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Functional integration of parietal lobe activity in early Alzheimer disease

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ABSTRACT

Objectives: Parietal lobe dysfunction is an important characteristic of early Alzheimer disease (AD). Functional studies have shown conflicting parietal activation patterns indicative of either compensatory or dysfunctional mechanisms. This study aimed at examining activation differences in early AD using a visuospatial task. We focused on functional characteristics of the parietal lobe and examined compensation or disconnection mechanisms by combining a fMRI task with effective connectivity measures from Granger causality mapping (GCM).

Methods: Eighteen male patients with amnestic mild cognitive impairment (aMCI) and 18 male cognitively healthy older individuals were given a mental rotation task with different rotation angles.

Results: There were no behavioral group differences on the fMRI task. Separate measurements at each angle revealed widespread activation group differences. More temporal and parietal activation in the higher angle condition was observed in patients with aMCI. The parametric modulation, which identifies regions associated with increasing angle, confirmed these results. The GCM showed increased connectivity within the parietal lobe and between parietal and temporal regions in patients with aMCI. Decreased connectivity was found between the inferior parietal lobule and posterior cingulate gyrus. Connectivity patterns correlated with memory performance scores in patients with aMCI.

Conclusions: Our results demonstrate increased effective temporoparietal connectivity in patients with aMCI, while maintaining intact behavioral performance. This might be a compensational mechanism to counteract a parietal-posterior cingulate gyrus disconnection. These findings highlight the importance of connectivity changes in the pathophysiology of AD. In addition, effective connectivity may be a promising method for evaluating interventions aimed at the promotion of compensatory mechanisms. *Neurology*® 2012;78:352–360

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnestic mild cognitive impairment; **CDR** = Clinical Dementia Rating; **CSTE** = Cluster-level Statistical Threshold Estimator; **DMN** = default mode network; **FA** = flip angle; **FOV** = field of view; **GCM** = Granger causality mapping; **MCI** = mild cognitive impairment; **MTL** = medial temporal lobe; **MUMC+** = Memory Clinic of the Maastricht University Medical Center; **ROI** = region of interest; **RT** = reaction time; **TE** = echo time; **TR** = repetition time.

Parietal lobe dysfunction in early Alzheimer disease (AD) has been shown abundantly in both postmortem[1,2] and neuroimaging[3,4] studies. fMRI studies in early AD have shown indications for either compensation or functional loss.[5–8] Compensatory mechanisms have been observed in medial temporal but also in parietal areas.[5,7,9] Early AD has been associated with a disconnection between lobes with increased intralobe connectivity,[10] although some studies have reported interlobe disconnection.[10,11] Compensation reflects increased activation in one or more regions in order to maintain behavioral performance, while disconnection implies a disturbed communication between 2 functionally related regions.

Supplemental data at www.neurology.org

Supplemental Data

From the School for Mental Health and Neuroscience, Alzheimer Centre Limburg (H.I.L.J., M.P.J.V.B., E.H.B.M.G., W.H.B., I.H.G.B.R., J.J., F.R.J.V.), and European Graduate School of Neuroscience EURON (H.I.L.J., M.P.J.V.B., E.H.B.M.G., I.H.G.B.R., J.J.), Maastricht University, Maastricht, the Netherlands; Cognitive Neurology Section (H.I.L.J.), Institute of Neuroscience and Medicine-3, Research Centre Jülich, Jülich, Germany; Brain Innovation (A.H.), Maastricht; Department of Radiology (W.H.B.), Maastricht University Medical Center, Maastricht; and AZIRE Research Institute (J.J.), Faculty of Psychology and Education, VU University, Amsterdam, the Netherlands.

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Compensation and disconnection could act in concert and influence each other over time (i.e., functional integration). This can be investigated through Granger causality mapping (GCM),[12] a method to measure effective connectivity.

This study aimed at investigating activation differences between patients with early AD vs patients with mild cognitive impairment (MCI) and controls in response to increasing task demands using a mental rotation task. This task relies on parietal activity[13–19] and has been investigated in persons genetically predisposed to AD.[20] We expected 1) increased brain activity with increasing task load for the total group, and 2) that this effect, especially in parietal areas, would be larger in patients with MCI, reflecting compensatory mechanisms. Therefore, we expected increased effective connectivity within parietal areas (but not between areas of different lobes) in patients with MCI. Investigation of effective connectivity can teach us more about brain network changes in MCI and AD and might provide a new perspective for interventions.

