ALZHEIMER’S DISEASE

Reduced grid-cell-like representations in adults at genetic risk for Alzheimer’s disease

Lukas Kunz,1,2 Tobias Navarro Schröder,3 Hweeling Lee,1 Christian Montag,4 Bernd Lachmann,5 Rayna Sariyska,4 Martin Reuter,4,6 Rüdiger Stirnberg,1 Tony Stöcker,1 Paul Christian Messing-Floeter,7,8 Juergen Fell,9 Christian F. Doeller,10,11 Nikolai Axmacher1,4,7†

Alzheimer’s disease (AD) manifests with memory loss and spatial disorientation. AD pathology starts in the entorhinal cortex, making it likely that local neural correlates of spatial navigation, particularly grid cells, are impaired. Grid-cell-like representations in humans can be measured using functional magnetic resonance imaging. We found that young adults at genetic risk for AD (APOE-ε4 carriers) exhibit reduced grid-cell-like representations and altered navigational behavior in a virtual arena. Both changes were associated with impaired spatial memory performance. Reduced grid-cell-like representations were also related to increased hippocampal activity, potentially reflecting compensatory mechanisms that prevent overt spatial memory impairment in APOE-ε4 carriers. Our results provide evidence of behaviorally relevant entorhinal dysfunction in humans at genetic risk for AD, decades before potential disease onset.

Late-onset AD is the most common form of dementia and one of the most challenging diseases of modern society (1). Curative therapies are still lacking, presumably because they start too late (2). Therefore, the elucidation of early pathomechanisms underlying symptoms of AD is of high interest. We aimed at identifying one of the potentially earliest neurocognitive pathomechanisms in the development of AD symptoms: We hypothesized entorhinal dysfunction in young APOE-ε4 carriers. Our hypothesis was built on three previous findings: First, the ε4 allele of the APOE gene is the strongest genetic risk factor for late-onset AD (3). Individuals carrying one APOE-ε4 allele are at threefold increased risk of AD, and those carrying two APOE-ε4 alleles are at more than 10-fold increased risk (4). Second, early AD histopathology appears in the entorhinal cortex (EC) (5), where tau abnormalities can already be observed in adults under the age of 30 (6), especially in APOE-ε4 carriers (7). Third, the EC contains grid cells, a cell type involved in spatial navigation. Grid cells fire whenever animals (8) or humans (9) traverse the vertices of an internally generated grid tiling the spatial environment into equilateral triangles. Their function has been linked to path integration (10, 11), error correction (12), and the maintenance of place cells (13), which exhibit only a singular firing field (14). Hence, a possible dysfunction of grid cells may provide an explanation for the symptom of spatial disorientation in patients suffering from AD. Proxies for grid cells, termed grid-cell-like representations, are detectable in humans by functional magnetic resonance imaging (fMRI). The blood oxygenation level-dependent signal of the EC depends on movement direction with sixfold rotational symmetry. More specifically, the contrast of brain activity during movements aligned versus misaligned to the main axes of a putative grid in a virtual arena leads to a macroscopically visible fMRI signal in the right EC (15).

We examined the effect of APOE-ε4 on grid-cell-like representations by comparing two groups of healthy young adults (n = 38 APOE-ε4/ε3 carriers, termed “risk participants” from now on; n = 37 ε3/ε3 carriers, “control participants”; table S1). Participants completed a previously established...
We anticipated hippocampal task-related activity to be a compelling option for a potential compensatory mechanism because the importance of the hippocampus for spatial memory is well established (20), and hippocampal activity is altered in APOE-e4 carriers (21). Hippocampal task-related activity (contrast of task versus implicit baseline; methods and table S6) was negatively correlated with grid-cell–like representations across all participants (bilateral hippocampus: Pearson’s r = −0.317, P = 0.006; Fig. 2; right hippocampus: r = −0.292, P = 0.011; left hippocampus: r = −0.320, P = 0.005). Particularly in the posterior hippocampus, which is especially relevant for spatial navigation (the bilateral posterior third; see (22)), this relationship was significantly more pronounced in risk participants than in control participants (risk participants: r = −0.545, P < 0.001; control participants: r = −0.064, P = 0.707; difference between correlation coefficients, z = −2.27, P = 0.023; fig. S7). Because reduced grid-cell–like representations were also correlated with increased task-related activity of the EC and amygdala (fig. S8), we then examined the behavioral relevance of hippocampal task-related activity. Detailed analyses revealed that increased task-related activity, particularly in the left posterior hippocampus, was associated with better spatial memory performance (supplementary text, tables S3 and S7, and fig. S9). In short, increased hippocampal activity could serve as a behaviorally relevant compensatory mechanism for reduced grid-cell–like representations. Nevertheless, increased hippocampal activity may also indicate a broader disruption of medial temporal lobe computations promoting pathological processes [(23, 24); for further discussion, see the supplementary text].

