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Impairment of place and grid cells and their effect on spatial cognition in Alzheimer's Disease

Jente Kuiper

Faculty of science and engineering

Supervised by Eddy van der Zee

university of groningen

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Summary

Alzheimer's disease (AD) is a neurodegenerative disease associated with spatial disorientation and loss of spatial memory. The onset of AD begins decades before the onset of spatial orientation deficits, which is why there is a need for biomarkers that can detect AD in a preclinical stage. The impairment of place and grid cells due to the progression of AD is thought to underly the loss of spatial memory and navigation. To find biomarkers, the deterioration of place and grid cells due to AD progression, needs to be fully understood. In this paper, it becomes clear that the deterioration of place and grid cells starts with the impairment of signal transfer towards grid neurons. A subsequent dysfunction of grid cells leads to impaired signal transfer between place and grid cells. Place cells begin to deteriorate after grid cells begin to lose their function. These network dysfunctions will eventually lead to spatial memory and navigation deficits. It has been suggested that the impaired signal transfer could be used as an early biomarker, along with the impairment of grid cells. In addition can the performance of preclinical AD risk patients in a path integration task be used as an early biomarker.

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Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease marked by three pathological characteristics. Amyloid-beta (AB) plaque accumulation (Yarns et al., 2022), misfolded hyperphosphorylated tau proteins (Ossenkoppele et al., 2022) and a reduction in brain volume (Du et al., 2007). AD pathology starts decades before the onset of cognitive deficits found in AD patients. (Tan et al., 2014). For this reason, there is a need to find biomarkers that can detect AD in a preclinical stage. As of yet, no effective cure has been found to treat AD (Chen & Zhang, 2022). It has been proposed that early biomarkers and possible therapeutic targets can be found by uncovering the underlying network dysfunction found in patients with AD (Canter et al., 2016).

A symptom found in patients with AD is their spatial disorientation associated with a loss of spatial navigation and memory (Allison et al., 2016). Spatial navigation is a cognitive function that allows a person to navigate through an environment. It is based upon the formation of a 'cognitive map'; a neuronal representation of the environment (Moser et al., 2015). Impairments to this cognitive map are thought to underly the loss of spatial memory and reduced spatial navigation in patients with AD. Part of the cognitive map are place cells, location-specific cells of the hippocampus that fire selectively in specific locations within the environment (O'Keefe & Dostrovsky, 1971). Every place cell has its own place field that represents a part of the environment (fig. 1). Together, they form a map of the environment (Moser et al., 2015) (Derdikman & Moser, 2011).

In 2005, another spatially sensitive neuron was found, the grid cells of the entorhinal cortex (EC) (Hafting et al., 2005). A grid cell has multiple place fields which are organised in a grid-like pattern across the environment (fig.1) (Derdikman & Moser, 2011). Grid cells fire in a non-topographic manner, meaning that neighbouring cells do not necessarily represent neighbouring locations in the environment (Moser et al., 2015). The scale of the environment they encode for increases from neurons found in the dorsal area to neurons in the ventral area of the EC (Brun et al., 2008). The firing rate of place cells changes when minor alterations are made to the environment, which is called rate remapping (Muller & Kubie, 1987). When exploring an entirely different environment, the location of place fields and grid fields changes as well as the firing rate, causing a global remapping of the representation of the environment (Muller & Kubie, 1987). This place and grid cell remapping allows an individual to distinguish between environments (Colgin et al., 2008).

To navigate through the environment, the brain is thought to use two mechanisms. The first one relies on the use of spatial land marks, the other one is based on path integration (Jayakumar, 2019). Path integration is a process in which the current location is measured based on distance and direction travelled from a starting point (Etienne & Jeffery, 2004). This is measured by integrating information about self-motion cues and visual land marks (Jayakumar, 2019). Next to place and grid cells, other neurons have been found in the entorhinal-hippocampal network that contribute to positional information. It seems that head-direction cells and speed encoding cells continuously interact with grid cells as an environment is explored, to update information about the current position (Sargolini, 2006).

Network dysfunctions of place and grid cells are thought to underly deficits in spatial navigation and memory (Jun et al., 2020). Neurofibrillary tau protein formation begins in the EC, then propagates to the hippocampus and the neocortex (Pooler et al., 2013), whereas AB pathology starts in the neocortex and then spreads to allocortical regions, including the hippocampus and the EC (Thal et al., 2002). Both AB pathology and neurofibrillary tau pathology are associated with impairments in place and grid cell functioning (Ying et al., 2022; Atsmon & Slutsky, 2020). To find early AD detection biomarkers, the effect of AD pathology on place and grid cells needs to be further understood. This review paper will therefore make an overview of what is known about the deterioration of place and grid cells in relation to AD, what network dysfunctions underly place and grid cell dysfunction and how the impairments of place and grid cells lead to spatial memory and navigation dysfunction. For this, the effect of AD on place and grid cells will first be discussed.

