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Neural and behavioral substrates of disorientation in mild cognitive impairment and Alzheimer's disease

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Abstract

Background: The neural and cognitive substrates of measures of orientation as used in clinical trials and examinations have not been comprehensively examined.

Methods: We studied 473 subjects diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD) at baseline in Alzheimer's Disease Neuroimaging Initiative. Regression analyses at baseline were conducted to find significant predictors of orientation score among cognitive, brain morphometry, and glucose metabolism measures. Mixed model longitudinal analysis was performed to examine consequences of orientation on functional decline, and Cox hazard models examined the risk of conversion to AD in the MCI group.

Results: In MCI and AD subjects, orientation was predicted by poorer neurocognitive performance on immediate and delayed episodic memory and attention and processing speed. Among magnetic resonance imaging measures, orientation was predicted by entorhinal cortex thickness, hippocampal volume, and inferior temporal cortex thickness. Glucose metabolism in both middle-inferior temporal cortex and hippocampus were also predictive of orientation score. Functioning was significantly lower in disoriented subjects after 4 years of follow-up, and MCI patients who also were disoriented showed a higher rate of conversion to AD with a hazard ratio of 1.5.

Conclusions: Orientation is associated with medial temporal lobe structure, temporal lobe glucose metabolism, and episodic memory function. In MCI individuals orientation was a risk factor for progression to AD, also associated with rapid functional decline and worse prognosis. Thus, orientation may serve as a surrogate for episodic memory in clinical examination. These results have direct implications for the use of orientation in MCI and AD clinical trials including ceiling effects in healthy controls and issues of redundancy with measures of memory, when both are used in composite scores.

Keywords: Mild cognitive impairment; Alzheimer's disease; Memory; Structural magnetic resonance imaging; FDG-PET

1. Background

Tests of orientation to time, date, and place are widely used in clinical psychiatric and neurologic examinations and for staging and monitoring progression in research studies and clinical trials involving individuals with dementia or its antecedents. Pragmatically, orientation may be useful as an indicator of decline in the Alzheimer's disease (AD) spectrum [1,2], and can also be used to discriminate between AD and other neurodegenerative

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp- content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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disorders, that is, frontal temporal dementia [3]. Neurocognitive studies examining the relationship between orientation and cognition have found correlations between episodic memory and working memory and/or executive impairment and orientation [4–7]. Several lesion and neuroimaging studies have implicated multiple brain areas (presumably subserving different cognitive operations) as being involved in orientation, including the hippocampus [8], medial temporal and parietal cortical areas [9], and orbitofrontal cortex [10] in various disorders. However, few studies have examined the neural substrates of orientation in the context of mild cognitive impairment (MCI) or AD. A single fluorodeoxyglucose positron emission tomography (FDG-PET) study of patients with mild-to-moderate AD found that temporal disorientation was related to reduced glucose metabolic rate in the posterior cingulate gyri and in the right middle temporal gyrus, but cognition was not examined [11].

Beyond its routine use in the clinic, orientation has come to be viewed as increasingly important in tracking neurodegenerative disease progression [2,12]. Recently several so-called composite measures of cognition have identified orientation as a key component in the battery [12,13]. Selection was made after analyses revealed that orientation (scored on the Mini-Mental State Examination or MMSE) demonstrated consistent decline in MCI and AD groups over time (i.e., had robust signal to noise properties using mean/standard deviation ratios). Further adjustments for group, namely individuals who remained cognitively normal versus those who progressed or showed practice effects were sometimes made [2,12]. However, selection criteria did not include redundancy with other measures (e.g., episodic memory), nor applicability to preclinical AD given the possibility of ceiling effects [14]. For the Preclinical Alzheimer Cognitive Composite (PACC) selection of items including MMSE orientation was based on a literature review. The resulting composite was used retrospectively in measuring change in various groups with preclinical AD and setting aside the possibility of tautology, was able to track "progressors" in various groups [13].

