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Novelty-Related fMRI Responses of Precuneus and Medial Temporal Regions in Individuals at Risk for Alzheimer Disease

Ornella V. Billette, PhD,* Gabriel Ziegler, PhD,* Merita Aruci, MSc, Hartmut Schütze, PhD, Jasmin M. Kizilirmak, PhD, Anni Richter, PhD, Slawek Altenstein, Dipl-Psych, Claudia Bartels, PhD, Frederic Brosseron, PhD, Arturo Cardenas-Blanco, PhD, Philip Dahmen, MSc, Peter Dechent, PhD, Laura Dobisch, MSc, Klaus Fliessbach, MD, Silka Dawn Freiesleben, MSc, Wenzel Glanz, MD, Doreen Göerß, MD, John Dylan Haynes, PhD, Michael T. Heneka, MD, Ingo Kilimann, MD, Okka Kimmich, MD, Luca Kleineidam, PhD, Christoph Laske, PhD, Andrea Lohse, Ayda Rostamzadeh, MD, Coraline Metzger, MD, Matthias H. Munk, PhD, Oliver Peters, MD, Lukas Preis, MSc, Josef Priller, MD, Klaus Scheffler, PhD, Anja Schneider, MD, Annika Spottke, MD, Eike Jakob Spruth, MD, Alfredo Ramirez, MD, Sandra Röske, PhD, Nina Roy, PhD, Stefan Teipel, MD, Michael Wagner, MD, Jens Wiltfang, MD, Steffen Wolfsgruber, PhD, Renat Yakupov, PhD, Peter Zeidman, PhD, Frank Jessen, MD, Björn H. Schott, MD, Emrah Düzel, MD, and Anne Maass, PhD, on behalf of the DELCODE Study Group

Correspondence
Dr. Maass
annemaass85@gmx.de

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Abstract

Background and Objectives

We assessed whether novelty-related fMRI activity in medial temporal lobe regions and the precuneus follows an inverted U-shaped pattern across the clinical spectrum of increased Alzheimer disease (AD) risk as previously suggested. Specifically, we tested for potentially increased activity in individuals with a higher AD risk due to subjective cognitive decline (SCD) or mild cognitive impairment (MCI). We further tested whether activity differences related to diagnostic groups were accounted for by CSF markers of AD or brain atrophy.

Methods

We studied 499 participants aged 60–88 years from the German Center for Neurodegenerative Diseases Longitudinal Cognitive Impairment and Dementia Study (DELCODE) who underwent task-fMRI. Participants included 163 cognitively normal (healthy control, HC) individuals, 222 SCD, 82 MCI, and 32 patients with clinical diagnosis of mild AD. CSF levels of β-amyloid 42/40 ratio and phosphorylated-tau181 were available from 232 participants. We used region-based analyses to assess novelty-related activity (novel > highly familiar scenes) in entorhinal cortex, hippocampus, and precuneus as well as whole-brain voxel-wise analyses. First, general linear models tested differences in fMRI activity between participant groups.

*These authors contributed equally to this work.

From the German Center for Neurodegenerative Diseases (DZNE) (O.V.B., G.Z., M.A., A.C.-B., W.G., C.M., R.Y., E.D., A.M.), Magdeburg; Institute of Cognitive Neurology and Dementia Research (IKND) (O.V.B., G.Z., H.S., A.C.-B., L.D., C.M., R.Y., E.D.), Otto-von-Guericke University, Magdeburg; German Center for Neurodegenerative Diseases (DZNE) (J.M.K., J.W., B.H.S.), Goettingen; Department of Behavioral Neurology (A. Richter, B.H.S.), Leibniz Institute for Neurobiology, Magdeburg; German Center for Neurodegenerative Diseases (DZNE) (S.A., P. Dahmen, S.D.F., O.P., L.P., J.P., E.J.S.), Berlin; Department of Psychiatry and Psychotherapy (S.A., A.L., J.P., E.J.S.), Charité; Department of Psychiatry and Psychotherapy (C.B., J.W., B.H.S.), University Medical Center Goettingen, University of Goettingen; German Center for Neurodegenerative Diseases (DZNE) (F.B., K.F., M.T.H., O.K., L.K., A. Schneider, A. Spottke, A. Ramirez, S.R., N.R., M.W., S.W., F.J.), Bonn; University of Bonn Medical Center (F.B., K.F., M.T.H., L.K., A. Schneider, A. Ramirez, M.W., S.W.); Department of Neurodegenerative Disease and Geriatric Psychiatry/Psychiatry, Bonn; MR-Research in Neurosciences (P. Dechent), Department of Cognitive Neurology, Georg-August-University Göttingen; Department of Psychosomatic Medicine (D.G., I.K., S.T.), Rostock University Medical Center; Bernstein Center for Computational Neuroscience (J.D.H.), Charité—Universitätsmedizin, Berlin; German Center for Neurodegenerative Diseases (DZNE) (I.K., S.T.), Rostock; German Center for Neurodegenerative Diseases (DZNE) (C.L., M.H.M.), Tübingen; Section for Dementia Research (C.L.), Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen; Department of Psychiatry (A. Rostamzadeh), Medical Faculty, University of Cologne; Department of Psychiatry and Psychotherapy (C.M.), Otto-von-Guericke University, Magdeburg; Systems Neurophysiology (M.H.M.), Department of Biology, Darmstadt University of Technology, Germany; Campus Benjamin Franklin, Department of Psychiatry (O.P, L.P.), Charité-Universitätsmedizin Berlin; Department for Biomedical Magnetic Resonance (K.S.), University of Tübingen; Department of Neurology (A. Spottke), University of Bonn; Division of Neurogenetics and Molecular Psychiatry (A. Ramirez, F.J.), Department of Psychiatry, Medical Faculty, University of Cologne; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) (A. Ramirez, F.J.), University of Cologne, Köln, Germany; Department of Psychiatry & Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases (A. Ramirez), San Antonio, TX; Neurosciences and Signaling Group (J.W.), Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Portugal; and Wellcome Centre for Human Neuroimaging (P.Z.), London, UK.

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Glossary

AD = Alzheimer disease; **AIC** = Akaike information criterion; **ANOVA** = analysis of variance; **CERAD** = Consortium to Establish a Registry of AD; **DMN** = default mode network; **FWE** = family-wise error; **FWHM** = full width at half maximum; **GLM** = general linear model; **GM** = gray matter; **HC** = healthy control; **MANCOVA** = multivariate analysis of covariance; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurological Institute; **MTL** = medial temporal lobe; **ROI** = region of interest; **SCD** = subjective cognitive decline; **SPM** = statistical parametric mapping; **VBM** = voxel-based morphometry.