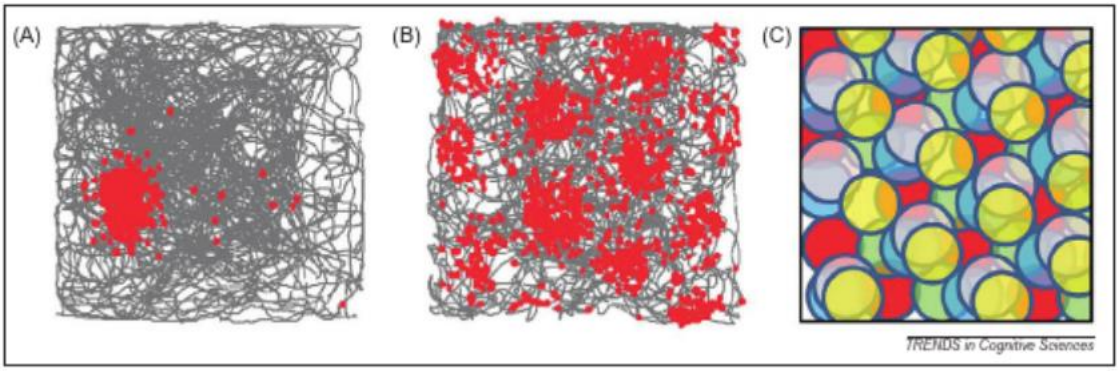

Figure 1. Neuronal representation of place and grid cells of an open field. Red dots and gray lines denote spike position and animal trace in the open field, respectively. A) Place field of a place cell. B) Grid-pattern of one grid cell. C) Firing fields of a population of grid cells. Different colours represent grids from different grid cells. Source: Derdikman, D., Moser, E. I. (2011). A manipfold of spatial maps in the brain. Dehaene, S., & Brannon, E. (Red.) Space, time and number in the brain : searching for the foundations of mathematical thought (41-57). Geraadpleegd op 24 juni 2023, https://ebookcentral.proquest.com/lib/rug/reader.action?docID=692428&ppg=4#

Place cell pathology

The deterioration of place cells due to AD has been thoroughly investigated. Recent research has focused on the underlying deficits caused by AD that lead to a decline in the ability of place cells to form an accurate map of the environment. A temporal relationship has been found between AB plaque formation, neuronal deficits and spatial memory deficits (Zhang et al., 2023).

In a 5xFAD mouse model by Zhang et al. (2023), they found a correlation between neuronal deficits and loss of spatial memory, where neuronal deficits precede spatial memory deficits. This model shows AB plaque formation after four months, accompanied by several neurological impairments, while spatial memory deficits, shown by an object location memory (OLM) task, only start after eight months. After four months, 5xFAD mice show impairments in global remapping of place cells. In addition, they show a reduced neuronal calcium activity in CA1 neurons, which remains consistent with age, while in WT mice, neuronal calcium activity decreases with age (fig. 1). They measured calcium activity to look at neuronal activity in the CA1 region. Interestingly, the reduction in calcium activity is only observed in immobile state. Previous research has shown that during movement, hippocampal place cells fire in theta oscillations, while in resting state, the hippocampus shows irregular activity, disturbed by intervals of sharp-wave ripples (SWR) (Buzsáki et al., 1992). SWR are associated with memory consolidation (Dupret et al., 2010). Zang et al. (2023) have shown that the reduction in calcium activity predicts OLM deficits found in eight month old mice, suggesting that the decrease of calcium event rates during immobility lies at the root of memory deficits found in later stages of AD. Interestingly, they found an increase in spatial information score across all ages in an open field task, which is usually a sign of increased spatial specificity. However, as place cells show unreliable mapping at four months, they looked for a different interpretation of this result and investigated the sparsity (amount of area covered by place field in relation to environment) and coherence (spatial consistency of firing) of place cell firing. They found lower sparsity across all ages and a lower coherence after 8-10 months, meaning that spatial tuning is reduced in 5xFAd mice. Concurrently with the onset of spatial memory deficits, spatial field stability and spatial tuning to location of objects decrease after 8-10 months. This suggests that the impaired OLM is induced by reduced place field stability and spatial tuning (Zang et al., 2023). In addition, the reduced neuronal activity and impaired global remapping at four months were predictors for spatial memory deficits at 8-10 months old.

Zang et al. (2023) show that deficits in place cell functioning are found together with AB plaque formation and made predictions on what underlies the spatial memory deficits found in AD. They do not, however, look at what underlies the neuronal deficits. In a previous study of the same group (Zhang et al., 2021), they propose that synapse loss could be a driver of neuronal deficits.

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Synapse loss precedes cellular loss in AD and is strongly associated with the progression of cognitive decline in patients with AD (Chabrier et al., 2014). Place cells receive input from, amongst others, grid cells and inhibitory interneurons (Booker & Vida, 2018; Nilsson et al., 2019). Zang et al. (2021) aimed to find out what the effect of synapse loss with these classes of neurons are on the deterioration of place cells in a computational model of AD. They appointed grid cells as excitatory neurons and interneurons as inhibitory. They found that a loss of synapses with excitatory neurons lead to a reduced number of place cells over time and low place map stability. This means that due to excitatory synapse loss, the specific place map of active cells in an environment is inconsistent. When the inhibitory input from interneurons is lacking, they found an increase in place cell activity and abundancy. However, the amount of place cells that produce a significant place field went down. Most importantly, the place field width increased, meaning a reduction in the spatial tuning of place cells. When both inhibitory and excitatory signals fell out, both place field stability and spatial tuning went down. Interestingly, activity of place cells initially increased, but gradually decreased. It would be expected that activity only decreases with progression of AD, however, this observation has also been found in mouse models with AD pathology. This model from Zhang et al. provides a possible explanation on the neuronal deficits underlying place cell deterioration. Synapse loss, resulting in impoverished inhibitory signal from interneurons and excitatory signals from grid cells, could very well be the leading cause of place cell deficits later on in AD.