In this article we examine spatial and temporal disorientation in the context of AD dementia and MCI, disorders in which disorientation may be a frequently observed symptom [15]. This study is the first to comprehensively examine cognitive, structural magnetic resonance imaging (MRI) brain morphometry, and positron emission tomography (PET) functional glucose metabolism substrates of orientation in a single large sample of MCI and AD patients. We predicted that orientation would be associated with (1) cognitive operations involving episodic memory, given demands for acquisition, and recall of new information in specific contexts; (2) executive processes involving cognitive estimation, updating, and management of interference between similar items ("remembering to remember" to advance the date after time has passed); and (3) semantic knowledge to parse meaning based on attributes (e.g., a city is different than a county), that is, a network involving higher integrative processes. These operations would engage such brain regions as the medial temporal lobe (episodic memory), prefrontal cortex (updating and estimating), and lateral temporal lobe (semantic knowledge). However, our results strongly supported a more restricted conceptualization of orientation involving episodic memory and its medial temporal lobe substrate and to a lesser extent, lateral temporal lobe glucose metabolism (perhaps impacting semantic knowledge). In an extension of our approach to examine prognosis, we examined the consequences of disorientation on longitudinal functional capacity (over 4 years of follow-up), and specifically in the context of MCI, the influence of disorientation on conversion to AD, and demonstrated that it was a robust and negative prognostic indicator. Our findings also have clear implications for orientation's possible use in clinical trials in various AD subpopulations.

2. Methods

2.1. Study population

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Only subjects diagnosed with MCI and AD at study entry were included in the analyses. Inclusion criteria for MCI and AD patients are described elsewhere [16,17] and on the ADNI website (http://www.adni-info.org). Briefly, healthy controls (HC) had no memory complaints aside from those common in other individuals of that age range, a Mini-Mental State Examination (MMSE) [18] score between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) [19] score equal to 0, and absence of significant levels of impairment in cognitive functions or activities of daily living. MCI patients had MMSE scores between 24 and 30 (inclusive), a memory complaint, objective memory loss, a CDR score of 0.5, and absence of significant impairment in other cognitive domains, and preserved activities of daily living. AD patients had MMSE scores between 20 and 26 (inclusive), memory complaint, objective memory loss, a CDR score of 0.5 or 1, and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders criteria for probable AD [20].

This study included both MCI and AD subjects in a single pool to extend the range of orientation scores and the likelihood that multiple brain regions would be compromised to greater and lesser degrees. Additionally, our rationale was based on our own work in the ADNI sample and consequent Pittsburgh compound B (PIB) imaging studies, in that most MCI patients had pathology consistent with AD (i.e., suffered from prodromal AD) and also converted to AD in the course of the study [16,17]. All participants signed written informed consent for participation in the ADNI initiative, as approved by the institutional board at each participating center.

2.2. Measurements

2.2.1. Orientation

Orientation was examined as a single composite including both spatial and temporal items, using the Folstein's MMSE orientation section, which contains five spatial orientation and five temporal orientation items. In a further set of analyses, we also took into account the temporal and spatial domains of orientation independently (see Supplementary Material).

2.2.2. Cognitive assessment

Cognitive measures were entered into analyses individually and were not statistically combined into domains. Cognitive domains assessed included those linked to the brain structures described previously: immediate and delayed episodic verbal memory were measured by Logical Memory immediate recall and delayed recall of the Wechsler Memory Scale (WMS) [21] and immediate and delayed recall of the Auditory Verbal Learning Test (AVLT) [22], attention was measured by Trail Making Test part A (23), working memory was measured by digit span, semantic memory and visuospatial ability were measured by clock drawing score [23], language ability was measured by semantic fluency (22), speed of processing was measured by digit symbol score [24], and executive function was measured by Trail Making Test part B (23). Clock drawing scores were log-transformed because of a skewed distribution. All measures were obtained at baseline.

