The lower hippocampus global connectivity, the higher its local metabolism in Alzheimer disease

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ABSTRACT

Objectives: Based on the hippocampus disconnection hypothesis in Alzheimer disease (AD), which postulates that uncoupling from cortical inputs contributes to disinhibition-like changes in hippocampus activity, we suggested that in patients with AD, the more the intrinsic functional connectivity between hippocampus and precuneus is decreased, the higher hippocampal glucose metabolism will be.

Methods: Forty patients with mild AD dementia, 21 patients with mild cognitive impairment, and 26 healthy controls underwent simultaneous PET/MRI measurements on an integrated PET/MR scanner. ^{18}F-fluorodeoxyglucose-PET was used to measure local glucose metabolism as proxy for neural activity, and resting-state functional MRI with seed-based functional connectivity analysis was performed to measure intrinsic functional connectivity as proxy for neural coupling. Group comparisons and correlation analysis were corrected for effects of regional atrophy, partial volume effect, age, and sex.

Results: In both patient groups, intrinsic connectivity between hippocampus and precuneus was significantly reduced. Moreover, in both patient groups, glucose metabolism was reduced in the precuneus (AD < mild cognitive impairment < controls) while unchanged in the hippocampus. Critically, the lower connectivity between hippocampus and precuneus was in patients with AD dementia, the higher was hippocampus metabolism.

Conclusion: Results provide evidence that in patients with AD dementia, stronger decrease of intrinsic connectivity between hippocampus and precuneus is linked with higher intrahippocampal metabolism (probably reflecting higher neuronal activity). These data support the hippocampus disconnection hypothesis, i.e., uncoupling from cortical inputs may contribute to disinhibition-like changes of hippocampal activity with potentially adverse consequences on both intrahippocampal physiology and clinical outcome. *Neurology*® 2015;84:1956–1963

GLOSSARY

AD = Alzheimer disease; **ANCOVA** = analysis of covariance; **BOLD** = blood oxygen level–dependent; **CDR** = Clinical Dementia Rating; **DMN** = default mode network; **FDG** = ^{18}F-fluorodeoxyglucose; **FDR** = false discovery rate; **FOV** = field of view; **iFC** = intrinsic functional connectivity; **MCI** = mild cognitive impairment; **MP-RAGE** = magnetization-prepared rapid-acquisition gradient echo; **PVC** = partial volume correction; **ROI** = region of interest; **rs-fMRI** = resting-state fMRI; **TUM** = Technische Universität München; **VBM** = voxel-based morphometry.

Hippocampus and retrosplenial cortex are central parts of the default mode network (DMN).[1] The DMN is an intrinsic brain network characterized by synchronous ongoing activity (i.e., intrinsic functional connectivity [iFC]). It is primarily affected in Alzheimer disease (AD) by β-amyloid and tau pathology, atrophy, and reduced iFC.[2–6] For example, β-amyloid pathology is already present in the retrosplenial cortex in the preclinical stages of AD,[4,5] while tau pathology and atrophy start in the transentorhinal region and hippocampus when first clinical symptoms appear.[7] Aberrant hippocampus activity has special characteristics in early AD. First, during

Supplemental data at Neurology.org

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memory processes, hippocampus activity has been demonstrated to be increased in mild cognitive impairment (MCI; a high-risk state for AD) while reduced in AD dementia,[8] with the degree of hyperactivity being linked with the level of structural parietal DMN degradation.[9] Since antiepileptic drugs normalize hippocampus hyperactivity with simultaneous memory improvement, hippocampus hyperactivity may represent an adverse consequence of AD instead of a beneficial compensation.[10] Second, beyond memory-related activity, synchronous ongoing intrahippocampal activity is progressively increased in MCI and AD dementia, with such increased local synchrony being associated with both patients' memory deficits and progressively reduced hippocampus iFC within the DMN.[11,12] Together, these findings suggest that hippocampus uncoupling from its main cortical input system may lead to disinhibition-like changes of intrahippocampal activity ("hippocampus disconnection hypothesis").[11–13] Accordingly, we hypothesized that the more iFC between hippocampus and precuneus is reduced, the higher intrahippocampal glucose metabolism (as a proxy for local hippocampus activity) may be found in patients with AD dementia.

