The brain structural and functional anomaly associated with simultanagnosia in patients with posterior cortical atrophy

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Research

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Abstract

Backgroud

Posterior cortical atrophy (PCA) is a rare neurodegenerative disease characterized by impairments in visual processing and in other relatively selective posterior cortical functions, mainly involving occipito-parietal regions. As the most common and important clinical manifestation, simultanagnosia is a profound inability of a patient with PCA to integrate multiple visual elements and to precept the global precedence within a scene. With few reports, the structural and functional changes in the brain associated with simultanagnosia are still yet comprehended more fully.

Methods

This study recruited 18 PCA patients with simultanagnosia, 29 patients with Alzheimer's disease (AD) and 20 cognitively normal controls (NC). All subjects underwent a full neuropsychological evaluation, picture-/computer-based simultanagnosia tests, structural and resting-state functional MRI. Grey matter volume (GMV) was assessed by voxel-based morphometry, while seed based intrinsic functional connectivity (iFC) was evaluated based on the PCA-specific grey matter injuries in contrast to AD. Finally, the correlations between the statistically significant structural or functional MRI features and the simultanagnosia were evaluated in PCA patients.

Results

We found that, between PCA and AD patients, there was no significant difference in clinical dementia rating, immediate memory and delayed memory, while the marked difference was exhibited in neuropsychological assessments, and also in the picture-based and computer-based test score ($P<0.01$). In addition to brain areas where both PCA and AD patients had compatible regional GMV reduction each in contrast with NC group, the left middle occipital gyrus and ventral occipital areas were specifically affected by PCA relative to AD. Also in contrast to AD, PCA had lower iFC from left middle occipital gyrus, left lingua gyrus and right middle occipital gyrus. Moreover, we found that GMV of left middle occipital gyrus, its functional coupling to right superior occipital gyrus, the GMV of left inferior occipital gyrus and the iFC from right middle occipital gyrus to left superior parietal gyrus were each correlated to simultanagnosia ($r=0.670$, $p=0.002$; $r=-0.517$, $p<0.001$; $r=0.605$ $p=0.008$; $r=0.778$, $p<0.001$, respectively) in PCA patients.

Conclusions

Simultanagnosia is associated with the lower structural GMV and lower iFC in the left middle occipital gyrus and the left inferior occipital gyrus in PCA.

Background

First described by Benson in 1988[1], posterior cortical atrophy (PCA) is a clinical syndrome characterized by visual impairment and the associated parietal occipital cortical atrophy, with the same pathologies as with Alzheimer's disease(AD).[2] Typically, a PCA patient has marginal memory impairment in his/her early stage, but with distinctive symptoms such as space/objective perception deficit, constructional dyspraxia, and, the most representatively, the simultanagnosia. As reported in previous researches, simultanagnosia is the only performance deficit in 85% of PCA patients in their early stage.[3, 4]

Patients with simultanagnosia can't recognize and classify objects when they appear together but can perfectly when each of the objects appears separately. For a given scene/picture, they can describe each isolated element in the picture, but are unable to perceive the overall meaning of the picture as a whole or multiple things together.[5] For more complete and accurate observation of objects, they prefer a longer distance and a smaller object to see.[6] In the typical picture-based simultanagnosia test, they can only recognize 1 or 2 objects in a picture containing overlapping objects such as umbrella, tea cup, saw and pear, resulted from the impairment of perceiving multiple visual locations simultaneously.[6]