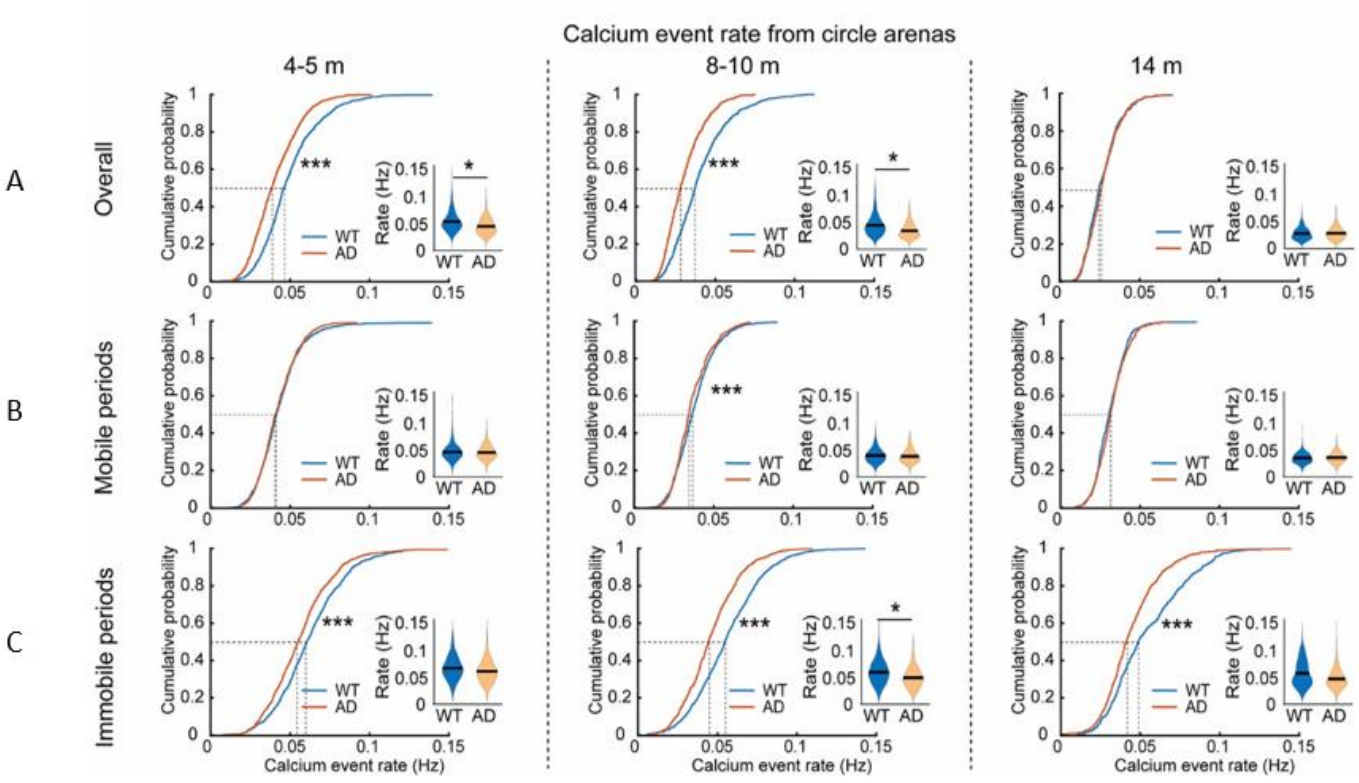

Figure 2. Calcium activity of CA1 neurons in mobile and immobile periods across different ages (4-5 months, 8-10 months and 14 months). A) The Z-scored calcium event rates during the entire session of recording. The calcium activity of WT mice decreases across ages, while the AD mice have decreased activity from 4-5 months already. B) The Z-scored calcium event rates during mobile periods of recording. Shows that the difference in activity cannot be explained by mobile periods. C) The Z-scored calcium activity during immobile states of recording. Shows the difference in calcium activity of CA1 neurons between WT and AD mice is observed mostly in immobile states. Source: Zhang H, Chen L, Johnston KG, Crapser J, Green KN, Ha NM, Tenner AJ, Holmes TC, Nitz DA, Xu X. Degenerate mapping of environmental location presages deficits in object-location encoding and memory in the 5xFAD mouse model for Alzheimer's disease. Neurobiol Dis. 2023 Jan;176:105939. doi: 10.1016/j.nbd.2022.105939. Epub 2022 Dec 1. PMID: 36462718; PMCID: PMC10187684

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Grid cell pathology

AD affects the medial Azhinal cortex (MEC) as well as the hippocampus. Especially the grid cells of the MEC are impaired due to AD. A lot of research has been conducted to uncover what deficits underly the impairment of grid cells and how the deterioration of grid cell is associated with spatial navigation deficits. In research conducted by Ying et al. (2022), they endeavoured to uncover how the network of grid cells is impacted in AD. They used a J20 transgenic familial AD mouse model, were the APP gene is a mutated version of the human APP gene. It was found that after 4.5-7 months, grid cells of the J20 mice begin to show impaired spatial periodicity and spatial information. In addition, grid cells have an increased firing field after 4.5-7 months, suggesting decreased spatial tuning of the grid cells. In contrast, there were no deficits found in the spatial tuning of Head-Direction cells or non-grid spatially tuned neurons of the MEC. Ying et al. looked at what network dysfunctions could possibly underly grid cell impairment. They found that the firing rate of interneurons from the MEC increases along with age in mice with mutated APP, which suggests that the inhibitory network is altered. Correspondingly they found slower theta waves and reduced theta power, resulting in a reduced synchrony between grid cells and interneurons after 3-4.5 months, preceding grid cell periodicity impairment (fig. 3) . The same decrease in synchrony was found between grid cells and head-direction cells (fig. 3). This suggests that the inability to integrate inhibitory signals from upstream interneurons, plays a role in the loss of spatial periodicity found in grid cells at later stages of AD. Contradictory to what previous research has shown, Ying et al. have not found grid cell impairment preceding spatial navigational deficits. Their mice show spatial navigation deficits in the Morris water maze after 3-4 months, however, no grid cell spatial tuning impairments have been found after 3-4.5 months. They did find deficits in path integration across different ages in comparison to age matched controls, which is correlated with the grid cell impairments.

