



RESEARCH ARTICLE

A unified brain system of orientation and its disruption in Alzheimer's disease

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Abstract

Objective: To investigate whether a unified brain system manages one's orientation to different places, events and people in one's environment, and test the hypothesis that failure of this system (disorientation) is an early sign of Alzheimer's disease (AD). **Methods:** A total of 46 participants (patients along the AD continuum and cognitively normal control subjects) were tested in a personalized, ecologically valid task of orientation relating to the participant's own world in space, time and person under high-density electroencephalography. As a first step, we used evoked potential mapping to search for brain topography correlated with participants' performance in orientating themselves to different places (space), events (time) and people (person) (Experiment 1). We then compared behavioral and electrophysiological changes in patients along the AD continuum (Experiment 2). **Results:** We identified a specific brain topography ("orientation map") that was active for orientation in space, time and person in correlation to participants' performance. Both performance and the map's strength gradually decreased from health to mild cognitive impairment (MCI) and from MCI to AD. Another map, immediately preceding the orientation map, showed the longest activity in patients with MCI, significantly more than both patients with AD and cognitively normal controls. **Interpretation:** Our findings demonstrate that the same brain topography accounts for orientation in the different domains of space, time and person and provide a nexus between deterioration in patients' orientation with the aggravation of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) accounts for an estimated 60–80% of dementia cases, laying an enormous burden – mental, physical and financial – on individuals, families and societies.¹ Accurately diagnosing the disease at an early stage is critical as it provides the opportunity to intervene before extensive neuronal death takes place. This has been proven difficult largely due to the long pre-clinical phase of the disease, with the initial deposition of AD pathology estimated to begin more than a decade prior to the onset of clinical symptoms.² Consequently, research criteria for the disease have been recently redefined to be based exclusively on neuropathological changes detected by biomarkers.³ Nevertheless, how may preclinical-AD be screened on a phenomenological or neuropsychological basis?

Emerging evidence suggests that deficits in the cognitive faculty of mental-orientation have high sensitivity and specificity to AD.⁴ Mental-orientation is defined as the "tuning between the subject and the internal representation of the corresponding public reference system"⁵ and is the bedrock of clinical neuropsychiatric evaluation. Current evaluations of so-called orientation test the patient's knowledge about the current location and present date, which carry very low sensitivity for AD.^{4,6,7} However, recent investigative efforts gave rise to several ecologically valid personalized tests for orientation and navigation with very-high sensitivity to AD.⁸ For instance, Monacelli and colleagues tested AD patients' landmark orientation with a real-world navigational task in the hospital's lobby.⁶ The four-mountains test⁹, which examines allocentric spatial memory through manipulation of a computer-generated landscape, was found to be highly accurate (100%