METHODS

Overview. Participants (table) were scanned on an integrated PET/MR scanner using ^{18}F-fluorodeoxyglucose-PET (FDG-PET), resting-state fMRI (rs-fMRI), and structural MRI. FDG-PET was used to measure local glucose metabolism, which reflects local glutamate-dependent synaptic activity,[14,15] seed-based functional connectivity analysis of rs-fMRI data with a seed in the precuneus was used to assess coherent blood oxygen level–dependent (BOLD) activity between hippocampus and precuneus (i.e., functional connectivity between these regions),[16] and voxel-based morphometry (VBM) of structural MRI was used to estimate and control for regional gray matter volumes.[11,16,17] Both the whole hippocampus and precuneus seed were used for further region-of-interest (ROI)-based analysis. Specifically, ROI-averaged values for iFC, FDG metabolism, and VBM values were obtained for all subjects. Analysis of covariance (ANCOVA) was applied for group comparisons of local metabolism and iFC. Partial correlation analysis was performed between local hippocampus metabolism (FDG-PET) and iFC between hippocampus and precuneus (rs-fMRI). All across-subject analyses were controlled for effects of age, sex, regional gray mater volume, and partial volume effects. Further methodologic details and additional confirmatory analyses are presented in appendix e-1 on the *Neurology*® Web site at Neurology.org.

Subjects. Forty-two patients with mild AD dementia, 24 patients with MCI, and 26 healthy controls participated in this study. Patients were recruited from the Memory Clinic of the Department of Psychiatry and Psychotherapy, and healthy controls by word-of-mouth advertising. Examination of every participant included medical history, neurologic examination, informant interview (Clinical Dementia Rating [CDR]),[18] neuropsychological assessment (Consortium to Establish a Registry for Alzheimer's Disease),[19] and blood tests (for patients only). Criteria for MCI (CDR global = 0.5) included reported and neuropsychologically assessed cognitive impairments and largely intact activities of daily living, and excluded dementia.[20] Patients with AD dementia fulfilled criteria for mild dementia (CDR global = 1) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for AD and dementia.[21] Exclusion criteria were other neurologic, psychiatric, or systemic diseases (e.g., stroke, acute depressive episode, substance/drug abuse) or clinically remarkable structural MRI (e.g., cerebrovascular lesions) potentially related to cognitive impairment. Twelve patients with AD dementia/8 patients with MCI/6 healthy controls were treated for hypertension (β-blockers, ACE [angiotensin-converting enzyme] inhibitors, and calcium channel blockers), 10/6/3 for hypercholesterolemia (statins), 2/1/0 had diabetes mellitus, 6/3/0 received antidepressant medication (mirtazapine, citalopram), and 35/0/0 received cholinesterase inhibitors.

Standard protocol approvals, registrations, and patient consents. The study was approved and registered by the medical ethical board of Technische Universität München (TUM) in line with Human Research Committee guidelines of TUM. All subjects provided informed consent in accordance with the standard protocol approvals.

Data acquisition. Scanning was performed on an integrated Siemens Biograph mMR scanner (Siemens, Erlangen, Germany)

Table Demographic and clinical data of participants

	CON (n = 26)	MCI (n = 21)	AD dementia (n = 40)	*p* Value
Age, y, mean (SD)	55.58 (10.21)	66.81 (9.77)	70.83 (8.18)	0.056
Sex, female	9	14	20	0.109
Education, y	10.10 (1.51)	10.02 (1.69)	9.84 (2.03)	0.406
MMSE score, mean (SD)	29.51 (1.02)	26.93 (2.26)	22.03 (4.61)	0.000
CERAD total, mean (SD)	86.10 (8.13)	69.61 (10.44)	53.65 (12.58)	0.000