2.2.3. MRI acquisition and analysis

The scans used in this study were obtained from 1.5 Tesla scanners at different sites involved in ADNI with minor variations in the MRI protocol based on the specific configuration of each scanner. For the purpose of this study, volumetric measures of the whole brain, cerebral white matter, and left and right hippocampus, and cortical thickness measures of both hemispheres were combined and extracted from the following medial temporal, frontal, and parietal lobe's areas: parahippocampal, entorhinal, middle temporal, inferior temporal, superior temporal, medial orbital frontal, rostral middle frontal, superior frontal, posterior cingulate, precuneus, superior parietal, and inferior parietal. These measures were derived by Freesurfer (http://surfer.nmr.mgh.harvard.edu/). We excluded full MRI scans for subjects who had failed or partially failed the cortical reconstruction in any of the brain regions that we examined. Detailed description of MRI protocol and methods is available at ADNI webpage and on request by the authors. All measures were obtained at baseline.

2.2.4. FDG-PET acquisition and processing

A specified reconstruction algorithm for each scanner type was implemented according to a standardized protocol to acquire FDG-PET data (http://adni.loni.usc.edu/about/centers-cores/pet-core/). All images were preprocessed by the ADNI PET coordinating center. Three predefined regions of interest (ROIs) including both right and left hemispheres, based on coordinates frequently cited in FDG-PET studies of MCI and AD, were analyzed [25]: middle-inferior temporal gyrus, posterior cingulate cortex, and angular gyrus. Briefly, processing of images consisted of spatial normalization in Statistical Parametrical Mapping (SPM) software to the Montreal Neurological Institute (MNI) MNI PET template and extraction of the mean counts from the regions of interest (ROIs) computing the intensity values with SPM subroutines; subsequently each ROI mean was intensity normalized by dividing it by a reference region mean (pons/cerebella vermis). An additional fourth ROI with both hippocampi was included. This latter measurement was performed through HIPMASK [26], a technique specifically developed to measure hippocampal metabolism sampling that overcomes errors in spatial alignment of small structures such as the hippocampus and with an anatomically variable position; it is an automated technique based on the optimization of positive likelihood ratio that enables rapid PET sampling of brain subregions. Mean glucose metabolism intensity data were extracted for both left and right hippocampus normalized to pons as the reference region. All measures were obtained at baseline.

2.2.5. Functional assessment

The functional assessment questionnaire (FAQ) [27] was used as a measure of functional ability. Data at baseline, 1 year, 2 years, and 3 years were used in a longitudinal framework analysis.

2.2.6. MCI to AD progression

Progression from MCI to AD is a primary outcome measure in ADNI. First, each site physician reviewed visit measures and completed diagnosis formulation. Second, site's clinical monitor reviewed CDR and resolved any issues with site Principal Investigator. Finally, the Conversion Committee reviewed reports, resolved differences, and completed diagnosis formulation. Conversions were counted over a 4-year period.

2.3. Data analyses

First, we performed a series of linear multiple regression analyses to identify the cognitive processes, MRI morphometry, and PET cerebral glucose metabolism measures that predicted orientation (treated dimensionally as a continuous dependent variable). We used a forward stepwise method that seeks to maximize the amount of explained variance (SAS PROC REG with MAXR selection method). We also present the results obtained when orientation was split into temporal and spatial domains (see Supplementary Material).

Second, as a confirmatory approach, we subjected the models obtained in the stepwise regressions to a k-fold cross-validation procedure to determine the robustness of

Table 1
Demographic characteristics

	MCI/AD (N = 473)
Age, mean (SD)	75.11 (7.39)
Range	55–91
Gender M/F	283/190
Education, mean (SD)	15.46 (3.04)
Range	6–20
CDR, mean (SD)	0.58 (0.18)
Range	0.5–1
MMSE orientation, mean (SD)	8.47 (1.47)
Range	4–10
MMSE total score without orientation items, mean (SD)	17.43 (1.69)
Range	13–20

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; SD, standard deviation; M, Male; F, Female; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

our findings. In this procedure, the sample is split into k randomly chosen subgroups (i.e., k training and test data sets). We performed a k-fold (k = 5) cross-validation (SAS 9.3. PROC GLMSELECT) specifying the adjusted r square as the stopping criterion to maximize the amount of explained variance. We chose k = 5 because it yielded reasonably large training and test sets (Table 3).