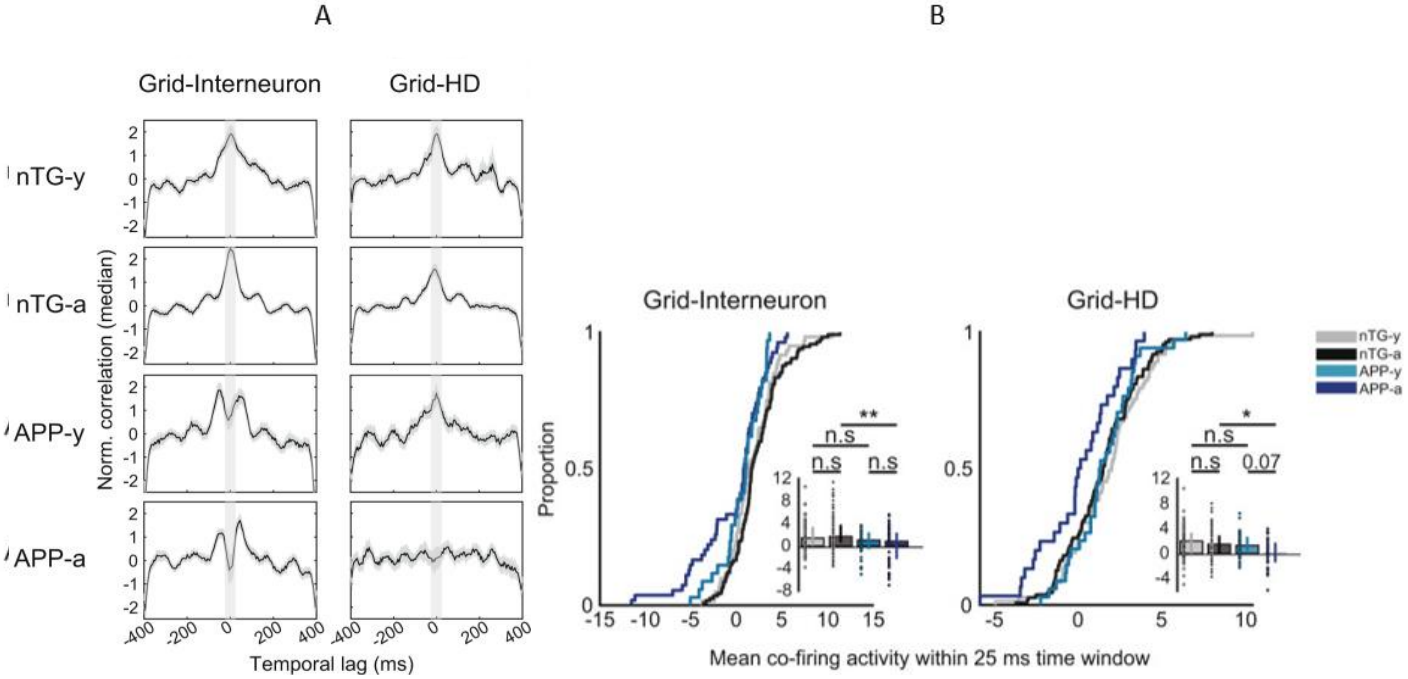

Figure 3. reduced synchrony between interneurons and grid cells and head-direction (HD) cells and grid cells. A) spike-time cross-correlations between grid cells and interneurons (left) and grid cells and HD cells (right). nTG-y is WT strain young mice, nTG-a is WT adult mice, APP-y mutated APP mouse strain young mice and APP-a is mutated APP mouse strain adult mice. Young is 3-4.5 months, adult is 4.5-7 months. The grey area in every panel is the 25 ms time window in each lag direction. APP mice grid cells are anti-synchronous with both interneurons and HD cells. This effect increases with age for HD cells. B) The mean co-activity within a 25 ms time-frame for grid-interneuron pairs (left) and grid-HD pairs (right). Grid-interneuron synchrony and grid-HD synchrony was not significantly reduced between age groups, but was significantly impaired between genotypes, meaning that synchrony was impaired across ages. Source: Ying J, Keinath AT, Lavoie R, Vigneault E, El Mestikawy S, Brandon MP. Disruption of the grid cell network in a mouse model of early Alzheimer's disease. Nat Commun. 2022 Feb 16;13(1):886. doi: 10.1038/s41467-022-28551-x. PMID: 35173173; PMCID: PMC8850598.

In contrast to what Ying et al. found, Jun et al. (2020) showed that grid cell impairment precedes spatial memory deficits. In a mouse model from Jun et al. (2020), they generated a knock-in APP gene, to resemble the human $APP^{NL\text{-}F\text{-}G\ gene}$ (APP-KI). These mice start to exhibit spatial memory deficits after six months. To show that grid cell impairment starts before spatial memory deficits, the MEC of young mice (3-5 month old) was recorded with a 64-channel customized drive. Already after 3-5 months, the APP-KI mice show impaired spatial tuning and decreased remapping properties in the absence of spatial memory deficits (fig. 4). This is accompanied by moderate plaque formation in the MEC.

Bierbrauer et al. (2020), believed that the early deterioration of the MEC would suggest a decreased performance in path integration related tasks in preclinical patients. In spite of previous research, which has shown no spatial memory deficits in the preclinical stage of AD, Brierbrauer et al. tested their hypothesis. In humans, the APOE ε4 gene indicates an increased risk of developing late-onset AD (Corder et al., 1993). Bierbrauer et al. could not find a predictive function of having the APOE ε4 gene on performance in path integration by young preclinical risk carriers (18-41 y). They did find this predictive function in older preclinical risk carriers (42-75 y). These results were found by creating three tasks of which one task contained spatial cues, one task contained border cues, and the last contained no cues at all, so the participants would have to rely purely on their path integration abilities, uncorrected by visual cues. They could find a decrease in performance across all age groups in the task without cues, when compared to the other two tasks. In addition, participants with the APOE ε4 gene were found to have a decreased performance when the distance to the goal was higher in the task without cues, in relation to the other tasks. However, when comparing participants with the APOE ε4 gene to controls, they could only find an effect of long distance towards a goal in older participants. In conclusion, they could find an effect of age and APOE ε4 gene on worse performance in path integration task of preclinical AD risk carriers. Bierbrauer et al. attribute the non-significant findings compared to controls to a small sample size and did find a trend of worse performance in participants with the APOE ε4 gene across all ages. In addition, they found strong evidence for deficits the MEC to be the leading cause for path integration impairment, as they found an association between path integration performance and the strength of grid like representation in the task without spatial cues. They suggest that impaired MEC will result in the use of compensatory mechanisms, like using the posterior cingulate/retrosplenial cortex (PC/RSC). These regions determine location and direction based on viewpoint (Bierbrauer et al., 2020). This would lead to hyperactivity of these regions, which ultimately leads to deterioration of these regions as well, so patients with AD are no longer able to know where they are.

