were calculated with type of memory details (internal vs. external) and memory recency (remote vs. recent) as within-subject factors and group (aphantasics vs. controls) as between-subject factor. Afterwards, Bonferroni-corrected t-tests were conducted for specific internal (time, place, internal event, perception, emotion) and external (external event, semantic, repetition, other) memory details. Differences in memory ratings (confidence, episodic richness), self-reported visualization scores, debriefing questions, and behavioral responses during fMRI scanning were also assessed via two sample t-tests.

Hippocampal activity associated with autobiographical memory in native space

In order to examine hippocampal activity associated with autobiographical memory, we extracted signal intensity values for both AM and MA trials for each participant for our manually segmented anatomical masks of the left and right, anterior and posterior portions of the hippocampus using the MATLAB-based Response Exploration toolbox (REX; https://www.nitric.org/projects/rex/). We then calculated for each participant for each anatomical mask the difference between AM and MA signal intensities. Afterwards, group differences between aphantasics and controls with respect to the laterality effects and effects between the anterior and posterior hippocampus were assessed using a two-way ANOVA with a post-hoc Tukey's multiple comparison test, applying a significance threshold of α=.05.

Whole-brain fMRI activation analyses

After focusing on the hippocampus, we examined group differences of whole-brain activation associated with AM and MA following the standard GLM procedure in SPM12. Owing to the prominence of mental imagery during the elaboration phase of AM retrieval, we analyzed the last 8 s of the AM and MA trials prior to the display of the vividness rating. These trials were modelled as mini blocks in the GLM with motion correction regressors included as covariate of no interest. We specified our main contrast of interest, that is AM versus MA on the first level, which was then brought to the second group level using a one-sample t-test. Finally, the activation maps of the two groups were compared using a two-sample t-test. For whole-brain analysis, we applied a significance threshold of $p<0.001$, and voxel cluster size of 10 adjacent voxels, uncorrected.

ROI-to-ROI functional connectivity analyses

One of our main a priori hypotheses stated that the hippocampus and the visual-perceptual cortex show differential engagement during AM retrieval associated with aphantasia which was confirmed by our whole-brain activation analyses. Based on these results, we sought to examine the functional connectivity between those two areas. Towards this end, we created regions of interest (ROIs, spheres with a diameter of 10 mm consisting of 536 voxels) around the three peaks of the activation differences, following the whole-brain fMRI activation analyses, using the MarsBaR HBM toolbox (***Brett et al., 2002***). The ROIs comprised (1) the right hippocampus, MNI: x=39, y = –31, z = –13, (2) the right visual cortex, MNI: x=12, y = –79, z=5, and (3) the left visual cortex, MNI: x = –9, y = –76, z=29. Using CONN, we examined functional connectivity (i.e. Generalized Psycho-Physiological Interactions, weighted general linear model with bivariate correlation) between the hippocampal ROI and the ROIs situated in the visual-perceptual cortex during AM task-based fMRI and during resting-state. Furthermore, in order to examine how well functional connectivity between hippocampus and the visual cortex reflected an individuals' ability to visualize mental events, we examined a regression model with the visualization scores of the AI as criterion and resting state connectivity values, group allocation and the interaction term of the connectivity values and group allocation as predictors. For these a priori driven analyses, we applied a significance threshold of $p<0.05$, small volume corrected, and a voxel cluster threshold of 10 adjacent voxels.

Acknowledgements

CM was supported by the German Research Foundation (DFG, MC244/3-1) and the DZNE Foundation (DZNE Stiftung-Forschung für ein Leben ohne Demenz, Parkinson & ALS). We thank Anke Rühling and Jennifer Schlee for their technical support during scanning and Yilmaz Sagik for serving as the secondary scorer for the Autobiographical Interview. In addition, we would like to thank all participants for their time and effort to share their memories with us.

Additional information

Funding

Funder	Grant reference number	Author
Deutsche Forschungsgemeinschaft	MC244/3-1	Cornelia McCormick
Deutsches Zentrum für Neurodegenerative Erkrankungen	BN059K	Cornelia McCormick

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Author contributions

Merlin Monzel, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing; Pitshaporn Leelaarporn, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review and editing; Teresa Lutz, Data curation, Formal analysis, Investigation; Johannes Schultz, Conceptualization, Supervision, Validation, Methodology, Writing – review and editing; Sascha Brunheim, Software, Supervision, Validation, Investigation, Methodology, Writing – review and editing; Martin Reuter, Conceptualization, Resources, Supervision, Validation, Methodology, Project administration, Writing – review and editing; Cornelia McCormick, Conceptualization, Resources, Data curation, Formal analysis, Supervision, Funding acquisition, Validation, Methodology, Project administration, Writing – review and editing

Author ORCIDs

Merlin Monzel https://orcid.org/0000-0001-7012-9350
Pitshaporn Leelaarporn http://orcid.org/0000-0001-8755-875X
Sascha Brunheim https://orcid.org/0000-0001-9341-797X

Ethics

Oral and written informed consent was obtained from all participants prior to the commencement of the experimental procedure in accordance with the Declaration of Helsinki (World Medical Association, 2013) and the local ethics board of the University Hospital Bonn.

Peer review material

Reviewer #1 (Public Review): https://doi.org/10.7554/eLife.94916.3.sa1
Reviewer #2 (Public Review): https://doi.org/10.7554/eLife.94916.3.sa2
Author response https://doi.org/10.7554/eLife.94916.3.sa3

Additional files

Supplementary files

- MDAR checklist

Data availability

We do not have ethical approval of our research institution and our participants to share the raw brain imaging data publically. However, the processed data can be accessed via Dryad. We also hold the permission to share raw data with scientific collaborators (no commercial research), so that interested researchers may contact cornelia.mccormick@dzne.de. There is no need for a research proposal.

The following dataset was generated:

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Monzel M, Leelaarporn P, Lutz T, Schultz J, Brunheim S, Reuter M, McCormick C	2024	Data from: Hippocampal-occipital connectivity reflects autobiographical memory deficits in aphantasia	https://doi.org/10.5061/dryad.fbg79cp48	Dryad Digital Repository, 10.5061/dryad.fbg79cp48

References

Addis DR, Moscovitch M, Crawley AP, McAndrews MP. 2004. Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus* **14**:752–762. DOI: https://doi.org/10.1002/hipo.10215, PMID: 15318333

Addis DR, Wong AT, Schacter DL. 2007. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* **45**:1363–1377. DOI: https://doi.org/10.1016/j.neuropsychologia.2006.10.016, PMID: 17126370

Albers AM, Kok P, Toni I, Dijkerman HC, de Lange FP. 2013. Shared representations for working memory and mental imagery in early visual cortex. *Current Biology* **23**:1427–1431. DOI: https://doi.org/10.1016/j.cub.2013.05.065, PMID: 23871239

Bainbridge WA, Pounder Z, Eardley AF, Baker CI. 2021. Quantifying aphantasia through drawing: Those without visual imagery show deficits in object but not spatial memory. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* **135**:159–172. DOI: https://doi.org/10.1016/j.cortex.2020.11.014, PMID: 33383478

Baudson TG, Preckel F. 2015. mini-q: Intelligenzscreening in drei Minuten. *Diagnostica* **01**:a000150. DOI: https://doi.org/10.1026/0012-1924/a000150

Bauer PJ, Pathman T, Inman C, Campanella C, Hamann S. 2017. Neural correlates of autobiographical memory retrieval in children and adults. *Memory* **25**:450–466. DOI: https://doi.org/10.1080/09658211.2016.1186699, PMID: 27224534

Bayley PJ, Hopkins RO, Squire LR. 2006. The fate of old memories after medial temporal lobe damage. *The Journal of Neuroscience* **26**:13311–13317. DOI: https://doi.org/10.1523/JNEUROSCI.4262-06.2006, PMID: 17182781

Bergmann J, Ortiz-Tudela J. 2023. Feedback signals in visual cortex during episodic and schematic memory retrieval and their potential implications for aphantasia. *Neuroscience and Biobehavioral Reviews* **152**:105335. DOI: https://doi.org/10.1016/j.neubiorev.2023.105335, PMID: 37524137

Blomkvist A. 2023. Aphantasia: in search of a theory. *Mind & Language* **38**:866–888. DOI: https://doi.org/10.1111/mila.12432

Brenner D, Stirnberg R, Pracht ED, Stöcker T. 2014. Two-dimensional accelerated MP-RAGE imaging with flexible linear reordering. *Magnetic Resonance Materials in Physics, Biology and Medicine* **27**:455–462. DOI: https://doi.org/10.1007/s10334-014-0430-y

Brett M, Anton JL, Valabregue R, Poline JB. 2002. Region of interest analysis using an SPM toolbox. 8th International Conference on Functional Mapping of the Human Brain. .

Brown TI, Rissman J, Chow TE, Uncapher MR, Wagner AD. 2018. Differential medial temporal lobe and parietal cortical contributions to real-world autobiographical episodic and autobiographical semantic memory. *Scientific Reports* **8**:6190. DOI: https://doi.org/10.1038/s41598-018-24549-y, PMID: 29670138

Burgess N, Maguire EA, O'Keefe J. 2002. The human hippocampus and spatial and episodic memory. *Neuron* **35**:625–641. DOI: https://doi.org/10.1016/s0896-6273(02)00830-9, PMID: 12194864

Burianova H, McIntosh AR, Grady CL. 2010. A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *NeuroImage* **49**:865–874. DOI: https://doi.org/10.1016/j.neuroimage.2009.08.066, PMID: 19744566

Chen D, Kunz L, Lv P, Zhang H, Zhou W, Liang S, Axmacher N, Wang L. 2021. Theta oscillations coordinate grid-like representations between ventromedial prefrontal and entorhinal cortex. *Science Advances* **7**:eabj0200. DOI: https://doi.org/10.1126/sciadv.abj0200

Ciaramelli E, De Luca F, Monk AM, McCormick C, Maguire EA. 2019. What "wins" in VMPFC: Scenes, situations, or schema? *Neuroscience & Biobehavioral Reviews* **100**:208–210. DOI: https://doi.org/10.1016/j.neubiorev.2019.03.001

Cui X, Jeter CB, Yang D, Montague PR, Eagleman DM. 2007. Vividness of mental imagery: individual variability can be measured objectively. *Vision Research* **47**:474–478. DOI: https://doi.org/10.1016/j.visres.2006.11.013, PMID: 17239915

Danker JF, Anderson JR. 2010. The ghosts of brain states past: remembering reactivates the brain regions engaged during encoding. *Psychological Bulletin* **136**:87–102. DOI: https://doi.org/10.1037/a0017937, PMID: 20063927

D'Argembeau A, Van der Linden M. 2006. Individual differences in the phenomenology of mental time travel: The effect of vivid visual imagery and emotion regulation strategies. *Consciousness and Cognition* **15**:342–350. DOI: https://doi.org/10.1016/j.concog.2005.09.001, PMID: 16230028

Dawes AJ, Keogh R, Andrillon T, Pearson J. 2020. A cognitive profile of multi-sensory imagery, memory and dreaming in aphantasia. *Scientific Reports* **10**:10022. DOI: https://doi.org/10.1038/s41598-020-65705-7, PMID: 32572039

Dawes AJ, Keogh R, Robuck S, Pearson J. 2022. Memories with a blind mind: Remembering the past and imagining the future with aphantasia. *Cognition* **227**:105192. DOI: https://doi.org/10.1016/j.cognition.2022.105192, PMID: 35752014

Dentico D, Cheung BL, Chang J-Y, Guokas J, Boly M, Tononi G, Van Veen B. 2014. Reversal of cortical information flow during visual imagery as compared to visual perception. *NeuroImage* **100**:237–243. DOI: https://doi.org/10.1016/j.neuroimage.2014.05.081, PMID: 24910071

Dijkstra N, Zeidman P, Ondobaka S, van Gerven MAJ, Friston K. 2017. Distinct top-down and bottom-up brain connectivity during visual perception and imagery. *Scientific Reports* **7**:5677. DOI: https://doi.org/10.1038/s41598-017-05888-8, PMID: 28720781

Fulford J, Milton F, Salas D, Smith A, Simler A, Winlove C, Zeman A. 2018. The neural correlates of visual imagery vividness - An fMRI study and literature review. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* **105**:26–40. DOI: https://doi.org/10.1016/j.cortex.2017.09.014, PMID: 29079342

Greenberg DL, Eacott MJ, Brechin D, Rubin DC. 2005. Visual memory loss and autobiographical amnesia: a case study. *Neuropsychologia* **43**:1493–1502. DOI: https://doi.org/10.1016/j.neuropsychologia.2004.12.009, PMID: 15989939

Greenberg DL, Knowlton BJ. 2014. The role of visual imagery in autobiographical memory. *Memory & Cognition* **42**:922–934. DOI: https://doi.org/10.3758/s13421-014-0402-5

Hassabis D, Kumaran D, Vann SD, Maguire EA. 2007. Patients with hippocampal amnesia cannot imagine new experiences. *PNAS* **104**:1726–1731. DOI: https://doi.org/10.1073/pnas.0610561104

Jessen F, Spottke A, Boecker H, Brosseron F, Buerger K, Catak C, Fliessbach K, Franke C, Fuentes M, Heneka MT, Janowitz D, Kilimann I, Laske C, Menne F, Nestor P, Peters O, Priller J, Pross V, Ramirez A, Schneider A, et al. 2018. Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). *Alzheimer's Research & Therapy* **10**:1–10. . DOI: https://doi.org/10.1186/s13195-017-0314-2

Kay L, Keogh R, Andrillon T, Pearson J. 2022. The pupillary light response as a physiological index of aphantasia, sensory and phenomenological imagery strength. *eLife* **11**:e72484. DOI: https://doi.org/10.7554/eLife.72484, PMID: 35356890

Keogh R, Pearson J. 2018. The blind mind: No sensory visual imagery in aphantasia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* **105**:53–60. DOI: https://doi.org/10.1016/j.cortex.2017.10.012, PMID: 29175093

Keogh R, Bergmann J, Pearson J. 2020. Cortical excitability controls the strength of mental imagery. *eLife* **9**:e50232. DOI: https://doi.org/10.7554/eLife.50232, PMID: 32369016

Langille JJ, Gallistel CR. 2020. Locating the engram: Should we look for plastic synapses or information-storing molecules? *Neurobiology of Learning and Memory* **169**:107164. DOI: https://doi.org/10.1016/j.nlm.2020.107164, PMID: 31945459

Leelaarporn P, Dalton MA, Stirnberg R, Stöcker T, Spottke A, Schneider A, McCormick C. 2024. *Hippocampal subfields and their neocortical interactions during autobiographical memory*. Imaging Neuroscience.

Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. 2002. Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychology and Aging* **17**:677–689. DOI: https://doi.org/10.1037/0882-7974.17.4.677, PMID: 12507363

Maguire EA, Mullally SL. 2013. The hippocampus: a manifesto for change. *Journal of Experimental Psychology. General* **142**:1180–1189. DOI: https://doi.org/10.1037/a0033650, PMID: 23855494

Marks DF. 1973. Visual imagery differences in the recall of pictures. *British Journal of Psychology* **64**:17–24. DOI: https://doi.org/10.1111/j.2044-8295.1973.tb01322.x, PMID: 4742442

Marks DF. 1995. New directions for mental imagery research. *Journal of Mental Imagery* **19**:153–167.

McCormick C, St Laurent M, Ty A, Valiante TA, McAndrews MP. 2015. Functional and effective hippocampal-neocortical connectivity during construction and elaboration of autobiographical memory retrieval. *Cerebral Cortex* **25**:1297–1305. DOI: https://doi.org/10.1093/cercor/bht324, PMID: 24275829

McCormick C, Rosenthal CR, Miller TD, Maguire EA. 2017. Deciding what is possible and impossible following hippocampal damage in humans. *Hippocampus* **27**:303–314. DOI: https://doi.org/10.1002/hipo.22694, PMID: 27997994

McCormick C, Ciaramelli E, De Luca F, Maguire EA. 2018a. Comparing and contrasting the cognitive effects of hippocampal and ventromedial prefrontal cortex damage: a review of human lesion studies. *Neuroscience* **374**:295–318. DOI: https://doi.org/10.1016/j.neuroscience.2017.07.066, PMID: 28827088

McCormick C, Rosenthal CR, Miller TD, Maguire EA. 2018b. Mind-wandering in people with hippocampal damage. *The Journal of Neuroscience* **38**:2745–2754. DOI: https://doi.org/10.1523/JNEUROSCI.1812-17.2018, PMID: 29440532

McCormick C, Barry DN, Jafarian A, Barnes GR, Maguire EA. 2020. vmPFC drives hippocampal processing during autobiographical memory recall regardless of remoteness. *Cerebral Cortex***30**:5972–5987. DOI: https://doi.org/10.1093/cercor/bhaa172, PMID: 32572443

Mechelli A, Price CJ, Friston KJ, Ishai A. 2004. Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cerebral Cortex* **14**:1256–1265. DOI: https://doi.org/10.1093/cercor/bhh087, PMID: 15192010

Miller TD, Chong TT-J, Aimola Davies AM, Johnson MR, Irani SR, Husain M, Ng TW, Jacob S, Maddison P, Kennard C, Gowland PA, Rosenthal CR. 2020. Human hippocampal CA3 damage disrupts both recent and remote episodic memories. *eLife* **9**:e41836. DOI: https://doi.org/10.7554/eLife.41836, PMID: 31976861

Milton F, Fulford J, Dance C, Gaddum J, Heuerman-Williamson B, Jones K, Knight KF, MacKisack M, Winlove C, Zeman A. 2021. Behavioral and neural signatures of visual imagery vividness extremes: aphantasia versus hyperphantasia. *Cerebral Cortex Communications* **2**:tgab035. DOI: https://doi.org/10.1093/texcom/tgab035

Monk AM, Dalton MA, Barnes GR, Maguire EA. 2021. The role of hippocampal-ventromedial prefrontal cortex neural dynamics in building mental representations. *Journal of Cognitive Neuroscience* **33**:89–103. DOI: https://doi.org/10.1162/jocn_a_01634, PMID: 32985945

Monzel M, Keidel K, Reuter M. 2021. Imagine, and you will find – Lack of attentional guidance through visual imagery in aphantasics. *Attention, Perception, & Psychophysics* **83**:2486–2497. DOI: https://doi.org/10.3758/s13414-021-02307-z

Monzel M, Mitchell D, Macpherson F, Pearson J, Zeman A. 2022a. Proposal for A consistent definition of aphantasia and hyperphantasia: A response to Lambert and Sibley (2022) and Simner and Dance (2022). *Cortex* **152**:74–76. DOI: https://doi.org/10.1016/j.cortex.2022.04.003

Monzel M, Vetterlein A, Reuter M. 2022b. Memory deficits in aphantasics are not restricted to autobiographical memory - Perspectives from the Dual Coding Approach. *Journal of Neuropsychology* **16**:444–461. DOI: https://doi.org/10.1111/jnp.12265, PMID: 34719857

Monzel M, Keidel K, Reuter M. 2023. Is it really empathy? The potentially confounding role of mental imagery in self-reports of empathy. *Journal of Research in Personality* **103**:104354. DOI: https://doi.org/10.1016/j.jrp.2023.104354

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, McAndrews MP, Levine B, Black S, Winocur G, Nadel L. 2005. Functional neuroanatomy of remote episodic, semantic and spatial memory: A unified account based on multiple trace theory. *Journal of Anatomy* **207**:35–66. DOI: https://doi.org/10.1111/j.1469-7580.2005.00421.x, PMID: 16011544

O'Keefe J. 1991. The hippocampal cognitive map and navigational strategies. *Nature Communications* **14**:2946. DOI: https://doi.org/10.1093/oso/9780198542841.003.0016

Pace T, Koenig-Robert R, Pearson J. 2023. Different mechanisms for supporting mental imagery and perceptual representations: modulation versus excitation. *Psychological Science* **34**:1229–1243. DOI: https://doi.org/10.1177/09567976231198435, PMID: 37782827

Pearson J, Clifford CWG, Tong F. 2008. The functional impact of mental imagery on conscious perception. *Current Biology* **18**:982–986. DOI: https://doi.org/10.1016/j.cub.2008.05.048, PMID: 18583132

Pearson J, Rademaker RL, Tong F. 2011. Evaluating the mind's eye: the metacognition of visual imagery. *Psychological Science* **22**:1535–1542. DOI: https://doi.org/10.1177/0956797611417134, PMID: 22058106

Pearson J. 2019. The human imagination: the cognitive neuroscience of visual mental imagery. *Nature Reviews. Neuroscience* **20**:624–634. DOI: https://doi.org/10.1038/s41583-019-0202-9, PMID: 31384033

Rosenbaum RS, Moscovitch M, Foster JK, Schnyer DM, Gao F, Kovacevic N, Verfaellie M, Black SE, Levine B. 2008. Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. *Journal of Cognitive Neuroscience* **20**:1490–1506. DOI: https://doi.org/10.1162/jocn.2008.20105, PMID: 18303977

Schwitzgebel E. 2002. How well do we know our own conscious experience? The case of visual imagery. *Journal of Consciousness Studies* **9**:35–53.

Sheldon S, Levine B. 2013. Same as it ever was: vividness modulates the similarities and differences between the neural networks that support retrieving remote and recent autobiographical memories. *NeuroImage* **83**:880–891. DOI: https://doi.org/10.1016/j.neuroimage.2013.06.082, PMID: 23845428

Steinvorth S, Levine B, Corkin S. 2005. Medial temporal lobe structures are needed to re-experience remote autobiographical memories: evidence from H.M. and W.R. *Neuropsychologia* **43**:479–496. DOI: https://doi.org/10.1016/j.neuropsychologia.2005.01.001, PMID: 15716139

St Laurent M, Moscovitch M, Levine B, McAndrews MP. 2009. Determinants of autobiographical memory in patients with unilateral temporal lobe epilepsy or excisions. *Neuropsychologia* **47**:2211–2221. DOI: https://doi.org/10.1016/j.neuropsychologia.2009.01.032, PMID: 19524089

Svoboda E, McKinnon MC, Levine B. 2006. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* **44**:2189–2208. DOI: https://doi.org/10.1016/j.neuropsychologia.2006.05.023, PMID: 16806314

Treder MS, Charest I, Michelmann S, Martín-Buro MC, Roux F, Carceller-Benito F, Ugalde-Canitrot A, Rollings DT, Sawlani V, Chelvarajah R, Wimber M, Hanslmayr S, Staresina BP. 2021. The hippocampus as the switchboard between perception and memory. *PNAS* **118**:1–10. DOI: https://doi.org/10.1073/pnas.2114171118, PMID: 34880133

Wagner S, Monzel M. 2023. Measuring imagery strength in schizophrenia: no evidence of enhanced mental imagery priming. *Brain and Behavior* **13**:e3146. DOI: https://doi.org/10.1002/brb3.3146, PMID: 37411000

Wicken M, Keogh R, Pearson J. 2021. The critical role of mental imagery in human emotion: insights from fear-based imagery and aphantasia. *Proceedings. Biological Sciences* **288**:20210267. DOI: https://doi.org/10.1098/rspb.2021.0267, PMID: 33715433

World Medical Association. 2013. World medical association declaration of helsinki: ehtical principles for medical research involving human subjects. *JAMA* **310**:2191. DOI: https://doi.org/10.1001/jama.2013.281053

Zeidman P, Maguire EA. 2016. Anterior hippocampus: the anatomy of perception, imagination and episodic memory. *Nature Reviews. Neuroscience* **17**:173–182. DOI: https://doi.org/10.1038/nrn.2015.24, PMID: 26865022

Zeman A, Dewar M, Della Sala S. 2015. Lives without imagery - Congenital aphantasia. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* **73**:378–380. DOI: https://doi.org/10.1016/j.cortex.2015.05.019, PMID: 26115582

Zeman A, Milton F, Della Sala S, Dewar M, Frayling T, Gaddum J, Hattersley A, Heuerman-Williamson B, Jones K, MacKisack M, Winlove C. 2020. Phantasia-The psychological significance of lifelong visual imagery vividness extremes. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* **130**:426–440. DOI: https://doi.org/10.1016/j.cortex.2020.04.003, PMID: 32446532

3.3 Publication 3: Increased T- and B-cells associated with the phenotype of autoimmune limbic encephalitis with mainly memory dysfunction

Journal of Translational Autoimmunity 5 (2022) 100167

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Increased T- and B-cells associated with the phenotype of autoimmune limbic encephalitis with mainly memory dysfunction

Niels Hansen [a,d,*], Guido Widman [a], Demet Önder [a], Kerstin Schwing [a], Pitshaporn Leelaarporn [a], Indra Prusseit [b], Randi von Wrede [a], Rainer Surges [a,c], Albert J. Becker [b], Juri-Alexander Witt [a], Christian E. Elger [a], Christoph Helmstaedter [a]

[a] Department of Epileptology, University Hospital Bonn, Venusberg - Campus 1, 53127, Bonn, Germany
[b] Department of Neuropathology, University of Bonn Medical Center, Venusberg - Campus 1, 53127, Bonn, Germany
[c] Center for Rare Diseases Bonn (ZSEB), University of Bonn, Germany
[d] Department of Psychiatry and Psychotherapy, Von-Siebold- Str. 5, University of Göttingen, 37075, Göttingen, Germany

ARTICLE INFO

Keywords:
Autoimmune encephalitis
Immune cells
Phenotype
Neuropsychology
Autoantibodies
Verbal memory

ABSTRACT

Background: Our goal is to investigate the autoantibodies' presence and immune cells in the bioprobes of autoimmune encephalitis (AE) patients with distinct phenotypes as a promising target in AE.
Methods: We retrospectively analyzed immune cells via flow cytometry, serum and cerebrospinal fluid (CSF) autoantibodies, electroencephalography, magnetic resonance imaging in 94 AE patients with suspected temporal lobe epilepsy and classified neuropsychological phenotypes according to their occurrence.
Results: We detected different phenotypes in 94 AE patients [10.6% with isolated memory dysfunction (MEM), 11.7% with mood-dysfunction, 12.7% with mood and memory dysfunction, 13.8% with memory and attention dysfunction, 18.1% with memory, mood and attention disturbances and 20.2% with no mood, memory or attention dysfunction]. We did discern a relevant association of phenotypes and CSF antibody-positivity on CSF $CD4^+$ T-cells, CD8+T-cells and HLADR + CD8+T-cells in our patients with MEM presenting elevated CD8+T-cells and HLADR + CD8+T-cells. Furthermore, CSF CD19+B-cells differed significantly between phenotypes in patients with MEM.
Discussion: Taken together, the phenotypes in combination with CSF antibody-positivity are biomarkers for stratifying patients. Furthermore, our results confirm the role of $CD4^+$ T-cells, CD8+T-cells and CD19+B-cells in AE patients with a memory dysfunction, providing insights into AE pathogenesis. Our preliminary results should be confirmed by larger-scale investigations.

1. Introduction

Immune-cell subsets are interesting candidates for advancing the diagnosis and treatment of autoimmune encephalitis (AE) - a dynamic disease comprising different clinical features ranging from seizures to cognitive, memory, mood alterations or psychosis [1–3]. The underlying pathomechanism involved in most clinical features is unknown. Although very seldom, specific clinic phenomena such as faciobrachial dystonic seizures might suggest the underlying pathomechanism of encephalitis, such as LGI1-antibodies in AE with faciobrachial dystonic seizures [4]. Such specific clinical features are important to enable a rapid therapeutic intervention to prevent further cognitive deterioration [5]. However, as neuropsychiatric features often overlap in patients, it is difficult to differentiate clinical syndromes and plan treatment strategies. It is therefore highly relevant to have additional biomarkers that can be used to identify patients for early immunotherapy. Flow cytometry is an interesting tool for investigating immune cells as biomarkers, as it is easy to perform and has delivered promising results, especially regarding its clinical applicability in patients with neuropsychiatric disorders [6–11]. We thus explored the usefulness of flow cytometry to immunophenotype patients with distinct neuropsychological phenotypes of AE. Furthermore, we aim to explore the significance of the presence of serum neural and intracellular autoantibodies for cognitive and mood functions in AE phenotypes.

