Abnormal Regional Brain Activities Along the Dorsal Stream During Visuospatial Processing in Alzheimer's Disease: A Magnetoencephalography Study

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Abstract

The dorsal stream is responsible for visuospatial processing, and visuospatial impairment is common in Alzheimer's disease (AD). Using magnetoencephalography (MEG) during visuospatial processing, we investigated neural activity in the dorsal stream in patients with clinically diagnosed AD dementia (the dementia group), patients with amnesic mild cognitive impairment (the aMCI group), and cognitively unimpaired subjects (the CU group). We estimated the powers of neural responses induced by optic flow tasks in the five regions that form the dorsal stream, namely medial ventral occipital cortex (MVOcC), lateral occipital cortex, precuneus (Pcun), inferior parietal lobule (IPL), and superior parietal lobule, and compared two-region power ratios in the dementia group ($n = 13$), aMCI group ($n = 11$), and CU group ($n = 20$). Two of the two-region power ratios, namely IPL/Pcun and IPL/MVOcC, were found to be significantly higher in the dementia group than in the CU and aMCI groups, indicating that neural activity during visuospatial processing changes with the progression of AD, and a compensatory mechanism may be present in IPL, Pcun, and MVOcC of patients with AD. Thus, MEG during optic flow tasks may be useful for the investigation of neural activity in the dorsal stream in patients with AD.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, and it accounts for about 70% of all cases of dementia¹. Visuospatial impairment is common in AD², and it is observed even in the early stage of AD³. Since visuospatial ability is essential for adapting to an environment, its impairment directly affects quality of life. However, there are no established diagnostic imaging tools for the detection of visuospatial impairment.

Regarding visuospatial processing, visual motion perception is executed in the dorsal stream⁴. The dorsal stream consists of V1, V5, or middle temporal visual area (V5/MT), inferior parietal lobule (IPL), V6 (located in the parieto-occipital sulcus)⁵, and superior parietal lobule (SPL)⁶. Visuospatial impairment in AD dementia involves deterioration of object-motion perception^{7,8} and impairment of self-motion perception⁹. A sense of self-motion is induced by optic flow stimuli, which are visual stimuli presented as numerous dots that move radially from the center of a screen¹⁰. Optic flow stimuli activate V1, V6, medial superior temporal area (MST), and IPL in the dorsal stream^{11–15}. They also activate V5/MT and SPL, but to a lesser degree^{13,15,16}. A meta-analysis on ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed that, in the early stages of AD dementia, dysfunction occurs in two brain areas, namely the precuneus (Pcun), which includes V6, and IPL¹⁷. It was reported in previous studies that maximum source-localized power of the dorsolateral prefrontal cortex (DLPFC) during optic flow stimuli is higher in patients with amnesic mild cognitive impairment (aMCI) and suspected AD than in cognitively unimpaired (CU) subjects¹⁸, and event-related potentials on optic flow over the parietal electrode were reported to be lower in patients with AD dementia than in CU subjects^{15,19}. However, it is still unclear how neural activity in the dorsal stream changes with developing cognitive decline in patients with AD. We hypothesized that neural activity during optic flow tasks in patients with aMCI (the aMCI

group) and patients with clinically diagnosed AD dementia (the dementia group) differs from that in CU subjects (the CU group).

This study had two aims. The first aim was to identify neural responses in the dorsal stream during optic flow tasks using magnetoencephalography (MEG) imaging and to determine the differences in response between the aMCI, dementia, and CU groups. The second aim was to investigate the clinical usefulness of responses in the dorsal stream during optic flow tasks in terms of discriminating between the three groups.

Results

Subject characteristics

Table 1 shows the demographic and clinical characteristics of the CU, aMCI, and dementia groups. Twenty CU subjects, 11 patients with aMCI, and 13 patients with dementia were included in this study. Three patients with dementia had visuospatial problems, which were assessed by conducting the intersecting pentagon copying test. Five patients with aMCI and five patients with dementia had high likelihood of AD, while six patients with aMCI and eight patients with dementia had intermediate likelihood of AD. All the patients with aMCI converted to patients with clinically diagnosed AD dementia ²⁰ within 36 months after MEG measurement.