Finally, for the purpose of examining the consequences of disorientation over time in a longitudinal framework, orientation and disorientation was treated categorically by median split resulting in two groups: oriented subjects (MMSE score greater than 8), and disoriented subjects (MMSE score less than or equal to 8). Mixed model analysis (SAS 9.3. PROC MIXED) with three factors (group, time, and group × time) was performed to examine the consequences of disorientation on functional capacity. In this mixed model, covariance pattern was set as autoregressive, time (follow-ups) was included as a repeated factor, and group (oriented vs. disoriented) as a between-subjects factor. Subject was the random factor. In addition, Cox proportional hazard regression analysis was performed to ascertain the hazard rate of conversion to AD in the MCI sample. Kaplan-Meier survival analysis was used to illustrate conversion in MCI individuals with intact orientation compared with disorientation.

Age, gender, educations (in years), and apolipoprotein E (*APOE*) ε4 status (carriers versus noncarriers) were forced in all regression and longitudinal mixed models.

3. Results

3.1. Orientation score distribution: HC

In the HC group, the mean orientation score was 9.79 (standard deviation or SD = 0.45) (of 10). Examination of the distribution confirmed a pronounced ceiling effect. Thus, no further analyses were undertaken in this group.

3.2. Demographic and cognitive characteristics: MCI/AD

Demographic information for the combined MCI/AD sample is described in Table 1. Average score on CDR was 0.58. The mean MMSE score on the 10 orientation items was 8.47 (SD = 1.47). The mean MMSE score exclusive of orientation items was 17.43 (SD = 1.69).

3.3. Neurocognitive predictors of disorientation

Orientation score was predicted by poorer performance on immediate and delayed recall on the WMS logical memory subtest, the AVLT delayed memory subtest, and the digit symbol test (Table 2). As can be seen in Table 2, episodic memory tests accounted for approximately 20% of the total variance in the regression analysis. When only AD patients were considered, disorientation was only predicted by the poorer performance of delayed recall on the WMS logical memory subtest.

3.4. Brain structural MRI predictors of disorientation

Among the significant brain morphometry predictors (Fig. 1), entorhinal cortex thickness entered first in the regression analysis, accounting for 17% of the variance in orientation score. Hippocampus volume added 2% more, and inferior temporal cortex thickness accounted for an additional 1% of the variance. Results were similar when analyzing MCI and AD subjects separately.

3.5. Brain functional FDG-PET predictors of disorientation

Glucose metabolism normalized to pons for both middle-inferior temporal cortex and hippocampus was predictive of orientation score in the combined sample (Fig. 2), accounting for 21% of the variance. In AD patients, only hippocampus metabolism was predictive of disorientation.

Table 2
Neurocognitive predictors of orientation

	F8, 423 = 17.201, $P < .0001$, adjusted $R^2 = 0.231$							
Model	DF	B	CI	t	*P*	Standardized estimate	Adjusted R^2	VIF
Logical memory immediate	1	0.094	0.044–0.144	3.69	.0003	0.213	0.174	1.868
Digit symbol	1	0.021	0.011–0.032	3.97	<.0001	0.179	0.030	1.138
AVLT delayed	1	0.047	0.014–0.081	2.75	.006	0.127	0.019	1.191
Logical memory delayed	1	0.076	0.011–0.140	2.32	.02	0.139	0.008	2.022

Abbreviations: DF, degrees of freedom; CI, confidence interval; VIF, variance inflation factor; AVLT, Auditory Verbal Learning Test.