* Corresponding author.Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Von-Siebold-Str. 5, 37075 Göttingen, Germany.
E-mail address: niels.hansen@med.uni-goettingen.de (N. Hansen).

https://doi.org/10.1016/j.jtauto.2022.100167
Received 20 August 2022; Received in revised form 24 September 2022; Accepted 25 September 2022
Available online 28 September 2022

2. Methods

In this retrospective, observational study we included 94 patients with possible and definitive AE according to the Graus criteria [1] and suspected temporal lobe epilepsy suggesting limbic encephalitis and without any immunotherapy ≤3 month prior to flow cytometry. They underwent flow cytometry in the Department of Epileptology, University of Bonn. Patients were classified as "antibody-positive" if actual antibodies were detected in the CSF or PB. Previous detection of antibodies and/or antibody proof at the detection limit in patients were categorized as "antibody-negative" patients. Furthermore, thyrosine peroxidase (TPO) or antinuclear antibodies (ANA) as the only presenting antibodies were categorized as "antibody-negative" patients, as these autoantibodies might argue for an underlying autoimmune disorder other than autoimmune encephalitis, such as autoimmune thyroiditis. The presence of additional unknown bands in western blot, as well as cytoplasmatic immunoreactivity in cerebellar and hippocampal rat brain sections after incubation with the patient's serum were further characterized as "antibody-positive" patients. Specific antibodies were detected in the neuropathology laboratory at the University of Bonn via immunoblots [paraneoplastic antibodies: Amphiphysin, collapsing response mediator protein 5 (CRMP5)/cronveinten 2 (CV2), Hu, Ma-2/Ta, Recoverin, Ri, SOX1, Titin and Yo] and cell-based assays [Aquaporin 4 receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) 1, AMPAR2, contactin-associated protein 2 (CASPR2), Gamma-aminobutyric acid A/B (GABAA/B) receptors, glutamic acid decarboxylase 65/67 (GAD65/67), leucine-rich glioma inactivated 1 (LGI1) and *N*-methyl-D-aspartate (NMDA) receptor]. All patients underwent electroencephalography (EEG), magnetic resonance imaging (MRI) and neuropsychological assessment (see section neuropsychological assessment). A 3 T MRI was used to conduct neuroimaging of the brain at the Life and Brain Institute (Magnetom Trio, Siemens, Germany) and/or in the Department of Neuroradiology (Philips Medical Systems, Germany), University of Bonn. To assess signal changes in the temporal lobe typical for encephalitis, we applied a sum score previously described in more details [6,7]. We employed these specifications: 1 = unilateral hippocampal or amygdalar signal or volume increase, unilateral blurring of the interior hippocampus part or unilateral volume decrease in hippocampus, 2 = bilateral volume increase in hippocampal or amygdalar volume or bilaterally-blurred interior hippocampus or bilaterally-decreased volume of the hippocampus. All patients underwent EEG (System Plus evolution, Micromed S. p.A, Treviso, Italy) to diagnose epilepsy and AE. An EEG criterion for AE according to Graus [1] was fulfilled if epileptic potentials or slow waves were observed in the temporal lobe. To score CSF parameters, we applied these specifications relying on laboratory records from the Department of Clinical Chemistry and Clinical Pharmacology, University of Bonn: the existence of a blood-brain barrier dysfunction was rated according to these specifications based on the albumin-quotient: 0 = no blood-brain barrier disturbance and 1 = blood-brain barrier disturbance. In addition, the presence or absence of intrathecal immunoglobulin (IgG) synthesis in the CSF relies on the Reiber formula [12] with this classification system: 0 = absence of intrathecal immunoglobulin (IgG) synthesis and 1 = presence of intrathecal IgG synthesis. The presence of intrathecal IgG synthesis is attributable to the presence of oligoclonal bands, which were evaluated in the Department of Clinical Chemistry and Clinical Pharmacology at the University of Bonn via isoelectric focusing and an electrophoresis system. The presence of isolated oligoclonal bands in cerebrospinal fluid was considered pathological. Lack of oligoclonal bands or the conjunction of oligoclonal CSF ligaments as well as serum oligoclonal ligaments were considered non-pathological. All these CSF investigations were conducted by employees in the Department of Clinical Chemistry and Clinical Pharmacology, University of Bonn. All patients agreed to these clinical procedures via informed consent before the investigations. Our study concurred with the Declaration of Helsiniki and was approved by our local ethics committee in the Medical Faculty of the University of Bonn.

2.1. Neuropsychological assessment

Every patient underwent a test battery examining verbal, figural memory and attentional-executive function. We used the revised version "Diagnosticum for Cerebralschädigung" (DCS-R) to measure figural memory capacity [13] and to assess verbal memory function, we utilized the "Verbaler Lern-und Merkfähigkeitstest" (VLMT) [14]. Each patient's neuropsychological performance was scored on a numerical rating scale in relation to standard performance - meaning that the performance is classified as 0 = if lower than 3-fold below the standard deviation of the mean, 1 = if two-fold below the standard deviation of the mean, 2 = if 1-fold below the standard deviation of the mean, 3 = if within ±1 standard deviation of the mean and 4 = if one-fold above the standard deviation of the mean.

2.2. Phenotype classification

Patients were subdivided according to these neuropsychological and clinical assessments into four categories: (1) memory impairment affecting verbal and/or figural capacity (score ≤2) (MEM), (2) impaired attentional-executive function with a score ≤2 (ATT), and (3) evidence of mood dysfunction in patient history (score = 1 means mood dysfunction, score = 0 no mood dysfunction) (PSY). We further categorized phenotypes due to their occurrence. We considered only phenotypes with patient numbers ≥10 as relevant. The mixed phenotype affecting mood and attentional functions (PSY + ATT) only appeared in three patients and was thus not further considered a relevant phenotype. No patients presented the pure phenotype ATT. In addition, mixed phenotypes affecting memory and mood (MEM + PSY), memory, attention and mood (MEM + PSY + ATT) were selected. We observed patients who revealed no dysfunctionality in memory, mood and attention measures (MEM-ATT-PSY-).

2.3. Immune cells

We assessed immune cells in CSF and PB via flow cytometry using a BD LSR Fortessa flow cytometer (BD Bioscience, California, USA). One investigator blinded to the patients analyzed the flow cytometry with the gating strategy of leukocytes using Kaluza software (Beckman Coulter GmbH, Life Science, Krefeld, Germany). The gating strategy we applied to differentiate T- and B-cell subsets has been described via commonly used cell-subset markers [10]. CSF samples were obtained via lumbar punctures that were then processed via polypropylenes tubes. Blood samples were put into EDTA monovettes. Cells were separated from CSF by centrifugation steps (first: 290 g, 15 min, 4°; second/third: 290 g, 15 min, 21°). In addition, Versa Lyse buffer (Beckman Coulter, Germany) was used to segregate cells from CSF and blood. In this study, we examined two important immune cell populations: T lymphocytes (T-cells) and B lymphocytes (B-cells). These immune cells were grouped according to their differentiation cluster (CD) as well as cellular surface receptors and major histocompatibility class II into human leukocyte antigen DR isotypes (HLA-DR+) $CD4^+$ T cells, HLA-DR + $CD8^+$ T cells, CD138+ B cells and $CD19^+$ B cells from blood and CSF. The CSF HLA-DR+/CD8+ T-cells represent only the activated $CD8^+$ T-cells, whereas the CSF HLA-DR+/CD4+ T-cells depict only the activated $CD4^+$ T-cells. For immune cell specification, we referred to these fluorochromo-conjugated antibodies in T- and B-lymphocyte populations: (Beckman-Coulter) CD19-Alexafluor700, CD138-PE, HLA-DR-ECD, CD4-APC and 700CD8-PacificBlue. As a gating strategy for selecting blood and CSF leukocyte subpopulations, we applied mainstream cell line markers [10]. Our main focus was on B- and T-cell populations, which likely play a relevant role in limbic encephalitis according to published evidence [8,9]. We analyzed the following immune cells in PB and CSF applying a formula in the manufacturer's recommendations [$CD19^+$ B-cells, CD138+ B-cells, $CD4^+$ T-cells, human leukocyte antigen DR isotype (HLA-DR+) $CD4^+$ T-cells, $CD8^+$ T-cells

Table 1
Laboratory parameter of autoimmune encephalitis phenotypes.

PARAMETER	PHENOTYPES						
	MEM- PSY- ATT-	MEM	MEM + PSY	MEM + ATT	MEM + PSY + ATT	PSY	ANOVA
N	19	10	12	13	17	11	
Age at flow cytometry (y)	41 ± 14	47 ± 17	39.6 ± 15	48.2 ± 16	41.6 ± 12.5	40.3 ± 11.8	ns
Gender, female, N (%)	11 (59%)	2 (20%)	4/12 (33%)	5/13 (38%)	8 (47%)	5 (45%)	ns
CSF intrathecal IgG synthesis (%)	5 (%)	2 (20%)	3/12 (25%)	4/13 (31%)	8 (47%)	1 (9%)	ns
CSF BBB disturbance N (%)	3 (%)	4 (40%)	2/12 (16.6%)	0/13 (0%)	4 (24%)	0 (0%)	ns
CSF $CD19^+$ B-cells (cells/ml)	5 ± 1.17	181 ± 169	5.4 ± 2.2	112 ± 99	10 ± 4.05	4.1 ± 1.76	#
CSF CD138+ B-cells (cells/ml)	0.2 ± 0.08	50 ± 46	0.17 ± 0.09	2.9 ± 2.6	2 ± 1.74	0.07 ± 0.06	ns
CSF $CD4^+$ T-cells (cells/ml)	419 ± 149	2015 ± 1707	333 ± 156	863 ± 504	530 ± 155	422 ± 146	+
CSF HLA-DR + $CD4^+$ T-cells (cells/ml)	74 ± 35	366 ± 319	76 ± 39	124 ± 54	161 ± 58.3	109 ± 52	ns
CSF $CD8^+$ T-cells (cells/ml)	78 ± 31	785 ± 683	92 ± 43	120 ± 39	106 ± 28.7	115 ± 37	*
CSF HLA-DR + $CD8^+$ T-cells (cells/ml)	41 ± 12+	488 ± 431+	46 ± 21+	57 ± 19+	71 ± 23+	80 ± 29+	*
CSF CD4/8+ T-cells (cells/ml)	2.4 ± 0.55	4.59 ± 1.07	3.79 ± 0.47	5.5 ± 10.4	5.7 ± 1.5	5 ± 1.08	ns
Blood $CD19^+$ B-cells (cells/ml)	139,088 ± 31,066	122,332 ± 40,123	144,081 ± 40,581	166,704 ± 42,226	217,467 ± 111,329	118,317 ± 31,424	ns
Blood CD138+ B-cells (cells/ml)	1541 ± 725	22,146 ± 20,269	617 ± 257	3640 ± 1896	2571 ± 1519	874 ± 299	ns
Blood $CD4^+$ T-cells (cells/ml)	658,738 ± 129,022	378,388 ± 101,358	565,417 ± 133,429	689,650 ± 180,367	1,119,482 ± 525,249	501,683 ± 126,633	ns
Blood HLA-DR + $CD4^+$ T-cells (cells/ml)	31,347 ± 6329	22,345 ± 6411	29,707 ± 12,824	70,939 ± 30,126	72,584 ± 35,403	26,445 ± 6650	ns
Blood $CD8^+$ T-cells (cells/ml)	226,171 ± 48,933	201,179 ± 68,745	262,891 ± 116,597	222,782 ± 52,249	396,251 ± 207,454	193,980 ± 43,317	ns
Blood HLA-DR + $CD8^+$ T-cells (cells/ml)	23,787 ± 6871	34,098 ± 9868	19,341 ± 4952	57,164 ± 23,331	47,658 ± 19,611	26,964 ± 6450	ns
Blood CD4/8+ T-cells (cells/ml)	3 ± 0.35	3.03 ± 1.01	3.3 ± 0.68	3.66 ± 0.82	4 ± 0.83	3 ± 0.46	ns
MRI score (0–12)	2.19 ± 0.5	3.3 ± 0.36	2.1 ± 0.53	1.8 ± 0.31	2.2 ± 0.5	2 ± 0.69	ns
EEG score (0–6)	2.8 ± 0.51	3.4 ± 0.42	3.8 ± 0.39	2.7 ± 0.61	2.9 ± 0.51	3.4 ± 0.55	ns

Abbreviations: BBB = blood brain barrier, CSF = cerebrospinal fluid, EEG = electroencephalography, HLA-DR = human leukocyte antigen – DR isotype, IgG = immunoglobulin G, MRI = magnetic resonance imaging, ns = non-significant, y = years. *ANOVA with factor phenotype, CSF antibody positivity and interaction between factors; $p < 0.05$, #p ANOVA with factor phenotype, $p < 0.005$. + ANOVA with factor phenotype, and interaction between factors, $p < 0.005$.

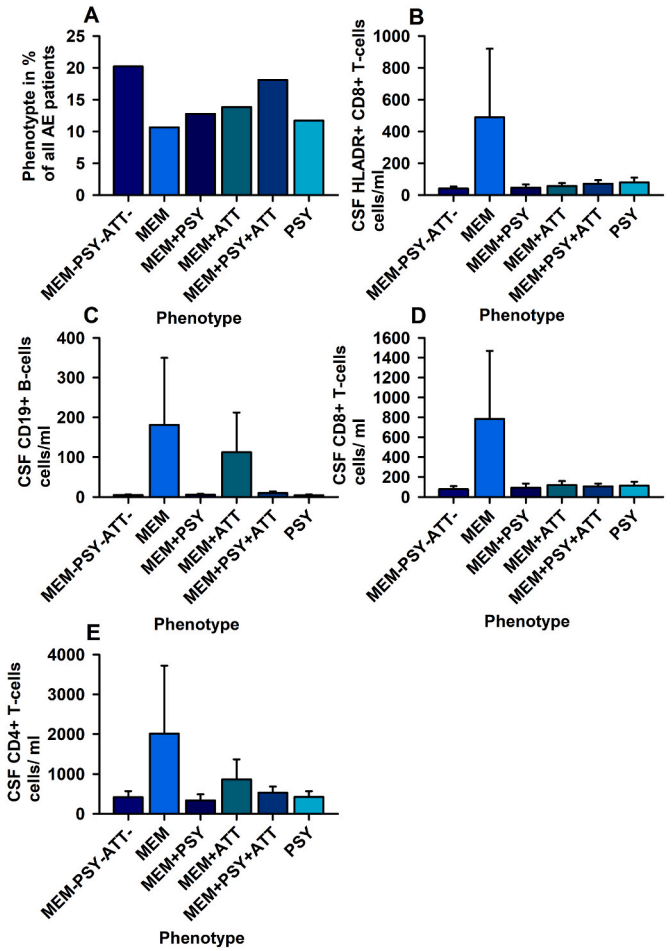

Fig. 1. Elevated $CD4^+$ T-cells, CD8+T cells and $CD19^+$ B-cells are associated with the phenotype of autoimmune encephalitis with mainly memory impairment. In A the distribution of phenotypes among our cohort of patients with autoimmune limbic encephalitis is shown. In B elevated HLADR + $CD8^+$ T-cells, in C ascended $CD19^+$ B-cells, in D increased $CD8^+$ T-cells and in E elevated $CD4^+$ T-cells are shown in MEM phenotype. The phenotype is a relevant factor determining the differences between HLADR + $CD8^+$ T-cells in B, $CD19^+$ B-cells in C, $CD8^+$ T-cells in D and $CD4^+$ T-cells in E among phenotypes. *$p < 0.005$ two factorial ANOVA. Abbreviations: MEM = phenotype with memory dysfunction, PSY = phenotype with mood dysfunction, MEM + PSY = phenotype with mood and memory dysfunction, MEM + ATT = phenotype of memory and attentional dysfunction, MEM + PSY + ATT = phenotype of memory, attentional-executive and mood dysfunction, MEM-PSY-ATT- = phenotype without affection of memory, mood and attentional-executive functions.

and HLA-DR + $CD8^+$ T-cells as well as CD4/8+ T-cell ratio in PB and CSF]. We determined absolute cell numbers following the manufacturer's guidelines in the Kaluza software instructions of Beckman Coulter GmbH.