No significant differences in sex, age, and educational level were observed between the three groups. However, significant differences in MMSE score were observed between the groups ($p < 0.001$). Post hoc analysis revealed that MMSE scores were significantly higher in the CU group than in the aMCI and dementia groups ($p < 0.05$ and $p < 0.001$, respectively).

Table 1
Demographics of the CU, aMCI, and dementia groups. Values of age, educational level, and MMSE score are presented as mean (standard deviation). Statistical analyses such as chi-square test (n) and analysis of variance (others) were performed.

	CU group	aMCI group	Dementia group	p-value
Gender (F/M)	13/7	5/6	5/8	0.321
Age	73.50 (5.15)	69.63 (9.99)	76.38 (5.36)	0.168
Educational level	10.95 (2.60)	10.81 (2.56)	10.30 (1.60)	0.738
MMSE score	28.40 (1.81)	26.00 (2.64)	22.30 (3.98)	< 0.001

Abbreviations: CU, cognitively unimpaired; aMCI, amnesic mild cognitive impairment; MMSE, Mini-Mental State Examination

Source localization map and waveforms from evoked responses

Figure 1 shows grand-averaged ROI time-courses determined by multiplying voxel-level source time-courses by the singular vector of largest singular value among the voxel-level source time-courses for CU, aMCI, and dementia in the dorsal stream. The time-courses of the dorsal stream have latencies of about 150 ms.

Figure 2 shows the grand-averaged source localization map on voxel-level source power at 150 ms after optic flow stimuli onset in the CU, aMCI, and dementia groups. The power in the dorsal stream increased for all three groups.

Supplementary material number 1 (a movie) shows the grand-averaged source localization map on voxel-level source power from 100 ms to 300 ms after optic flow stimuli onset in the CU group. First, the power in the medial dorsal stream, namely MVOcC and Pcun, increased at about 120 ms. Next, the power in the medial and lateral dorsal stream, namely MVOcC, LOcC, Pcun, and IPL, increased at about 150 ms.

Group differences in the two-region power ratios

There were significant differences in the power ratios IPL/MVOcC ($p = 0.002$) and IPL/Pcun ($p = 0.004$) (Figure 3). Post hoc analysis revealed that the power ratio IPL/MVOcC was significantly higher in the dementia group than in the CU and aMCI groups ($p = 0.003$ and $p = 0.016$, respectively). Further, the power ratio IPL/Pcun was significantly higher in the dementia group than in the CU and aMCI groups ($p = 0.005$ and $p = 0.022$, respectively). In contrast, there were no significant differences in the ratios including LOcC and SPL between the three groups.

When we analyzed only subjects with high likelihood of AD, we observed marginally significant differences in IPL/Pcun between the CU, aMCI ($n = 5$), and dementia ($n = 5$) groups ($p = 0.068$). Post hoc analysis revealed that IPL/Pcun was marginally higher in the dementia group than in the CU group ($p = 0.053$).

ROC analysis

We evaluated the power ratios to distinguish dementia from CU and aMCI. We calculated the following three statistics from the ROC plots: sensitivity, specificity, and AUC. The ROC plots are shown in Figure 4, with the diamond symbols denoting points of maximum accuracy. The AUCs of IPL/MVOcC and IPL/Pcun were 0.84 and 0.82, respectively. Furthermore, the sensitivity and specificity of IPL/MVOcC were 0.69 and 0.94, respectively, and the sensitivity and specificity of IPL/Pcun were 0.85 and 0.72, respectively.

Discussion

We used MEG to investigate neural activity in the dorsal stream in the CU, aMCI, and dementia groups during the optic flow task. We observed activity in the dorsal stream in the three groups at latencies of about 150 ms. Furthermore, we observed significant differences in the power ratios IPL/MVOcC and IPL/Pcun between the dementia group and the CU and aMCI groups ($p = 0.002$ and $p = 0.004$,

respectively). When we restricted subjects with high likelihood of AD, we observed marginally significant differences in IPL/Pcun between the CU and dementia groups ($p = 0.053$). Visuospatial impairment caused by progression of neurodegeneration in AD may affect differences of the active region between the three groups.