It has been shown in other research that grid cell firing patterns break down in response to reduced input from spatially sensitive neurons (Brandon et al., 2011) (Koenig et al., 2011). This finding is supported by research from Ridler et al. (2020). In their rTg4510 mouse model they discovered that grid cells are unable to integrate information about speed in their spatial code due to tau pathology. In healthy mice, theta oscillation frequencies and amplitude change in response to locomotor activity. However, locomotor activity does not seem to have an effect on theta power in rTg4510 mice, suggesting that these mice are unable to provide a neuronal representation of running speed. This is shown in the reduced speed encoding found in MEC neurons. Previous research has shown that fire frequencies of speed encoding cells decrease in a small proportion of cells in response to locomotion (Hinman et al., 2016). In the rTg4510 mice, however, the proportion of cells with a decreased firing rate in MEC is significantly higher than found in WT mice. This data suggests that with the loss of theta modulation in repose to locomotion, speed encoding in grid cells is impaired. The impaired speed encoding could, however, also be explained by the reduction in

interneurons found in rTg4510 mice, as Ying et al. also suggest an effect of decreased interneuron input on grid cell functioning.

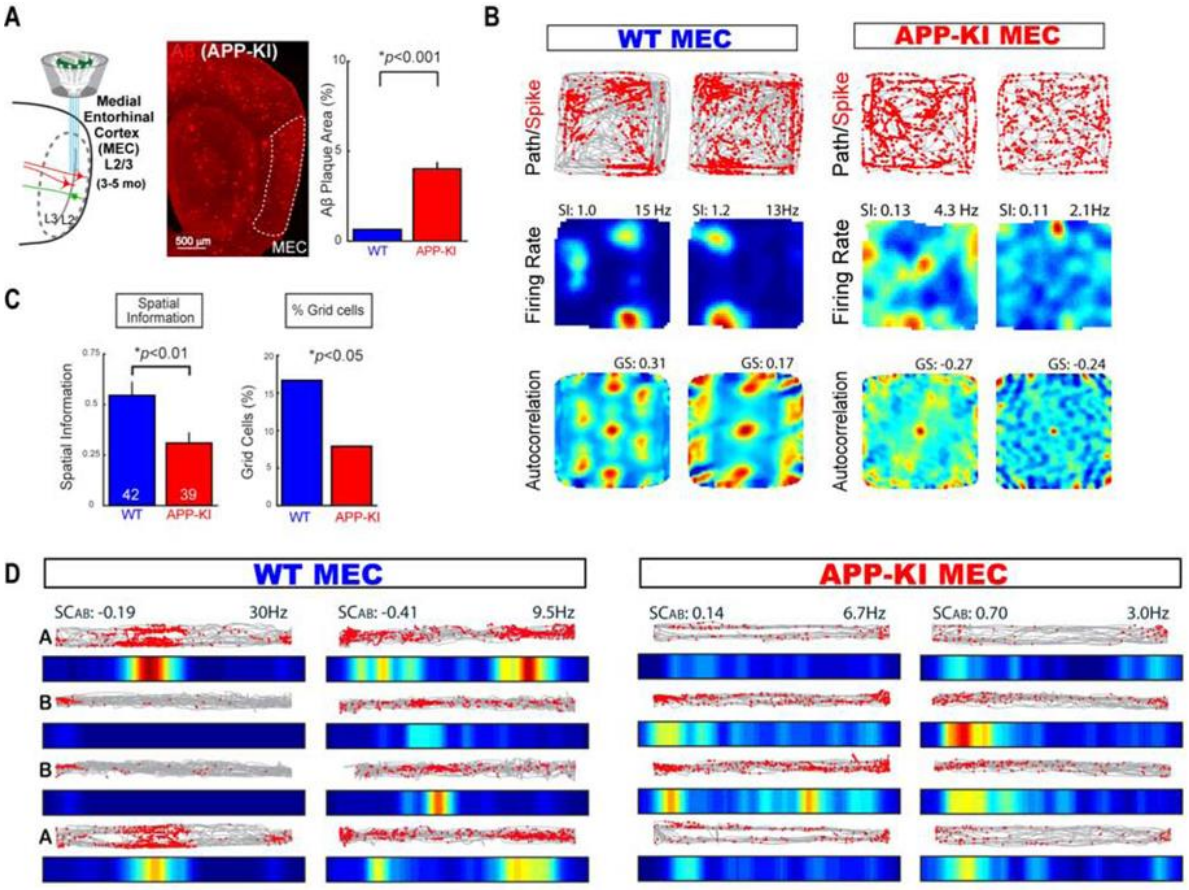

Figure 4. MEC neurons of young mice have disrupted remapping properties and diminished spatial tuning. (A) A sagittal section with anti-Ab immunostaining from 3-month-old APP-KI mouse (center), and percentage of area with Ab plaques in the MEC. (B) Two representative MEC neurons from WT and APP-KI mice recorded in the open field. (C) Young APP-KI mice showed reduced spatial information score (left), meaning diminished spatial tuning, and percentage of grid cells than in young WT mice. (D) Two representative MEC neurons from WT and APP-KI mice recorded on linear tracks. The first and last row represent recording on track A, the middle rows represent track B. In APP-KI mice, the neurons record at almost the same place on both linear track, meaning the neurons are unable to distinguish between the two tracks. Jun H, Bramian A, Soma S, Saito T, Saido TC, Igarashi KM. Disrupted Place Cell Remapping and Impaired Grid Cells in a Knockin Model of Alzheimer's Disease. Neuron. 2020 Sep 23;107(6):1095-1112.e6. doi: 10.1016/j.neuron.2020.06.023. Epub 2020 Jul 21. PMID: 32697942; PMCID: PMC7529950.