2.4. Statistics

Statistical analysis was done via Sigma Statistics (Version 11, 2008, San Jose, California, USA). In addition figures were constructed by CorelDraw (Graphics Suite Version 11, Ontario, Canada). Two two-way ANOVAs with (1) phenotype and (2) autoantibody positivity in PB as factors as well as (1) phenotype and (2) autoantibody positivity in CSF as factors served to evaluate differences between immune cells and other laboratory parameters such as oligoclonal bands and a blood-brain barrier disturbance in the CSF, MRI scores, and in EEG scores. The receiver operating characteristic curves (ROC) analyses were performed using the software Excel Analyse-it. A p-level of <0.05 was considered as significant.

3. Results

3.1. Phenotyping of patients

We investigated 94 patients aged on average 43 ± 15 years with possible und definitive AE and suspected temporal lobe epilepsy (Table 1). We detected these clinical phenotypes: 10 of 94 (10.6%) patients with MEM, 11 of 94 patients (11.7%) with PSY, 12 of 94 patients (12.7%) with MEM + PSY, 13 of 94 patients (13.8%) with MEM + ATT, 17 of 94 patients (18.1%) with MEM + PSY + ATT and finally 19 of 94 patients (20.2%) MEM-PSY-ATT-.

3.2. Neural autoantibodies in patients

The AE patients comprised 29/94 (31%) antibody-positive patients (n = 5 GAD65 PB + CSF, n = 2 GAD65 PB, n = 1 GAD65 CSF, n = 1 CASPR2 PB + CSF, n = 1 CASPR2 CSF, n = 2 NMDAR PB, n = 2 Recoverin PB, n = 1 Zic4 PB, n = 1 Titin PB, n = 1 Yo PB, n = 1 LG1 PB, n = 1 CV2, n = 1 Ri CSF, n = 2 additional bands in western blot CSF + PB, n = 4 additional bands in western blot, unspecific neuronal binding pattern in rat brain sections n = 2 PB, n = 1 cytoplasmatic binding pattern in rat brain sections CSF + PB), and 65/94 (69%) antibody-negative patients.

3.3. Association of phenotypes, serum and CSF antibody positivity with immune cells

The phenotypes and CSF and serum antibody-positivity factors demonstrate no relevant association with immune cells in the PB ($CD19^+$ B-cells, CD138+ B-cells, $CD4^+$ T-cells, HLA-DR + $CD4^+$ T-cells, $CD8^+$ T-cells, HLA-DR + $CD8^+$ T-cells and CD4/8+ T-cell ratio; data not shown). However, the phenotype and CSF serum antibody positivity factors showed a relevant association with CSF $CD8^+$ and CD4+T-cell differences with a rise in CSF $CD8^+$ T-cells (Factor phenotype: $CD8^+$ T-cells: ANOVA $F = 8.2$, $p < 0.001$; factor CSF antibody positivity: $F = 5.3$, $p < 0.05$; interaction between phenotype and CSF antibody positivity: $F = 8.6$, $p < 0.001$; Fig. 1), $CD4^+$ T-cells (Factor phenotype: $CD8^+$ T-cells: ANOVA $F = 5.7$, $p < 0.001$; factor CSF antibody positivity: ns; interaction between phenotype and CSF antibody positivity: $F = 7.0$, $p < 0.001$; Fig. 1), and HLADR + $CD8^+$ T-cell differences with increased HLADR + $CD8^+$ T-cells (HLADR + $CD8^+$ T-cells: Factor phenotype, ANOVA: $F = 8.2$, $p < 0.001$; factor CSF antibody positivity, ANOVA: $F = 5.3$, $p < 0.05$; interaction between these factors, ANOVA: $F = 8.7$, $p < 0.001$; Fig. 1), but not on other immune cell subsets in CSF (CD138+ B-cells, $CD4^+$ T-cells HLA-DR + $CD4^+$ T-cells and CD4/8+ T-cell ratio). However, post hoc testing revealed no relevant differences in CSF $CD4^+$ T-cells, $CD8^+$ T-cells, HLADR + $CD8^+$ T-cells and HLADR + $CD4^+$ T-cells between clinical phenotypes. The phenotype is also a relevant factor for differentiating $CD19^+$ B-cells in patients (ANOVA: $F = 4$, $p < 0.005$) with the MEM and MEM + ATT phenotype showing a rise in $CD19^+$ B-cells (Fig. 1). In addition, post hoc testing revealed no relevant differences in CSF $CD19^+$ B-cells between clinical phenotypes. The serum antibody-positivity factor had no relevant association with CSF immune cells ($CD19^+$ B-cells, CD138+ B-cells, $CD4^+$ T-cells, LA-DR + $CD4^+$ T-cells, $CD8^+$ T-cells, HLA-DR + $CD8^+$ T-cells and CD4+/8+ T-cell ratio).

Furthermore, we determined optimized thresholds of $CD19^+$ B-cells, $CD4^+$ T-cells, $CD8^+$ T-cells and HLADR + $CD8^+$ T-cells to distinguish between unaffected patient (MEM-ATT-PSY- phenotype) and affected patient phenotypes (all other phenotypes pooled together) [CD19+B-cells: AUC = 0.51, p = 0.90, optimal threshold: 0.35 cells/ml, TPF (sensitivity) = 0.84, FPF (1- specificity) = 0.77; CD4+T-cells: AUC = 0.54, p = 0.62, optimal threshold: 65.42 cells/ml, TPF = 0.84, FPF = 0.63; CD8+T-cells: AUC = 0.51, p = 0.86, optimal threshold: 6.06 cells/ml, TPF = 0.95, FPF = 0.86; HLADR + $CD8^+$ T-cells: AUC = 0.50, p =

0.95, optimal threshold: 223.39 cells/ml, TPF = 1, FPF = 0.89] as well as those patients with the MEM + phenotype and all other phenotypes [CD19+B-cells: AUC = 0.55, p = 0.70, optimal threshold: 0.66 cells/ml, TPF = 0.78, FPF = 0.50; CD4+T-cells: AUC = 0.55, p = 0.68, optimal threshold: 1376 cells/ml, TPF = 0.93, FPF = 0.80; CD8+T-cells: AUC = 0.531, p = 0.764, optimal threshold: 0.86 cells/ml, TPF = 0.99, FPF = 1; HLADR + $CD8^+$ T-cells: AUC = 0.52, p = 0.86, threshold: 0 cells/ml, TPF = 0.99, FPF = 1]. In addition, we calculated optimized thresholds of $CD19^+$ B-cells, $CD4^+$ T-cells, $CD8^+$ T-cells and HLADR + $CD8^+$ T-cells to distinguish between patients with blood-brain barrier dysfunction and those without a blood -brain barrier dysfunction [CD19+B-cells: AUC = 0.55, p = 0.62, optimal threshold: 35.35 cells/ml, TPF = 0.96, FPF = 0.85; CD4+T-cells: AUC = 0.55, p = 0.55, optimal threshold: 3.07 cells/ml, TPF = 1, FPF = 0.33; CD8+T-cells: AUC = 0.52, p = 0.85, optimal threshold: 7265.24 cells/ml, TPF = 1, FPF = 0.92; HLADR + $CD8^+$ T-cells: AUC = 0.53, p = 0.67, threshold: 322.96 cells/ml, TPF = 1, FPF = 0.85)]. These results fail to support these biomarkers in differentiating between clinical phenotypes.

3.4. Association with phenotypes, serum and CSF antibody positivity on CSF, EEG and MRI parameter

Serum autoantibody positivity was a relevant factor for the presence of oligoclonal bands (ANOVA: F = 11.3, $p < 0.05$). Furthermore, the phenotype had an relevant association with blood brain barrier disturbance (ANOVA F = 2.7, $p < 0.05$). Phenotypes, serum, and CSF antibody positivity have no relevant influence on EEG and MRI scores.

4. Discussion

Our main findings suggest that $CD8^+$ T-cell subsets in CSF serve as biomarkers to distinguish AE's neuropsychological phenotypes. The phenotype primarily characterized by isolated memory impairment is associated with more CSF $CD8^+$ T-cells. Elevated $CD8^+$ T-cells in CSF in patients with pure memory dysfunction is further corroborated by autoantibody positivity in CSF. A relevant interaction between CSF autoantibody positivity and phenotypes in elevated $CD8^+$ indicates that both autoantibodies and $CD8^+$ T-cells might contribute to the primarily memory impairment phenotype in AE. Nevertheless, CSF autoantibody positivity's contribution must be interpreted with caution, as we had too few CSF autoantibody-positive patients to draw robust conclusions. The $CD8^+$ T-cells thus are helpful to characterize the memory impairment phenotype in comparison with other phenotypes that are probably accompanied by a relevant T-cell immunopathology to stratify patients more accurately for immunotherapeutic approaches. The relevant role of $CD8^+$ T-cells in the pathogenesis of autoimmune limbic encephalitis was recently shown for anti-GAD65 limbic encephalitis [15], limbic encephalitis in temporal lobe epilepsy patients [16] and GABA-B receptor limbic encephalitis [17], thus confirming our findings. However, no study so far has addressed the exclusive role of activated $CD8^+$ T-cells in a phenotype of limbic encephalitis involving prominent memory disturbances behind the $CD8^+$ T-cell driven pathophysiology of memory dysfunction in limbic circuits. Our findings also suggest that the phenotype of a pure memory impairment or demarcation of other phenotypes might give us some hints about AE's underlying pathophysiology. On the functional level, our findings do reveal the presence of CSF $CD19^+$ B-cells that play a crucial role in producing autoantibodies and are associated with impaired memory performance in AE patients. Moreover, and in line with these observations, is the recent evidence that $CD19^+$ B-cells as antibody-producing cells play a role in figural memory performance [18]. The key role of autoantibodies in verbal memory dysfunction might be related to (1) the known deposition of autoantibodies in the human hippocampus in autoimmune encephalitis with limbic features known from neuroimaging studies [19,20] after a postulated transient breakdown of the blood-brain barrier, and (2) the human hippocampus' crucial role in verbal memory formation [21–23]. Other functions such as attention, global cognition, or mood often involve temporal and extratemporal brain networks that might be dysfunctional in AE [24], but they are less often affected by immunoglobulin depositions in various AE-associated antibody subtypes. We postulate a temporal location of immunoglobulin depositions in our patients with suspected temporal lobe epilepsy due to antibody-positive AE. The prominent role of human neuronal autoantibodies in memory performance associated with AE has been confirmed in murine passive transfer models of AE from men to mice, revealing that human cerebrospinal fluid NMDA receptor antibodies induce AE [25] affecting memory performance [26,27] by disrupting NMDA receptor synaptic function. There is indirect evidence from antibody-mediated memory-dysfunction research in humans, as memory disturbances in NMDA receptor encephalitis patients were reversed by depleting B-cells via rituximab [28]. Together with those studies, our findings highlight the important role autoantibodies and $CD19^+$ B-cells play in disease-related memory dysfunction - probably due to structural changes in the temporal lobe [29]. Several autoantibodies which were also present in our phenotype subgroups, such as GAD65-, LGI1-, and NMDA receptor-antibodies are known to be associated with verbal memory decline [29,30] in patients with AE, although each antibody exhibits its own mechanism, ie, synaptic-receptor dysfunction in the case of NMDA receptors or LGI1-antibodies [25,26], or altered synaptic transmission via presynaptic alterations in GABA release due to GAD65-antibodies acting in concert with additional antibodies [31]. Despite subordinate mechanisms in autoantibody-mediated encephalitis, the crucial role antibodies and $CD19^+$ B-cells play in memory dysfunction with therapy implications must be kept in mind when treating patients with predominant or pure memory disturbances.

4.1. Limitations

As patients often display impairment in various functional aspects such as mood, cognition, and memory [3], clinical phenotypes often cannot be strictly differentiated from each other. However, careful observation is necessary to differentiate a purely clinical phenotype with a memory or psychiatric manifestation. Often clinical phenotypes show a substantial overlap between neuropsychological subdomains such as cognition, memory, and mood functions, as recently shown in conjunction with NMDA-receptor encephalitis [32], so that our investigation has to be proven in more large cohort studies to be of practical feasibility. Another critical issue is our small cohort of heterogeneous subgroups with serum and even less CSF antibodies, limiting our findings' significance. Another limitation is that we could not draw clinically relevant conclusions related to the question of cerebrospinal fluid autoantibodies associated with memory function due to too small samples of CSF autoantibodies. Furthermore, it would make sense to investigate these T- and B-cell subsets in limbic encephalitis with memory dysfunction in comparison to control subjects. Another aspect to carefully consider is that the level of $CD8^+$ T-cells and $CD19^+$ B-cell expression might change as the disease develops. This might explain why our results reveal discrepancies in B-cell subset populations ($CD19^+$ vs. CD138+ B-cells). This point should be kept in mind taking a longitudinal approach in future research. In addition, note that it would be of great interest to investigate kappa-free light chains in conjunction with oligoclonal bands in a future study to better distinguish non-inflammatory and inflammatory diseases, and to evaluate intrathecal IgG synthesis, as recently illustrated in a study by Konen et al. [33].