We found significant grid-cell–like representations in control participants (ROI; Fig. 2D) across all voxels in the right EC reflect the magnitude of grid-cell–like representations [exemplary participant-specific EC region of interest (ROI); Fig. 2D]. We found significant grid-cell–like representations in control participants (t_{40} = 2.318, P = 0.026) but not in risk participants (t_{72} = 1.730, P = 0.092). In fact, the magnitude of grid-cell–like representations was strongly reduced in risk participants as compared to control participants (t_{72} = 2.875, P = 0.005; Fig. 2; two-way genotype × sex analysis of variance (ANOVA): main effect of genotype, F_{1,72} = 8.695, P = 0.004; no main effect of sex, F_{1,72} = 0.709, P = 0.403; no interaction, F_{1,72} = 1.838, P = 0.179). Control analyses showed that our finding in control participants was specific for sixfold rotational symmetry and specific for the right EC (fig. S3). No structural changes of the right EC, which could potentially account for the functional changes, were observed (fig. S4).

In contrast to the genotype effect on grid-cell–like representations, both genetic subgroups showed similar spatial memory performance (t_{40} = −0.109, P = 0.913; Fig. 1) as well as similar basic behavioral characteristics (table S2). We assume that the detrimental effect of APOE-e4 on spatial memory becomes apparent only at older age (17), when histopathological changes due to presymptomatic AD have reached adjacent limbic regions such as the hippocampus. However, risk participants exhibited altered navigational behavior: They showed a reduced preference to navigate in the center of the arena (“central navigational preference”; methods) as compared to control participants (t_{40} = 2.551, P = 0.014; Fig. 1 and fig. S1; two-way genotype × sex ANOVA: main effect of genotype, F_{1,71} = 6.293, P = 0.014; no main effect of sex, F_{1,71} = 0.094, P = 0.761; no interaction, F_{1,71} = 1.978, P = 0.164). This finding was also reflected in a greater mean distance of all virtual positions relative to the arena center in risk participants (t_{73} = −3.003, P = 0.004; fig. S5). Next, we examined whether the APOE-dependent changes of grid-cell–like representations and central navigational preference were related to spatial memory performance. Using linear multiple regression (Table 1), we found that greater grid-cell–like representations (in addition to higher values of central navigational preference, younger age and male sex) were positively related to spatial memory performance (supplementary text and fig. S6). This result strengthens the hypothesis that EC-specific representations of space guide behavior in humans (15, 18). Nevertheless, this result also seemed paradoxical to us: Given that APOE-e4 reduces grid-cell–like representations and that reduced grid-cell–like representations are associated with impaired spatial memory performance, how can we explain similar performance between both genetic subgroups? Therefore, we hypothesized that there are compensatory mechanisms in risk participants (19).
Next, we aimed at understanding the reduction of grid-cell–like representations in risk participants in greater detail. In principle, reduced grid-cell–like representations in fMRI could be due to (i) temporal instability of the putative grid axes across the entire experiment, (ii) spatial instability of the putative grid axes within each half of the experiment, or—similar temporal and spatial stability between genetic subgroups in smaller data segments provided—(iii) a relatively weaker right EC contrast of aligned versus misaligned movements. We sought to disentangle this ambiguity by first calculating one temporal stability and one spatial stability value for each participant (methods; Fig. 3). Temporal stability values differed between genetic subgroups ($t_{52} = 2.408, P = 0.019$), were positively correlated with grid-cell–like representations (Pearson’s $r = 0.736, P < 0.001$; Fig. 3B), and were also negatively correlated with hippocampal task-related activity ($r = -0.311, P = 0.007$). Reduced temporal stability values were related to decreased functional connectivity between the right EC and hippocampus, possibly indicating a decoupling of both regions associated with entorhinal dysfunction ($r = 0.298, P = 0.009$; supplementary text and fig. S10). In contrast, spatial stability values did not differ between genetic subgroups and were not related to the grid-cell–like representations ($t_{52} = -0.143, P = 0.887; r = -0.079, P = 0.501$; Fig. 3). Finally, to disentangle reduced grid-cell–like representations from reduced temporal stability, we analyzed grid-cell–like representations on shorter data segments (methods). This analysis revealed significant grid-cell–like representations in control participants ($t_{36} = 2.708, P = 0.010$) but not in risk participants ($t_{37} = -0.788, P = 0.436$), with a significant difference between both groups ($t_{52} = 2.315, P = 0.023$; fig. S11), although the corresponding temporal and spatial stability values did not differ between groups (temporal stability: $t_{52} = 1.469, P = 0.149$; spatial stability: $t_{52} = -0.421, P = 0.675$). Taken together, this demonstrates that grid-cell–like representations in risk participants were less robust than in control participants (on a shorter time scale) and that the grid orientations of potential grid-cell–like representations were additionally temporally unstable in risk participants (on a longer time scale).