Abbreviations: AD = Alzheimer disease; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CON = healthy controls; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.
Analysis of variance, $p < 0.05$ as threshold of significance, except of sex (Kruskal-Wallis test).

capable of simultaneously acquiring PET and MRI data using the vendor-supplied 12-channel phase-array head coil. PET images, magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) T1-weighted anatomical images, and T2-weighted echo planar imaging MRI data were acquired using the following scanning parameters. PET: list-mode acquisition, 30 minutes after injection, 15 minutes acquisition time, 128 slices (gap 0.5 mm) covering the whole brain; field of view (FOV) 450 mm; matrix size 192 × 192; voxel size: 3.7 × 2.3 × 2.7 mm. Echo planar imaging: repetition time/echo time/α = 2.000 milliseconds (ms)/30 ms/90°; 35 slices (gap 0.6 mm) aligned to AC/PC covering the whole brain; FOV 192 mm; matrix size 64 × 64; voxel size 3.0 × 3.0 × 3.0 mm. Each measurement consists of 240 acquisitions in interleaved mode with a total scan time of 8 minutes, 08 seconds. MP-RAGE: repetition time/echo time/α = 2.300 ms/2.98 ms/9°; 160 slices (gap 0.5 mm) covering the whole brain; FOV 256 mm; matrix size 256 × 256; voxel size 1.0 × 1.0 × 1.0 mm.[22]

Preprocessing of imaging data. Preprocessing of PET and rs-fMRI data was adapted from previous studies[16,22] and is described in detail in appendix e-1. Briefly, after discarding the first 3 volumes, rs-fMRIs were realigned and coregistered with FDG-PET and T1-weighted images to create subject-specific multimodal datasets. These data were normalized to MNI (Montreal Neurological Institute) space. The rs-fMRI and PET images were resampled to the isotropic voxel size of 3 × 3 × 3 mm.

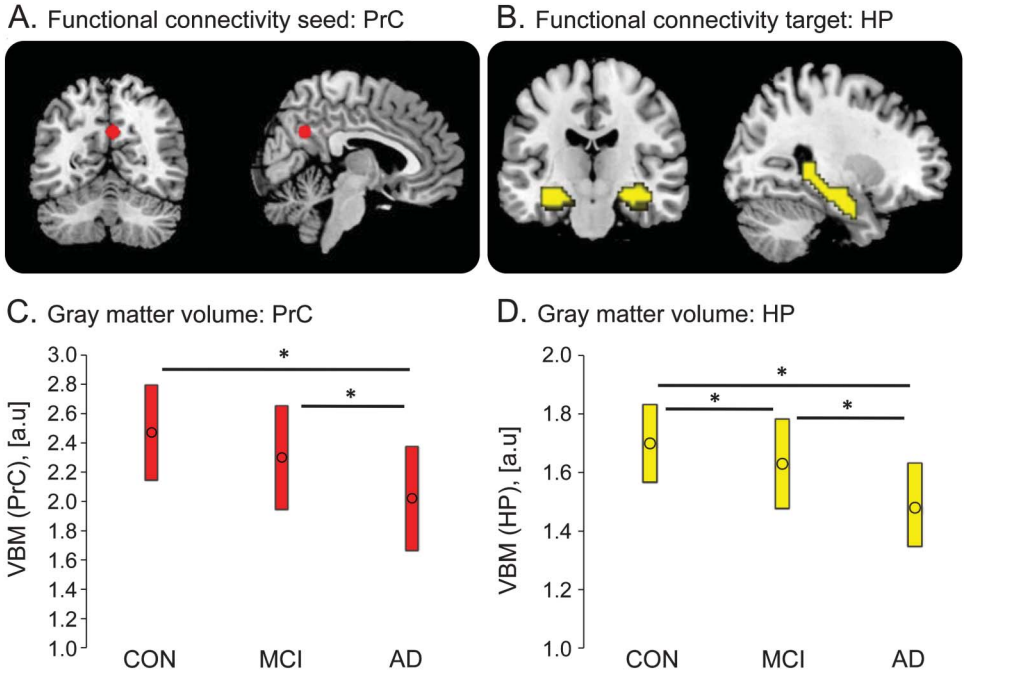
After smoothing (full width at half maximum gaussian kernel 8 × 8 × 8 mm), rs-fMRI data were intensively controlled for movement-induced artifacts[23] (i.e., excessive head movements, point-to-point translational and rotational movements, temporal signal-to-noise ratio) with no significant differences being found across groups (see appendix e-1).