4.2. Conclusions

Taken together, our study reveals that $CD8^+$ T-cells and $CD19^+$ B-cells might play a relevant role as an additional biomarker by which (1) to differentiate the often overlapping neuropsychological phenomenology of AE patients and (2) further to stratify patients for

immunotherapy. However, the relevance of the biomarkers of $CD4^+$ T-cells, $CD8^+$ T-cells and activated $CD8^+$ T-cells is not supported by our ROC analysis. Thus, these cells might play key roles in the pathophysiology of AE, although these biomarkers do not seem suitable via the current assessment strategy for distinguishing clinical phenotypes, including those associated with memory dysfunction. Novel techniques should be developed to exploit the potential of standard flow cytometry. Such an enriched flow cytometry technique would include the potential assessment of the flow-cytometric functional immune phenotyping matrix as described in the literature [34,35] to delineate differences of the immune repertoire between clinical phenotypes. The pure manifestation of memory impairment without affecting other neuropsychological functions are likely associated with elevated $CD4^+$ T-cells, $CD8^+$ T-cells and $CD19^+$ B-cells that might bear clues for the pathogenesis of memory dysfunction in these AE. In addition, for memory impairment in AE the occurrence of CSF autoantibodies and $CD8^+$ T-cells seems to be important although conclusions here are limited to the small patient size. We believe that our findings highlight the pathophysiological role of activated $CD8^+$ T-cells in deciphering AE phenotypes. Cutting-edge immunodiagnostics including flow cytometry help us to provide more insights into immune cells and their contribution to neuropsychological functions impaired by AE to be addressed in further large-scales studies.

Credit author statement

NH and CH conceptualized the study, **NH and JAW** wrote the manuscript, **DÖ and KS** contributed to data collection, all authors have read and revised for important intellectual content the published version of the manuscript.

Declaration of competing interest

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

Data availability

Data will be made available on request.

References

[1] F. Graus, M.J. Titulaer, R. Balu, S. Benseler, C.G. Bien, T. Celluci, I. Cortese, R. C. Dale, J.M. Gelfand, M. Geschwind, C.A. Glaser, J. Honnorat, R. Höftberger, T. Iizuka, S.R. Irani, E. Lancaster, F. Leypoldt, H. Prüss, A. Rae-Grant, M. Reindl, M. R. Rosenfeld, K. Rostásy, A. Saiz, A. Venkatesan, A. Vincent, K.P. Wandinger, P. Waters, J. Dalmau, A clinical approach to diagnosis of autoimmune encephalitis, Lancet Neurol. 15 (2016) 391–404, https://doi.org/10.1016/S1474-4422(15)00401-9.

[2] E. Kelleher, H. Barry, D.R. Cotter, A. Corvin, K.C. Murphy, Autoantibodies and psychosis, Curr Top Behav Neurosci 44 (2019) 85–123, https://doi.org/10.1007/7854_2019_90.

[3] J.A. Witt, C. Helmstaedter, Neuropsychological evaluation in limbic encephalitis, Brain Sci. 11 (2021) 576, https://doi.org/10.3390/brainsci11050576.

[4] S.R. Irani, A. Vincent, Voltage-gated potassium channel-complex autoimmunity and associated clinical syndromes, Handb. Clin. Neurol. 133 (2016) 185–197, https://doi.org/10.1016/B978-0-444-63432-0.00011-6.

[5] J. Thompson, M. Bi, A.G. Murchison, M. Makuch, C.G. Bien, K. Chu, P. Farooque, J. M. Gelfand, M.D. Geschwind, L.J. Hirsch, E. Somerville, B. Lang, A. Vincent, M. I. Leite, P. Waters, S.R. Irani, Faciobrachial Dystonic Seizures Study Group, Faciobrachial Dystonic Seizures Study Group. The importance of early immunotherapy in patients with faciobrachial dystonic seizures, Brain 141 (2018) 348–356, https://doi.org/10.1093/brain/awx323.

[6] N. Hansen, D. Önder, D, K. Schwing, G. Widman, L. Pitshaporn, I. Prusseit, et al., CD19+B-cells in autoantibody negative limbic encephalitis, Epilepsy Behav. 106 (2020), 107016.

[7] N. Hansen, K. Schwing, D. Önder, G. Widman, P. Leelaarporn, I. Prusseit, R. Surges, N. Melzer, C. Gross, A.J. Becker, J.-A. Witt, C.E. Elger, C. Helmstaedter, Low CSF CD4/CD8+T-cell proportions are associated with blood-CSF barrier dysfunction in limbic encephalitis, Epilepsy Behav. 102 (2020), 106682, https://doi.org/10.1016/j.yebeh.2019.106682.

[8] C. Helmstaedter , N. Hansen, P. Leelaarporn, K. Schwing , D. Oender , G. Widman , A. Racz , R. Surges , A. Becker , J.-A. Witt, Specific B- and T-cell populations are associated with cognition in patients with epilepsy and antibody positive and negative suspected limbic encephalitis, J. Neurol.. 268, 455-466. doi: 10.1007/s00415-020-10158-1.

[9] J. Lippert, P. Young, C. Gross, S.G. Meuth, B. Dräger, A. Schirmacher, A. Heidbreder, Specific T-cell activation in peripheral blood and cerebrospinal fluid in central disorders of hypersomnolence, Sleep 42 (2019) 2, https://doi.org/10.1093/sleep/zsy223.

[10] G. Lueg, C.C. Gross, H. Lohmann, A. Johnen, A. Kemmling, M. Deppe, J. Groger, J. Minnerup, H. Wiendl, S.G. Meuth, T. Duning, Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease, Neurobiol. Aging 36 (2015) 81–89, https://doi.org/10.1016/j.neurobiolaging.2014.08.008.

[11] A. Schulte-Mecklenbeck, I. Kleffner, C. Beuker, T. Wirth, M. Hartwig, A. Schmidt-Pogoda, L. Klotz, W. Hansen, H. Wiendl, S.G. Meuth, C.C. Gross, J. Minnerup, Immunophenotyping of cerebrospinal fluid cells in ischaemic stroke, Eur. J. Neurol. 26 (2019) 919–926, https://doi.org/10.1111/ene.13909.

[12] H. Reiber, K. Felgenhauer, Protein transfer at the blood cerebrospinal fluid barrier and the quantification of the humoral immune response within the central nervous system, Clin. Chim. Acta 163 (1987) 319–328, https://doi.org/10.1016/0009-8981(87)90250-6.

[13] C. Helmstaedter, C. Pohl, C.E. Elger, Eine modifizierte Version des Diagnostikums für Cerebralschäden (DCS) zur Diagnostik räumlich-visueller Gedächtnisdefizite bei Patienten mit Temporallappenepilepsie, in: D. Scheffner (Ed.), Epilepsie 90. Reinbek, vol. 272, Einhorn Presse, 1991, p. 9.

[14] C. Helmstaedter, M. Lendt, S. Lux, VLMT: verbaler lern-und merkfähigkeitstest. Testhandbuch, Hofgrefe, Göttingen, 2000.

[15] A. Dik, G. Widman, A. Schulte-Mecklenbeck, J.-A. Witt, J. Pitsch, K.S. Golombeck, J. Wagner, M. Gallus, C. Strippel, N. Hansen, C. Mönig, S. Räuber, H. Wiendl, C. E. Elger, R. Surges, S.G. Meuth, C. Helmstaedter, C.C. Gross, A.J. Becker, N. Melzer, Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis, Ann Clin Transl Neurol 8 (2021) 2289–2301, https://doi.org/10.1002/acn3.51486.

[16] J. Pitsch, K.M.J. van Loo, M. Gallus, A. Dik, D. Kamalizade, A.-K. Baumgart, V. Gnatkovsky, J.A. Müller, T. Opitz, G. Hicking, V.N. Naik, L. Wachsmuth, C. Faber, R. Surges, C. Kurts, S. Schoch, N. Melzer, A.J. Becker, CD8+ T-lymphocyte driven limbic encephalitis results in temporal lobe epilepsy, Ann. Neurol. 89 (2021) 666–685, https://doi.org/10.1002/ana.26000.

[17] K.S. Golombeck, K. Bönte, C. Mönig, K.M. van Loo, M. Hartwig, W. Schwindt, G. Widman, M. Lindenau, A.J. Becker, M. Glatzel, C.E. Elger, H. Wiendl, S. G. Meuth, H. Lohmann, C.C. Gross, N. Melzer, Evidence of a pathogenic role for CD8(+) T cells in anti-GABAB receptor limbic encephalitis, Neurol Neuroimmunol Neuroinflamm 3 (2016) e232, https://doi.org/10.1212/NXI.0000000000000232.

[18] C. Helmstaedter, J.A. Witt, P. Leelaarporn, K. Schwing, D. Oender, G. Widman, et al., Is There a Clinical Relevance of T- and B-Cell Activity for Cognition and Behavior in Epilepsy Patients with Evident or Suggested Limbic Encephalitis? Bangkok - IEC, 2019, p. 389, 2019.

[19] J. Heine, H. Prüss, T. Bartsch, C.J. Ploner, F. Paul, C. Finke, Imaging of autoimmune encephalitis - relevance for clinical practice and hippocampal function, Neuroscience 309 (2015) 68–83, https://doi.org/10.1016/j.neuroscience.2015.05.037.

[20] A. Hanert, J. Rave, O. Granert, M. Ziegler, A. Pedersen, J. Born, C. Finke, T. Bartsch, Hippocampal dentate gyrus atrophy predicts pattern separation impairment in patients with LGI1 encephalitis, Neuroscience 400 (2019) 120–131, https://doi.org/10.1016/j.neuroscience.2018.12.046.

[21] S. Jun, J.S. Kim, C.K. Chung, Direct stimulation of human Hippocampus during verbal associative encoding enhances subsequent memory recollection, Front. Hum. Neurosci. 13 (2019) 23, https://doi.org/10.3389/fnhum.2019.00023.

[22] J.A. Witt, R. Coras, A.J. Becker, C.E. Elger, I. Blümcke, C. Helmstaedter, When does conscious memory become dependent on the hippocampus? The role of memory load and the differential relevance of left hippocampal integrity for short- and long-term aspects of verbal memory performance, Brain Struct. Funct. 224 (2019) 1599–1607, https://doi.org/10.1007/s00429-019-01857-1.

[23] J.A. Witt, R. Coras, J. Schramm, A.J. Becker, C.E. Elger, I. Blümcke, C. Helmstaedter, C, The overall pathological status of the left hippocampus determines preoperative verbal memory performance in left mesial temporal lobe epilepsy, Hippocampus 24 (2014) 446–454, https://doi.org/10.1002/hipo.22238.

[24] J. Heine, H. Prüss , U.A. Kopp , F. Wegner , F.T. Bergh , T. Münte, K.-P. Wandinger, P. Friedemann , T. Bartsch , C. Finke, Beyond the limbic system: disruption and functional compensation of large-scale brain networks in patients with anti-LGI1 encephalitis, J. Neurol. Neurosurg. Psychiatry. 89: 1191-1199. DOI: 10.1136/jnnp-2017-317780.

[25] J. Kreye, N.K. Wenke, M. Chayka, J. Leubner, R. Murugan, N. Maier, B. Jurek, L.-T. Ly, D. Brandl, B.R. Rost, A. Stumpf, P. Schulz, H. Radbruch, A. E Hauser, F. Pache, A. Meisel, L. Harms, F. Paul, U. Dirnagl, C. Garner 2, D. Schmitz, H. Wardemann 3, H. Prüss, Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis, Brain 139 (2016) 2641–2652, https://doi.org/10.1093/brain/aww208.

[26] J. Planagumà, F. Leypoldt, F. Mannara, J. Gutiérrez-Cuesta, E. Martín-García, E. Aguilar, M.J. Titulaer, M. Petit-Pedrol, A. Jain, R. Balice-Gordon, M. Lakadamyali, F. Graus, R. Maldonado, J. Dalmau, Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice, Brain 138 (2015) 94–109, https://doi.org/10.1093/brain/awu310.

[27] H. Haselmann, F. Mannara, C. Werner, J. Planagumà, F. Miguez-Cabello, L. Schmidl, B. Grünewald, M. Petit-Pedrol, K. Kirmse, J. Classen 6, F. Demir 7, N. Klöcker, D. Soto, S. Doose, J. Dalmau, S. Hallermann, C. Geis, Human autoantibodies against the AMPA receptor subunit GluA2 induce receptor

reorganization and memory dysfunction, Neuron 100 (2018) 91–105, https://doi.org/10.1016/j.neuron.2018.07.048.

[28] Y. Hachiya, A. Uruha, E. Kasai-Yoshida, K. Shimoda, I. Satoh-Shirai, S. Kumada, E. Kurihara, K. Suzuki, A. Ohba, S. Hamano, H. Sakuma, Rituximab ameliorates anti-N-methyl-D-aspartate receptor encephalitis by removal of short-lived plasmablasts, J. Neuroimmunol. 265 (2013) 128–130, https://doi.org/10.1016/j.jneuroim.2013.09.017.

[29] C. Finke, H. Prüss, J. Heine, S. Reuter, U.A. Kopp, F. Wegner, F.T. Bergh, S. Koch, O. Jansen, T. Münte, G. Deuschl, K. Ruprecht, W. Stöcker, K.-P. Wandinger, F. Paul, T. Bartsch, Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with leucine-rich, glioma-inactivated 1 antibodies, JAMA Neurol. 74 (2017) 50–59, https://doi.org/10.1001/jamaneurol.2016.4226.

[30] N. Hansen, L. Ernst, T. Rüber, G. Widman, A.J. Becker, C.E. Elger, C. Helmstaedter, Pre- and long-term postoperative courses of hippocampus-associated memory impairment in epilepsy patients with antibody-associated limbic encephalitis and selective amygdalohippocampectomy, Epilepsy Behav. 79 (2018) 93–99, https://doi.org/10.1016/j.yebeh.2017.10.033.