We evaluated the clinical usefulness of responses in the dorsal stream during the optic flow task in discriminating between the three groups. Regarding the accuracy of discrimination of the dementia group, the AUCs of the power ratios IPL/MVOcC and IPL/Pcun were 0.84 and 0.82, respectively. Hence, MEG imaging during optic flow task may be considered useful for the detection of dementia.

The difference in IPL/Pcun between the CU and dementia groups indicates the presence of a compensatory mechanism. In a previous study, it was reported that dysfunction may explain the low activation of the Pcun¹⁷. The anatomical connection of IPL to a subregion of the Pcun partially supports the possibility of compensation by the IPL^{21,22}, as do the following two previous studies. First, a functional MRI (fMRI) study reported that spontaneous activity in the bilateral Pcun decreased significantly in the AD dementia group compared to the CU and aMCI groups, while spontaneous activity in the left IPL increased significantly in the aMCI group compared to the CU group²³. Second, a MEG resting state study reported that functional connectivity between Pcun and IPL increased significantly in the A β -positive CU group compared to the A β -negative CU group²⁴.

In addition, it is important to note that IPL is known as an impaired region in patients with typical AD dementia¹⁷. However, as gray matter atrophy occurs in the Pcun of patients with aMCI²⁵, dysfunction in the IPL may occur later than dysfunction in the Pcun. In our study, the mean MMSE score of patients with dementia was 22.3, which indicates early stage of disease. These findings may explain the increased activation in the IPL observed in the dementia group in our study during the optic flow task.

When we restricted our subjects to those with high likelihood of AD, we observed no significant differences in power ratios between the three groups. However, we observed marginally significant differences in IPL/Pcun between the CU and dementia groups ($p = 0.053$). These results support the hypothesis that IPL is compensatorily activated by failure of the Pcun in patients with AD.

Dysfunction in a part of the MVOcC and in the Pcun was reported in patients with AD dementia²⁶, while low destruction of the V1 subregion of MVOcC was reported in patients with AD dementia²⁷. Thus, it is reasonable to expect that the power of the MVOcC during the optic flow task will be lower in the dementia group than in the CU group and that the power ratio IPL/MVOcC in the dementia group will be high.

In our previous study, we found that neural activity in the DLPFC was significantly higher in the aMCI group than in the CU group¹⁸. However, in this study, which analyzed the same subjects, no significant differences in the power ratios in the dorsal stream were observed between the aMCI and CU groups, but median neural activity of the IPL/Pcun and IPL/MVOcC increased in the CU, aMCI, and dementia groups, with the lowest increase in the CU group and the highest increase in the dementia group. It was

suggested that functional decline of the dorsal stream began early in the aMCI group and that the DLPFC was activated in compensation for the functional decline in aMCI.

Our results showed that the SPL was commonly inactive in the three groups and that there were no significant differences in the ratios that include SPL and LOcC. One possible reason for these findings is that the SPL is reported not to be responsible for self-motion perception induced by the optic flow stimuli¹⁵. Further, a previous fMRI study reported that the LOcC, which includes MST, may be activated by the optic flow stimuli¹³. However, detection of the activity of MST, which lies deep in the cortex, using MEG may be difficult²⁸, and we posited that the estimated activity of LOcC is mainly leakage of activity from the adjacent IPL or MVOcC.

Our study shows that the neural activity of dorsal streams can be evaluated using MEG data of subjects passively looking at a screen that is projecting optic flow stimuli. Based on the AUC of 0.82, the ability of MEG imaging to distinguish the dementia group from the aMCI and CU groups is high. In other words, by performing MEG imaging during optic flow tasks, self-motion perception caused by impairments of the dorsal stream in patients with AD dementia can be detected. Furthermore, by performing MEG imaging during optic flow tasks, visuospatial impairment may also be detected.

This study has some limitations. First, the number of subjects was small; therefore, it is necessary to conduct validation studies. Second, pathological verification of AD diagnosis was not obtained for any patient. Third, to verify that the MEG findings in this study are specific for AD dementia, further studies of patients with various types of dementia should be conducted.