Table 3
Cross-validation sample sizes for training and test sets in each of the five folds; (a) cross-validation details for cognitive model; (b) cross-validation details for MRI model; and (c) cross-validation details for fluorodeoxyglucose positron emission tomography (FDG-PET) model

	Observations		
Fold	Fitted	Left out	CV PRESS
(a) Cognition cross-validation details			
1	355	85	121.980
2	351	89	162.675
3	349	91	153.430
4	348	92	132.004
5	357	83	168.486
Total			738.575
(b) MRI cross-validation details			
1	242	60	64.054
2	243	59	151.751
3	240	62	83.292
4	235	67	110.579
5	248	54	134.694
Total			544.371
(c) FDG-PET cross-validation details			
1	147	37	61.626
2	152	32	39.477
3	142	42	87.610
4	141	43	87.118
5	154	30	57.267
Total			333.098

Abbreviation: MRI, magnetic resonance imaging; CV PRESS, cross-validation predicted residual sum of squares.

3.6. k-fold cross-validation analyses

We subjected the models obtained in the previous series of regression analyses to a k-fold cross-validation. Results were confirmatory. We present the sample size for training and test sets in the cross-validation procedure in Table 3, showing that k-fold method with k = 5 provided reasonable sample sizes in each of the folds. The cross-validation predicted residual sum of squares (CVPRESS) values, another index of fit examining residuals between observed and predicted scores, are shown in Table 3.

3.7. Consequences of disorientation over 4 years of follow-up

For this set of analyses, two groups were created according to MMSE orientation score at baseline with the score of 8 as a cutoff for disorientation (see Data Analysis section). For the combined group of AD and MCI individuals, functioning level, as measured by FAQ, was significantly lower in disoriented subjects. FAQ scores systematically declined over 4 years, as indicated by the group × time interaction factor ($F_{4,\ 437} = 5.21$, $P = .0004$) in the mixed model analysis, that is, those patients who showed disorientation at baseline declined to a greater extent on their everyday functioning level (Supplementary Table 7 and Supplementary Fig. 1). This finding remained unchanged when analyzing both groups separately, although as expected, it was of greater statistical significance for AD patients compared with MCI patients.

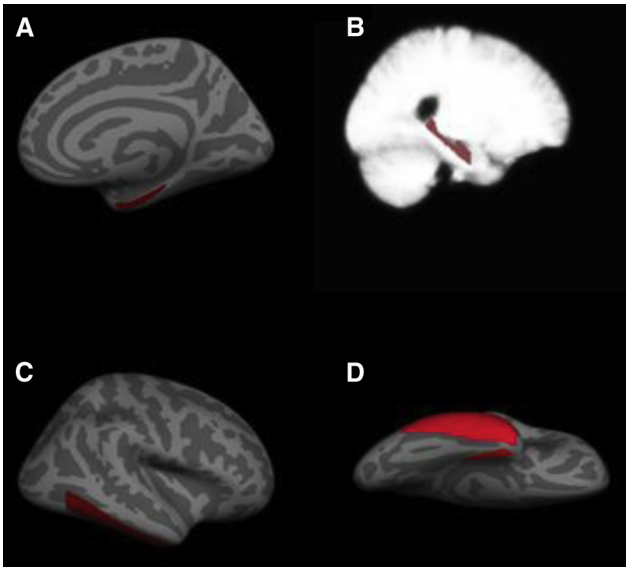

Fig. 1. Magnetic resonance imaging (MRI) morphometric predictors of orientation in individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Brain areas that significantly predicted orientation are highlighted in red. The overall significance of the predictive model was: $F_{7,\ 294} = 12.583$, $P < .0001$, adjusted $R^2 = 0.212$. (A) Decreased entorhinal cortex thickness predicted poorer orientation, accounting for 17% of the variance (adjusted $R^2 = 0.174$); individual estimates: b = 0.523 (confidence interval or CI 0.067–0.979), t = 2.26, $P = .025$, standardized b = 0.175, variance inflation factor or VIF = 2.298. (B) Smaller hippocampal volume predicted disorientation, accounting for 2% of the variance (adjusted $R^2 = 0.025$); individual estimates: b = 0.0005 (CI 0.0001–0.001), t = 2.43, $P = .015$, standardized b = 0.177, VIF = 2.015. (C) Decreased thickness of the inferior temporal cortex predicted disorientation, explaining 1% of the variance (adjusted $R^2 = 0.014$); individual estimates: b = 1.307 (CI 0.470–2.145), t = 3.07, $P = .002$, standardized b = 0.207, VIF = 1.726. (D) Represents both entorhinal and inferior-temporal cortices from a basal plane, illustrating the importance of medial temporal lobe areas in disorientation. NB: The colored area represents the region under study; it is not a heat map.