METHODS

Participants. Eighteen patients with amnestic MCI (aMCI) (mean age 65.1 years ± 4.5 SD) were recruited from the Memory Clinic of the Maastricht University Medical Center (MUMC+). These patients were matched for age and education with 18 cognitive healthy participants (mean age 64.6 years ± 3.4 SD). Patients were included if they met the following criteria: diagnosis of aMCI established by a clinical expert (F.R.J.V.) with at least an impairment in the memory domain (−1.5 SD) according to the Petersen criteria[21] and a Clinical Dementia Rating (CDR) score of 0.5.[22] Fourteen of the included 18 patients (78%) showed medial temporal lobe (MTL) atrophy (measured by visual rating scales) of whom 6 converted to AD within 1.5 years.[23] Of these 6 patients, 3 had abnormal tau concentrations in the CSF. According to recent criteria,[24] these observations increase the likelihood that we recruited patients with prodromal AD. Control participants were recruited by advertisements in local newspapers. They were required to have a CDR score of 0, no cognitive complaints, and no evidence of cognitive deficits on testing. Hypertensive status was based on the medical history. Because of lateralization effects in visuospatial tasks, we selected only right-handed men.[25] All participants underwent a neuropsychological assessment examining various cognitive functions. Details of exclusion and inclusion criteria and the neuropsychological assessment are described in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Standard protocols, registration, and patient consents. The local Medical Ethics Committee approved the study and written informed consent was obtained from all participants.

MRI. MRI examination was performed using a 3.0 T whole-body magnetic resonance system release 2.0 (Philips Achieva, Philips Medical Systems, Best, the Netherlands) equipped with an 8-element head coil (SENSE, factor 2).

Functional scans were collected using a T2* echoplanar imaging sequence (repetition time [TR] = 1,500 msec, echo time [TE] = 30 msec, flip angle [FA] = 90°, field of view [FOV] = 224 × 224 mm, voxel size = 3.5 mm isotropic, matrix size = 64 × 64, and number of slices = 26).

Anatomic images were acquired with a T1 gradient echo sequence (TR = 8 msec, TE = 3.7 msec, FA = 8°, FOV = 240 × 240 mm, voxel size = 1 mm isotropic, matrix size = 240 × 240, number of slices = 180).

Experimental paradigm. ***Mental rotation task.*** For the visual task, we used the Shepard and Metzler structures[13] (figure 1). The objects were presented in congruent or incongruent pairs on a white background. Different levels of difficulty were included, based on the amount of angular disparity (0°, 40°, 60°, and 120°). Twenty trials per condition were presented in random order to prevent subjects from developing a degree-specific mapping strategy. Half of the trials consisted of congruent stimuli and the other half of incongruent stimuli. No object pair was presented twice. Once the object pair appeared, participants were asked to decide, as quick as possible, whether it was a congruent (left button) or incongruent pair (right button), while keeping the number of errors to a minimum. The task was set up in a mixed fMRI design (appendix e-2). The total time required for task execution was 22 minutes.

Data analysis. ***Behavioral data analysis.*** Behavioral data were analyzed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 15.0. Demographic and cognitive group differences were investigated with an independent t test for continuous variables and a χ^2 test for categorical variables. For the functional task, reaction time (RT) and accuracy group differences were analyzed with analysis of variance for the various rotation angles. Statistical significance threshold was set at $p < 0.05$.