VBM of structural MRI data was performed as described previously[11,16,17] and in appendix e-1.

rs-fMRI data analysis. For seed-based iFC analysis, we used MarsBaR (http://marsbar.sourceforge.net) to create a spherical ROI in the precuneus with center coordinates (7, −60, 21) and radius of 6 mm (figure 1A). This region was described by Sheline et al.[24] as that part of the DMN with highest levels of β-amyloid plaque load in persons at risk of AD; because of the critical role of β-amyloid pathology in AD, we suggested this region as surrogate for DMN changes in early AD and used it as representative for potential AD-induced iFC changes. After Butterworth bandpass-filtering of all voxel time courses for frequencies from 0.009 to 0.08 Hz, voxel time courses of the seed ROI were extracted and then reduced to ROI-representative time courses by singular value decomposition. We put each time course into the first-level fixed-effects general linear model in SPM8, and iFC analysis was performed for each subject. For each model, additional regressors for global gray matter, white matter, CSF BOLD signal, and 6 movement parameters (translational and rotational movement) were considered as regressors of no interest.

Subsequently, to define iFC of the precuneus with the hippocampus, we restricted our iFC model to a bilateral whole hippocampus mask, which was derived from WFU-PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas, version 2.5.2) (figure 1B). From precuneus and hippocampus ROIs, we extracted and

Figure 1 ROI based on resting-state functional connectivity



The study focused on the relationship between hippocampal local glucose metabolism and resting-state functional connectivity between precuneus (PrC) and hippocampus (HP) in patients with Alzheimer disease (AD) dementia or mild cognitive impairment (MCI), by the use of region-of-interest (ROI)-based approach. (A) The chosen ROI in the PrC is involved in the earliest stages of AD based on previous studies, and serves as seed for a seed-based functional connectivity analysis. (B) The bilateral whole HP region as a target based on WFU-PickAtlas. (C) Averaged voxel-based morphometry (VBM) revealed volume reductions in patients with AD dementia in the PrC and (D) HP (analysis of variance and post hoc *t* tests, $p < 0.05$). For such structural changes, subsequent analyses in correspondent functional connectivity and local metabolism have been controlled. CON = controls.

averaged values from single-subject iFC maps, FDG metabolism maps, and regional brain volume maps (as described below). Averaged values were fed into further group comparisons and correlation analyses in SPSS version 20 (IBM Corp., Armonk, NY). In the group comparisons, sex, age, and regional gray matter volumes were included as covariates of no interest.

PET data analysis. Preprocessed PET images were scaled by normalization of whole-brain FDG uptake values to cerebellar vermis FDG uptake[25] and were spatially smoothed using a gaussian kernel full-width at half-maximum of 12 mm. To correct FDG-PET data for a potential influence of partial volume effects, correction for partial volume effects (PVC) was performed by the use of segmented individual T1-weighted MRI in gray matter, white matter, and CSF. An algorithm implemented in the PMOD software package (PMOD Technologies Ltd., Adliswil, Switzerland) was applied for PVC, which has been suggested and described previously.[26,27] Afterward, from both ROIs, we extracted and averaged FDG metabolism values from the normalized FDG map of each subject. Group comparisons were performed of values obtained in the ROIs (hippocampus and precuneus) by the use of ANCOVA and corresponding least significant difference post hoc *t* tests including covariates of no interest (sex, age, and gray matter values of precuneus and hippocampus) with a threshold of $p < 0.05$.