Relation between place and grid cells in Alzheimer's Disease

AD affects place and grid cells independently from each other. The interconnected network of place and grid cells (Nilsson et al., 2019) would, however, suggest the deterioration of place and grid cells to have an effect on each other. As suggested by the computational model of Zhang et al. (2021), the impairment of grid cell input on place cells indeed likely results in reduced place map stability of place cells. Recent research on a mouse model of AB plaque pathology, has also shown a correlation between the deterioration of grid cells and the deterioration of place cells (Jun et al. 2020).

With their research, Jun et al. (2020) provide strong arguments for a causal relationship of place and grid cell deterioration. They suggest that AB plaque formation underlies grid cell impairment. That the dysfunction of grid cells lead to place cell impairments and that place cell impairments eventually lead to the memory deficits found in AD patients. These speculations can be made, based on the results they found in their APP knockin (APP-KI) mouse model. Their mouse model has a mutated APP gene, so it resembles the human APP^{NL-F-G} gene (Saito et al., 2014). With this model, they analysed the temporal progression of AD induced impairments in the CA1 and the

MEC. After 3-5 months, APP-KI mice show AB plaque formation in the CA1 region of the hippocampus as well as in the MEC. They found that place cells remained intact as they had no deficits in spatial tuning or remapping properties. Controversially, grid cells of the MEC did show disrupted functioning as they found a mild decrease in remapping and spatial tuning properties of grid cells (fig. 4). This suggests that impairments in CA1 place cells are not a direct consequence of AB plaque formation and it shows that spatial tuning impairment occurred earlier in MEC grid cells. In older mice (7-13), CA1 neurons begin to deteriorate and show diminished spatial tuning to the environment. Place cells of the CA1 show a disruption in their remapping properties (fig. 5). The number of place cells also decreased, but the spatial stability remained intact (fig. 5). The deficits in MEC neurons increased where the number of grid cells was severely reduced, and the spatial tuning was severely disrupted along with remapping properties. They found that the impaired remapping of place cells was independent from their diminished spatial tuning. The reduced remapping and spatial tuning of grid cells did show a negative correlation. In addition to a decrease in spatial representation of place and grid cells, Jun et al. (2020) also show a diminished signal transfer between place and grid cells. First, a disruption of fast gamma oscillations in the CA1 was discovered. They found reduced fast oscillation, while slow gamma oscillations remained intact (fig.6). Then they found that fast gamma oscillation coupling to theta oscillation in the CA1 of APP-KI mice was lacking (fig. 6).. Furthermore, the neuronal activity spikes from the MEC were not phase-locked with fast gamma oscillations (fig. 6). As a result, the fast gamma oscillations in the MEC were desynchronised with fast gamma oscillations in the CA1. In healthy brains, fast gamma oscillation are highly synchronised with fast gamma oscillation of the MEC, which suggests that fast gamma oscillations are necessary for signal transfer between the CA1 and the MEC (Colgin et al., 2009). This desynchronisation in APP-KI mice possibly leads to a deteriorated signal transfer between MEC and CA1.

The same model was used in a different study, to investigate the deterioration of sharp wave ripples (SWR) in preclinical AD brains (Funane et al., 2022). Long-duration SWR are associated with memory consolidation and previous research has shown that SWR occur in lower density in the CA1 of several AD mouse models (Iaccarino et al., 2016; Jones et al., 2019; Benthem et al., 2020; Witton et al., 2016) and that SWR have a shorter duration in the CA1 (Prince et al., 2021). Funane et al. investigated the characteristics of SWR in MEC of preclinical AD mice and found that SWR of the MEC are not affected by AD in a preclinical stage. In accordance with previous research, they did see a lower density of SWR in the CA1, meaning that the number of SWR events per time has reduced. In addition, they found a reduced duration of SWR in the CA1. The researchers could not find impaired SWR in the MEC of preclinical AD mice, but they did find a diminished SWR coordination between the MEC and the CA1. In the healthy mouse model of Funane et al., SWR of the MEC precede SWR of the CA1 with 32.2 ± 4.6 ms. In AD mice, the SWR of the MEC took place 8.9 ± 5.6 ms after the SWR of CA1. This suggests that the contribution of the MEC to long-duration SWR propagating into the CA1 is diminished. The loss of long-duration SWR in the hippocampus may underly spatial memory consolidation found in later stages of AD.