Simultanagnosia has always been an interesting research topic because of its particularity. However, its pathogenesis remains unclear. Though PCA was medically recognized till 1988, medical professional observed simultanagnosia as early as in World War I and World War II in wounded veterans with visual spatial impairment.[7] Moreover, they hypothesized that simultanagnosia is associated with parietal lobe damage.[7] However, studies on PCA and/or simultanagnosia were in general rarely reported. In recent years, only few studies investigating the neuroimaging characteristics of patients with simultanagnosia were found in the literature.[8–11] Amongst these few were two case reports about the the specific encephalic changes of cerebral ischemia patients who had simultanagnosia using structural magnetic resonance imaging (sMRI) and single photon emission computed tomography. [8, 9] The authors suggested that simultanagnosia was related to the right temporoparietal area in one patient and the left parietooccipital lobe in the other.[8, 9] A case-control study published in 2016 comparing sMRI findings between 12 PCA subjects and 12 healthy controls, reported the white matter atrophy within the left association fiber pathway resulted in simultanagnosia. As the authors pointed out in their report, the impact of cognitive impairment on the sMRI based findings could not be assessed due to the lack of cognition-matched group.[10] Another research included AD group and PCA group with matched MMSE scores, and found that the hypoperfusion in the right inferior occipital gyrus, middle occipital gyrus and left middle occipital gyrus were related to simultanagnosia through SPECT technique.[11]

Aimed to better understand the simultanagnosia's pathogenesis, our current research is intended to systematically investigate the association of the visual impairment with both structural sMRI and functional anomaly using sMRI and resting-state functional MRI (rs-fMRI) techniques in patients with PCA. For rs-fMRI, we primarily considered intrinsic functional connectivity (iFC). To eliminate the influence of cognitive impairment, we especially enrolled disease-course and dementia-severity matched AD patients as well as cognitively normal controls (NC) group in order to characterize the unique correlate in

PCA patients. In this research, we attempted to explore the onset locus of simultanagnosia and explain its causes, providing a basis for further research on early diagnosis and treatment of this syndrome.

Methods

Participants

From August 2017 to June 2018, eighteen patients with PCA, twenty-nine patients with AD and twenty NC were recruited by the Department of Neurology in Xuanwu Hospital. We obtained written informed consent of individuals themselves or their families for participating in this study according to the Declaration of Helsinki. The informed consent form was approved by the ethics committee of Xuanwu Hospital, Capital Medical University on Human Clinical Research.

All the participants accomplished detailed clinical history interview, physical examination and neuropsychological assessment. Every patient with PCA fulfilled the diagnostic criteria developed in 2017, especially with deficits of simultaneous perception.[12] Patients with AD met the diagnosis criteria established by the International Working Group (IWG-1).[13] In addition, subjects in NC group were above the cut-off values for the education-adjusted Mini Mental State Examination (MMSE, > 19 for illiterate, 22 for primary school and 24 for secondary school and above), and for Montreal Cognitive Assessment (MoCA, 13, 19 and 24 separately for illiterate, primary and secondary schools).[14, 15] Moreover, all NC subjects had 0 score for Clinical Dementia Rating scale (CDR) sum of boxes.[16] As detailed below, all subjects finished the whole neuropsychological examination and imaging examination, without any other disease such as depression, cerebrovascular disease, poisoning, infection and metabolic diseases that can explain the patient's memory impairment and related symptoms.

Neuropsychological assessment

Global cognitive function was assessed by MMSE and MoCA, as well as the severity of dementia was detected by CDR. Episodic memory was evaluated by the World Health Organization University of California-Los Angeles Auditory Verbal Learning Test (AVLT), including the AVLT-immediate, AVLT-delay and AVLT-clue subtests.[17] Language ability was assessed using the Boston Naming Test (BNT), meanwhile the attention and executive function were detected by the modified Trail Making Test (TMT) parts A.[18–20]

Simultanagnosia and visuospatial construction test

Two methods were used to assess the simultaneous perception of participants. The first is the classical picture-based test, which asked the subject to respectively name each individual object which overlaps with each other in a given figure.[21] The other method is a computer-based test designed and developed

by Beijing Normal University. In the computer-based test, the subjects sat in a chair with their eyes about 50 cm away from the computer screen on which a large geometric shape composing of a number of small but identical geometric shapes such as triangle, square or circle was randomly presented. This test was divided into two parts– local shape test and global shape test. In the local shape test, participants were required to ignore the shape of whole figure and determine the shape of the same small ones, and in the global shape test they had the opposite requirement. Each of two parts contains 54 geometric shapes, with five trials before the test. Participants' responses were recorded by the computer and one point was awarded for each correct answer. In addition, the response time was also automatically recorded by the computer. (see Additional file 1)