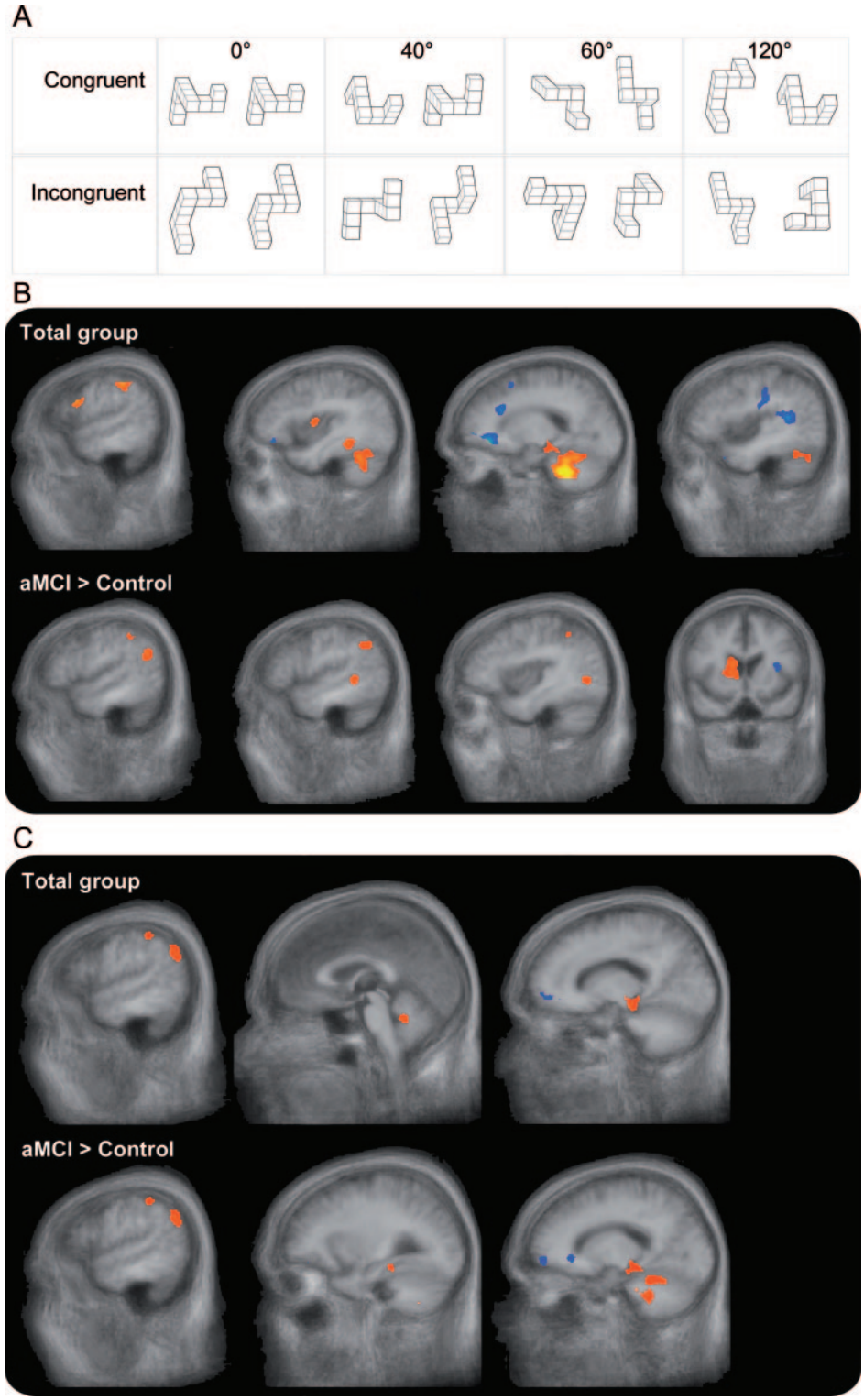
fMRI data analysis. fMRI data analysis and visualization were performed with Brainvoyager QX version 1.10.4 (Brain Innovation, the Netherlands; http://www.brainvoyager.com).[26] Functional scans were first corrected for slice timing, movement, and intensity inhomogeneities. The first 3 volumes were discarded to remove magnetic T1 saturation effects. Functional volumes for every subject underwent spatial smoothing with an isotropic Gaussian kernel (full width at half maximum = 8 mm). Temporal filtering consisted of linear trend removal and reduction of low-frequency fluctuations by means of a high-pass filter. Functional and anatomic scans were spatially coregistered. The functional data were normalized to Talairach space and linearly interpolated to 3 × 3 × 3 mm resolution.

Main and group by task effects for each rotation angle were calculated, as well as the parametric effects for the total group and group comparison (appendix e-2). Statistical maps were thresholded at $p < 0.05$ (Bonferroni corrected). All clusters of active voxels were provided with an anatomic label using MRIcro 1.40 (www.mricro.com) as guideline.