[31] C. Werner, H. Haselmann, A. Weishaupt, K.V. Toyka, C. Sommer, C. Geis, Stiff person-syndrome IgG affects presynaptic GABAergic release mechanisms, J. Neural. Transm. 122 (2015) 357–362, https://doi.org/10.1007/s00702-014-1268-1.

[32] A. Al-Diwani, A. Handel, L. Townsend, T. Pollak, M.I. Leite, P.J. Harrison, R. Belinda, Lennox, D. Okai, S.G. Manohar, S. R Irani, The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data, Lancet Psychiatr. 6 (2019) 235–246.

[33] F.F. Konen, P. Schwenkenbecher, K.F. Jendretzky, S. Gingele, T. Witte, K.W. Sühs, et al., Kappa free light chains in cerebrospinal fluid in inflammatory and non-inflammatory neurological diseases, Brain Sci. 12 (2022) 475, https://doi.org/10.3390/brainsci12040475.

[34] L.A. Gerdes, C. Janoschka, M. Eveslage, et al., Immune signatures of prodromal multiple sclerosis in monozygotic twins, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 21546–21556.

[35] T. Ruck, S. Barman, A. Schulte-Mecklenbeck, S. Pfeuffer, F. Steffen, C. Nelke, et al., Alemtuzumab-induced immune phenotype and repertoire changes: implications for secondary autoimmunity, Brain 145 (2022) 1711–1725, https://doi.org/10.1093/brain/awac064.

4. Summary

This thesis focuses on the investigation of the neural basis of E-AM retrieval and visual-perceptual mental imagery, involving the hippocampus and its neocortical connections Additionally, identifying different immune cell populations incurring the damage to the hippocampus may provide the hint into the inflammatory process of episodic memory dysfunction.

The 1st study incorporated in this thesis (Leelaarporn et al., 2024) examines the role of six hippocampal subfields along their longitudinal axis during the vivid re-experiencing of E-AM in healthy young adults. Although all subfields along their entire length were found to be engaged during E-AM retrieval in comparison to a mental arithmetic (MA) task, the pre-/parasubiculum within the anterior body of the hippocampus displayed greater involvement than its neighbors (along the long-axis of the hippocampus as well as the adjacent anatomical subfields) during E-AM recall. Furthermore, the anterior body of the pre-/parasubiculum revealed stronger functional connectivity towards other cortical regions, such as the vmPFC and the medial/lateral parietal regions, known to be typically associated with E-AM. Our findings suggest that vivid E-AM, which presumably involves visual mental imagery, is supported by the pre-/parasubiculum, mainly in the anterior body of the hippocampus.

In the 2nd study (Monzel, Leelaarporn et al., 2024), the identical E-AM versus MA tasks as described in the 1st study were conducted with 16 healthy controls and 14 individuals with congenital aphantasia. In addition to providing less detailed E-AM reports on the AI, aphantasics showed reduced activation of the right hippocampus in comparison to the controls during E-AM retrieval. Conversely, greater activation in the visual-perceptual cortices was found in the aphantasics compared to the controls. Additionally, we observed stronger functional connectivity between the right hippocampus and the visual-perceptual cortices in the controls, which was also correlated with higher visualization abilities during E-AM retrieval. Together, these behavioural and neural group differences indicate that visual mental imagery is an integral part of vivid, detail-rich E-AM.

The results from the 3rd study (Hansen et al., 2022) suggest that elevated levels of specific immune lymphocyte populations, including CD4+ T-cells, CD8+ T-cells, and CD19+ B-cells, are correlated with episodic memory impairment, affecting verbal and/or figural abilities in autoantibody-positive LE patients. Furthermore, the increase of CD19+ B-cells in CSF has been shown to be correlated with impairment in figural or visual episodic memory performance in autoantibody-negative LE patients (Hansen et al., 2020a). This suggests that the presence of accumulated relevant lymphocytes can factor into the detrimental changes in the brain structures. The impact may contribute to the clinical conditions with memory dysfunction.

5. Discussion and future directions

The overall aim of the current thesis was to examine the relationship between hippocampal-dependent episodic memory and visual-perceptual processing. The main aspects cover the use of ultra-high field neuroimaging technique, exploring E-AM in the absence of visual imagery, and the presence of autoantibodies in episodic memory dysfunction. Further imminent future directions involving the visuospatial world in the episodic aspect of AM are highlighted. Ultimately, the key elements are emphasized to present a novel neural model of the construction of the movies of our minds.

5.1 Using 7 Tesla fMRI to examine the link between E-AM and visual-perceptual processing

Leveraging the benefits of 7 T over 3 T fMRI, we used a novel submillimeter fMRI sequence to examine E-AM processes in hippocampal subfields and their neocortical connectivity. We opted to employ a previously known, robust E-AM task (Recall AMs versus MA task) to ensure hippocampal engagement. We found that the precise location of the anterior body of the pre-/parasubiculum was more engaged during E-AM than math solving. While this finding meshes well with our predictions that the pre-/parasubiculum may be a central hippocampal hub for scene-based cognition, there are much more cognitive differences between E-AM and mental arithmetic solving than scene-based cognition, such as retrieval processes, emotional influences, etc. Therefore, in a sequential study, one could employ the same 7 T fMRI sequence, and examine a much tighter contrast to disentangle the engagement of the pre-/parasubiculum in scene versus object construction. For example, participants could be asked to construct single scenes (like a scenic postcard) or single objects in front of a white background. Conducting the same analysis procedure as set out during study 1 of the current thesis, we would predict that the anterior body of the pre-/parasubiculum is more engaged during the scene condition than the object condition. Furthermore, we would expect that this hippocampal subregion may be functionally stronger connected to the visual-perceptual cortices during scene than object construction.

5.2 E-AM in the absence of visual-perceptual processing

In line with the literature, we have demonstrated that Aphantasia is associated with a E-AM deficit. We have added to the literature that this E-AM deficit is reflected neurally by altered patterns of activation and connectivity of the hippocampus and visual-perceptual cortex. Together, these findings support the hypothesis that the visual imagery maybe essential for E-AM retrieval and that this link is facilitated by the connectivity between hippocampus and visual-perceptual cortex. Of note, and in line with previous work on hemispheric lateralization, the peak of the group differences was located in the right posterior hippocampus. One possible explanation involves the pre-described functions of the right hippocampus, such as processing of visual or figurative information (Gleiβner et al., 1998). Complementing our current FC analysis, future studies could examine the white matter pathways between the hippocampus and the visual-perceptual cortex using diffusion tensor imaging (DTI) (Basser et al., 1994). Moreover, effective connectivity analysis, such as Dynamic Causal Modelling, could investigate the directionality of these connections to study how the hippocampus may influence or be influenced by the other regions (Rolls, 2022).

Additionally, an intriguing question arising from the 2nd study is how congenitally blindness may affect E-AM and its underlying neural networks. Surprisingly, there is a scarcity of research on E-AM of blind individuals (Raz et al., 2005; Tekcan et al., 2015), particularly of fMRI studies. Such an exploration may provide even deeper insights into the hippocampal relationship between E-AM and visual-perceptual processing.

5.3 Specific immune cell population and hippocampal dysfunction in LE

Due to the unknown underlying processes causing cognitive dysfunction and neuroimaging pattern in LE, the search for the biomarkers is still ongoing (Day et al., 2021; Wesselingh et al., 2023). Our results propose the elevated presence of CD8+ T-cell population in CSF as the main biomarker for isolated memory dysfunction in LE, while CD4+ T-cells and CD19+ B-cells could also attest for both memory and attention-

executive function impairments. The prominent level of CD8+ T-cells has also been shown in various subtypes of LE with different autoantibody statuses (Dik et al., 2021; Golombeck et al., 2016; Pitsch et al., 2021). This hints the role of inflammatory cells in memory impairment-related disease.

Furthermore, hippocampal volume is generally found to be correlated with neuropsychological assessment, where the decrease in the volume due to autoantibody deposition has been show to indicate extensive memory deficits in LE (Finke et al., 2016; Miller et al., 2017; Shibata et al., 2024). MRI reconstruction of the hippocampus and its subfields has been attempted previously (Finke et al., 2017; Harms et al., 2023; Heine et al., 2020; Wagner et al., 2015). The pronounced episodic verbal memory impairment in LE patients can be correlated with the left CA2/3 volume shrinkage. Automated hippocampus subfields segmentation with higher accuracy for volumetric analysis in conjunction with functional imaging could contribute to the characterization of the disease progression as well as the cause for memory performance decline.

5.4 A neural model of the movies in our minds

The research presented in my thesis points to the crucial role of the hippocampus and its associated neural network to support vivid, detail-rich episodic memory. In the following, I will set out a hierarchical neural network of the vmPFC, hippocampus (particularly the anterior body of the pre-/parasubiculum), and the visual-perceptual cortices to support a more comprehensive neural model of the construction of the movies in our minds.

Firstly, the vmPFC initiates the overall process of E-AM retrieval, stimulating the hippocampal-dependent E-AM reconstruction. The responding activation of the vmPFC due to AM recall has been found to direct the hippocampal activation (McCormick et al., 2020). Secondly, the influenced hippocampus plays an essential role in reconstructing detail-rich scenes by integrating visuospatial information. The pre-/parasubiculum, one of the hippocampal subfields, receives direct information from the parieto-medial temporal pathway. It is likely that this projection allows for the visuo-spatial access (Dalton und Maguire, 2017). Thirdly, the visual-perceptual cortex provides the hippocampus with

detailed visual input necessary for the vividness of visual imagery. Increased signal intensity in the hippocampus and reduced visual-perceptual cortex activity during complex scene construction has previously been described in healthy individuals (McCormick et al., 2021). Thus, the changes in hippocampal activation we observed may be due to the limited/excessive visual information flow from the visual processing regions, occurring during the assimilation of lucid details during E-AM. Further examination in different portions along the longitudinal axis of the hippocampal subfields could pinpoint the responsible area and the link to other cortical regions for more comprehension of visual information pathways in E-AM. Together, these regions enable the vivid and accurate recollection of past experiences, highlighting the complex interplay between E-AM and visual imagery.

6. Conclusion

The hippocampus emerges as one of the key players linking vivid visual mental imagery and scene construction during episodic autobiographical memory retrieval. Suggested by our observations, the anterior body of the pre-/parasubiculum is demonstrated to be strongly engaged during scene-based reconstruction. Characterizing the performance of the hippocampal subfields during memory retrieval and visual imagery supports the understanding of autonoetic cognition. To this end, we proposed a process consisting of a whole-brain hierarchical network, where the hippocampus facilitates the detail-rich memories with non-specific visual information supplied by visual-perceptual cortex and the chain of command begun in the vmPFC. Disruptions in this hierarchy impede proper event recall and can lead to reduced or absent visual imagery. Novel 7 T fMRI sequence with higher resolution and increased sensitivity in the tasks design would allow for more accurate mapping the hippocampal-neocortical network during episodic memory and imagination in individuals with different memory circumstances. In due course, our findings promote our comprehension of neural architecture during hippocampal-dependent scene constructing processes.

7. References

Addis DR, Moscovitch M, Crawley AP, McAndrews MP. Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. Hippocampus. 2004; 14: 752-762.

Addis DR, Wong AT, Schacter DL. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia. 2007; 45: 1363-1377.

Aly M, Ranganath C, Yonelinas AP. Detecting changes in scenes: the hippocampus is critical for strength-based perception. Neuron. 2013; 78: 1127-1137.

Anderson RJ, Dewhurst SA, Dean GM. Direct and generative retrieval of autobiographical memories: The roles of visual imagery and executive processes. Conscious Cogn. 2017; 49: 163-171.

Arcangeli M. Aphantasia demystified. Synthese. 2023; 201.

Bainbridge WA, Pounder Z, Eardley AF, Baker CI. Quantifying aphantasia through drawing: Those without visual imagery show deficits in object but not spatial memory. Cortex. 2021; 135: 159-172.

Bartsch T, Döhring J, Rohr A, Jansen O, Deuschl G. CA1 neurons in the human hippocampus are critical for autobiographical memory, mental time travel, and autonoetic consciousness. Proceedings of the National Academy of Sciences. 2011; 108: 17562-17567.

Bauer PJ, Pathman T, Inman C, Campanella C, Hamann S. Neural correlates of autobiographical memory retrieval in children and adults. Memory. 2016; 25: 450-466.

Berron D, Schutze H, Maass A, Cardenas-Blanco A, Kuijf HJ, Kumaran D, Duzel E. Strong Evidence for Pattern Separation in Human Dentate Gyrus. Journal of Neuroscience. 2016; 36: 7569-7579.

Berron D, Vieweg P, Hochkeppler A, Pluta JB, Ding SL, Maass A, Luther A, Xie L, Das SR, Wolk DA, Wolbers T, Yushkevich PA, Düzel E, Wisse LEM. A protocol for manual segmentation of medial temporal lobe subregions in 7 Tesla MRI. NeuroImage: Clinical. 2017; 15: 466-482.

Bien CG. Limbic encephalitis. Hrsg. The Temporal Lobe. 2022: 467-487.

Boccara CN, Sargolini F, Thoresen VH, Solstad T, Witter MP, Moser EI, Moser M-B. Grid cells in pre- and parasubiculum. Nature Neuroscience. 2010; 13: 987-994.

Bonnici HM, Chadwick MJ, Maguire EA. Representations of recent and remote autobiographical memories in hippocampal subfields. Hippocampus. 2013; 23: 849-854.

Butler AC, Rice HJ, Wooldridge CL, Rubin DC. Visual imagery in autobiographical memory: The role of repeated retrieval in shifting perspective. Conscious Cogn. 2016; 42: 237-253.

Chadwick MJ, Bonnici HM, Maguire EA. CA3 size predicts the precision of memory recall. Proceedings of the National Academy of Sciences. 2014; 111: 10720-10725.

Cîrneci D, Onu M, Papasteri CC, Georgescu D, Poalelungi C, Sofonea A, Puşcaşu N, Tanase D, Rădeanu T, Toader M-Y, Dogaru AL, Podină IR, Berceanu AI, Carcea I. Neural Networks Implicated in Autobiographical Memory Training. eneuro. 2022; 9.

Conway MA. Episodic memories. Neuropsychologia. 2009; 47: 2305-2313.

Dalton MA, Maguire EA. The pre/parasubiculum: a hippocampal hub for scene-based cognition? Current Opinion in Behavioral Sciences. 2017; 17: 34-40.