Optic ataxia was assessed through the method described by Karnath and Perenin[22]. Visuospatial function was assessed by the revised Rey-Osterrieth Complex Figure Test (ROCFT) (16-point scoring), meanwhile rapid automatized naming test was used to exam the reading ability.[23, 24]Besides, facial agnosia was evaluated by accurate naming a total of 10 celebrity avatars (including national leaders and actors).

All participants underwent detailed neuropsychological and specific visuospatial construction tests. The time interval was less than one month between the cognitive test and the MRI scan visits.

MRI scanning and imaging parameters

Magnetic resonance scanning was performed on a GE Signa PET/MR 3.0 T scanner (GE Healthcare, Milwaukee, WI) in Xuanwu Hospital, Capital Medical University. During the scanning, participants were asked to remain quiet and eyes-closed, and to think of nothing in particular. High-resolution T1-weighted structural images and resting state functional images were acquired from all participants with following parameters: structural data were collected using 3D magnetization prepared rapid gradient echo sequences [192 sagittal slices, repetition time/echo time = 6.9/3.0 ms, slice thickness = 1 mm, flip angle = 12°, acquisition matrix = 256 × 256, field of view = 256 mm × 256 mm], and functional data were obtained with an echo-planar imaging sequence [repetition time/echo time = 2000/30 ms, flip angle = 90°, 36 slices, slice thickness = 3.5 mm, acquisition matrix = 64 × 64, field of view = 230 mm × 230 mm, 240 images].

Data processing and analyses

Structural image preprocessing and analysis

The CAT12 toolbox (www.neuro.uni-jena.de/cat) was used to preprocess the images with all default settings. The images were bias-corrected, tissue classified, and normalized to Montreal Neurological Institute (MNI) space using linear (12-parameter affine) and nonlinear transformations, within a unified model including the high-dimensional DARTEL normalization.[25, 26] Grey and white matter segments were modulated to preserve actual tissue amount locally, and after QC and homogeneity inspections, all

images were smoothed with a Gaussian kernel of 8 mm full-width-half-maximum. We conducted voxel-based morphometry (VBM) analyses to explore grey matter volume differences among the PCA, AD and NC groups, by analyses of covariance (ANCOVA) with age, gender, years of education and the intracranial volume as covariates, and the significance was judged when $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons. Mean value of significant clusters identified were then extracted for further analyses.

Resting state functional image preprocessing and analysis

Images were processed using Data Processing & Analysis for Brain Imaging toolbox. [27]The first ten volumes from each scan were excluded as dummy scans to allow stability of magnetization. Slice timing correction and image realignment to correct the head motion were followed, and after the segmentation of co-registrated T1-weighted structural images, realigned functional images were spatial normalized to MNI space at 3 mm isotropic voxel resolution based on transformation parameters computed with the DARTEL tool. The linear trend, head motion parameter measured by the Friston-24 model, white matter, and cerebrospinal fluid signals were further regressed out as nuisance covariates.[28] Then the resultant images were temporal filtered (0.01–0.1 Hz) and smoothed with a 4 mm FWHM Gaussian kernel.

To inspect how group differences in GMV impact the cortical functional coupling, we constructed iFC based on the peak coordinates of clusters identified in structural VBM analyses which identified the difference between AD and PCA. We drew 5-mm radius balls as regions of interest (ROI) at one of these given peaks as the seed ROI. To from the iFC map, we extracted the rs-fMRI mean time series from those ROIs, and calculated the Pearson's correlation coefficient between each of those and time series of every voxel in the brain, and after normalization of the correlation maps with Fisher's r to z transformation. The z-score images as the iFC maps were compared among groups by the means of voxel-wise ANCOVA with Statistical Parametric Mapping toolbox (SPM12, https://www.fil.ion.ucl.ac.uk/), and Monte Carlo simulation was used for multiple comparison corrections ($p < 0.001$ uncorrected, 10,000 iterations) to achieve a cluster-level false-positive rate of 0.05. For significant clusters found in pairwise comparisons, mean iFC over a given cluster was extracted for subsequent correlation analyses with simultanagnosia measure within PCA group.