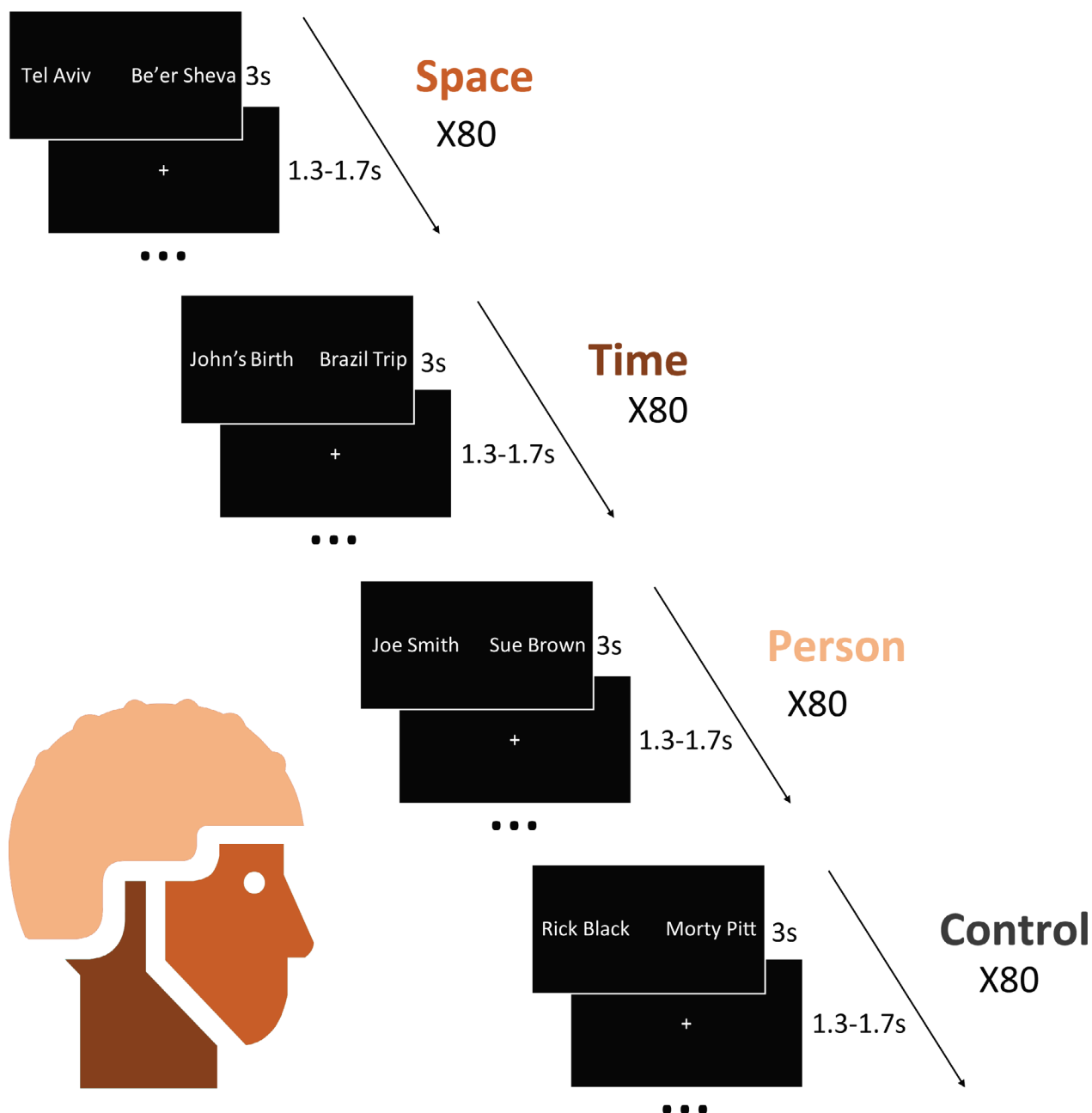


Figure 1. The orientation paradigm. Multi-channel (64 electrodes) electroencephalography (EEG) was recorded while subjects performed an individually tailored mental-orientation task. In this task subjects were presented with two stimuli from the same orientation domain (space, time, person), and were asked to determine which of the two stimuli was closer to them: spatially closer to their current location (for space stimuli), temporally closer to the current time (for time stimuli), or personally closer to themselves (for person stimuli). Additionally, subjects performed a similar lexical control condition in which they were required to determine which of the two words contained the letter 'A'. Response times (RTs) and success rates (SRs) were recorded and efficiency scores (ESs) were calculated.

sensitivity and 78% specificity) classifying whether AD biomarkers were present in a cohort of mild cognitive impairment (MCI) patients.¹⁰ Performance of patients along the AD continuum in virtual-reality and real-world navigation tests was found to correlate with clinical

aggravation.¹¹ Similarly, the Sea Hero Quest, a spatial cognition test applied on more than 4 million people worldwide, showed high efficacy in discriminating healthy aging from genetically at-risk individuals of AD.^{12–14} The so-called orientation task added personalization and ecological

validity by testing subject's relations to personally significant events, people and places.¹⁵ In light of the role of orientation in AD, the aforementioned task differentiated patients along the AD continuum with higher accuracy than the Addenbrooke's Cognitive Examination and the Mini-Mental State Examination MMSE (95%, 71% and 70% of accuracy, respectively).⁴ Together, these results point at real-world, self-referenced, egocentric–allocentric transforming tests to be highly responsive to AD pathology, thereby holding considerable diagnostic potential.

Functional neuroimaging further supported the central role of orientation and navigation in AD. For example, young adults at genetic risk for AD (APOE-ε4 carriers) exhibited reduced grid-cell-like representations under functional magnetic resonance imaging (fMRI) and altered navigational behavior in a virtual arena.¹⁶ Administering the orientation task under fMRI revealed that orientation in space, time and person is managed by a specific brain system with a highly ordered internal organization, closely related to the default-mode network (DMN),¹⁵ a network involved in self-referential processes¹⁷ that was previously associated with AD.¹⁸ Moreover, the orientation task selectively recruited brain regions exhibiting early AD-related atrophy.⁴

Previous functional neuroimaging data showed how the orientation system consists of distinct domain-specific subdivisions and a common functional core.¹⁵ Accordingly, we used here high-density electroencephalography (HD-EEG) and evoked potential (EP) mapping with high-temporal resolution to, first, identify a “core” orientation topography common to all domains; and then detect its characteristics in patients along the AD continuum from cognitively normal (CN) to MCI to AD.