Our results (summarized in fig. S12) support the hypothesis that AD involves the dysfunction of entorhinal grid cells. Adults at genetic risk for AD exhibit strongly reduced fMRI representations of grid cells, and reduced grid-cell–like representations are related to impaired spatial memory performance (for a speculative interpretation of the underlying mechanistic basis, see the supplementary text). We also found a reduced preference of risk participants to navigate in the center of a virtual arena. This change in navigational strategy may be interpreted (i) as an attempt to correct errors in the grid code by encounters with environmental boundaries (25), (ii) as an uncertainty to rely on entorhinal path integration mechanisms, (iii) as a shift toward a response-based strategy relying on different mountain-wall conjunctive features, or (iv) as a result of inaccurate place fields in the arena center due to impaired grid cell input on place cells (26). Moreover, our results offer an explanation for the previously observed hyperactivity of certain brain areas in APOE-ε4 carriers (27): They may compensate for entorhinal dysfunction. Specifically, our data would be in line with behaviorally relevant compensatory hyperactivity of the hippocampus that could indicate a stronger hippocampus-dependent boundary-based strategy (28) or enhanced hippocampal path integration computations (29, 30) to counter impaired entorhinal path integration. Such neuronal hyperactivity could cause partial benefits at a young age (31) but may induce further pathological spreading afterward (24), including the degradation of place cell firing, which has already been shown in a mouse model of AD (32). Thus, the increased hippocampal activation may also reflect an adverse condition. Our results could provide a
new basic framework for preclinical research on AD and may provide a neurocognitive explanation of spatial disorientation in AD. We emphasize their early occurrence in young adulthood, which may help to determine treatment onset and to establish entorhinal dysfunction as a prognostic marker. The amelioration of entorhinal dysfunction might be a new therapeutic target in the treatment of AD.

REFERENCES AND NOTES

16. Materials and methods are available as supplementary materials on Science Online.

Fig. 3. Stability metrics of grid-cell–like representations. (A) Exemplary plots from one participant per group show temporally stable grid orientations (connected by green lines) and temporally unstable grid orientations (red lines) of individual voxels, leading to one percentage value per participant (“temporal stability”). The exemplary plot for the risk participant indicates that the voxel-wise grid orientations change between the two halves of the data (lines between circles), but that within each half, the voxel-wise grid orientations are clustered (dots placed on the different circles, see spatial stability). (B) Temporal stability values show a reduction in risk participants and are highly correlated with grid-cell–like representations (P < 0.001), suggesting temporal instability as a cause of reduced grid-cell–like representations. (C) Exemplary plots showing spatially stable grid orientations estimated from the first half of the data (Rayleigh’s z > 11 for both). (D) Contrarily to temporal stability, spatial stability values do not differ between genetic subgroups and are not related to grid-cell–like representations. All bars show mean and SEM across participants, separately for both groups. Green dots represent control participants; red dots represent risk participants. Units of all contrasts are parameter estimates. *P < 0.05, **P < 0.01, ***P < 0.001.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Figs. S1 to S12

Tables S1 to S7

References (33–62)

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