Complementary regression models tested quadratic relationships between memory impairment and activity. Second, relationships of activity with AD CSF biomarkers and brain volume were analyzed. Analyses were controlled for age, sex, study site, and education.

Results

In the precuneus, we observed an inverted U-shaped pattern of novelty-related activity across groups, with higher activity in SCD and MCI compared with HC, but not in patients with AD who showed relatively lower activity than MCI. This nonlinear pattern was confirmed by a quadratic relationship between memory impairment and precuneus activity. Precuneus activity was not related to AD biomarkers or brain volume. In contrast to the precuneus, hippocampal activity was reduced in AD dementia compared with all other groups and related to AD biomarkers.

Discussion

Novelty-related activity in the precuneus follows a nonlinear pattern across the clinical spectrum of increased AD risk. Although the underlying mechanism remains unclear, increased precuneus activity might represent an early signature of memory impairment. Our results highlight the nonlinearity of activity alterations that should be considered in clinical trials using functional outcome measures or targeting hyperactivity.

Network-level dysfunction occurs early in Alzheimer disease (AD) and can be measured indirectly with fMRI. Task-based fMRI studies have yielded increased activity in medial temporal lobe (MTL) regions and the precuneus in older adults with mild cognitive impairment (MCI) compared with healthy controls (HCs).[1-3] Similar or reduced activity compared with HCs has been found in patients with AD dementia.[4] Studies with AD biomarkers suggest that early increased activity in individuals without dementia is related to increased Aβ burden or MTL tau pathology,[5-10] and late reduced activity accompanied by clinical impairment is linked to pronounced AD pathology and neurodegeneration. It remains unclear whether increased brain activity reflects early pathology or rather compensatory mechanisms that enable sustained memory performance.[7,11,12] The activity pattern changes across the spectrum from HC to groups with increased AD risk, such as subjective cognitive decline (SCD) and MCI,[13,14] toward patients with AD dementia have been described as an inverted U or J shape.[15-17] Individuals with SCD—a relatively young diagnosis[13]—are twice as likely to develop dementia as individuals without SCD,[14] and its functional characterization is crucial for clinical trials. fMRI studies in SCD indicate increased task-related parietal and frontal activity.[17-19] However, these studies were limited by small sample sizes and lacked AD CSF biomarkers. Therefore, we examined how fMRI-task activity during novelty processing differs across the AD risk spectrum using the German Center for Neurodegenerative Diseases Longitudinal Cognitive Impairment and Dementia Study (DELCODE) cohort.[20] We expected a nonlinear pattern with increased activity in the MTL and precuneus in SCD and MCI explained by CSF biomarkers of AD pathology, followed by decreased activity with clinical progression and more advanced AD pathology. We further investigated the regional pattern of activity deviations and how this compares to the pattern of atrophy by means of whole-brain analyses.

Methods

Participants

The DELCODE study is a German multicentric observational study, and details are provided in reference 20 and the eMethods (links.lww.com/WNL/C105). Here, we analyzed baseline data from 499 participants who completed a task fMRI. CSF samples were available for 232 participants (Table 1) and APOE ε4 status for 488 participants. Our study sample included 163 HC, 222 SCD, 82 MCI, and 32 patients with a clinical diagnosis of AD dementia. HC was defined as having memory test performances within 1.5 SD of the age-, sex-, and education-adjusted normal performance on all subtests of the Consortium to Establish a Registry of AD (CERAD) test battery. SCD was defined as the presence of SCD as expressed to the physician of the memory center[13] and normal cognition as assessed with the CERAD. Participants were classified as MCI when displaying an age-, sex-, and education-adjusted performance below −1.5 SD on the delayed recall trial of the

Table 1 Sample Characteristics

Feature	HC	SCD	MCI	AD-dementia	Statistics
N MRI	163	222	82	32	
Age (y)	69 ± 5	70 ± 6	73 ± 5	73 ± 5	$p < 0.001$ HC < SCD < MCI/AD
N female (%)	102 (63)	100 (45)	42 (51)	21(66)	$p < 0.01$ HC/AD > SCD
Years of education	15 ± 3	15 ± 3	14 ± 3	13 ± 3	$p < 0.001$ MCI/AD < HC/SCD,
N APOE ε4+ (%)	35_3 (22)	68_6 (31)	36_2 (45)	21 (66)	$p < 0.001$ HC < SCD < MCI < AD
N CSF	64	99	48	21	
Aβ42/40	0.097 ± 0.020	0.097 ± 0.027	0.077 ± 0.031	0.048 ± 0.015	$p < 0.001$ HC/SCD < MCI < AD
N A+ (%)	6 (9)	26 (26)	22 (46)	20 (95)	$p < 0.001$ HC < SCD < MCI < AD
p-tau181 (pg/mL)	47.9 ± 15.1	55.5 ± 23.9	67.2 ± 29.4	97.4 ± 46.7	$p < 0.001$ HC < SCD < MCI < AD
N T+ (%)	16 (25)	34 (34)	29 (60)	17 (81)	$p < 0.001$ HC/SCD < MCI/AD
MMSE	29.4 ± 0.83	29.2 ± 1.10	27.0 ± 1.52	24.3 ± 3.39	$p < 0.001$ HC > SCD > MCI > AD
Memory factor	0.65 ± 0.42	0.41_1 ± 0.58	−0.72 ± 0.62	−1.74 ± 0.61	$p < 0.001$ HC > SCD > MCI > AD

Abbreviations: AD = Alzheimer disease; ANOVA = analysis of variance; APOE ε4 = carriers of apolipoprotein E ε4 allele; T+ ~ p-tau >57 pg/mL; A+~ Aβ42/40 < 0.09; HC = healthy control; MMSE = Mini-Mental State Examination; MCI = mild cognitive impairment; SCD = subjective cognitive decline.
Unless otherwise stated, variables denote mean ± SD. Subscripts denote the number of missing values. Percentages are based on the number of valid cases; statistics show p values for the effect of group in ANOVAs or χ^2 tests (without additional covariates). Significant differences (at $p < 0.05$ uncorrected) for paired group comparisons are further denoted.

CERAD word-list episodic memory tests. Finally, only participants with a clinical diagnosis of mild AD[21] obtaining ≥18 points on the Mini Mental State Examination (MMSE) were included in DELCODE.

All participants were aged 60 years or older, fluent speakers of German, and had a relative who completed informant questionnaires. Exclusion criteria are described in the eMethods (links.lww.com/WNL/C105).[20]

Standard Protocols, Approvals, Registrations, and Patient Consents

The study protocol was approved by Institutional Review Boards of all participating study centers of the DZNE.[20] The process was led and coordinated by the ethical committee of the medical faculty of the University of Bonn (trial registration number 117/13). All participants provided written informed consent.