Materials and Methods

Experiment 1 – characterizing the brain topography of mental-orientation

Participants

Eighteen healthy volunteers (see supplemental material).

Stimuli and procedures

In the mental-orientation task^{4,15} participants were presented with pairs of stimuli consisting of names of either two cities, two events, or two people, and were asked to determine which of the two was closer to themselves (See Fig. 1 for study design): spatially closer to their current location (which location is physically closer to you: “Tel-Aviv” or “Haifa”), chronologically closer to the present time (which event occurred more

recently: “Retirement party” or “Silver wedding”), or personally closer to themselves (which person do you feel closer to: name of sister or name of colleague). Therefore, the task and instructions were similar for each orientation domain (space, time and person). Stimuli were presented in separate blocks for the space, time and person orientation domains, with each block containing 80 consecutive trials in randomized order. In addition, in a separate block, subjects performed a lexical control task, in which they viewed similar stimuli, but were instructed to determine which of the two words contained the letter ‘A’. For stimuli presentation see supplemental material.

To obtain stimuli, 1–2 weeks prior to performing the task, participants were presented with a list of potential stimuli and regarding each were asked to approximate either its location (for space stimuli) or year (for time stimuli). Space stimuli consisted of names of cities in Israel, distanced 7–175 km from the experimental location (Jerusalem, Israel). Time stimuli consisted of two-word descriptions of common events from the subject's personal life (e.g., “College Graduation”) or nonpersonal world/national events (e.g., “Barak Elected”). Failing to reference both the relevant region of the country and at least one nearby landmark (space) or miscalculating by more than 5 years (time), resulted in the specific stimuli to be removed from further testing. In addition, participants were asked to generate a list of 10 close family members and best friends (e.g. name of life-partner), 10 colleagues, friends and distant relatives (e.g. name of colleague from work) and 10 acquaintances (e.g. name of barber).

Analysis of behavioral data

See supplemental material.

Electroencephalography (EEG) recording, evoked potential (EP) mapping and source estimation

See supplemental material.

Experiment 2 – mental-orientation in clinical groups along the AD continuum

Participants

Twenty-eight individuals (16 females, mean age: 75.32 ± 6.81 years) participated in the study: 14 patients along the AD continuum (seven with AD and seven with MCI) and 14 age-matched cognitively normal subjects. Participants underwent a full neurological examination as

well as neuropsychological evaluation that included a semistructured interview, the Addenbrooke's Cognitive Examination (ACE), the frontal assessment battery (FAB) and Hachinski Ischemic Scores. Patients were recruited from the memory disorders clinic at the Hadassah Medical Center and met the National Institute on Aging and Alzheimer's Association clinical criteria for AD and MCI.^{19,20} All individuals with MCI met the research criteria for amnesic MCI.²¹ All participants provided written informed consent, and the study was approved by the ethics committee of the Hadassah Medical Center.

Stimuli and procedures

The mental-orientation task was performed under continuous EEG as described in Experiment 1, with adjustments to the elderly population (see supplemental material).

Analysis of behavioral data

See supplemental material.

Electroencephalography (EEG) recording, evoked potential (EP) mapping and source estimation

See supplemental material.

Results

Experiment 1: brain topography of mental-orientation

Our behavioral data showed that efficiency scores (ES) for the space domain (0.73 ± 0.02 , mean \pm standard error) were significantly higher than the time domain (0.57 ± 0.01) but lower than the person domain (0.89 ± 0.03) ($F_{(3,68)} = 71.28$, $P < 0.001$, one-way ANOVA, $F = 11.49$ and $P = 0.001$ for both comparisons, planned contrasts with Bonferroni correction; Fig. 2A), corroborating previous behavioral results.^{4,15} EP mapping of the group-averaged data revealed a distinct brain segment of stable topography (or EP map; Fig. 2B, orange) appearing between 220 and 460 msec after stimulus presentation that had significantly higher global field power (GFP) for orientation conditions ($2.64 \pm 0.3 \mu\text{V}$) compared to the control condition ($1.65 \pm 0.3 \mu\text{V}$) ($F_{(3,60)} = 3.31$, $P = 0.026$, one-way ANOVA, $F = 6.31$, $P < 0.05$, orientation vs. control planned contrast; Fig. 2C), similar to the behavioral results (n.s.). Additionally, this map showed higher global explained variance (GEV) for the orientation conditions compared to the control condition (Table S3). No other map showed such

distinctions. We refer to this EP map as the "orientation map" (Fig. 2D). There was no significant effect with respect to the duration of brain activation in the orientation conditions versus the control condition. A linear inverse solution²² (sLORETA) localized this map to the entorhinal cortex, rostral anterior cingulate, lateral orbitofrontal, and medial orbitofrontal cortices bilaterally (Fig. 2E).