Granger causality mapping. In GCM analysis, effective connectivity maps were computed from blood oxygenation level–dependent response time courses to identify regions that were influenced by the reference region of interest (ROI) (X→Y; positive influences) and regions that influenced the reference ROI (Y→X, negative influences). Statistical significance thresholds for effective connectivity maps were computed by bootstrapping.[27]

Parietal lobe clusters from the parametric group comparison analyses were used as reference ROI. In order to prevent loss of

Figure 1 Example of task stimuli and activation patterns



Pairs of Shepard and Metzler structures were shown at 0°, 40°, 60°, or 120° rotation angle (A). Participants had to decide whether pairs were congruent or incongruent. The whole brain analysis (B) for the whole group (top row) and for the comparison between patients with amnestic mild cognitive impairment (aMCI) and controls (bottom row) are shown for the 120° rotation condition. In the whole group increased activation was found in frontal, temporal, parietal, and cerebellar regions, and deactivation was found in frontal and parietal areas. The group comparison showed increased activation in temporal and parietal areas, and deactivation in the insula. (C) Shows regions associated with parametric modulation common to both groups (top row) and the comparison between patients with aMCI and controls (bottom row). Increased load was associated with increased activation (red) in temporal and parietal areas and less activation (blue) in frontal areas in the whole group. The same patterns were found when comparing the aMCI group with the control group, but involved activation in additional regions.

temporal details and cluttering, ROIs were eroded to 200–300 voxels. Positive and negative influences were split into separate individual maps to allow separate group comparisons on each direction. A t test comparing both groups was performed at $p < 0.05$. False-positive activations were minimized by applying the Cluster-level Statistical Threshold Estimator (CSTE) plug-in for multiple comparisons[26,28] (appendix e-2).

The advantages of GCM over other effective connectivity methods such as structural equation modeling or dynamic causal modeling is that GCM is less affected by a selection bias, being more data-driven (exploratory) than model-driven, and that GCM intends to estimate the directionality of the signal in the networks.

RESULTS **Behavioral data.** There were no group differences on the Hamilton Depression Rating Scale, hypertension status ($\chi^2 = 4.39$, $p = 0.11$), or total white matter hyperintensities volume (table 1). The aMCI group performed worse on the Mini-Mental State Examination, Verbal Learning Task (immediate recall and delayed recall), Letter Digit Substitution Task, Concept Shifting Task (card 3), and fluency (naming professions and words that start with the letter M). There were no group differences on the total score or RT for the various angles of rotation of our fMRI task.

Table 1 Characteristics of the 2 groups[a]

	Controls (n = 18), mean (SD)	aMCI (n = 18), mean (SD)	Group difference	
			t	p
Age, y	64.6 (3.4)	65.1 (4.5)	−0.417	0.680
Educational level	4.2 (1.4)	3.9 (1.8)	0.728	0.472
MMSE	28.9 (1.0)	27.6 (2.3)	2.191	0.035[b]
Hamilton Depression Rating Scale score	0.6 (1.2)	1.6 (1.9)	−1.754	0.088
Total VLT, words	37.5 (7.6)	26.1 (9.8)	3.910	<0.001[c]
VLT: delayed recall, words	8.6 (3.4)	3.7 (2.8)	6.165	<0.001[c]
Stroop card 3, s	108.1 (19.7)	118.5 (45.8)	−0.883	0.383
LDST in 60 s, items	32.6 (5.9)	26.7 (8.3)	2.428	0.021[b]
CST card 3, s	36.6 (13.1)	49.0 (19.9)	−2.221	0.033[b]
Fluency animals, n	23.2 (5.3)	21.4 (5.4)	0.993	0.328
Fluency professions, n	19.8 (4.3)	15.3 (5.9)	2.632	0.013[b]
Fluency letter M, n	15.8 (5.5)	11.4 (5.6)	2.366	0.024[b]
Total white matter hyperintensities volume	6.53 (4.08)	5.22 (3.34)	1.033	0.309
Score 0° rotation	15.9 (2.3)	15.4 (2.3)	0.722	0.475
Score 40° rotation	15.1 (2.3)	14.8 (2.4)	0.422	0.676
Score 60° rotation	12.9 (1.8)	11.8 (1.9)	1.798	0.081
Score 120° rotation	12.8 (2.4)	11.0 (3.3)	1.843	0.074
Reaction time[d] 0° rotation	3,085.8 (649.2)	2,940.1 (778.9)	0.610	0.546
Reaction time 40° rotation	3,560.1 (524.1)	3,420.2 (704.4)	0.676	0.504
Reaction time 60° rotation	3,761.8 (596.3)	3,485.4 (493.7)	1.515	0.139
Reaction time 120° rotation	3,808.9 (642.9)	3,470.2 (499.2)	1.765	0.087

Abbreviations: aMCI = amnestic mild cognitive impairment; CST = Concept Shifting Task; LDST = Letter-Digit Substitution Test; MMSE = Mini-Mental State Examination; VLT = Verbal Learning Test.
[a] Independent t tests were used to calculate group differences for the continuous variables; a standardized 8-point scale was used to indicate educational level (1 = primary school; 8 = university degree).
[b] $p < 0.05$.
[c] $p < 0.001$.
[d] Reaction times are expressed in milliseconds.