Partial correlation analysis. To evaluate the expected relationship between intrahippocampus activity and hippocampus-precuneus iFC, partial correlation analyses were performed for the FDG metabolism in the hippocampus and precuneus and iFC between these regions. Partial correlation is defined here as the relationship between 2 different variables controlled for the influence of another variable such as age, sex, and regional gray matter volume.[28] We performed partial correlation analyses for each patient group separately, controlling for the mentioned covariates of no interest.

Control analyses. To control for critical methodologic steps, we performed additional analyses concerning the effect of PVC of PET data, voxel-wise vs ROI-based correlation between iFC and metabolism, and the effects of global gray matter signal regression (see appendix e-1).

RESULTS

Reduced gray matter volume in precuneus and hippocampus of patients with AD. VBM revealed that gray matter volume of hippocampus ($F_{4,86} = 17.58$, $p < 0.001$) and precuneus ($F_{4,86} = 6.98$, $p < 0.001$) was different across groups (ANCOVA controlled for age and sex, $p < 0.05$). Post hoc tests revealed atrophy for precuneus (controls > AD, $p < 0.001$; MCI > AD, $p = 0.001$) and hippocampus (controls > AD, $p < 0.001$; MCI > AD, $p < 0.001$; and controls > MCI, $p = 0.049$) in patients with AD (figure 1, C and D).

Patients had reduced intrinsic connectivity between precuneus and hippocampus. Restricted to the whole hippocampus region (figure 1B), ANCOVA on averaged iFC values demonstrated iFC difference across groups ($F_{5,86} = 3.40$, $p = 0.038$; controlled for age, sex, and hippocampus volume). Post hoc *t* tests revealed that compared with healthy controls, iFC was reduced for patients with AD dementia ($p = 0.017$) and MCI ($p = 0.043$), and there was no difference between patients with AD dementia and patients with MCI (figure 2A).

Patients had progressive hypometabolism in precuneus but unchanged metabolism in hippocampus. Averaged FDG-PET values were different across groups for the precuneus (ANCOVA, $F_{5,86} = 29.23$, $p < 0.001$) but not for the hippocampus. Post hoc *t* tests revealed progressive decrease of glucose metabolism in the precuneus along patient groups (controls > AD, $p < 0.001$; controls > MCI, $p = 0.006$; and MCI > AD, $p = 0.009$) (figure 2C.a). FDG metabolism in the hippocampus was unchanged across groups (figure 2B.a).