MCI patients who were disoriented converted at a higher rate to AD (61%) than MCI patients who were oriented (42%) over a 5-year period ($X^2 = 8.45$, $P = .004$). The mean follow-up time in months for disoriented MCI patients who developed AD was 24.09 (SD = 12.60) and 28.04 (SD = 12.19) for oriented patients. Cox hazard ratio regression model to estimate the risk of conversion to AD according to orientation status at baseline showed that the hazard ratio was 1.5 ($P = .0001$), 95% confidence interval (CI) 1.28–1.75, that is, disoriented MCI patients showed approximately 1.5 times the risk of conversion per month as compared with oriented patients. In addition, Kaplan-Meier survival analysis revealed that subjects with MCI converted at a higher rate to AD if they also had disorientation compared with MCI patients with relatively intact orientation (Fig. 3).

4. Discussion

Although orientation has long been used as a measure of global mental status in neurological and psychiatric

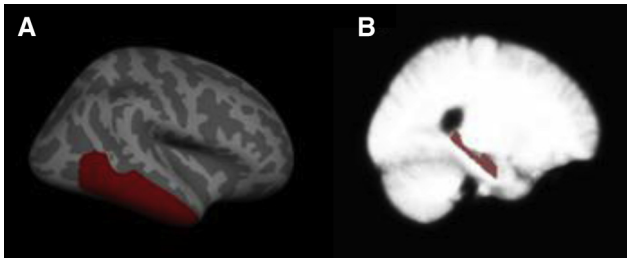

Fig. 2. Fluorodeoxyglucose positron emission tomography (FDG-PET) measures of glucose metabolism predictors of orientation in individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Brain areas that significantly predicted orientation are highlighted in red. The overall significance of the predictive model was: $F_{6,\ 183} = 9.314$, $P < .0001$, R^2 adjusted = 0.214. (A) Glucose hypometabolism in the middle and inferior temporal cortex was predictive of disorientation, explaining almost 18% of the variance (adjusted $R^2 = 0.186$); individual estimates: b = 3.934 (confidence interval or CI 2.474–5.393), t = 5.32, $P < .0001$, standardized b = 0.375, variance inflation factor or VIF = 1.154. (B) Glucose hypometabolism in the hippocampus was also predictive of disorientation, explaining almost 3% of the variance (adjusted $R^2 = 0.028$); individual estimates: b = 2.185 (CI 0.602–3.768), t = 2.72, $P = .007$, standardized b = 0.194, VIF = 1.178. NB: The colored area represents the region under study; it is not a heat map.

assessment [28], research has been sparse on the cognitive operations involved in orientation abilities and the neural substrates that support them. The current findings provide convergent evidence that episodic memory ability and both structure and metabolic function of medial temporal brain areas are primary predictors of disorientation in the context of MCI and AD. We also found evidence for a role of lateral temporal cortex in orientation ability. This region has been thought to support semantic knowledge, including featural attributes and has been compromised in MCI and AD [29]. Importantly, our results were robustly supported by k-fold cross-validation analyses in which shrinkages were very small.