Experiment 2: EP mapping of orientation along the AD continuum

In experiment 2 we utilized the knowledge gained in experiment 1 to investigate the differences in the identified orientation map between patients along the AD continuum. Behaviorally, cognitively normal (CN) subjects (0.42 ± 0.02 , mean \pm standard error) showed significantly higher mental-orientation ES compared to patients along the AD continuum (AD-con) (0.26 ± 0.02) ($F_{(2,25)} = 22.47$, $P < 0.001$, one-way ANOVA, $F = 30.7$, $P < 0.001$, CN vs. MCI + AD planned contrast with Bonferroni correction; Fig. 3A), corroborating previous results⁴. Microstate analysis of the group average data revealed an EP map appearing between 340 and 580 msec after stimulus presentation (Fig. 3B, orange) which was highly similar to the orientation EP map found in experiment 1 (Fig. 3C, right) (see Fig. S2 for topographic analysis of variance (TANOVA)²³ between the topographies of the two experiments). This orientation map showed higher global field power for CN ($2.1 \pm 0.21 \mu\text{V}$) compared to the AD-con group ($1.37 \pm 0.11 \mu\text{V}$) ($F_{(2,20)} = 3.81$, $P = 0.039$, one-way ANOVA; $F = 11.8$, $P < 0.05$, CN vs. MCI + AD planned contrast; Fig. 3D, upper right). Applying linear inverse solution,²² the orientation map was localized to regions of the right entorhinal, rostral anterior cingulate, lateral orbitofrontal, and bilateral medial orbitofrontal cortices (Fig. 3E). Interestingly, an EP map preceding the orientation map which appeared between 220 and 400 msec after stimulus presentation (Fig. 3B, purple) showed longer duration in patients with MCI (184 ± 42 msec) compared to AD (42 ± 12 msec) and CN (79 ± 18 msec) ($F_{(2,25)} = 7.69$, $P = 0.003$, one-way ANOVA, $F = 9.59$ and $F = 14.3$, $P = 0.005$ and $P = 0.001$, CN vs. MCI and MCI vs. AD planned contrasts respectively; Fig. 3D, lower left). We refer to this EP map as the "preorientation map" (Fig. 3C, left). Applying linear inverse solution,²² the pre orientation map was localized to the orbitofrontal cortex bilaterally (Fig. S3C).

Discussion

EP mapping and electrical neuroimaging identified a specific brain topography corresponding to the