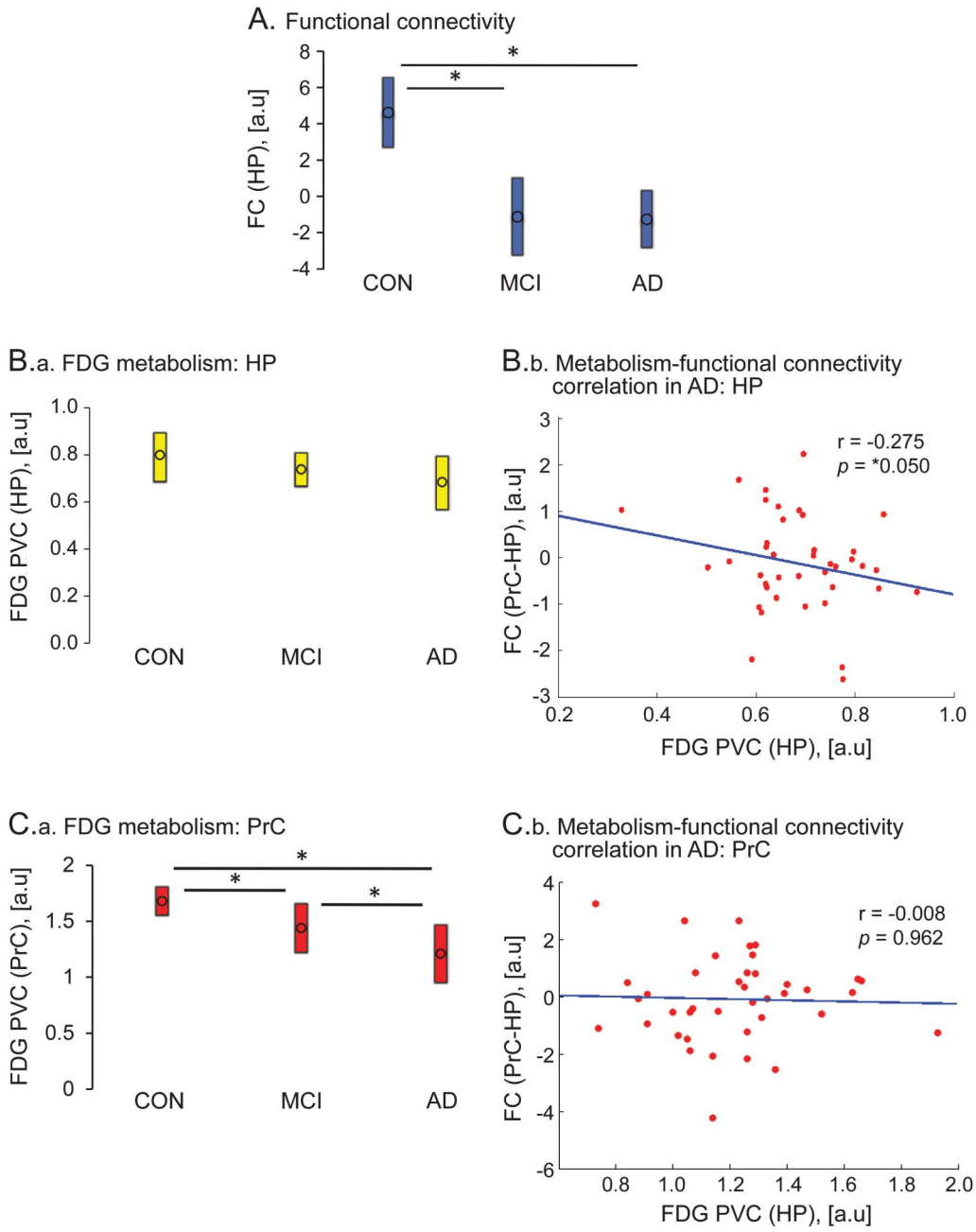
The lower extrahippocampal iFC, the higher hippocampus metabolism in patients with AD dementia. Of note, partial correlation analyses demonstrated that lower precuneus-hippocampus iFC is associated with higher FDG metabolism for the hippocampus, only in patients with AD dementia ($r = -0.275$, $p = 0.050$) (figure 2B.b). For patients with MCI, there was no such correlation ($R = -0.036$, $p = 0.44$). Furthermore, there was no association between iFC and FDG metabolism for the precuneus in both groups ($r = -0.008/0.326$, $p = 0.962/0.174$ for AD/MCI) (figure 2C.b).

Our finding was controlled for different methodologic factors. First, partial correlation between precuneus-hippocampus iFC and hippocampal non-PVC FDG values also demonstrated a similar link between iFC and FDG metabolism in patients with AD dementia ($r = -0.291$, $p = 0.041$) (figure e-1). Second, to confirm the results of the ROI-based approach, we performed a voxel-wise analysis (see methods and appendix e-1), which revealed that higher hippocampus FDG metabolism is linked with lower hippocampal iFC with both the angular gyrus (−48, −64, 40; cluster size = 157, *p* value false discovery rate [FDR]-corrected = 0.028) and the precuneus (0, −49, 52; cluster size = 141, *p* value FDR-corrected = 0.028) (figure e-2). Third, to control the effect of global gray matter regression on the association between hippocampus metabolism and connectivity, we performed alternative preprocessing, which was based on global brain signal regression derived from the white matter and CSF signal as described before.[29,30] We found almost identical results in patients with AD dementia as for the previous analysis based on global gray matter regression, i.e., the lower hippocampus connectivity, the higher its local metabolism ($r = -0.273$, $p = 0.051$; supplement 5 in appendix e-1).