Brain activity per angle condition. Several temporal and parietal areas showed increased activation in each angle condition compared to baseline in the total group. The superior frontal gyrus, right supramarginal gyrus, and anterior cingulum showed less activation in all conditions compared to baseline in the total group (figure 1 and table e-1).

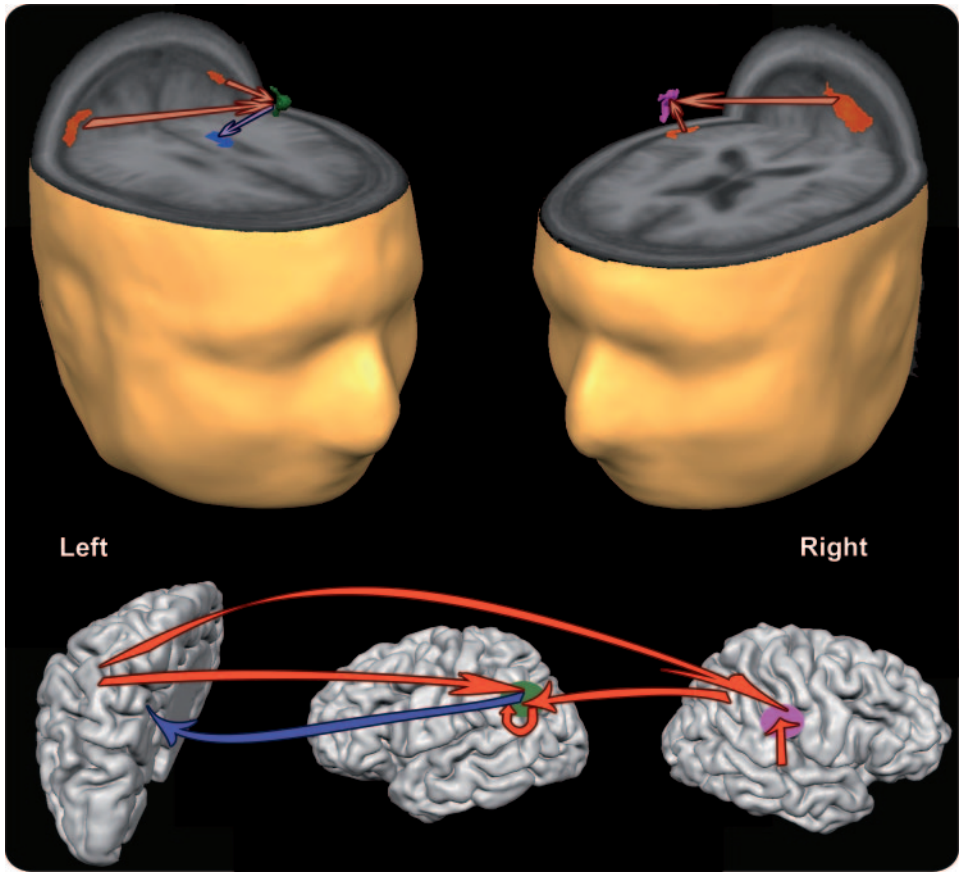
Increased activation in patients with aMCI compared to controls was observed in several temporal and parietal areas when comparing the different rotation angle conditions to the baseline: the middle temporal gyrus, inferior parietal lobule, and angular gyrus (figure 2 and table e-1).

Parametric effects. Table 2 shows the parametric effects for the total group. Areas that showed increased activation with increasing rotation angles were mainly found in the temporal and parietal lobe (figure 1).

Patients with aMCI showed increased activation with increasing rotation angles compared to controls in several temporal (middle, superior, and inferior temporal gyri, parahippocampal gyrus, hippocampus) and parietal areas (supramarginal gyrus, inferior parietal lobule, angular gyrus). Areas where patients with aMCI showed less activation with increasing rotation angles than controls were the superior frontal gyri and anterior cinguli (table 2 and figure 1).