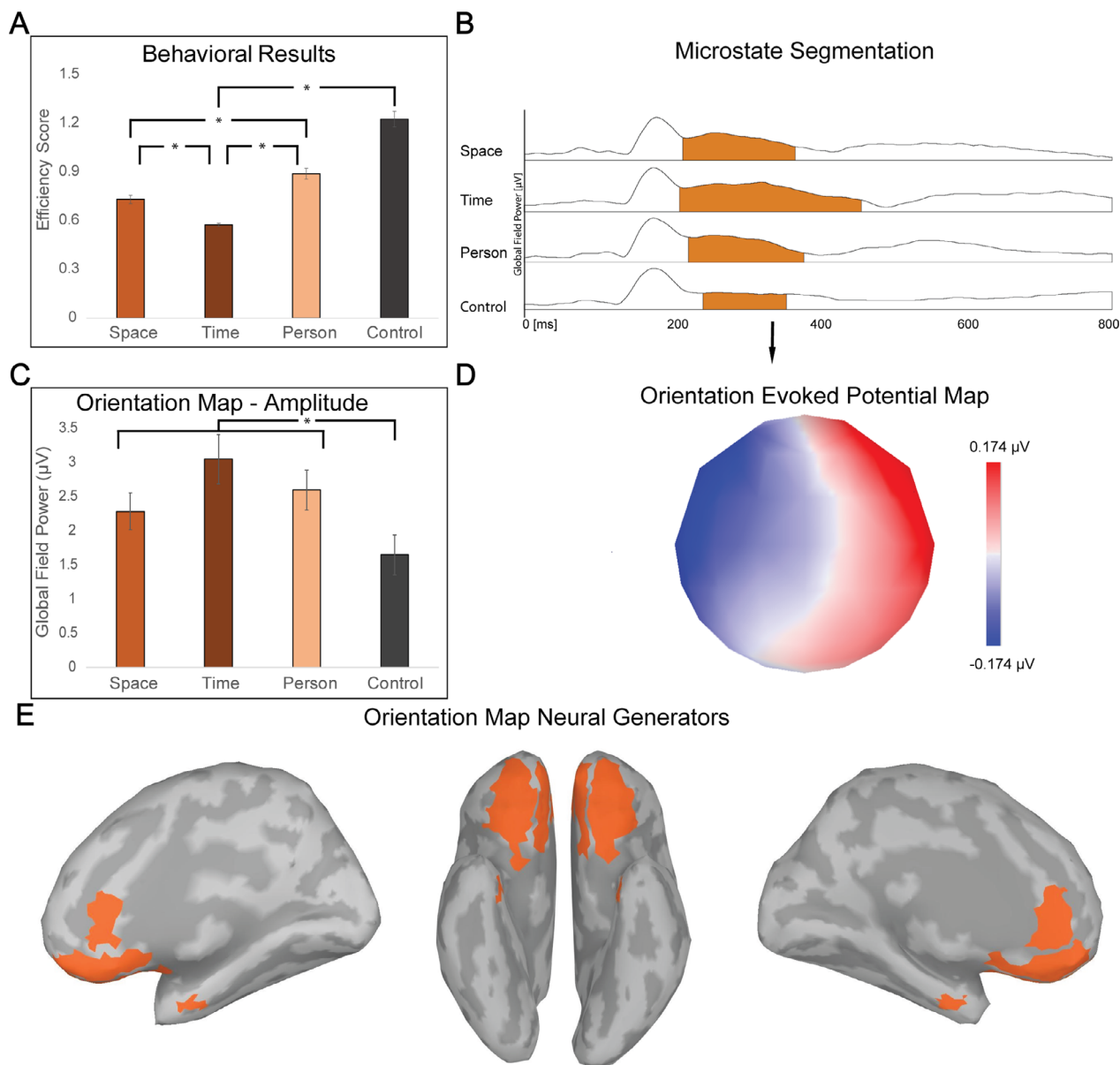
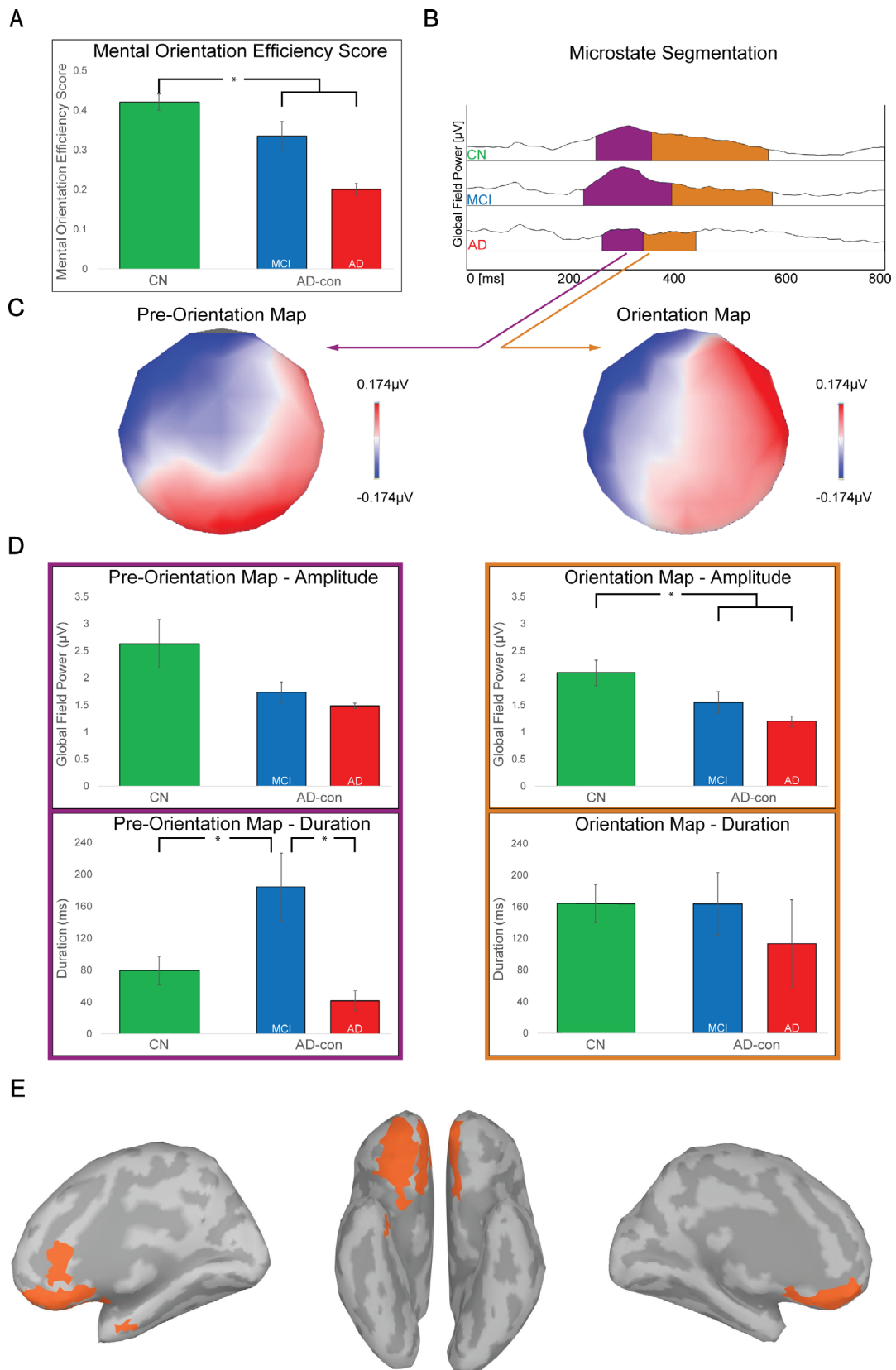