Cognitive Measures

We assessed memory performance by a latent cognitive factor score for learning and memory, derived from a confirmatory factor analysis from the extensive DELCODE neuropsychological battery (see eMethods, links.lww.com/WNL/C105) as described previously.[22]

CSF Measures

Procedures of CSF acquisition, processing, and analysis in the DELCODE cohort have been previously described.[20] Here, we focused on Aβ42/Aβ40 and phospho-tau181 (p-tau) CSF measures of Aβ (A) and tau pathology (T) as well as on the ratio CSF-Aβ42/p-tau as a single continuous measure of AD pathology. For supplementary group analyses, we categorized individuals according to the AT(N) biomarker classification system[23] based on cutoffs reported elsewhere.[20] (T+ ~ p-tau >57 pg/mL; A+ ~ Aβ42/40 <0.07).

(f)MRI Acquisition and fMRI Task

The T1-weighted structural image (1 mm^3 isotropic resolution) and fMRI data (3.5 mm isotropic resolution) were acquired at 3T, and sequences are reported in the eMethods (links.lww.com/WNL/C105).[20,24] Subjects performed a modified version of an incidental encoding task lasting about 9 minutes originally reported in another study.[24,25] Participants were presented with 88 novel scenes (half outdoor/half indoor) and 44 repetitions of 2 prefamiliarized scenes (1 indoor and 1 outdoor, presented 22 times each) using Presentation (Neurobehavioral Systems Inc). Participants were instructed to classify each scene as indoor or outdoor by pressing a button. Each scene presentation lasted 2500 ms, with an optimized intertrial jitter for statistical

efficiency. After a retention delay of 60 minutes, memory was tested with a 5-point recognition-confidence rating for the former novel images and new distractor scenes to assess successful incidental encoding. The current study focused on the novel >familiar contrast, which is independent of later memory performance, owing to the poor recognition-memory performance in the MCI/AD dementia groups. Associations between fMRI task-memory performance, hippocampal activity, and Aβ × tau interactions in the groups without dementia with CSF data have been examined by other studies.[24,26]

fMRI Preprocessing and First-Level Analysis

Preprocessing included slice-time correction, unwarping, realignment, and spatial smoothing with an isotropic Gaussian kernel of full width at half maximum (FWHM) 6 mm in SPM12 (r7771, Wellcome Trust Centre for Human Neuroimaging). First-level general linear models (GLMs) were calculated in native space using a hemodynamic response function with a 128-second high-pass filter, no global scaling. The first-level GLM included a maximum of 12 regressors of interest: 5 regressors for novel images ordered by subsequent confidence rating plus 1 regressor for the familiar image, each separately for indoor and outdoor images. Six motion regressors from the realignment process were also included. Familiar and novel stimuli (irrespective of confidence rating) were used to calculate a novelty contrast (novel >familiar).

Spatial Normalization to Template Space

T1-weighted images were processed using SPM and CAT-Toolbox (r1615, Structural Brain Mapping Group, Jena University Hospital, neuro.uni-jena.de/cat/). First, a correction for field inhomogeneities was applied. Thereafter, images were segmented into gray matter (GM), white matter, and CSF maps that were iteratively warped to generate a study-specific template in Montreal Neurological Institute (MNI) space using the Geodesic Shooting approach.[27] The first-level fMRI contrast images from presmoothed data were warped to MNI space using the obtained deformation fields and smoothed further by 2 mm FWHM. The spatially normalized fMRI novelty contrast images (further referred to as activity) were used for (1 region-based analyses using a priori defined regions of interests (ROIs) and (2) whole-brain voxel-wise analyses as outlined below. Activation (deactivation) refers to positive (negative) contrast values (activity). GM tissue maps were warped and modulated by the Jacobian determinant to enable voxel-based comparisons of local GM volume across subjects and smoothed with 6 mm FWHM.

ROI-Based Measures

Based on previous fMRI studies showing increased task-related activation in early preclinical stages of AD, we focused on 3 ROIs: entorhinal cortex,[8] hippocampus,[7] and precuneus.[5] Although the entorhinal cortex and hippocampus within the MTL show early tau pathology, the precuneus shows early Aβ burden.[28] The postcentral gyrus was used as a control region because it is only affected by AD pathology in the latest stages of AD.[29] ROIs were derived from the Desikan-Killiany atlas[30] in FreeSurfer 6.0 (surfer.nmr.mgh.harvard.edu/). To extract regional activity in MNI space, we used the FreeSurfer MNI aparc + aseg.mgz template and resliced ROIs to echo-planar imaging space. We also derived corresponding regional volumes by segmentation of the individual T1 images with FreeSurfer, which were adjusted for total intracranial volume. Bilateral means were calculated because we had no hemisphere-specific hypotheses. For ROI analyses, we excluded 13 subjects with extreme activity values (eMethods, links.lww.com/WNL/C105), leaving 486 subjects of whom 224 had CSF data (122 A−T−, 10 A+T−, 59 A+T+, and 33 A−T+).

Statistical Analyses

Cognitive, demographic, and ROI data were analyzed using SPSS 24 (IBM). Demographic variables were compared between groups with analysis of variance (ANOVAs), *t* tests, and χ^2 tests. Differences in activity were assessed in ROI-based and whole-brain analyses, as described below. For all analyses, if not otherwise stated, we included the fMRI site (n = 8), age, sex, and years of education as covariates.

ROI-Based Analyses

We performed 3 complementary types of analyses to test for an inverted U-shaped pattern of activity across the continuum from HC to at-risk stages for AD to AD dementia. First, we assessed differences in activity between diagnostic groups, hypothesizing a pattern of increased activity in participants with subjective or mild objective memory deficits followed by similar/decreased activity in participants with AD dementia relative to HCs. To test this hypothesis, we computed a multivariate analysis of covariance (MANCOVA) to predict activity in the 3 a priori–defined ROIs by diagnostic group. Significant MANCOVAs were followed by univariate ANCOVAs for each ROI and post hoc *t* tests using Bonferroni-Holm correction for multiple comparisons (1-tailed *p* values, 5 group comparisons to test the U-shaped pattern AD < HC < SCD/MCI). Furthermore, a univariate ANOVA was performed for a control region, the postcentral gyrus, in which we did not expect activity differences between groups. Second, we performed supplementary nonparametric Spearman rank correlations between activity in each ROI and diagnostic groups recoded by the order of expected activity increases. Third, the nonlinear pattern of activity increases and decreases with increasing memory deficits was tested by quadratic models using memory performance as a continuous measure instead of diagnostic groups. The Akaike information criterion (AIC) was used to determine which model (e.g., linear or quadratic) better fit the data while also accounting for model complexity. A smaller AIC value indicates a better model.