Granger causality mapping. The parietal regions from the parametric group comparison were chosen as reference ROI. Applying the CSTE plug-in yielded no significant group differences in positive or negative influences for the left supramarginal gyrus. For the left inferior parietal lobule we found less connectivity to the left posterior cingulate gyrus in patients with aMCI compared with controls. More connectivity in patients with aMCI was found from the right middle occipital/angular gyrus, left inferior parietal lobule, and left superior occipital/superior parietal lobule toward the inferior parietal lobule. With the left angular gyrus as reference ROI, we found comparable patterns as for the inferior parietal lobule, viz. more connectivity in patients with aMCI from the left superior occipital/superior parietal lobule and right middle occipital/angular gyrus toward the ROI. Finally, for the right supramarginal gyrus as reference ROI, we found more connectivity in patients with aMCI from the left superior occipital/superior pari-

Figure 2 Effective connectivity differences between the 2 groups



Granger causality mapping with either the left inferior parietal lobule (left figure, green) or the right supramarginal gyrus (right figure, pink) as region of interest. Blue indicates regions where patients with amnestic mild cognitive impairment (aMCI) showed less effective connectivity than controls (posterior cingulate gyrus). Red indicates regions where patients with aMCI showed more effective connectivity than the control group (inferior parietal lobule, superior occipital/parietal lobule, middle occipital/angular gyrus, and superior and middle temporal gyri).

etal lobule and right middle/superior temporal gyrus toward the ROI (figure 2). Significant correlations with the delayed recall score of the verbal word learning task were found for the left posterior cingulate gyrus (positive correlation: lower memory performance was associated with loss of connectivity), right middle occipital/angular gyrus, left superior occipital/superior parietal lobule, and middle/superior temporal gyrus (negative correlations: increased connectivity was associated with lower memory performance) (table 3).

DISCUSSION We provide evidence of increased neural activity in parietal and temporal areas in patients with aMCI during a mental rotation task. Patients and controls showed no differences in behavioral performance. Our results suggest an underlying compensatory mechanism. In addition, our GCM analyses suggest that this compensation is associated with increased intraparietal and parietal-temporal effective connectivity, in order to counteract loss of effective connectivity involving the posterior cingulate gyrus, an area commonly affected in AD.[4] This study is thus able to integrate compensation with connectivity loss underlying task performance and lends credibility to the capacity for functional reorganization and for the development of neural compensation in patients with aMCI. This notion may have therapeutic implications. The outcome of new interventions could be evaluated to the extent that they promote compensatory mechanisms. Brain activity in combination with effective connectivity could potentially be used as a measure of treatment success.

As for the brain activation related to the mental rotation task, the total group showed increased activation in lateral and medial temporal and parietal areas, evidencing that our task was well designed and able to elicit regions associated with this task in healthy participants and persons genetically at risk of AD.[14,18,20]

The group comparison showed that patients with MCI displayed more activation with increasing

Table 2 Whole brain parametric analyses for the mental rotation task

Region of interest	Hemisphere	BA	Peak *t* value	Talairach coordinates *x*, *y*, *z*	Size, mm^3
Whole group: regional activations significant at $p < 0.05$ (Bonferroni corrected) with cluster threshold of at least 270 mm^3					
Middle temporal gyrus	RH	22	5.76	65, −41, 0	1,364
Middle temporal gyrus	RH	22	4.26	65, −47, 15	520
Middle temporal gyrus	LH	22	4.45	−64, −41, 12	1,394
Superior temporal gyrus	RH	22/42	3.87	62, −53, 21	384
Parahippocampal gyrus	RH	36	4.43	17, −23, −12	747
Superior frontal gyrus	RH	10	−3.78	11, 55, −6	704
Superior frontal gyrus	LH	10	−3.76	−13, 61, 0	382
Inferior parietal lobule	LH	39	4.40	−58, −35, 42	327
Angular gyrus	LH	39	5.01	−58, −59, 27	986
Vermis	–	NA	3.78	2, −35, −6	396
Vermis	–	NA	5.16	−1, −47, −27	781
Cerebellum	LH	NA	4.62	−22, −41, −33	499
aMCI > control: regional activations significant at $p < 0.05$ (Bonferroni corrected) with cluster threshold of at least 243 mm^3					
Inferior temporal gyrus	RH	37	4.14	53, −68, −12	649
Middle temporal gyrus	RH	22	4.17	53, −68, 0	364
Middle temporal gyrus	LH	22	4.45	−64, −41, 12	3,066
Middle temporal gyrus	RH	22	5.76	65, −41, 0	3,513
Superior temporal gyrus	RH	22/42	3.87	62, −53, 21	1,124
Hippocampus	RH	NA	3.87	35, −11, −12	454
Parahippocampal gyrus	RH	36	4.43	17, −23, −12	1,003
Superior frontal gyrus	LH	10	−3.76	−13, 61, 0	1,866
Superior frontal gyrus	RH	10	−3.78	11, 55, −6	4,263
Inferior frontal/anterior cingulum	LH	11	−3.81	−16, 31, 0	314
Anterior cingulum	RH	32/34	−3.99	17, 43, 6	466
Supramarginal gyrus	LH	40	3.58	−61, −23, 27	627
Inferior parietal lobule	LH	39	4.40	−58, −35, 42	1,417
Angular gyrus	LH	39	5.01	−58, −59, 27	2,362
Supramarginal gyrus	RH	40	4.19	65, −41, 36	1,884
Vermis	–	NA	3.61	−1, −35, −6	350
Vermis	–	NA	5.03	0, −47, −27	1,567
Cerebellum	LH	NA	4.62	−22, −41, −33	5,288