Figure 2. Experiment 1: Characterizing the brain topography of orientation. (A) Behavioral results. Efficiency scores showed significantly lower results for the orientation conditions compared to the control condition ($P < 0.05$). (B) Microstate segmentation. Segments of stable map topography in the three orientation domains and lexical control task under the global field power curve from 0 to 800 msec. A segment representing an evoked potential (EP) map (“orientation map”) was found at 220–460 msec and had (C) significantly higher global field power for the orientation conditions as compared to the control condition ($P < 0.05$). (D) The orientation EP map topography is shown. (E) Neural generators of the orientation map were localized to the entorhinal, rostral anterior cingulate, lateral orbitofrontal, and medial orbitofrontal cortices bilaterally.

Figure 3. Experiment 2: Mental-orientation in subjects along the Alzheimer’s disease continuum. (A) AD continuum (AD-con) patients had significantly lower efficiency scores in the orientation task than cognitively normal age-matched control subjects. (B) Segments of stable map topography in the three clinical groups under the global field power curve from 0 to 800 msec are shown. A segment (orange) representing an EP map highly similar to the orientation map found in Experiment 1 (C, right) found at 340–580 msec, was found significantly higher for CN than patients (D, upper right; $P < 0.05$). Another segment (purple) preceding the orientation map (“preorientation map”, 220–400 msec; C, left), was found longer for the MCI condition than CN and AD (D, lower left; $P < 0.05$). (E) Neural generators of the orientation map were localized to the right entorhinal, rostral anterior cingulate, lateral orbitofrontal, and bilateral medial orbitofrontal cortices.



orientation system in space, time and person in CN (“orientation map”). The orientation map was found to be strongest in CN and appeared to deteriorate gradually from CN to MCI to AD. Remarkably, another EP map was found significantly longer in MCI, more than both CN and AD. We discuss our results with respect to an ongoing debate concerning the role of the orientation system in the different domains of space, time and person, and draw similarities between its disturbance in AD as found here to emerging evidence demonstrating increased neuronal activity at early stages of the disease.