In a next step, we tested our hypothesis that the pattern of increased activity in AD-risk stages followed by relatively decreased activity in AD dementia would be explained by AD biomarkers or measures of atrophy (in a quadratic manner). To do so, we performed 3 sets of analyses. First, we tested whether activity differences between diagnostic groups were accounted for by measures of pathology or atrophy by including measures of CSF Aβ42/40, p-tau, Aβ42/p-tau, or ROI volume as covariates in our ANCOVAs. Second, we ran

regression models (without diagnostic group as factor) to directly test for a U-shaped relationship by predicting ROI activity by continuous measures of Aβ42/40, p-tau, Aβ42/p-tau, or volume including linear and quadratic effects. Third, group comparisons also assessed the effect of AD pathology on activity by binary categorization of individuals according to the AT-biomarker classification scheme hypothesizing increased activity in the presence of abnormal Aβ levels followed by decreased activity when also CSF p-tau becomes abnormal (A+T+ < A−T− < A+T−). We excluded the A−T+ with suspected non-AD pathologic change from the analysis because we had no hypothesis for this group. Finally, we explored in supplementary analyses whether activity differences were related to APOE ε4 status, which has been related to increased activity in previous fMRI studies.[31]

Whole-Brain Voxel-Wise Second-Level Analyses

Complimentary to our ROI analyses, we performed whole-brain exploratory analyses to assess the spatial pattern of activity deviations to test the same hypotheses for effects of diagnostic status and AD pathology using continuous measures and categorical AT staging on novelty responses. ANCOVAs with planned post hoc independent samples *t* tests were performed in statistical parametric mapping (SPM) 12. Results are family-wise error (FWE) corrected at the cluster level with $p_{cluster}$ <0.05 using a cluster-forming threshold of p_{voxel} <0.005 (uncorrected). For this purpose, an explicit whole-brain GM mask excluding the cerebellum and basal ganglia was applied.

Similarly, voxel-based morphometry (VBM) analyses were conducted to examine the patterns of local morphologic differences in terms of GM volumes in the same groups and to explore whether the pattern of activity alterations is seen in areas of reduced GM, and whether functional alterations precede or follow reduced GM volume, which could indicate compensatory mechanisms. Total intracranial volume was included as an additional covariate. VBM results are reported at $p_{cluster}$ <0.05 using FWE cluster-level correction and a cluster-forming threshold of p_{voxel} <0.001 (uncorrected).

Data Availability

Data, study protocol, and biomaterials can be shared with partners based on individual data and biomaterial transfer agreements.

Results

Participants and Demographics

Demographics are reported in Table 1. Diagnostic groups significantly differed in age, years of education, sex, APOE ε4 status, Aβ42/40, p-tau, MMSE, and memory performance factor (see Table 1 for statistics and pairwise group comparisons). Compared with HC, the SCD group was significantly older by 1 year, included fewer females, had more APOE ε4 carriers, had higher CSF p-tau concentrations, and had worse cognition (as reported previously[22]).

Differences in Regional Activity Across the Clinically Defined AD-Risk Spectrum

We conducted MANCOVAs to examine diagnostic group differences in activity in the 3 a priori ROIs (Figure 1A). The effect of diagnostic group was significant (Pillai trace = 0.044, $F(9, 1416) = 2.37$, $p = 0.012$; partial eta^2 = 0.015, power = 0.921). Follow-up univariate ANCOVAs revealed a significant effect of diagnostic group on activity in the hippocampus ($F(3,472) = 2.79$, $p = 0.040$) and precuneus ($F(3,472) = 4.31$, $p = 0.005$). The group effect in the entorhinal cortex was not significant but trending ($F(3,472) = 2.57$, $p = 0.054$). Univariate ANCOVAs on activity in the postcentral gyrus as a control region showed no significant effect of group ($F(3,472) = 2.32$, $p = 0.0745$). Post hoc *t* tests (Table 2) showed reduced hippocampal activity in the AD dementia group relative to MCI, SCD, and HC but no difference between SCD or MCI and HC.

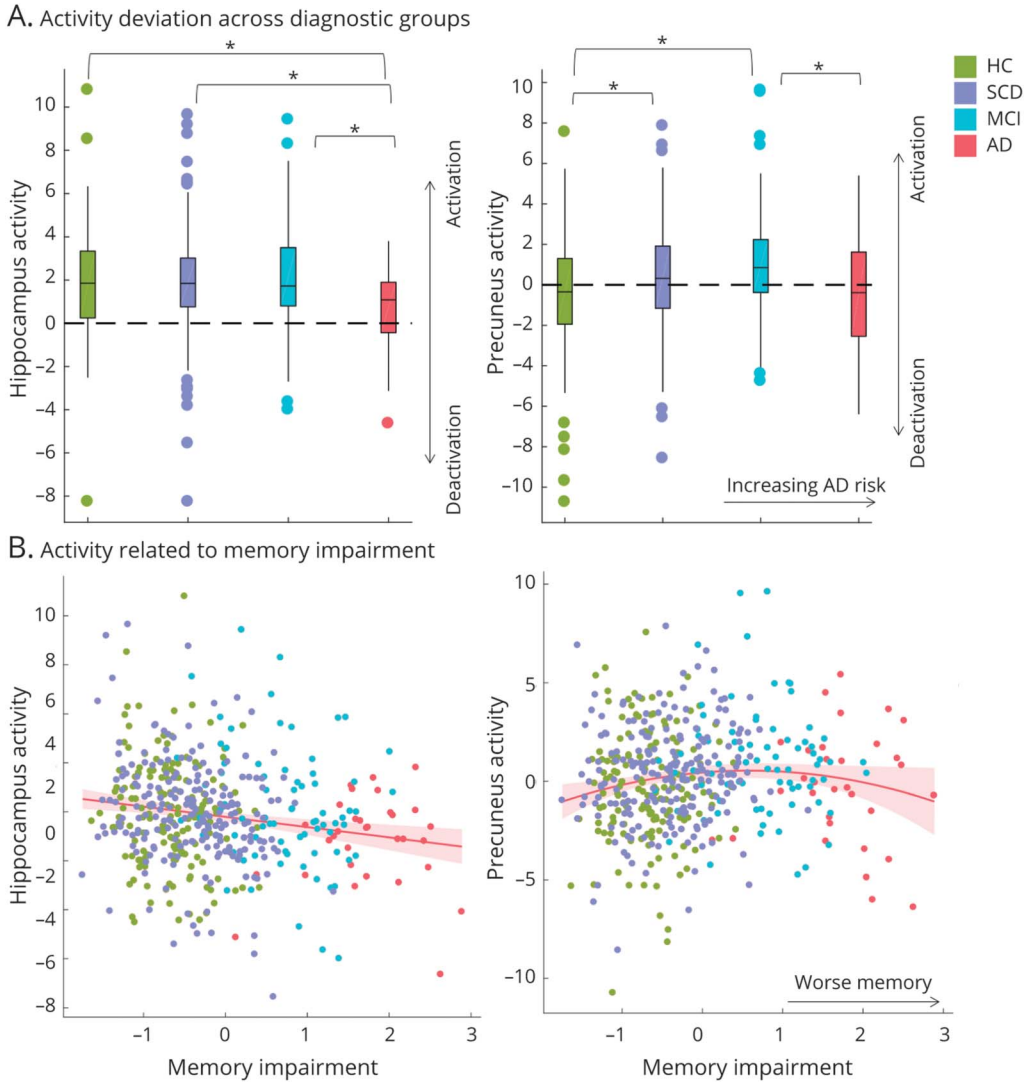
In the precuneus, novelty-related activity was higher in the MCI group compared with HC and compared with AD dementia. Precuneus activity was also higher in the SCD group relative to HC. Precuneus activity did not significantly differ between the AD dementia group and HC. Thus, activity in the precuneus follows an inverted U-shaped pattern with increased activity in SCD and MCI, but similar activity levels as HC in the AD dementia group, which was further confirmed by supplementary Spearman correlations between ROI activity and diagnostic group ranked by expected activity increases (eResults 1, links.lww.com/WNL/C105).