Dalton MA, Zeidman P, Barry DN, Williams E, Maguire EA. Segmenting subregions of the human hippocampus on structural magnetic resonance image scans: An illustrated tutorial. Brain and Neuroscience Advances. 2017; 1.

Dawes AJ, Keogh R, Robuck S, Pearson J. Memories with a blind mind: Remembering the past and imagining the future with aphantasia. Cognition. 2022; 227.

Day GS, Yarbrough MY, Kortvelyessy P, Pruss H, Bucelli RC, Fritzler MJ, Mason W, Tang-Wai DF, Steriade C, Hebert J, Henson RL, Herries EM, Ladenson JH, Lopez-Chiriboga AS,

Graff-Radford NR, Morris JC, Fagan A. Prospective Quantification of CSF Biomarkers in Antibody-Mediated Encephalitis. Neurology. 2021; 96: e2546-e2557.
De Luca F, McCormick C, Ciaramelli E, Maguire EA. Scene processing following damage to the ventromedial prefrontal cortex. Neuroreport. 2019; 30: 828-833.
Dik A, Widman G, Schulte-Mecklenbeck A, Witt JA, Pitsch J, Golombeck KS, Wagner J, Gallus M, Strippel C, Hansen N, Monig C, Rauber S, Wiendl H, Elger CE, Surges R, Meuth SG, Helmstaedter C, Gross CC, Becker AJ, Melzer N. Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis. Ann Clin Transl Neurol. 2021; 8: 2289-2301.
Ding SL. Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum in human, monkey, and rodent. Journal of Comparative Neurology. 2013; 521: 4145-4162.
Finke C, Kopp UA, Pajkert A, Behrens JR, Leypoldt F, Wuerfel JT, Ploner CJ, Pruss H, Paul F. Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Biol Psychiatry. 2016; 79: 727-734.
Finke C, Pruss H, Heine J, Reuter S, Kopp UA, Wegner F, Then Bergh F, Koch S, Jansen O, Munte T, Deuschl G, Ruprecht K, Stocker W, Wandinger KP, Paul F, Bartsch T. Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies. JAMA Neurol. 2017; 74: 50-59.
Ganis G, Schendan HE. Visual imagery. Wiley Interdiscip Rev Cogn Sci. 2011; 2: 239-252.
Gibson LL, McKeever A, Coutinho E, Finke C, Pollak TA. Cognitive impact of neuronal antibodies: encephalitis and beyond. Transl Psychiatry. 2020; 10: 304.
Gleißner U, Helmstaedter Ca, Elger C. Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 1998; 65: 665-669.
Golombeck KS, Bonte K, Monig C, van Loo KM, Hartwig M, Schwindt W, Widman G, Lindenau M, Becker AJ, Glatzel M, Elger CE, Wiendl H, Meuth SG, Lohmann H, Gross CC, Melzer N. Evidence of a pathogenic role for CD8(+) T cells in anti-GABAB receptor limbic encephalitis. Neurol Neuroimmunol Neuroinflamm. 2016; 3: e232.
Greenberg DL, Knowlton BJ. The role of visual imagery in autobiographical memory. Memory & Cognition. 2014; 42: 922-934.
Hansen N. Long-Term Memory Dysfunction in Limbic Encephalitis. Frontiers in Neurology. 2019; 10.
Hansen N, Önder D, Schwing K, Widman G, Leelaarporn P, Prusseit I, Surges R, Becker AJ, Witt J-A, Helmstaedter C, Elger CE. CD19 + B-cells in autoantibody-negative limbic encephalitis. Epilepsy & Behavior. 2020a; 106.
Hansen N, Schwing K, Önder D, Widman G, Leelaarporn P, Prusseit I, Surges R, Melzer N, Gross C, Becker AJ, Witt J-A, Elger CE, Helmstaedter C. Low CSF CD4/CD8 + T-cell proportions are associated with blood–CSF barrier dysfunction in limbic encephalitis. Epilepsy & Behavior. 2020b; 102.
Hansen N, Widman G, Önder D, Schwing K, Leelaarporn P, Prusseit I, von Wrede R, Surges R, Becker AJ, Witt J-A, Elger CE, Helmstaedter C. Increased T- and B-cells associated with the phenotype of autoimmune limbic encephalitis with mainly memory dysfunction. Journal of Translational Autoimmunity. 2022; 5.
Harms A, Bauer T, Witt JA, Baumgartner T, von Wrede R, Racz A, Ernst L, Becker AJ, Helmstaedter C, Surges R, Ruber T. Mesiotemporal Volumetry, Cortical Thickness, and Neuropsychological Deficits in the Long-term Course of Limbic Encephalitis. Neurol Neuroimmunol Neuroinflamm. 2023; 10.
Heine J, Prüss H, Bartsch T, Ploner C, Paul F, Finke C. Imaging of autoimmune encephalitis–Relevance for clinical practice and hippocampal function. Neuroscience. 2015; 309: 68-83.

Heine J, Pruss H, Scheel M, Brandt AU, Gold SM, Bartsch T, Paul F, Finke C. Transdiagnostic hippocampal damage patterns in neuroimmunological disorders. Neuroimage Clin. 2020; 28: 102515.
Helmstaedter C. Effects of chronic epilepsy on declarative memory systems. Progress in brain research. 2002; 135: 439-453.
Helmstaedter C, Gleissner U, Di Perna M, Elger CE. Relational verbal memory processing in patients with temporal lobe epilepsy. Cortex. 1997; 33: 667-678.
Helmstaedter C, Hansen N, Leelaarporn P, Schwing K, Oender D, Widman G, Racz A, Surges R, Becker A, Witt J-A. Specific B- and T-cell populations are associated with cognition in patients with epilepsy and antibody positive and negative suspected limbic encephalitis. Journal of Neurology. 2020; 268: 455-466.
Helmstaedter C, Lendt M, Lux S. VLMT: Verbaler Lern-und Merkfähigkeitstest. Beltz Test, 2001.
Helmstaedter C, Wietzke J, Lutz MT. Unique and shared validity of the “Wechsler logical memory test”, the “California verbal learning test”, and the “verbal learning and memory test” in patients with epilepsy. Epilepsy Research. 2009; 87: 203-212.
Helmstaedter C, Witt J-A. Clinical neuropsychology in epilepsy. Hrsg. Epilepsy. 2012: 437-459.
Hodgetts CJ, Voets NL, Thomas AG, Clare S, Lawrence AD, Graham KS. Ultra-High-Field fMRI Reveals a Role for the Subiculum in Scene Perceptual Discrimination. The Journal of Neuroscience. 2017; 37: 3150-3159.
Holland AC, Addis DR, Kensinger EA. The neural correlates of specific versus general autobiographical memory construction and elaboration. Neuropsychologia. 2011; 49: 3164-3177.
Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. J Neurol Neurosurg Psychiatry. 2007; 78: 917-928.
Irish M. Autobiographical memory in dementia syndromes—An integrative review. WIREs Cognitive Science. 2022; 14.
Irish M, Lawlor BA, O'Mara SM, Coen RF. Impaired capacity for autonoetic reliving during autobiographical event recall in mild Alzheimer's disease. Cortex. 2011; 47: 236-249.
Johnen A, Bertoux M. Psychological and Cognitive Markers of Behavioral Variant Frontotemporal Dementia–A Clinical Neuropsychologist's View on Diagnostic Criteria and Beyond. Frontiers in Neurology. 2019; 10.
Kopelman MD. The autobiographical memory interview (AMI) in organic and psychogenic amnesia. Memory. 1994; 2: 211-235.
Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: A new assessment of autobiographical and personal semantic memory in amnesic patients. Journal of Clinical and Experimental Neuropsychology. 2008; 11: 724-744.
Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. Trends in Cognitive Sciences. 2013; 17: 26-49.
Lad M, Mullally SL, Houston AL, Kelly T, Griffiths TD. Characterizing memory loss in patients with autoimmune limbic encephalitis hippocampal lesions. Hippocampus. 2019; 29: 1114-1120.
Leelaarporn P, Dalton MA, Stirnberg R, Stöcker T, Spottke A, Schneider A, McCormick C. Hippocampal subfields and their neocortical interactions during autobiographical memory. Imaging Neuroscience. 2024; 2: 1-13.
Lerma-Usabiaga G, Iglesias JE, Insausti R, Greve DN, Paz-Alonso PM. Automated segmentation of the human hippocampus along its longitudinal axis. Human Brain Mapping. 2016; 37: 3353-3367.
Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M. Aging and autobiographical memory: Dissociating episodic from semantic retrieval. Psychology and Aging. 2002; 17: 677-689.

Loane C, Argyropoulos GPD, Roca-Fernández A, Lage C, Sheerin F, Ahmed S, Zamboni G, Mackay C, Irani SR, Butler CR. Hippocampal network abnormalities explain amnesia after VGKCC-Ab related autoimmune limbic encephalitis. Journal of Neurology, Neurosurgery & Psychiatry. 2019; 90: 965-974.

Lutz MT, Helmstaedter C. EpiTrack: tracking cognitive side effects of medication on attention and executive functions in patients with epilepsy. Epilepsy Behav. 2005; 7: 708-714.

Maguire EA, Intraub H, Mullally SL. Scenes, Spaces, and Memory Traces. The Neuroscientist. 2016; 22: 432-439.

Marks DF. Visual Imagery Differences in the Recall of Pictures. British Journal of Psychology. 1973; 64: 17-24.

McAndrews MP, Cohn M. Neuropsychology in Temporal Lobe Epilepsy: Influences from Cognitive Neuroscience and Functional Neuroimaging. Epilepsy Research and Treatment. 2012; 2012: 1-13.

McCormick C, Barry DN, Jafarian A, Barnes GR, Maguire EA. vmPFC Drives Hippocampal Processing during Autobiographical Memory Recall Regardless of Remoteness. Cerebral Cortex. 2020; 30: 5972-5987.

McCormick C, Dalton MA, Zeidman P, Maguire EA. Characterising the hippocampal response to perception, construction and complexity. Cortex. 2021; 137: 1-17.

McCormick C, Moscovitch M, Valiante TA, Cohn M, McAndrews MP. Different neural routes to autobiographical memory recall in healthy people and individuals with left medial temporal lobe epilepsy. Neuropsychologia. 2018; 110: 26-36.

McCormick C, Rosenthal CR, Miller TD, Maguire EA. Deciding what is possible and impossible following hippocampal damage in humans. Hippocampus. 2017; 27: 303-314.

Miller TD, Chong TT, Aimola Davies AM, Ng TWC, Johnson MR, Irani SR, Vincent A, Husain M, Jacob S, Maddison P, Kennard C, Gowland PA, Rosenthal CR. Focal CA3 hippocampal subfield atrophy following LGI1 VGKC-complex antibody limbic encephalitis. Brain. 2017; 140: 1212-1219.

Miller TD, Chong TTJ, Aimola Davies AM, Johnson MR, Irani SR, Husain M, Ng TWC, Jacob S, Maddison P, Kennard C, Gowland PA, Rosenthal CR. Human hippocampal CA3 damage disrupts both recent and remote episodic memories. eLife. 2020; 9.

Miró J, Ripollés P, Sierpowska J, Santurino M, Juncadella M, Falip M, Rodríguez-Fornells A. Autobiographical memory in epileptic patients after temporal lobe resection or bitemporal hippocampal sclerosis. Brain Imaging and Behavior. 2019; 14: 1074-1088.

Monk AM, Dalton MA, Barnes GR, Maguire EA. The Role of Hippocampal–Ventromedial Prefrontal Cortex Neural Dynamics in Building Mental Representations. Journal of Cognitive Neuroscience. 2021; 33: 89-103.

Monzel M, Vetterlein A, Reuter M. Memory deficits in aphantasics are not restricted to autobiographical memory – Perspectives from the Dual Coding Approach. Journal of Neuropsychology. 2021; 16: 444-461.

Moscovitch M, Cabeza R, Winocur G, Nadel L. Episodic Memory and Beyond: The Hippocampus and Neocortex in Transformation. Annual Review of Psychology. 2016; 67: 105-134.

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, McAndrews MP, Levine B, Black S, Winocur G. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. Journal of anatomy. 2005; 207: 35-66.

Palombo DJ, Sheldon S, Levine B. Individual Differences in Autobiographical Memory. Trends in Cognitive Sciences. 2018; 22: 583-597.

Peters SL, Fan CL, Sheldon S. Episodic memory contributions to autobiographical memory and open-ended problem-solving specificity in younger and older adults. Memory & Cognition. 2019; 47: 1592-1605.

Pitsch J, van Loo KMJ, Gallus M, Dik A, Kamalizade D, Baumgart AK, Gnatkovsky V, Müller JA, Opitz T, Hicking G, Naik VN, Wachsmuth L, Faber C, Surges R, Kurts C, Schoch S, Melzer N, Becker AJ. CD8+ T-Lymphocyte–Driven Limbic Encephalitis Results in Temporal Lobe Epilepsy. Annals of Neurology. 2021; 89: 666-685.

Poiret C, Bouyeure A, Patil S, Grigis A, Duchesnay E, Faillot M, Bottlaender M, Lemaitre F, Noulhiane M. A fast and robust hippocampal subfields segmentation: HSF revealing lifespan volumetric dynamics. Front Neuroinform. 2023; 17: 1130845.

Raz N, Amedi A, Zohary E. V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb Cortex. 2005; 15: 1459-1468.

Robin J, Moscovitch M. The effects of spatial contextual familiarity on remembered scenes, episodic memories, and imagined future events. J Exp Psychol Learn Mem Cogn. 2014; 40: 459-475.

Ryan DH, Fallon MA, Horan PK. Flow cytometry in the clinical laboratory. Clinica chimica acta. 1988; 171: 125-173.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of neurology, neurosurgery, and psychiatry. 1957; 20: 11.

Setton R, Sheldon S, Turner GR, Spreng RN. Temporal pole volume is associated with episodic autobiographical memory in healthy older adults. Hippocampus. 2022; 32: 373-385.

Sheldon S, Levine B. Same as it ever was: Vividness modulates the similarities and differences between the neural networks that support retrieving remote and recent autobiographical memories. NeuroImage. 2013; 83: 880-891.

Shibata K, Attaallah B, Tai XY, Trender W, Hellyer PJ, Hampshire A, Irani SR, Manohar SG, Husain M. Remote digital cognitive assessment reveals cognitive deficits related to hippocampal atrophy in autoimmune limbic encephalitis: a cross-sectional validation study. EClinicalMedicine. 2024; 69: 102437.

Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: A meta-analysis. Neuropsychologia. 2006; 44: 2189-2208.

T. Vu A, Jamison K, Glasser MF, Smith SM, Coalson T, Moeller S, Auerbach EJ, Uğurbil K, Yacoub E. Tradeoffs in pushing the spatial resolution of fMRI for the 7T Human Connectome Project. NeuroImage. 2017; 154: 23-32.

Tang L, Pruitt PJ, Yu Q, Homayouni R, Daugherty AM, Damoiseaux JS, Ofen N. Differential Functional Connectivity in Anterior and Posterior Hippocampus Supporting the Development of Memory Formation. Frontiers in Human Neuroscience. 2020; 14.

Tekcan AI, Yilmaz E, Kiziloz BK, Karadoller DZ, Mutafoglu M, Erciyes AA. Retrieval and phenomenology of autobiographical memories in blind individuals. Memory. 2015; 23: 329-339.

Tulving E, Markowitsch HJ. Episodic and declarative memory: Role of the hippocampus. Hippocampus. 1998; 8: 198-204.

van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, Bowtell R. fMRI at 1.5, 3 and 7 T: Characterising BOLD signal changes. NeuroImage. 2009; 47: 1425-1434.

Wagner J, Witt JA, Helmstaedter C, Malter MP, Weber B, Elger CE. Automated volumetry of the mesiotemporal structures in antibody-associated limbic encephalitis. J Neurol Neurosurg Psychiatry. 2015; 86: 735-742.

Wesselingh R, Griffith S, Broadley J, Tarlinton D, Buzzard K, Seneviratne U, Butzkueven H, O'Brien TJ, Monif M. Peripheral monocytes and soluble biomarkers in autoimmune encephalitis. J Autoimmun. 2023; 135: 103000.

Winterburn JL, Pruessner JC, Chavez S, Schira MM, Lobaugh NJ, Voineskos AN, Chakravarty MM. A novel in vivo atlas of human hippocampal subfields using high-resolution 3 T magnetic resonance imaging. Neuroimage. 2013; 74: 254-265.

Wisse LEM, Daugherty AM, Olsen RK, Berron D, Carr VA, Stark CEL, Amaral RSC, Amunts K, Augustinack JC, Bender AR, Bernstein JD, Boccardi M, Bocchetta M, Burggren A, Chakravarty MM, Chupin M, Ekstrom A, de Flores R, Insausti R, Kanel P, Kedo O,

Kennedy KM, Kerchner GA, LaRocque KF, Liu X, Maass A, Malykhin N, Mueller SG, Ofen N, Palombo DJ, Parekh MB, Pluta JB, Pruessner JC, Raz N, Rodrigue KM, Schoemaker D, Shafer AT, Steve TA, Suthana N, Wang L, Winterburn JL, Yassa MA, Yushkevich PA, la Joie R. A harmonized segmentation protocol for hippocampal and parahippocampal subregions: Why do we need one and what are the key goals? Hippocampus. 2017; 27: 3-11.

Witt JA, Coras R, Becker AJ, Elger CE, Blumcke I, Helmstaedter C. When does conscious memory become dependent on the hippocampus? The role of memory load and the differential relevance of left hippocampal integrity for short- and long-term aspects of verbal memory performance. Brain Struct Funct. 2019; 224: 1599-1607.

Witt JA, Helmstaedter C. Neuropsychological Evaluations in Limbic Encephalitis. Brain Sci. 2021; 11.

Witt JA, Helmstaedter C. The impact of perampanel on cognition: A systematic review of studies employing standardized tests in patients with epilepsy. Seizure. 2022; 94: 107-111.

Yoo PE, John SE, Farquharson S, Cleary JO, Wong YT, Ng A, Mulcahy CB, Grayden DB, Ordidge RJ, Opie NL, O'Brien TJ, Oxley TJ, Moffat BA. 7T-fMRI: Faster temporal resolution yields optimal BOLD sensitivity for functional network imaging specifically at high spatial resolution. NeuroImage. 2018; 164: 214-229.

Zeidman P, Maguire EA. Anterior hippocampus: the anatomy of perception, imagination and episodic memory. Nature Reviews Neuroscience. 2016; 17: 173-182.

Zeidman P, Mullally SL, Maguire EA. Constructing, Perceiving, and Maintaining Scenes: Hippocampal Activity and Connectivity. Cerebral Cortex. 2015; 25: 3836-3855.

Zeman A, Dewar M, Della Sala S. Lives without imagery – Congenital aphantasia. Cortex. 2015; 73: 378-380.

8. Acknowledgements

I am deeply indebted to my primary supervisor, Dr. Cornelia McCormick, for her immense support and advice, both in terms of research and career guidance, throughout my doctoral years. I greatly appreciate her patience and mentorship during the data acquisition, analyses, and manuscript submission processes. Her thoughtful critiques and generous time have transformed this dissertation from an initial draft into its final, substantive form, providing me with a glimpse of scintillating vision of the end goal. Without her leap of faith, I would not have received the opportunity to learn new methods, collaborate with an outstanding team of physicians, physicists, and neuropsychologists, nor engage in these fascinating research studies that contribute to complementing our fundamental understanding of the human mind.

I would like to express my sincere gratitude to the following members of my Dissertation Committee: Prof. Dr. Christoph Helmstaedter, Prof. Dr. Anja Schneider, Prof. Dr. Michael Wagner, and Dr. Martin Reuter, for their constructive feedback on all of my projects during our three Thesis Advisory Committee (TAC) meetings. Special appreciation goes to Prof. Dr. Helmstaedter for his valuable advice and intriguing ideas that have shaped our collaboration and potential future projects.

I extend my deepest appreciation to Prof. Dr. Tony Stöcker and his MR Physics team, especially Anke Rühling, Sascha Brunheim, and Jennifer Schlee, for their support during the time-consuming data acquisition process. I am also very grateful to Dr. Martin Reuter and his Deep MI team for lending me with their Wacom Drawing Tablet for segmentation, and to Dr. Annika Spottke for the use of the workstation the German Center for Neurodegenerative Diseases (DZNE). Special thanks go to Yilmaz Sagik for his assistance with all the projects and for encouraging me to train for marathons over the years. Many thanks to Julia Taube for her compassion ears and emotional boost throughout the final state of writing this dissertation.

My thanks also go to NeurotechEU and Bonn International Graduate School Clinical and Population Science (BIGS CPS), for I have received many scholarships and financial aids that allowed me to attend various courses and conferences. Without their assistance, I would not have had the opportunity to further my knowledge and connect with peers and researchers in related fields.

Lastly, I wish to thank all of my co-authors and collaborators for their dedicated time in reviewing and providing feedback on the manuscripts. I am also genuinely appreciative of the other PhD students at the DZNE and the Universitätsklinikum Bonn (UKB) for their mellifluous cherished friendship and unwavering mental sustenance throughout my doctoral years.

I swear on my honour to continue my diligent efforts in future research, with the hope that it will benefit humankind and contribute valuable insights into the dynamic world of neuroscience.

กราบขอบพระคุณอาจารย์ที่ปรึกษา ทีมแพทย์ และนักวิจัยทุกท่าน
ที่สละเวลาให้ความช่วยเหลือและคำแนะนำที่มีคุณค่าแก่ข้าพเจ้าในการศึกษาค้นคว้างานวิจัย
และการจัดทำดุษฎีนิพนธ์ระดับปริญญาเอกครั้งนี้

กราบขอบพระคุณพระมารดา คุณยาย และสมาชิกครอบครัวอื่นๆ ของข้าพเจ้า ที่ให้การสนับสนุนการเรียนในครั้งนี้

Pitshaporn Leelaarporn

พิชชาพร ลีลาอาภรณ์

9. Publications

- **Leelaarporn, P.,** Monzel, M., Lutz, T., Schultz, J., Brunheim, S., Reuter, M., & McCormick, C. (2024). Hippocampal-occipital connectivity reflects autobiographical memory deficits in aphantasia. *eLife.* doi:10.7554/eLife.94916.1.
- **Leelaarporn, P.,** Dalton, M. A., Stirnberg, R., Stöcker, T., Spottke, A., Schneider, A., & McCormick, C. (2024). Hippocampal subfields and their neocortical interactions during autobiographical memory. *Imaging Neuroscience.* doi: 10.1162/imag_a_00105.
- Hansen, N., Widman, G., Önder, D., Schwing, K., **Leelaarporn, P.,** Prusseit, I., von Wrede, R., Surges, R., Becker, A.J., Witt, J.A. and Elger, C.E. (2022). Increased T-and B-cells associated with the phenotype of autoimmune limbic encephalitis with mainly memory dysfunction. *Journal of Translational Autoimmunity*. doi:10.1016/j.jtauto.2022.100167.
- Kongwudhikunakorn, S., Kiatthaveephong, S., Thanontip, K., **Leelaarporn, P.,** Piriyajitakonkij, M., Charoenpattarawut, T., Autthasan, P., Chaisaen, R., Dujada, P., Sudhawiyangkul, T., Senanarong, V., & Wilaiprasitporn, T. (2021). A Pilot Study on Visually Stimulated Cognitive Tasks for EEG-Based Dementia Recognition. *IEEE Transactions on Instrumentation and Measurement.* doi: 10.1109/TIM.2021.3120131.
- **Leelaarporn, P.,** Wachiraphan, P., Kaewlee, T., Udsa, T., Chaisaen, R., Choksatchawathi, T., Laosirirat, R., Lakhan, P., Natnithikarat, P., Thanontip, K., Sangnark, K., Chen, W., Mukhopadhyay, S.C., & Wilaiprasitporn, T. (2021). Sensor-Driven Achieving of Smart Living: A Review. IEEE Sensors J*ournal*. doi: 10.1109/JSEN.2021.3059304.
- Ueafuea, K., Boonnag, C., Sudhawiyangkul, T., **Leelaarporn, P.,** Gulistan, A., Chen, W., Mukhopadhyay., S. C., Wilaiprasitporn, T., & Piyayotai, S. (2020). Potential Applications of Mobile and Wearable Devices for Psychological Support During the COVID-19 Pandemic: A Review. *IEEE Sensors Journal*. doi: 10.1109/JSEN.2020.3046259.
- Banluesombatkul, N., Ouppaphan, P., **Leelaarporn, P.**, Lakhan, P., Chaitusaney, B., Jaimchariya, N., Chuangsuwanich, E., Chen, W., Phan, H., Dilokthanakul, N., & Wilaiprasitporn, T. (2020). Metasleeplearner: A pilot study on fast adaptation of bio-signals-based sleep stage classifier to new individual subject using meta-learning. *IEEE Journal of Biomedical and Health Informatics*. doi: 10.1109/JBHI.2020.3037693.
- Piriyajitakonkij, M., Warin, P., Lakhan, P., **Leelaarporn, P.**, Kumchaiseemak, N., Suwajanakorn, S., Pianpanit, T., Niparnan, N., Mukhopadhyay, S.C., & Wilaiprasitporn, T. (2020). SleepPoseNet: Multi-View for Sleep Postural Transition Recognition Using UWB. *IEEE Journal of Biomedical and Health Informatics.* doi: 10.1109/JBHI.2020.3025900
- Helmstaedter, C., Hansen, N., **Leelaarporn, P.**, Schwing, K., Oender, D., Widman, G., Racz, A., Surges, R., Becker, A., & Witt, J. A. (2020). Specific B-and T-cell populations are associated with cognition in patients with epilepsy and antibody positive and negative suspected limbic encephalitis. *Journal of Neurology*. doi: 10.1007/s00415-020-10158-1
- Chaisaen, R., Autthasan, P., Mingchinda, N., **Leelaarporn, P.**, Kunaseth, N., Tammajarung, S., Manoonpong, P., Mukhopadhyay, S.C., and Wilaiprasitporn, T. (2020) Decoding EEG Rhythms During Action Observation, Motor Imagery, and Execution for Standing and Sitting. *IEEE Sensors Journal*. doi: 10.1109/JSEN.2020.3005968.
- Choksatchawathi, T., Ponglertnapakorn, P., Ditthapron, A., **Leelaarporn, P.**, Wisutthisen, T., Piriyajitakonkij, M., & Wilaiprasitporn, T. (2020). Improving Heart Rate Estimation on Consumer Grade Wrist-Worn Device Using Post-Calibration Approach*. IEEE Sensors Journal*. doi: 10.1109/JSEN.2020.2979191.
- Hansen, N., Önder, D., Schwing, K., Widman, G., **Leelaarporn, P.**, Prusseit, I., Surges, R., Becker, A.J., Witt, J.A., Helmstaedter, C., & Elger, C. E. (2020). CD19+ B-cells in autoantibody-negative limbic encephalitis. *Epilepsy & Behavior.* doi.org/10.1016/j.yebeh.2020.107016

- Sawangjai, P., Hompoonsup, S., **Leelaarporn, P.**, Kongwudhikunakorn, S., and Wilaiprasitporn, T. (2020). Consumer grade EEG Measuring Sensors as Research Tools: A Review*. IEEE Sensors Journal*. doi:10.1109/JSEN.2019.2962874
- Hansen, N., Schwing, K., Önder, D., Widman, G., **Leelaarporn, P.**, Prusseit, I., Melzer, N., Gross, C., Becker, A.J., Witt, J.A., Helmstaedter, C., & Elger, C. E. (2020). Low CSF CD4/CD8+ T-cell proportions are associated with blood–CSF barrier dysfunction in limbic encephalitis. *Epilepsy & Behavior.* doi: 10.1016/j.yebeh.2019.106682
- Natnithikarat, S., Lamyai, S., **Leelaarporn, P.**, Kunaseth, N., Autthasan, P., Wisutthisen, T., & Wilaiprasitporn, T. (2019). Drowsiness Detection for Office-based Workload with Mouse and Keyboard Data. *12th Biomedical Engineering International Conference (BMEiCON) IEEE.*
- Lakhan, P., Banluesombatkul, N., Changniam, V., Dhithijaiyratn, A., **Leelaarporn, P.,** Boonchieng, E., Hompoonsup, S., & Wilaiprasitporn, T. (2019). Consumer Grade Brain Sensing for Emotion Recognition*. IEEE Sensors Journal*. doi: 10.1109/JSEN.2019.2928781