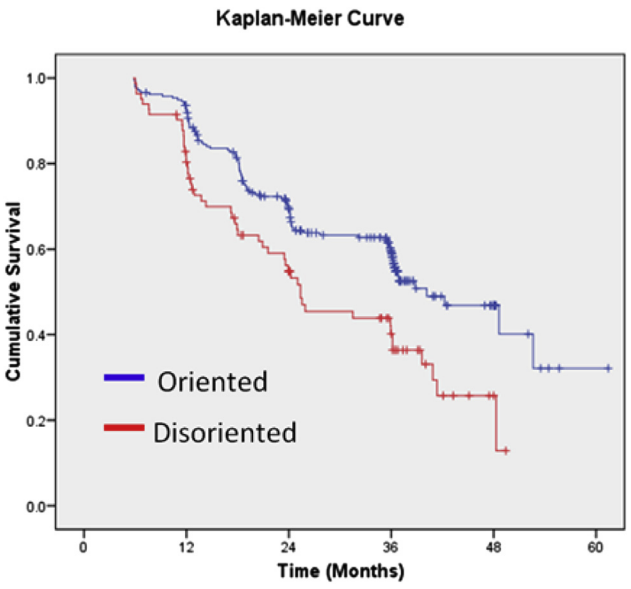

Fig. 3. Kaplan-Meier estimates of the rate of progression to Alzheimer's disease (AD) in mild cognitive impairment (MCI) patients who were either oriented or disoriented at baseline. MCI patients with disorientation converted to AD at a higher rate than MCI patients with intact orientation ability. The blue line represents oriented MCI individuals and the red line represents disoriented MCI individuals. The X-axis represents time and the Y-axis represents conversion from MCI to AD.

These results have important clinical implications in that the use of orientation as a measure can aid in the assessment of memory functioning. Additionally, it adds to prognostic information: more disoriented individuals were more likely to experience steeper declines such that they converted more rapidly than less disoriented individuals, and concomitantly also demonstrated reduced functional abilities over time. Based on the analyses presented here, orientation could be used as an outcome in clinical trials, given that it is valid on its face, can be objectively scored, and has plausible biological correlates. Given the relationship of disorientation to steeper decline in everyday function and MCI to AD conversion, it could also be used to enrich samples. Nevertheless, there are caveats. We found marked ceiling effects in HCs in ADNI (mean orientation score = 9.8 of 10) and so the measure may have limited utility in determining fine differences in medial temporal lobe integrity in this group.

As noted, little research has specifically focused on orientation items in relation to neurocognition and neurobiological variables in MCI or AD. Our initial hypothesis involved a large network of cognitive and regional neurobiological predictors. However, our findings, combining three different and complementary lines of evidence, pointed toward medial temporal lobe integrity and episodic memory as the critical factors that determine the presence of disorientation in MCI and AD. Although our findings may be attributed to orientation in MCI and AD having unique cognitive and neurobiological underpinnings, in our view, the locus of pathology, rather than its nature, more likely played a determining role [30]. In this respect, we acknowledge that there is evidence that AD pathology is often accompanied by other disease processes [31].

One point to take into consideration is the method by which orientation is measured. There is likely a difference in the cognitive domains needed to verbally "name" a location as opposed to navigating to the location. Questions of spatial orientation (e.g., state, country, name of building) may rely on new learning of the names of places rather than actual tracking of one's location in space. Similarly, temporal orientation may also be "memorized" to some degree (e.g., month, year). This may account for the seeming reliance of orientation on memory function and temporal lobe brain structures found in this study. It would be useful to examine other aspects of orientation, in which route-finding in space [32] and temporal monitoring might be used as orientation measures. It is worth noting here that when we separated spatial and temporal orientation, we found that predictors were generally the same, but the amount of variance accounted for was less in spatial orientation than temporal orientation. This perhaps suggests that predictors outside the domains included in ADNI's data

set may play a role or alternatively that there may have been a reduction in range for spatial orientation.