Third, evidence for a nonlinear pattern of precuneus activity deviations with increasing cognitive impairment was provided by quadratic models using the memory factor score as a continuous measure instead of diagnostic groups (Table 3 and Figure 1B). Although lower hippocampal activity was linearly predicted by higher memory impairment, precuneus activity followed a quadratic pattern, that is, increasing followed by decreasing activity with advancing memory deficits. Model comparisons (Table 3) supported that the linear model was favorable for the hippocampus (ΔAIC ~2) but the quadratic model for the precuneus (ΔAIC ~3). We further noted that higher precuneus activity was significantly related to more memory deficits (ascending branch of the inverted U) when excluding the patients with dementia ($r = -0.126$, $p = 0.007$).

Relationship Between Regional Activity and AD Biomarkers and APOE ε4 Status

We next tested our hypothesis that the inverted U-shaped pattern of precuneus activity would be accounted for by AD pathology or measures of atrophy (eTable 1, links.lww.com/WNL/C105). In the subsample of individuals with CSF markers, the effect of diagnostic group on precuneus activity remained significant with similar group differences as seen in the full sample (eTable 2), whereas the group effect on hippocampal activity was only marginal. When covarying for CSF biomarkers (eTable 1), the effect of diagnostic group on precuneus activity remained significant. Activity in the different diagnostic groups separated by A- or T-biomarker status is further displayed in eFigure 1.

Figure 1 Differences in Region-Specific Novelty Activity Between Diagnostic Groups and With Increasing Memory Impairment



(A) Mean fMRI activity (raw betas) for the novelty contrast (novel—familiar scenes) in the hippocampus and precuneus across diagnostic groups. Hippocampal activity was reduced in AD relative to all other groups. Precuneus activity followed an inverted U-shaped pattern with more advanced risk stages for AD. *Significant group differences surviving Bonferroni-Holm correction for the 5 group comparisons of interest (AD < HC < SCD/MCI) with $p < 0.05$. (B) Activation deviations related to memory performance as a continuous measure of clinical impairment. The memory factor score was inverted (*−1) to represent memory impairment for display purposes. The hippocampus showed a linear but the precuneus a quadratic pattern of activity deviations with increasing memory impairment. AD = Alzheimer disease dementia; HC = healthy control; MCI = mild cognitive impairment; SCD = subjective cognitive decline.

Subsequent regression models testing linear and quadratic (U-shaped) effects of AD pathology on activity directly are summarized in Table 3. Here, we found that hippocampal activity was significantly predicted by Aβ42/Aβ40 in a quadratic rather than in a linear manner (Table 3 and eFigure 2A, links.lww.com/WNL/C105), whereas linear or quadratic effects of p-tau or Aβ42/p-tau were not significant (all p values >0.055). Precuneus activity was not predicted by Aβ42/Aβ40 (Table 3), p-tau or Aβ42/p-tau, neither in models with linear nor quadratic effects (all p values >0.5). A MANCOVA on the effect of AT-biomarker groups (excluding A−T+) on activity revealed no significant multivariate effect of group (Pillai trace = 0.048, $F(6, 354) = 1.46$, $p = 0.190$; partial eta^2 = 0.024, power = 0.567). ROI-specific activity separated by the AT-biomarker group is depicted in eFigure 2b.

Similarly, we tested whether activity differences between diagnostic groups were explained by differences in regional volume. The effect of diagnostic group on hippocampal activity and precuneus remained significant when covarying for regional volume (eTable 1, links.lww.com/WNL/C105). Subsequent regression analyses did not reveal a significant linear or quadratic effect of ROI-specific volume on hippocampal or precuneus activity. However, we found a trend quadratic effect for the hippocampus ($F(1,473) = 3.84$, $p = 0.051$).

Table 2 Group Comparisons for Regional Activity Differences Between Diagnostic Groups in the Whole Sample

Group comparison	Mean difference	SE	P_{uncorr} (1 tailed)	P_{corr} (1 tailed)	*p* Value rank (lowest to highest)
Hippocampal activity					
MCI > AD	1.345	0.459	0.002	0.01[a]	1
SCD > AD	1.156	0.414	0.0025	0.01[a]	2
HC > AD	1.099	0.424	0.005	0.015[a]	3
MCI > HC	0.246	0.302	0.2085	0.417	4
SCD > HC	0.056	0.228	0.4025	0.4025	5
Precuneus activity					
MCI > HC	1.279	0.368	0.001	0.003[a]	1
MCI > AD	1.319	0.559	0.010	0.038[a]	2
SCD > HC	0.618	0.278	0.0135	0.041[a]	3
SCD > AD	0.658	0.504	0.096	0.192	4
HC > AD	0.040	0.516	0.469	0.469	5

Abbreviations: AD = Alzheimer disease; HC = healthy control; MCI = mild cognitive impairment; SCD = subjective cognitive decline; SE = standard error.
Post hoc *t* tests (after significant univariate ANCOVAs) in the whole cohort tested whether novelty activity differed between AD < HC < SCD/MCI (5 group comparisons). Corrected *p* values denote Bonferroni-Holm correction.
[a] *p* =<0.05.