Abbreviations: 270 mm^3 = 10 voxels; aMCI = amnestic mild cognitive impairment; BA = Brodmann area (approximate); LH = left hemisphere; NA = not applicable (no labeled Brodmann region); RH = right hemisphere.

task demand in lateral and medial temporal areas, and lateral parietal areas, confirming our hypothesis of increased parietal activity with increasing task demand.[19,20]

More deactivation was found in superior frontal gyri and cingulate areas, areas of the default mode network (DMN).[29–31] Disturbances of the DMN have been found in healthy and pathologic aging,[30,31] and an increase in deactivation might be interpreted as an increased effort to inhibit task-irrelevant activations.[32] This might seem conflicting with studies reporting failure to deactivate temporal and parietal areas in patients with MCI and AD. But it has been suggested that increased frontal deactivation is a compensational mechanism for this deactivating failure.[33] This increased frontal deactivation seems to contradict earlier findings of increased frontal activation in cognitively healthy subjects genetically at risk of AD.[20] This could be explained by sample-related differences, such as the cognitive and genetic status of participants, or gender. Women tend to use a more top-down approach engaging frontal and temporal regions, while men tend to prefer a bottom-up approach involving the postcentral gyrus, the precuneus, lateral parietal areas, and thalamus.[34]

Increased parietal activation reflects dorsal pathway involvement, while lateral and medial temporal activity reflects ventral pathway involvement for the recognition of the 3-dimensional figures, suggesting that performance entails activation of areas in both pathways.[18]

With respect to the parietal lobe, several studies reported greater involvement of the superior parietal lobule[14,19,20] instead of increased inferior parietal lobule activation. The superior parietal lobule is engaged in spatial manipulation of objects, while the inferior parietal lobule is involved in object recognition, spatial manipulation, and detection of salient stimuli, and together with the prefrontal cortex, plays a role in sustained attention.[19] Our patients with aMCI may have used another behavioral strategy that relies more on inferior parietal lobule functions.

The interpretation of increased activation in medial temporal lobe regions is not yet clear. It has been interpreted as a compensatory mechanism to counteract structural pathologic processes in order to maintain adequate performance,[35,36] but recently it has been suggested that it might also reflect a transitional stage to AD.[37] The increased activation might then be the result of amyloid-induced hyperexcitability of neurons and impending neuronal network breakdown. The fact that we observed no performance differences and that an increase in hippocampal activity was significantly associated with an increase in behavioral performance in patients with aMCI ($p = 0.038$) but not in controls ($p = 0.43$) (figure e-1) suggests that the activation increase is beneficial and might indeed reflect a compensatory mechanism. Compensation could take place at a neural network level or patients may adopt a different behavioral strategy. Patients would then have to build new connections to access other neurons or to address other regions, accommodating new strategies. However, activity changes can also be due to deficits in neuronal circuits, synaptic loss, sprouting,

Table 3 Effective connectivity correlated with memory performance (i.e., the delayed recall score of the verbal word learning task)[a]

Regions resulting from the Granger causality mapping	Hemisphere	Correlation (Pearson r)	
		Controls	aMCI
Reference ROI: left inferior parietal lobule			
Posterior cingulate gyrus (less connectivity)	LH	−0.174	0.540[b]
Middle occipital/angular gyrus	RH	−0.150	0.417
Inferior parietal lobule	LH	−0.106	0.301
Superior occipital/superior parietal lobule	LH	−0.244	−0.265
Reference ROI: left angular gyrus			
Middle occipital/angular gyrus	RH	−0.163	−0.472[b]
Superior occipital/superior parietal lobule	LH	0.047	−0.494[b]
Reference ROI: right supramarginal gyrus			
Superior occipital/superior parietal lobule	LH	−0.247	−0.318
Middle/superior temporal gyrus	RH	0.074	−0.483[b]