Neural activity during visuospatial processing changes with the progression of AD, and a compensatory mechanism may be present in the dorsal stream in patients with AD dementia. MEG imaging can be used to investigate neural activity in the dorsal stream and can be useful for the detection of functional changes in the dorsal stream in patients with AD.

Methods

Study population

We recruited patients with aMCI confirmed using the clinical criteria defined by Petersen et al.²⁹ and patients with dementia confirmed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association²⁰. Furthermore, these patients were assessed based on criteria developed by combining biomarkers and diagnostic guidelines for AD from the National Institute on Aging–Alzheimer's Association^{30,31}, and the patients were classified as having an intermediate or high likelihood of AD. We assessed biomarkers of amyloid β ($A\beta$) including cerebrospinal fluid (CSF) $A\beta_{42}$, amyloid PET images, biomarkers of tau including CSF-phosphorylated tau, neurodegeneration/neural injury (which refers to medial temporal lobe atrophy [MTA] on magnetic resonance imaging [MRI]), and temporoparietal/Pcun hypometabolism on FDG-PET³¹. Regarding CSF

markers, we set cut-off values of 490 pg/mL and 49 pg/mL for CSF A β ₄₂ and CSF-phosphorylated tau, respectively³². In the evaluation of amyloid PET, we considered cortical amyloid deposition, such as unilateral binding in one or more cortical brain regions, as positive for AD pathology³³. In the evaluation of FDG-PET, we used the following visual criteria for the assessment of neurodegeneration: reduction in metabolism in the temporoparietal lobe, Pccu, and/or posterior cingulate gyrus and relative sparing of metabolism in the sensorimotor cortex, occipital cortex, and cerebellum³². In the evaluation of MTA, we used the visual rating scale of MTA³⁴. MTA was rated on coronal T1-weighted images using a five-point visual rating scale, ranging from zero (no atrophy) to four (severe atrophy) based on the height of the hippocampal formation and the surrounding CSF space³⁴. We considered neurodegeneration as MTA $\geq$ 2³⁴. All patients were examined by neurologists, and patients on medications that act on the central nervous system (e.g., cholinesterase inhibitors, N-methyl-D-aspartate receptor antagonists, antipsychotics, anticholinergics, and antidepressants) were excluded from the study. Brain MRI was performed to rule out other potential medical conditions. The CU group was recruited from participants in the Nakajima study, which is a population-based longitudinal cohort study that investigated cognitive decline in residents aged $\geq$ 60 years in Nakajima, Ishikawa Prefecture, Japan³⁵. The CU group had no history of psychiatric or neurological diseases, were not on medications that can act on the central nervous system, and were assessed as having no cognitive impairment. The aMCI and dementia groups were recruited from participants in the Nakajima study and patients who visited our Memory Clinic at Kanazawa University Hospital. All the subjects in the three groups were recruited from 2010 to 2013. Cognitive profiles were evaluated using the Mini-Mental State Examination (MMSE)³⁶ and Wechsler Memory Scale-Revised. This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving human subjects were approved by the Kanazawa University Medical Ethics Review Board (study approval number: 2918). Written informed consent was obtained from all the subjects.

Optic flow task

Each subject was presented with visual stimuli on a screen and was required to maintain centered visual fixation throughout the presentation of all visual stimuli. Two types of stimuli were presented: stationary-dots stimuli and optic flow stimuli. The stationary-dots stimuli consisted of 1000 white dots presented randomly on a black background. The optic flow stimuli consisted of animated sequences of 1000 white dots moving radially outward at a mean dot speed of 15°/s. The subjects underwent a total of 360 trials (120 trials $\times$ three sets, with intervals of tens of seconds between sets). The optic flow stimuli and stationary-dots stimuli occurred 96 times and 264 times, respectively. The duration of each trial (for both stimuli types) was 2.7 s. Regarding the optic flow stimuli, each trial began with a fixation dot shown for a duration of 1000 ms, followed by stationary dots for 800 ms. After that, the dots moved radially outward from the center of the screen for 300 ms, and the stationary dots then appeared for 600 ms (Figure 5). Regarding the stationary-dots stimuli, each trial began with a fixation dot shown for a duration of 1000 ms, followed by stationary dots for 1700 ms (Figure 5). It was reported that brain activity evoked by visual motion, such as optic flow tasks, fluctuate easily because of long-term adaptation/habituation or

fatigue³⁷. To avoid fluctuation of neural responses to the optic flow stimuli, we randomly inserted stationary-dots stimuli, for an optic-flow-stimuli-to-stationary-dots-stimuli ratio of 4:11.