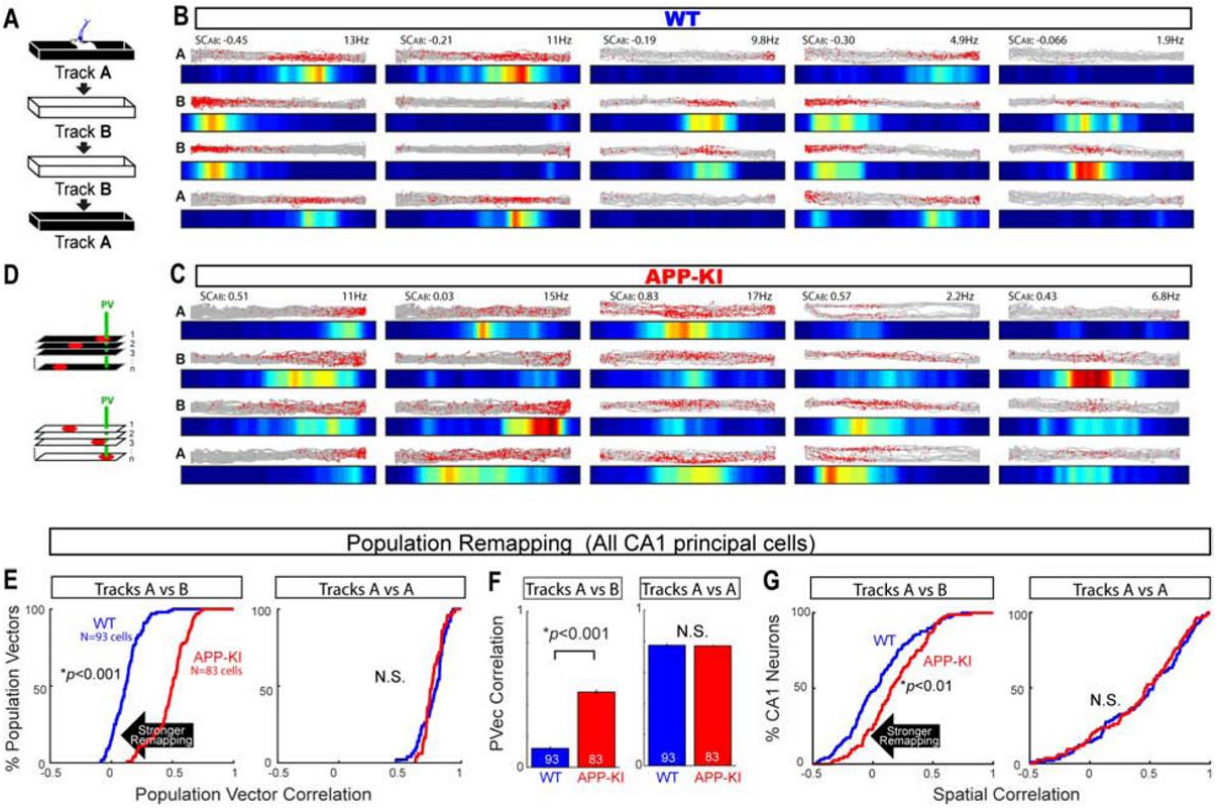

Figure 5. Hippocampal CA1 Neurons in Old APP-KI Mice Showed Disrupted Remapping, but intact spatial stability. (A) Remapping was tested in 1-m linear track A and track B with distinct colors and textures. (B) Five representative CA1 neurons in WT mice recorded on the tracks. The first and last row represent track A, the middle rows track B. Maximum firing rate (Hz) is shown at top right, the spatial correlation between track A and track B (SCAB) is shown at top left. (C) Five representative CA1 neurons from APP-KI mice are shown as in (B). The five neurons show almost no difference in firing position between track A and B, meaning they are unable to discriminate between the two tracks (impaired remapping). (D) The degree of remapping was assessed using population vector (PVec) correlation track A and track B. (E–G) Population remapping calculated using all recorded CA1 neurons. (E) Cumulative distribution plots for PVec correlation between track A and track B (left) and between 2 recordings in track A (right). The lower PVec correlation of ~0 denotes stronger remapping (black arrow). This shows that APP-KI have impaired remapping. The neurons do have strong spatial stability as seen by comparing firing properties of different session on the same track (right). (F) Left: mean PVec correlation between track A and track B. Right: mean PVec correlation between 2 recordings in track A did not differ, showing again spatial stability of CA1 neurons in APP-KI. (G) Cumulative distribution plots of spatial correlation between track A and track B (left) and between 2 recordings in track A (right). Source: Jun H, Bramian A, Soma S, Saito T, Saido TC, Igarashi KM. Disrupted Place Cell Remapping and Impaired Grid Cells in a Knockin Model of Alzheimer's Disease. Neuron. 2020 Sep 23;107(6):1095-1112.e6. doi: 10.1016/j.neuron.2020.06.023. Epub 2020 Jul 21. PMID: 32697942; PMCID: PMC7529950.