Abbreviations: aMCI = amnestic mild cognitive impairment; LH = left hemisphere; RH = right hemisphere; ROI = region of interest.
[a] Negative correlations indicate that lower effective connectivity is associated with lower memory performance. Positive correlations indicate that higher effective connectivity is associated with lower memory performance.
[b] $p < 0.05$.

or may reflect inefficient synaptic transmission.[38] Therefore, we investigated effective connectivity changes in patients with aMCI based on the activation patterns. We applied GCM to investigate how parietal activation increases were related to the recruitment of other areas, and thus to possible compensation or disconnection.

The GCM results showed that parietal regions have an increased effective intralobe connectivity but also an increased interlobe connectivity with the lateral temporal gyrus. This might reflect additional recruitment of regions outside the parietal lobe and possibly a change in strategic behavior typical of the ventral pathway. This would mean that patients with aMCI put more effort into visual recognition when determining the rotation angle, which is in agreement with the increased inferior parietal lobule and temporal lobe activation observed in the parametric modulation. This change in strategy might provide clinicians with new perspectives for interventions, for example in compensation training as part of cognitive rehabilitation.

Interestingly, patients with aMCI showed reduced effective connectivity from the inferior parietal lobule toward the posterior cingulate gyrus. It might be speculated that this reduction in effective connectivity is counteracted by an increase in the abovementioned connections. The effective connectivity patterns behind the increased parietal activation are supported by the correlations with the memory scores. Higher memory scores are associated with less connectivity loss in the posterior cingulate gyrus. The posterior cingulate gyrus plays a role in memory functions, evaluation of information, and object recognition.[39] Structural, functional, and metabolic changes in the posterior cingulate gyrus have been extensively reported in aMCI.[3,11,40]

Several limitations merit attention. First, our patients were recruited as patients with aMCI. Based on medial temporal lobe atrophy, CSF measurements, and the conversion rates to AD after 1.5 years, our patients are likely to represent patients with prodromal AD. Four patients did not have a positive biomarker at the time of scanning, suggesting the need for follow-up. Furthermore, we did not analyze differences between single-domain and multi-domain MCI, since only 2 patients fulfilled the criteria for single-domain MCI.

Second, GCM offers information on the direction of effective connectivity, but not on the strength or time delay of the influence, and the conclusions are bound to the ROI. Therefore the results of the GCM analysis have to be interpreted cautiously. Third, we interpreted activation differences in terms of compensation, but dedifferentiation cannot be excluded as an alternative explanation of our observations. The fact that performance levels remain intact and that we found significant correlations between activity and performance favors a compensatory view. More research is necessary to disentangle these mechanisms, although they could co-occur, combining age-related and neurodegenerative processes. Fourth, the apparent activation patterns might stem from differences in the hemodynamic response function between both groups. Although hemodynamic response function differences cannot be fully excluded, we found no group differences on vascular factors, such as hypertension or white matter hyperintensities.

Patients with early AD showed increased temporal and parietal activation during a mental rotation task with varying cognitive load. Activity levels were associated with adequate task performance, possibly indicating compensatory strategies. Compensation was expressed by extra effective connectivity in parieto-occipital and lateral temporal areas. The possible underlying neural mechanism might be disconnection between the posterior cingulate gyrus and the medial temporal lobe. Compensatory mechanisms as well as disconnection within the parietal lobe correlated with memory performance in patients with aMCI, which suggests the importance of these brain changes in the understanding of the pathophysiology of AD.

AUTHOR CONTRIBUTIONS

Dr. Jacobs: drafting the manuscript, study design, acquisition of data, statistical analysis, analysis and interpretation of data. Dr. van Boxtel:

revising the manuscript, study concept, study supervision. A. Heinecke: study design and analysis of data. Dr. Gronenschild: revising the manuscript, analysis of data. Dr. Backes: revising the manuscript, acquisition of data, coordination. Dr. Ramakers: revising the manuscript, acquisition of data. Dr. Jolles: revising the manuscript, study concept, obtaining funding. Dr. Verhey: revising the manuscript, study concept, study supervision, obtaining funding.

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