MEG recordings and MRI scans

MEG measurements were performed using a MEG system (MEG vision PQA160C; Ricoh Co. Ltd., Kanazawa, Japan). The system included a 160-channel whole-head coaxial gradiometer. The MEG signals were sampled at 1000 Hz with a 0.1–200 Hz analog band-pass filter. The position of the head within the helmet was determined by magnetic marker coils attached at five locations on the surface of the head as fiducial points to the landmarks (three points on the forehead and the left and right pre-auricular points). All the subjects underwent T1-weighted MRI studies using the Sigma Excite HD 1.5T System (GE Yokogawa Medical Systems Ltd., Milwaukee, WI, USA). For co-registration of MEG with structural MRI images, T1-weighted MRI was performed with spherical lipid markers placed at the five corresponding MEG fiducial points. These MRI images consisted of 158 sequential horizontal slices 1.2-mm thick, with a resolution of 512×512 points in a viewfield of 261×261 mm.

Data pre-processing

Data pre-processing was performed using FieldTrip, which is a MATLAB-based analysis software. As the first step of data pre-processing, data was digitally filtered using a 1–30 Hz band-pass filter, and cardiac artifacts and eye-movement were removed using independent component analysis. Ninety-six optic flow trials were identified using a measured trigger signal, and 96 epochs of interest were set from -300 to 1000 ms. Epochs with muscle artifacts were removed using an automatic artifact rejection tool in the FieldTrip toolbox³⁸, and the remaining cleaned epochs were averaged for each subject.

Source localization and two-region power ratios

An array-gain constraint minimum-norm spatial filter with recursively updated gram matrix (AGMN-RUG)³⁹ was applied to the epoch-averaged signals to obtain source power activities for all brain regions. As the AGMN-RUG consists of normalized lead-field vectors, false intensity increase around the center of the head is avoided. Furthermore, the AGMN-RUG has a small source location bias and robust to source correlation, which meets our need to distinguish the source power activities of adjacent regions in the dorsal stream. By applying the AGMN-RUG to the pre-processed sensor time-courses, voxel-level source time-courses were computed on 8-mm volumetric grids in the brain.

We defined the maximum-power time (peak latency) within the interval from 100 to 300 ms, given that we observed the event-related fields in the epoch-averaged signals in this time interval. We calculated the grand-averaged source localization map at latency in the three groups.

Using the Brainnetome atlas⁴⁰, we selected the following five regions in the dorsal stream as regions-of-interest (ROIs): medial ventral occipital cortex (MVOcC), lateral occipital cortex (LOcC), Pccun, IPL, and SPL. V1 and MST are subregions of MVOcC and LOcC, respectively, and V6 lies on the boundary between

MVOcC and Pccun. ROI time-course was taken as the time-course of the first principal component of the voxel time-courses within each ROI. In each subject, the response power in each ROI was computed by averaging the ROI time-courses over the time interval (latency – 50 ms, latency + 50 ms). In this study, we defined latency as the time at which an ROI time-course reaches a maximum value within 100 to 300 ms.

We introduced the two-region power ratios (i.e., SPL/IPL, SPL/LOcC, SPL/Pccun, SPL/MVOcC, IPL/LOcC, IPL/Pccun, IPL/MVOcC, LOcC/Pccun, LOcC/MVOcC, and Pccun/MVOcC). As the AGMN-RUG consists of normalized lead-field vectors, estimated regional powers depend on the distance between the MEG sensor array and the subject's brain region. Thus, taking the ratios may be helpful for reducing the inter-subject variability of the regional powers.