Partial correlations between brain activity, AD biomarkers, and brain volume are further reported in eTable 3 (links.lww.com/WNL/C105). In summary, AD biomarkers or regional volume did not account for the inverted U-shaped pattern of precuneus activity across groups. Supplementary analyses showed that the effect of diagnostic group on precuneus

Table 3 General Linear Models Predicting Regional Activity by Linear and Quadratic Effects of Memory or Aβ

Predicted variable	Model	Model AIC	Model F	Model p	Predictor	*B*	SE	*T*	*p* Value	Partial η^2	Observed power
Hippocampus activity	Linear	769	1.808	0.050	Memory	0.35	0.13	2.62	0.009[a]	0.014	0.742
Hippocampus activity	Quadratic	771	1.655	0.074	Memory	0.34	0.17	1.95	0.052	0.008	0.495
					Memory^2	−0.01	0.11	−0.12	0.905	0.000	0.052
Precuneus activity	Linear	966	1.556	0.109	Memory	−0.23	0.17	−1.39	0.164	0.004	0.285
Precuneus activity	Quadratic	963	1.827	0.042	Memory	−0.53	0.21	−2.45	0.015[b]	0.013	0.686
					Memory^2	−0.29	0.13	−2.16	0.031[b]	0.010	0.578
Hippocampus activity	Linear	374	0.813	0.627	Aβ42/40	7.02	5.69	1.24	0.218	0.007	0.233
Hippocampus activity	Quadratic	371	1.176	0.302	Aβ42/40	2.93	5.92	0.50	0.622	0.001	0.078
					Aβ42/40^2	−454.59	203.43	−2.23	0.026[b]	0.023	0.604
Precuneus activity	Linear	953	1.739	0.067	Aβ42/40	−4.28	6.55	−0.65	0.514	0.002	0.100
Precuneus activity	Quadratic	955	1.625	0.086	Aβ42/40	−5.68	6.90	−0.82	0.412	0.003	0.130
					Aβ42/40^2	−155.05	236.81	−0.66	0.513	0.002	0.100

Abbreviation: AIC = Akaike information criterion; SE = standard error.
Regression models tested whether novelty-related fMRI activity in the hippocampus and precuneus follows an inverted U-shaped curve across disease severity defined by memory performance (memory factor score) or the Aβ42/40 ratio as a marker of early AD pathology. To do so, models were run first including a linear term of the predictor and second adding a quadratic term. Note that predictor variables were mean centered beforehand and then squared. Additional covariates of no interest in all models included age, sex, years of education, and site. Only sex was a significant covariate in the linear model on precuneus activity predicted by memory (results for covariates not shown).
[a] *p* = <0.01.
[b] *p* = <0.05.

activity remained also significant when covarying for APOE ε4 status (eTable 2, links.lww.com/WNL/C105).

Whole-Brain Analyses (fMRI and VBM)

In HC, positive activity (i.e., activation) during processing of novel vs familiar scenes was found in frontal regions, the MTL, and occipital regions bilaterally (Figure 2A). In contrast, deactivation (novel < familiar) was evident in the lateral temporal cortex, precuneus, posterior cingulate, angular, and middle frontal gyrus (Figure 2B), covering parts of the default mode network (DMN[32]).

When assessing activity differences between diagnostic groups, significantly higher activity was found in the precuneus of the SCD and MCI groups compared with HC, confirming our ROI analyses (Figure 3, A and B). Notably, higher precuneus activity represented reduced novelty-related deactivation (Figure 2A). No significant decrease in activity was found in any diagnostic group compared with HC.

Morphometric analyses revealed reduced GM volume in the MCI group compared with HC in the hippocampus, amygdala, lateral orbital gyrus, middle frontal gyrus, angular gyrus, and precuneus (Figure 3B) but no volume differences between the SCD and HC. As depicted in Figure 3, regions of atrophy in the MCI group overlapped partly with regions of higher novelty-related activity, particularly in the precuneus. There were no significant associations between novelty-related activity and continuous measures of p-tau or Aβ42/40 and no differences between AT-biomarker groups when applying cluster-level correction.

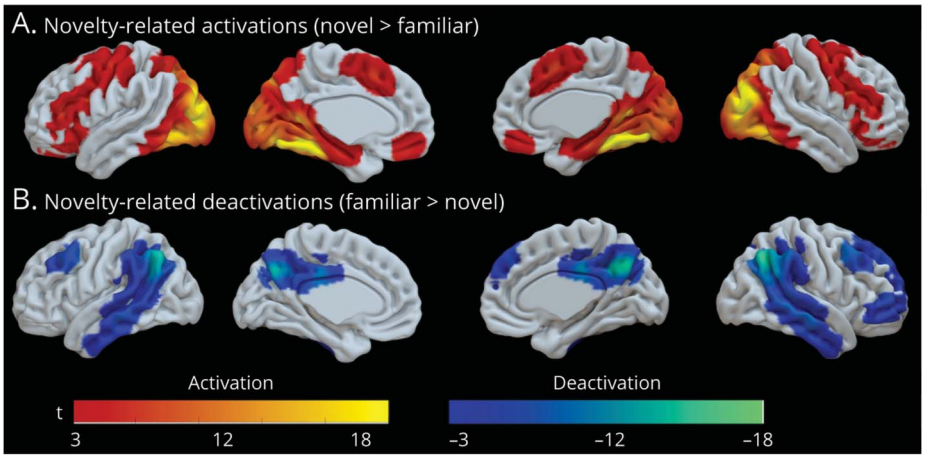
Discussion

The present study investigated how novelty-related fMRI activity in the MTL and the precuneus deviates with increasing clinical risk for AD in a large and well-characterized cohort. In the precuneus, we observed an inverted U-shaped pattern of activity alterations with higher fMRI activity in the precuneus of participants with SCD and MCI compared with HCs and lower activity in patients with AD dementia relative to MCI. This quadratic pattern of activity deviations with increasing memory deficits was further confirmed by regression analyses.

Higher precuneus activity in our study corresponded to a reduced deactivation during processing of novel vs familiar images. The precuneus is the most interconnected node of the DMN,[33] and our results are in line with previous studies reporting reduced task-related deactivation of DMN regions in at-risk stages of AD ranging from cognitively normal APOE ε4 carriers to patients with MCI.[31,34] A few previous studies have examined fMRI task activity in SCD. For example, increased activity in the prefrontal cortex[18,19] compared with HC was suggested to be compensatory in memory and attention tasks. A recent study[17] in 28 SCD-plus individuals (SCD with smaller hippocampal volumes compared with HC and/or with APOE ε4 positivity) observed increased encoding activity in the hippocampus, precuneus, temporal, and superior parietal cortex. Moreover, left superior parietal activity followed an inverted U-shaped pattern with proxies of pathology (i.e., atrophy and cognition). Together with our findings in a much larger sample, this suggests that fMRI activity is increased in individuals with SCD and MCI most prominently in posterior midline brain regions, which can be measured with different fMRI paradigms. In contrast to the precuneus, hippocampal activity was not increased in individuals with SCD or MCI relative to HC but was reduced in patients with AD dementia relative to all other groups.