DISCUSSION

To assess the relationship between precuneus-hippocampus iFC and intrahippocampal metabolism in early AD, we used simultaneous

Figure 2 Hippocampus and precuneus: Resting-state functional connectivity, local FDG metabolism, and their relationship in AD



(A) Reduced precuneus (PrC)-hippocampus (HP) functional connectivity (FC) in patients with mild cognitive impairment (MCI) and Alzheimer disease (AD) dementia (ANCOVA and post hoc *t* tests, $p < 0.05$). (B.a) Preserved fluorodeoxyglucose (FDG) metabolism in the HP of patients (ANCOVA, $p < 0.05$). (B.b) The lower PrC-HP FC, the higher HP metabolism in patients with AD dementia (partial correlation with additional covariates of age, sex, HP, and PrC gray matter volume; $p < 0.05$). (C.a) Progressively reduced FDG metabolism in the PrC of patients (ANCOVA, $p < 0.05$). (C.b) Not correlated PrC metabolism and PrC-HP FC in patients with AD dementia (partial correlation with additional variates of age, sex, HP, and PrC gray matter volume; $p < 0.05$). ANCOVA = analysis of covariance; CON = controls; PVC = partial volume correction.

rs-fMRI and FDG-PET in healthy controls and patients with MCI and AD dementia. We found that in patients with AD dementia, lower iFC between hippocampus and precuneus correlated with higher hippocampal metabolism, independent of hippocampal atrophy (figure 2B.b). This result provides evidence that functional disconnectivity of the hippocampus from regions outside the hippocampus is associated with increased intrahippocampal neuronal activity in patients with AD dementia. Complementing our previous findings, functional decoupling from the DMN appears to relate not only to increased synchrony[11] but also to an increased total amount of

hippocampal activity, supporting the hippocampus disconnection hypothesis of AD.

We hypothesized this result because of previously observed association between increased local and decreased global hippocampus resting-state functional connectivity in patients with AD.[11,12] To control for the influence of structural changes on the suggested relationship (figure 1, C and D), we applied a partial correlation approach, which accounts separately for influences of structural changes on local metabolism and global connectivity. Furthermore, neither partial volume effects on PET data (figure e-1) nor voxel-wise vs ROI-based approach (see figure e-2) influenced our finding. Finally, the result was also independent from age and sex for which we controlled our analysis.

While local metabolism was preserved in the hippocampus, patients' metabolism was progressively reduced in the precuneus (figure 2, B.a and C.a). Moreover, patients with AD dementia had atrophy in both hippocampus and precuneus (figure 1, C and D), in line with several previous studies.[31–33] These incongruent patterns of atrophy and metabolism indicate distinctive local activity changes for neocortical and hippocampal regions despite consistent volume reductions. We found reduced iFC between hippocampus and precuneus in both patient groups, in line with previous studies[2,34] (figure 2A). Of note, we observed that reduced hippocampus-precuneus intrinsic connectivity was linked with increased hippocampus metabolism. The observed link between iFC and FDG metabolism was specific for the hippocampus; no such relation was present for the precuneus (figure 2, B.b and C.b). This specificity indicates that in AD, reduced precuneus-hippocampus connectivity is associated with hippocampus metabolism rather than precuneus metabolism. To control whether the link between hippocampus connectivity and metabolism depends on the choice of the precuneus as a seed in the FC analysis, we repeated FC analysis but with the hippocampus as a seed region and found almost identical results (figure e-2). Furthermore, the association between hippocampus connectivity and metabolism was specific for patients with AD dementia, since it was not present in patients with MCI.