Investigation of orientation in young CN participants enabled us to characterize an EP map reflecting mental-orientation in space, time and person. The behavioral results showed lower ES for the time domain with respect to the person and space domain, corroborating previous studies.^{4,15,24,25} These differences may be related to different construal levels required to perform each condition successfully, with the person domain requiring an abstract and schematic mental representation of people (high-level construal) and the time domain requiring a more contextualized and detailed mental representation of events (low level construal).^{26–28} This suggestion is supported by the posterior-anterior organization of space-person-time activation as identified in high-resolution fMRI,¹⁵ compatible with recent investigations suggesting a general cortical organization scheme, where information gradually progresses from sensory regions to form high-level cognitive representations in the DMN.^{29,30} Alternatively, the time domain may require additional resources such as episodic memory retrieval, reflected by the related temporal activation,^{4,15} which may slow participants’ response, though the nature of the task does not allow much time for reflection. The amplitude of the orientation map for each domain complemented the behavioral results, suggesting that more complex orientation processing requires higher activation of the orientation system. The question of whether orientation in space, time, and person relies on a common brain system is under debate.^{5,31} While several previous studies investigated orientation-related activity,^{32–35} most of them investigated each domain (space, time, or person) separately. A recent fMRI study of the orientation system in these three domains revealed a common “core” network for orientation with segregation of the network to domain-specific regions, adjacent to each other.¹⁵ Comparison of each domain to a lexical control task revealed a significant overlap between the different orientation domains, supporting a model of a general orientation system with distinct domain-specific divisions and a common functional core. The design applied in experiment 1 compares a common activity for all three domains as well as activity for each domain to the

control task. The current results therefore are in-line with the fMRI studies since the same EP map accounts for orientation though its expression in the different domains is different. These findings can be explained by the general function of orientation, which processes the relations between the self and externally cued stimuli in general, though differences are evident in between domains.^{15,36}

fMRI studies of orientation have revealed the orientation system to include activations in the precuneus and posterior cingulate cortex, inferior parietal lobe, medial prefrontal cortex, and lateral frontal and lateral temporal cortices. These regions have been implicated in self-related aspects of space (navigation),³² time (autobiographical memory),^{35,37} and person (representation of self and others).^{34,38} In addition, these regions are involved in specifying relations between landmarks in each domain: cognitive mapping of the spatial environment, recency judgments of life-events, and social proximity and hierarchy judgments.^{32,36} Neural generators of the orientation map as found here were localized to temporal and frontal brain regions including the entorhinal, rostral anterior cingulate, lateral orbitofrontal, and medial orbitofrontal cortices bilaterally. While these results should be taken cautiously in view of the limited spatial resolution of scalp EEG, event-related potential (ERP) studies of self-other discrimination suggest that the activation captured at this specific time segment involves self-related anterior regions, potentially related to the P300 ERP component,^{34,39} more than posterior regions, which are related to magnitude, distance judgments or perspective taking.⁴⁰

Comparison of the orientation map between the clinical groups revealed a significant decrease in activation despite heterogenous disease severity in the AD-con group. This decrease in activation appears to progress gradually from CN through MCI to AD, similar to the monotonous decline pattern exhibited in the behavioral performance. These findings might represent the increasingly compromised orientation system as the disease progresses. Surprisingly, we identified a prolonged activation of the preorientation map for the MCI group (compared to both the AD and CN groups). Due to the small sample sizes of the MCI and AD subgroups this result should be regarded as a preliminary finding inviting further experimental support. Nonetheless, these results are in congruence with a growing body of evidence reporting a paradoxical increase in activity relative to baseline in patients at high risk for AD, rather than a loss of activity.^{41–43} For example, MCI patients performing an associative memory encoding task under fMRI showed greater hippocampal activation compared to control.⁴¹ Similarly, asymptomatic genetically at-risk individuals

such as carriers of familial early-onset AD (FAD)⁴⁴ and APOE- ϵ 4 carriers⁴⁵ demonstrated greater mean entorhinal⁴¹ or hippocampal^{44,45} task-related activation compared to noncarriers. Patients who had progressed to the AD stage exhibited decreased task-related hippocampal activity bilaterally⁴⁶ correlating with deteriorating memory performance.⁴⁷ Notably, increased activity was found not only on the neurocognitive level but also in the molecular and cellular level.⁴³ It remains unclear whether these increased activations play a compensatory role to maintain performance in the early stages of AD or a causal role, acting as a harbinger of imminent neuronal failure. While reports of increased activity in early stages of AD have mainly implicated the hippocampus, this phenomenon has been documented in the prefrontal cortex as well.^{46,48} For instance, AD patients who had higher activity in prefrontal areas were better able to perform tasks of semantic and episodic memory.⁴⁸ Nevertheless, while previous studies have identified hyperactivation of AD-related regions under fMRI,^{41,44–46} the high temporal resolution of our EEG data suggests two processes to be involved: one is a decrease in orientation-related activity along the AD continuum, while the other is a parallel increase of a distinct activity. The latter may be related to the previously reported MTL hyperactivity, which was found to be distinguished from orientation-related activity in previous studies. Further research involving multimodal functional neuroimaging in larger groups of preclinical AD population is needed to shed more light on this remarkable finding.