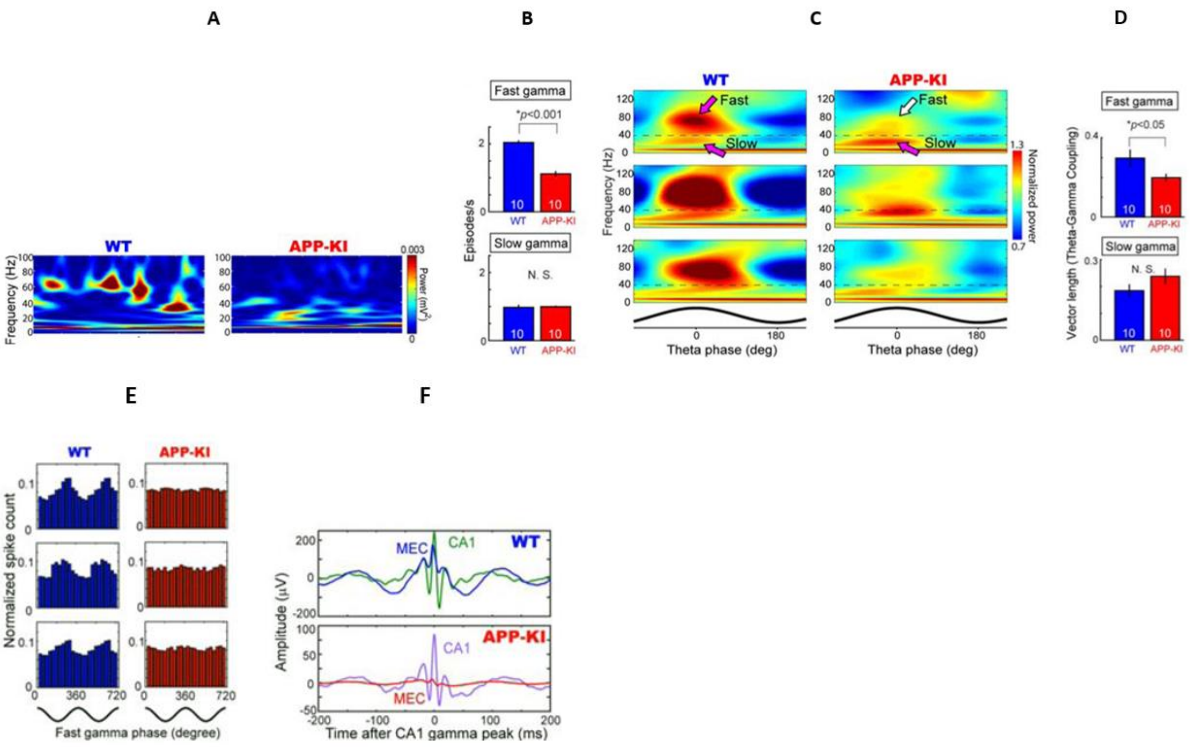

Figure 6. CA1 and MEC fast gamma oscillations are impaired. A) A representative time-resolved spectrogram showing gamma oscillation episodes in CA1 of a WT mouse (left) and an APP-KI mouse (right). Fast gamma oscillations are almost completely lacking. Only slow gamma waves are observed. B) Graph presentation of diminished gamma oscillations in APP-KI mice in the CA1. C) WT mice show phase-locking of fast and slow gamma oscillation with theta waves in CA1. APP-KI only have slow gamma oscillation theta wave phase-lock. D) graph presentation of theta-gamma coupling. Fast gamma waves are significantly less coupled to theta waves in CA1 of APP-KI than in WT. E) Spikes from MEC neurons are phase-locked to local fast gamma oscillations. An example of two fast gamma waves are depicted below the panels. Source: Jun H, Bramian A, Soma S, Saito T, Saido TC, Igarashi KM. Disrupted Place Cell Remapping and Impaired Grid Cells in a Knockin Model of Alzheimer's Disease. Neuron. 2020 Sep 23;107(6):1095-1112.e6. doi: 10.1016/j.neuron.2020.06.023. Epub 2020 Jul 21. PMID: 32697942; PMCID: PMC7529950.

Discussion

This review would suggest that the deterioration found in spatial tuning to the environment of place and grid cells, begins with the impairment of signal transfer towards these neurons. A reduced synchrony between grid cells and interneurons was found to precede grid cell impairment (Ying et al. 202..), which likely results in an inability to inhibit grid cells. Subsequent to a reduced synchrony, grid cells began to deteriorate. Jun et al. (2020) show reduced remapping properties and spatial tuning in grid cells before signal transfer between place and grid cells diminishes. In support of those findings, the computational model of Zhang et al. (2021), suggests that place cell deterioration starts with synapse loss between grid cells and interneurons, causing a disbalance between inhibitory and excitatory signals. Concurrently with reduced synchrony between place and grid cells, gamma oscillations of place cells are found to be disrupted, along with reduced SWR density and duration (Funane et al. 2022). The impaired gamma activity of place cells seems to be accompanied by a lack of phase locking of MEC activity spikes to fast gamma oscillations, which could result in the desynchronization of fast gamma oscillations between place and grid cells.

These network dysfunctions underly place and grid cells deterioration, but how does neuronal dysfunction lead to spatial disorientation found in AD patients. Zhang et al. (2023) show that the deterioration of place cell remapping and place cell tuning to the environment can predict object location memory deficits in later stages of AD. This suggests that the spatial memory deficits start with the deterioration of place cells. This is supported by the findings of previous research that show impairment of long-duration SWR in place cells, as long-duration SWR are associated with

memory consolidation. Funane et al. suggest that especially the uncoordinated SWR between the MEC and the CA1 found in preclinical AD mice, lead to the impaired memory consolidation in the CA1. Impaired remapping also contributes to spatial memory deficits, as Zhang et al (2023) showed that a decrease in remapping properties of place cells is a predictor for spatial memory deficits. The impaired remapping properties of place and grid cells. The deficits found in remapping are also associated with the inability to discriminate between environments (Zhang et al., 2023). The impairment in path integration found in AD patients, is likely correlated with impairment of the MEC (Bierbrauer et al., 2020). Ridler et al. showed that impaired speed encoding of the MEC is involved in the path integration deficits found in the MEC. The ability to integrate information about the running speed, is needed for a properly functioning path integration system.

Knowledge about the network dysfunctions can suggest potential biomarkers for the early detection of AD. The desynchronisation of SWR between place and grid cells found in preclinical AD mice is suggested by Funane et al. as a potential early biomarker. A correlation between grid cell impairment and performance in a path integration task was found by Ying et al. suggesting that performance in a path integration task could also be used as an early marker to test for AD. This hypothesis is also supported in humans by Bierbrauer et al., who show a correlation between APOE ε4 gene and path integration performance in humans. It should be taken into account that Bierbrauer et al. only show a correlation between APOE gene and path integration in older participants. These participants are preclinical, so detection of AD can still be valuable in these patients. Grid cell impairments can also be used to detect AD early, as Zhang et al. show that grid cells are impaired long before the widespread accumulation of AB plaques.

With this review, an overview was made of the effect of AD on place and grid cells, what network dysfunctions underly place and grid cell dysfunction and how the impairments of place and grid cells lead to spatial memory and navigation dysfunction. This overview was, however, made by integrating results from different papers, which mostly use different models. Conclusions made on the basis of these mouse models, should be met with caution, as behavioural and pathological deficits could arise from the transgene model, instead from the particular genetic deficit that mimics AD genetic deficits (Ridler et al., 2020). Every mouse model used, is either a model of taupathy or a model of AB plaque pathology and both could have different effects on neurodegeneration. This means that none of the models fully represent AD pathology (Ying et al., 2022).

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