The inverse relation between hippocampus connectivity and intrahippocampus activity lends support for the hippocampus disconnection hypothesis.[11–13] This hypothesis states that cortical disconnection leads to disinhibition-like changes of intrahippocampal activity, which is characterized by loop-like glutamate-dependent activity flow from entorhinal cortex to subiculum, dentate gyrus, CA3, CA1, and then back to entorhinal cortex.[35] While disrupted precuneus-hippocampus iFC is a proxy for hippocampal disconnection, hippocampal FDG metabolism may reflect intrahippocampal glutamate-based activity.[14,15] Also in line with the disconnection hypothesis, a previous study found that hippocampal diffusion tensor imaging–based diffusivity (a potential surrogate for hippocampal structural connectivity) is inversely related to hippocampal FDG metabolism.[36] Remarkably, our current results contrast in 2 aspects with our previous finding of progressively increased intrahippocampal synchrony along MCI and AD dementia.[11] First, reduced hippocampus connectivity was found to be inversely linked with increased synchrony in our previous study, while for metabolic activity, we found the same relation but metabolism was not increased in patients relative to healthy controls; this discrepancy between increased synchrony and preserved metabolic activity may indicate that the total amount of glutamate-dependent activity is unchanged but distinctively organized. Second, inverse connectivity-metabolism correlation was found only in patients with AD dementia, while an inverse relationship between global connectivity and local synchrony was also found in patients with MCI previously. In our study, the additional presence of hippocampus atrophy appeared to be a precondition for the inverse connectivity-metabolism relationship. Our findings suggest that such relationship reflects substantial hippocampus reorganization. We speculate whether such atrophy might be due to lasting hypersynchrony of ongoing hippocampus activity. Such hypersynchrony, in turn, might be associated with increased levels of synchronized synaptic glutamate, which is suggested to be detrimental for cellular integrity and therefore relevant for atrophy ("synaptic excitatory toxicity hypothesis"[37,38]). However, one should note that beyond global disconnection, additional other local factors might contribute to impaired hippocampus physiology in AD. For example, a recent rodent study has shown that β-amyloid plaque–induced hyperactivity within the hippocampus[39] and tau pathology, which affects the hippocampus very early in AD,[7] is associated with the local network hyperexcitability in mice correspondent with seizure frequency.[40]

Moreover, across the spectrum of Alzheimer disease, we observed a decline in connectivity and metabolism from cognitively normal to MCI to dementia. Mean levels of metabolism were slightly lower in AD dementia compared to MCI but showing a broader variance (figure 2, B.a). This indicates a general degradation in both parameters with ongoing neurodegeneration. Exclusively within the AD dementia group, we found the negative correlation between hippocampal metabolism and connectivity (figure 2, B.b). This is consistent with the hippocampus disconnection hypothesis but it did not result in an increase of HP metabolism above MCI levels in AD dementia. Furthermore, our findings may be

limited to moderate stages of AD and the observed phenomenon may disappear in later stages of disease.

Taken together, the current study provides evidence that in patients with AD dementia, a stronger decrease of intrinsic connectivity between hippocampus and precuneus is linked with higher intrahippocampal metabolism. Data are consistent with the hippocampus disconnection hypothesis suggesting that cortical uncoupling may contribute to disinhibition-like changes of hippocampus activity—with likely adverse consequences for hippocampus physiology and function.

AUTHOR CONTRIBUTIONS

All authors are fully responsible for the study. M.T., C.S., and A.D. designed the study. M.T., S.F., I.Y., T.G., J.D.-S., V.R., and A.D. recruited subjects and conducted the experiment. M.T., C.M., S.M.B., and K.S. analyzed the data. M. Schwaiger, C.S., and A.D. supervised the experiment. M.T., L.P., M. Scherr, A.D., and C.S. wrote the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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