Statistical analysis

Fisher's exact test was used to evaluate gender differences between the three groups (i.e., aMCI, dementia, and CU groups). Analysis of variance was used to evaluate the other clinical characteristics and the MMSE score between the groups.

We used Kruskal–Wallis test to compare two-region power ratios between the groups and obtain p-values. We considered $p < 0.005$ as statistically significant and used Bonferroni correction for a total of 10 components.

Receiver operating characteristics (ROC) curve analysis was conducted to distinguish between the dementia, CU, and aMCI groups. We obtained area under the ROC curve (AUC) as a complementary measure of a parameter's performance at discriminating between the three groups. We also calculated sensitivity and specificity based on an optimum threshold that maximizes accuracy.

Statistical analyses were performed using SPSS software package (version 26; SPSS Inc., Chicago, IL), MATLAB (R2019a), and R (version 3.5.3).

Declarations

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Author Contributions

MK, Conceptualization, Formal analysis, Validation, Methodology, Writing original draft

MN-S, HM, KK, ST, YM, JK, CA, MH, SK, Conceptualization, Validation, Methodology, Writing review & editing

YI, Conceptualization, Data curation, Writing original draft

MY, Conceptualization, Funding acquisition, Project administration, Writing review & editing, Supervision

KO, Writing review & editing, Supervision

Competing interests

M.K., H.M., K.K., S.T., and Y.M., are employed by a private company, Ricoh Company Ltd. M.N-S., J.K., C.A., and M.H., belong to an endowment department, supported with an unrestricted grant from Ricoh Company Ltd. These do not alter our adherence on the manuscript. The other authors declare no competing financial conflicts of interest to disclose.

Data availability

The informed consent did not include a declaration regarding public availability of data, and the datasets for this study will not be made publicly available. Source scripts for analysis and anonymized data are available from the corresponding author on reasonable request.

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Figures

Figure 1

Grand-averaged ROI time-courses (± 1 STD) determined by multiplying the voxel-level source time-courses by the singular vector of largest singular value among the time-courses for CU (blue lines), aMCI, and dementia (red lines) in the dorsal stream: MVOcC (upper left), LOcC (upper middle), Pcun (upper right), IPL (lower left), and SPL (lower right). The solid vertical lines indicate optic flow stimuli onset. The dashed vertical lines indicate 150 ms after optic flow stimuli onset. The time within the interval from 100 to 300 ms is highlighted in yellow.

Abbreviations:

ROI, region of interest; CU, cognitively unimpaired; aMCI, amnesic mild cognitive impairment; MVOcC, medial ventral occipital cortex; LOcC, lateral occipital cortex; Pcun, precuneus; IPL, inferior parietal lobule; SPL, superior parietal lobule

Figure 2

Grand-averaged source localization map on voxel-level source power at 150 ms after optic flow stimuli onset in the CU (upper left), aMCI (upper right), and dementia (lower left) groups. Regions of MVOC (green), LOC (orange), Pcun (blue), IPL (red), and SPL (pink) on source localization map (lower right)

Abbreviations:

CU, cognitively unimpaired; aMCI, amnesic mild cognitive impairment; MVOcC, medial ventral occipital cortex; LOcC, lateral occipital cortex; Pkun, precuneus; IPL, inferior parietal lobule; SPL, superior parietal lobule

Figure 3

Scatter plots showing the distributions of IPL/MVOcC (left) and IPL/Pkun (right). *p < 0.05, **p < 0.01

Abbreviations:

CU, cognitively unimpaired; aMCI, amnesic mild cognitive impairment; MVOcC, medial ventral occipital cortex; Pkun, precuneus; IPL, inferior parietal lobule

Figure 4

ROC curves of the power ratios IPL/MVOcC (blue line) and IPL/Pcun (red line) used to distinguish dementia from CU and aMCI. The diamond symbol () indicates the optimum threshold of each ROC curve.

Abbreviations:

CU, cognitively unimpaired; aMCI, amnesic mild cognitive impairment; MVOcC, medial ventral occipital cortex; Pkun, precuneus; IPL, inferior parietal lobule

Figure 5

Optic flow task

Supplementary Files

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- [Supplementarymaterialnumber1.mov](#)