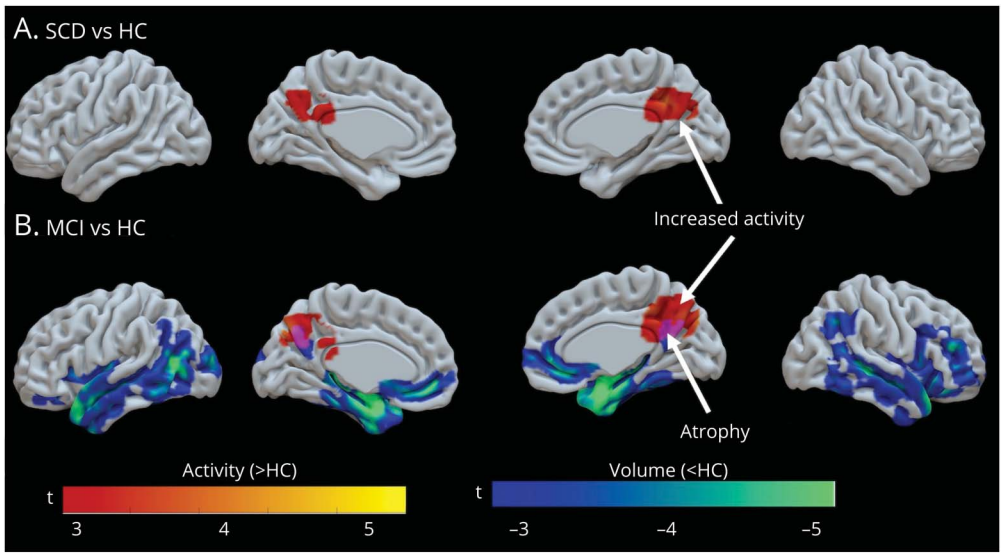
When considering AD biomarkers, most previous studies have linked increased task activity in HC and MCI to abnormal levels of Aβ using PET imaging.[5-8] More recently, with the advent of tau-specific PET tracers, a few studies in HCs have suggested that increased task activity in the hippocampus[9,10,35] and posterior-midline[9] regions is more

Figure 2 Whole-Brain Voxel-Wise Novelty Activation Pattern in Cognitively Normal Older Adults



(A) Higher fMRI activity for novel than familiar scenes in cognitively normal older adults (N = 163) is seen in a frontal network, the supplementary motor cortex, the medial temporal lobe including the hippocampus and parahippocampal cortex, and the occipital regions bilaterally. (B) Lower fMRI activity for novel compared with familiar scenes (i.e., novelty-related deactivation) is seen in the posterior midline, lateral temporal, temporo-parietal, and frontal regions. Results are depicted at <0.05 (FWE, cluster-level, cluster-forming threshold $p = 0.001$).

Figure 3 Whole-Brain Voxel-Wise Pattern of Increased Activity and Reduced GM Volume in SCD and MCI



Two-sample *t* tests revealed higher novelty activity in SCD (A) and MCI (B) relative to cognitively normal older adults in the precuneus (red colors), a region usually deactivating for novel relative to familiar scenes (Figure 2B). fMRI results are depicted at p_{voxel} <0.005 (uncorrected), $p_{cluster}$ <0.05 FWE corrected. Reduced gray matter volume was seen in the MCI only (B) comprising temporal lobe, frontal regions, and the precuneus (blue colors). Voxel-based morphometry results are depicted $p < 0.05$ (FWE, cluster-level, cluster-forming threshold $p = 0.001$). MCI = mild cognitive impairment; SCD = subjective cognitive decline.

strongly associated with temporal lobe tau than with Aβ burden. Together, these findings are in line with animal models in which Aβ or tau pathology has been linked to higher neural excitability.[36,37] However, in contrast to these previous studies, we did not find a relationship between CSF AD biomarkers and increased precuneus activity, neither when considering continuous levels of CSF Aβ42/40 or p-tau nor with categorical AT-staging. We note that only half of our sample provided CSF samples. However, despite the reduced sample size, we found similar group differences in precuneus activity as observed in the full sample, which remained significant when covarying for AD biomarkers or atrophy. Although further analysis in a bigger sample enriched for abnormal AD biomarkers in HC and SCD individuals would increase the power to detect such a relationship, the null findings observed here are unlikely to be explained solely by the lack of power. Hyperactivity in posterior-midline regions could be related to early MTL tau[9,35] pathology that is unlikely to be detected with CSF biomarkers. According to the cascading network model,[38] high MTL tau burden might be related to a compensatory load shift to the posterior DMN (that might relate to fMRI activity and connectivity changes), which fails before Aβ plaques are measurable. It appears to initiate a connectivity cascade that continues throughout the AD spectrum. Furthermore, at early stages of the disease, increased activation in the precuneus could represent a marker of a behavioral or clinical phenotype[39] that can be observed even before pathologic changes become measurable. In the presence of AD dementia, we observed reduced activity in the hippocampus. Regression models further suggested that hippocampal activity followed an inverted U-shaped dependency pattern on Aβ pathology, where activity slightly increased with mildly increased Aβ burden and then declined at high levels of pathologic Aβ. Recent findings from the DELCODE cohort, focusing on Aβ and tau interactions on hippocampal novelty responses in individuals without dementia, suggest that Aβ pathology is permissive for tau-related hippocampal dysfunction.[26] Together, these findings highlight the presence of nonlinear region-specific relationships between AD-related pathology, fMRI activity, and memory impairment.

It is debated whether increased activity in at-risk stages of AD represents compensation for early AD pathology or brain atrophy, or whether aberrant activity might be directly driving protein accumulation and vice versa. On the one hand, greater hippocampal task activation has been related to a faster cognitive decline in MCI[40] and reduced cortical thickness.[1] On the other hand, a study on episodic memory encoding of scenes found increased task-positive activation in A+ compared with A– HC in the hippocampus and occipital regions that was linked to more detailed memories, in accordance with compensation.[12] In our study, increased precuneus activity in SCD and MCI was not linked to AD CSF biomarkers or brain volume. Moreover, higher precuneus activity was related to worse memory performance in the groups without dementia. Previous longitudinal studies have shown that worse memory in SCD and MCI at baseline is also related to an increased risk for conversion to AD dementia.[41] Whether compensatory or not, our results support previous studies showing hyperactivity in the precuneus as an early signature of memory impairment that could arise before AD pathology is detected in CSF biomarkers.