While behavioral results in CN and deterioration along the AD continuum were correlated with the strength of the orientation map, the increased activity in the preorientation map was associated to map duration. The GFP amplitude refers to the average strength of the potentials being recorded across all electrodes.²³ Therefore, a GFP decrease in maps sharing the same topography reflects a proportional decrease of map strength in all active neural sources.⁴⁹ On the other hand, prolonged brain activation patterns have been proposed to depend on increased backward (top-down) connections, reflecting reentry dynamics of neuronal transients to lower-tier processing areas.^{50,51} The prolonged activity found in this study might therefore represent pathological processing in prefrontal regions related to altered top-down signals in MCI patients. Alternatively, extended activation at these regions may also be due to degraded functional connectivity between these regions. However, neuroimaging studies have highlighted increased functional connectivity within the prefrontal cortices in early AD patients compared to control.⁴⁸ Furthermore, as a stable map across time indicates that the same brain generators are

active and functionally connected across this time segment,⁵² it is improbable that degradation in connectivity would prolong a stable topographic map. Taken together, we propose the monotonic decrease in orientation is compensated by another prolonged process represented by the preorientation map.

A major limitation of this study is that while we recruited an overall large number of subjects for both experiments ($n = 46$) and while the total number of patients was comparable to other neuroimaging studies ($n = 14$),^{41,45,46} the subdivision into MCI and AD groups ($n = 7$) makes conclusions at this level of limited value. Another limitation is that the increase in familywise error rate across the reported EEG statistical analyses was not controlled. Nevertheless, here we are interested in testing a specific time period in between groups and analyzed data accordingly. Different reading speeds between the different clinical groups may pose an additional limitation, however this is less likely to significantly influence results since stimuli were restricted to 2-word phrases and EP maps were highly similar.

To conclude, we have identified a single brain topography underlying orientation in space, time and person. We provide functional neuroimaging evidence from patients along the AD continuum supporting the role of disorientation as a fundamental deficit in Alzheimer's disease. Our data also suggest a prolonged activation of another system prior to the recruitment of the orientation system for MCI patients. These findings invite novel insights into the core cognitive deficits in Alzheimer's disease and suggest increased activity as a functional biomarker to the disease's early stages. Future research incorporating key AD-related cognitive deficits and their underlying neuronal biomarkers may trailblaze the way to a better understanding of the disease pathology, and ultimately, to effective diagnostics and therapies.

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Author Contributions

AD contributed to conception and design of the study, acquisition and analysis of data and drafting the manuscript and figures. GF contributed to conception and

design of the study and critical review of the manuscript. SK contributed to the acquisition of data. SA contributed to conception and design of the study, analysis of data and drafting the manuscript and figures.

Conflict of Interest

The authors declare that they have no competing interests.

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Supporting Information

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

Data S1. Experiment 1 – Participants.

Data S2. Stimuli presentation.

Data S3. Experiment 1 – Analysis of behavioral data.

Data S4. Experiment 1 – Electroencephalography (EEG) recording, evoked potential (EP) mapping and source estimation.

Data S5. Experiment 2 – Stimuli and procedures.

Data S6. Experiment 2 – Analysis of behavioral data.

Data S7. Experiment 2 – Electroencephalography (EEG) recording, evoked potential (EP) mapping and source estimation.

Figure S1. Experiment 1: EEG microstate analysis.

Figure S2. Topographic analysis of variance (TANOVA) between the topographies in experiment 1 and 2.

Figure S3. Experiment 2: EEG microstate analysis.

Table S1. Analysis of variance (ANOVA) on the Global Field Power (GFP) of all EP maps between conditions in experiment 1.

Table S2. Analysis of variance (ANOVA) on the duration of all maps between conditions in experiment 1.

Table S3. Analysis of variance (ANOVA) on the global explained variance (GEV) of all maps between conditions in experiment 1.

Table S4. Analysis of variance (ANOVA) on the global field power (GFP) of the EP maps appearing between 220 and 460 msec after stimulus onset between the groups in experiment 2.

Table S5. Analysis of variance (ANOVA) on the duration of the EP maps appearing between 220 and 460ms after stimulus onset between the groups in experiment 2.

Table S6. Clinical groups demographics and neuropsychological scores.