Orientation has also been shown to be a significant predictor of further cognitive decline [1]. Our findings similarly suggest that individuals with MCI who were disoriented at baseline had higher hazard ratio for the conversion to AD compared with MCI individuals who were oriented at baseline. Furthermore, disoriented individuals declined in everyday function significantly more than oriented subjects. In this sense, greater atrophy and glucose hypometabolism in the hippocampal and middle temporal lobe brain region (beyond what is expected in prodromal AD) may indicate a more aggressive form of AD from which a primary clinical manifestation would encompass impairments in orientation ability. In keeping with this, clinicopathological studies of post-mortem brain tissue have found that disorientation was significantly correlated with neurofibrillary tangle density in CA1 field of the hippocampus and Brodmann's Areas 7 and 23 [33]. It may also be important in future studies to examine the covariance of orientation and its neural substrates monitored over time.

These findings have important implications for the use of orientation in preclinical and prodromal AD (i.e., MCI due to AD) clinical trials. First in healthy subjects, a ceiling effect may be present that could obscure subtle longitudinal change. Although the PACC was able to demonstrate sensitivity to various groups of "progressors" in preclinical AD or a possible surrogate based on *APOE* ε4 genotype, it is unclear if orientation directly contributed to sensitivity [13]. Second, the use of orientation may be redundant in composite test batteries with cognitive tests assaying episodic memory processes that engage medial temporal lobe. On the other hand, orientation does not overlap completely with episodic memory measures and thus may demand unique cognitive operations sensitive to functional decline (see point 4 below). Third, several composite batteries (ref e.g., PACC, ADCOM) and orientation scores are included from multiple sources (e.g., CDR, MMSE, and Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-Cog]) [34]. Thus, critical examination of subtle differences in administration and items in orientation may be necessary to more comprehensively understand what orientation, in its various implementations, is measuring. Fourth, disorientation was associated with steeper declines in MCI subjects in everyday function and ultimately to progression to AD, and may have prognostic advantages. Although we did not test this directly, orientation may not be subject to severe practice effects because of the necessity for the person to regularly update information, especially with respect to temporal items [35]. Thus, the use of orientation measures in translational interventions may be dependent on the group that is being monitored (preclinical, prodromal, and established AD), the length of time over which monitoring is to occur, and the type of treatment. Depending on the type of treatment, it is also worth considering whether orientation might be best be used as a "stand-alone" measure or be included in a composite.

In summary, in this, the largest and most comprehensive study of the neurobiological and behavioral components of orientation, we found that disorientation in the context of MCI and AD was predicted by reduced thickness in temporal and entorhinal cortex, and reduced volume of the hippocampus, and poorer performance on neurocognitive measures of immediate and delayed verbal memory. We also found that MCI subjects with signs of disorientation showed an increased risk of conversion, and in both AD and MCI, disoriented individuals had steeper decline in function than those with preserved orientation. Our findings support the perspective that orientation is an important clinical measure, as it may be considered an ecologically relevant surrogate for traditional laboratory tests of episodic memory in MCI and AD. Our findings also may usefully provide evidence-based knowledge so that an informed discussion of orientation's use in translational clinical trials can begin.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2015.04.002.

RESEARCH IN CONTEXT

1. Systematic review: We used a PubMed search for studies examining the relationship of neurocognition, regional brain morphometry, or glucose metabolism to disorientation. We interrogated the Alzheimer's Disease Neuroimaging Initiative database to derive orientation scores and their neural and cognitive predictors.
2. Interpretation: The study is the first to provide convergent evidence that medial temporal lobe morphometrics and glucose use, along with related episodic memory test scores, are associated with disorientation scores in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Disorientation in MCI also predicted decline in functional abilities and progression to AD.
3. Future directions: The study has implications that are directly relevant to the use of orientation measures as outcomes in clinical trials. First, in healthy subjects, a ceiling effect may be present that could obscure or constrain longitudinal change. Second, the use of orientation measures may be redundant in composite test batteries given their strong association with memory test scores. Last, the use of orientation scores from different sources (e.g. Mini-Mental State Examination, Clinical Dementia Rating, Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-Cog]) requires further analyses to determine their degree of similarity.

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