Our voxel-wise group comparisons of whole brain activity and GM volume further suggest that functional activity might

deviate from HC even without significant structural decline or cognitive impairment, as seen in the SCD group. In MCI, a diagnosis with higher conversion risk to AD,[42] the site of lower deactivation in the precuneus overlapped with regions of reduced GM volume, which additionally covered AD-typical regions of atrophy.[43] Individual differences in GM volume did not account for altered precuneus activity. Together, our results indicate that increased precuneus activity is not associated with GM loss. Our findings are in accordance with the hypothesized sequence that neural dysfunction precedes brain structural changes. Nevertheless, we note that altered precuneus activity might already reflect early neurodegeneration or synaptic damage not detectable with standard MRI.

Future studies will need to investigate what underlies and causes the increased novelty-related fMRI activity that we observed in SCD and MCI. We assume that the increased precuneus activity represents reduced deactivation during processing of novel stimuli compared with familiar stimuli.[5,35] However, this pattern could also reflect lower activation to familiar items in SCD and MCI compared with HC. The additional inclusion of a baseline condition could help to resolve this question. Furthermore, it is not clear whether increased fMRI activity represents aberrant neuronal activity or whether it also reflects altered microglia activity or vascular changes that affect the Blood-oxygen-level-dependent signal. Future studies, which further include measures of neuroinflammation and cerebral blood flow, will help to elucidate these questions. The additional assessment of brain metabolism via fluorodeoxyglucose-PET, which shows characteristic patterns of AD neurodegeneration earlier than MRI, could give further insight into the underlying mechanisms of altered fMRI activity. Although FDG data in SCD are scarce, 1 previous study found hypometabolism in the precuneus in SCD relative to HC.[44] Several other PET studies have reported a nonlinear pattern of metabolic changes across the AD continuum similar to fMRI findings, showing hypermetabolism in subjects with MCI or HCs with increased tau pathology[45-47] at low levels of Aβ but hypometabolism when Aβ becomes abnormal. Hyperactivity could be an early sign of subtle pathology that lasts until pathology is so advanced that the Blood-oxygen-level-dependent signal decreases. This might be coupled with changes in network connectivity that follow a similar nonlinear pattern of early hyperconnectivity, which has been also observed in the precuneus of individuals with SCD,[48] followed by hypoconnectivity and cortical network failure[38,49] when pathology and brain atrophy progress further toward AD.

This study has strengths and limitations. A major strength is the large SCD sample with more than 200 well-characterized individuals, of which about half had CSF measures of AD pathology. Moreover, the study included patients with MCI with and without abnormal AD biomarkers. A limitation is its cross-sectional nature, which allows only indirect inferences about activity changes with AD progression by comparing different groups. With the availability of follow-up fMRI and cognitive data, future studies will need to test whether precuneus activity increases with clinical progression and whether increased activity might serve as an early functional predictor of progression to AD.

In conclusion, our results highlight the nonlinearity of activity alterations that have to be considered when activity is used as an outcome measure, for example, in clinical trials. Although the drivers and consequences of fMRI hyperactivity in the precuneus are still to be determined, it might potentially serve as an early functional marker of pathologic changes observed in subjects at an increased risk for AD. Our findings further suggest that abnormally increased precuneus activity could be a potential biomarker to monitor early therapeutic interventions to reduce the risk to AD conversion, as has been proposed for hippocampal hyperactivation.[50] Although decreasing precuneus activity might be beneficial in diagnoses with an increased risk for cognitive decline, increasing its activity might be related to better cognitive performance in later stages of the disease. Moreover, as precuneus activity is apparent before brain atrophy, it might aid stratification in clinical trials for subjects at risk for cognitive decline.

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Disclosure

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Appendix 1 Authors

Name	Location	Contribution
Ornella V. Billette, PhD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Gabriel Ziegler, PhD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Merita Aruci, MSc	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

Appendix 1 *(continued)*

Name	Location	Contribution
Hartmut Schütze, PhD	Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Jasmin M. Kizilirmak, PhD	German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Anni Richter, PhD	Department of Behavioral Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Slawek Altenstein, Dipl.-Psych.	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Claudia Bartels, PhD	Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Frederic Brosseron, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Arturo Cardenas-Blanco, PhD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Philip Dahmen, MSc	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Peter Dechent, PhD	MR-Research in Neurosciences, Department of Cognitive Neurology, Georg-August-University Göttingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Laura Dobisch, MSc	Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Klaus Fliessbach, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Silka Dawn Freiesleben, MSc	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content

Appendix 1 *(continued)*

Name	Location	Contribution
Wenzel Glanz, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Doreen Göerß, MD	Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany	Drafting/revision of the manuscript for content, including medical writing for content
John Dylan Haynes, PhD	Bernstein Center for Computational Neuroscience, Charité—Universitätsmedizin, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Michael T. Heneka, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Ingo Kilimann, MD	Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany; German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Okka Kimmich, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Luca Kleineidam, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Christoph Laske, Phd	German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany; Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Andrea Lohse	Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Ayda Rostamzadeh, MD	Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Coraline Metzger, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany; Department of Psychiatry and Psychotherapy, Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Matthias H. Munk, PhD	German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany; Systems Neurophysiology, Department of Biology, Darmstadt University of Technology, Darmstadt, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Oliver Peters, MD	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Psychiatry, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Lukas Preis, MSc	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Psychiatry, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Josef Priller, MD	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Klaus Scheffler, PhD	Department for Biomedical Magnetic Resonance, University of Tübingen, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Anja Schneider, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Annika Spottke, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; Department of Neurology, University of Bonn, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Eike Jakob Spruth, MD	German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Alfredo Ramirez, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/Psychiatry, Bonn, Germany; Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Köln, Germany; Department of Psychiatry & Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, San Antonio, TX	Drafting/revision of the manuscript for content, including medical writing for content

Appendix 1 *(continued)*

Name	Location	Contribution
Sandra Röske, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Nina Roy, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Stefan Teipel, MD	Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany; German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Michael Wagner, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Jens Wiltfang, MD	German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany; Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany; Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal	Drafting/revision of the manuscript for content, including medical writing for content
Steffen Wolfsgruber, PhD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; University of Bonn Medical Center, Dept. of Neurodegenerative Disease and Geriatric Psychiatry/ Psychiatry, Bonn, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Renat Yakupov, PhD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Peter Zeidman, PhD	Wellcome Centre for Human Neuroimaging, London, UK	Drafting/revision of the manuscript for content, including medical writing for content
Frank Jessen, MD	German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany; Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Köln, Germany	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

Appendix 1 *(continued)*

Name	Location	Contribution
Björn H. Schott, MD	German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany; Department of Behavioral Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany; Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Emrah Düzel, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Anne Maass, PhD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C104.

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