Statistical analyses

ANOVA were administered to compare demographic data, neuropsychological score and visuospatial function among three groups in SPSS (version 22.0, IBM Inc., New York, NY). To explore the relationships between neuroimaging findings and simultanagnosia, partial correlation analyses were performed in PCA group between the results of simultanagnosia tests and GMV and the iFCs, considering the covariates such as age, gender, years of education and course of disease. A statistical significance level of $p < 0.05$ was used in these analyses.

Results

Demographic, neuropsychological and visuospatial assessment results

There was no statistically difference in age, years of education and sex ratio, while significant differences were showed in TMT A test ($F = 39.44$, $p < 0.01$), reading test ($F = 21.26$, $p < 0.01$) and face agnosia test ($F = 10.28$, $p < 0.01$) among the three groups, that the PCA group performed obviously worse than the other. Moreover, no significant difference was found in disease course, immediate or delayed memory and CDR scores between PCA and AD groups, suggesting that the degree of cognitive impairment was comparable in these two groups ($F = 46.20$, $p < 0.01$; $F = 181.23$, $p < 0.01$; $F = 49.58$, $p < 0.01$). The obviously lower scores of MMSE and MoCA in PCA group comparing to AD group also should be noticed ($t=-2.21$, $P = 0.03$; $t=-3.09$, $P = 0.004$).(Table 1)

Table 1

Demographics, neuropsychological and visuospatial construction assessment of three groups

	PCA group (n = 18)	AD group (n = 29)	NC group (n = 20)	F/χ 2	P
Gender (male/female)	7/11	12/17	13/7	3.42	0.18
Age (years)	57.56 ± 5.04	58.31 ± 5.22	57.10 ± 6.29	1.80	0.17
Years of education	9.22 ± 5.24	11.48 ± 3.38	11.50 ± 2.96	2.27	0.11
Age at onset (years)	53.61 ± 4.45	54.62 ± 5.86	—	-0.63	0.53
Disease duration (years)	3.94 ± 1.51	3.59 ± 1.70	—	0.73	0.47
General neuropsychological tests					
MMSE (30)	13.11 ± 5.26	17.28 ± 6.85	29.30 ± 0.80	49.80	< 0.01[a,b]
MoCA (30)	7.39 ± 3.84	12.41 ± 7.30	27.40 ± 1.60	76.82	< 0.01[a,b]
CDR (3)*	1.42 ± 0.55	1.26 ± 0.62	0.00 ± 0.00	49.58	< 0.01 [a]
Immediate memory (45)	7.22 ± 6.50	10.35 ± 5.96	24.10 ± 5.30	46.20	< 0.01 [a]
Delayed memory (15)	0.28 ± 0.67	1.03 ± 1.97	9.25 ± 1.83	181.23	< 0.01 [a]
BNT (30)	13.94 ± 5.41	17.69 ± 6.10	25.70 ± 2.25	27.57	< 0.01[a,b]
Attention—TMT A					
Time (150 s) **	150.00 ± 0.00	116.03 ± 47.07	47.65 ± 17.02	50.10	< 0.01[a,b]
No. of correct lines (24)	2.72 ± 5.22	13.07 ± 10.40	24.00 ± 0.00	39.44	< 0.01[a,b]
Visuospatial construction					
Optic ataxia test (4)	2.17 ± 1.76	3.72 ± 1.03	4.00 ± 0.00	14.63	< 0.01[a,b]
ROCFT (16)	1.11 ± 3.18	8.03 ± 6.52	15.05 ± 0.76	43.01	< 0.01[a,b]

a Significant when comparing both patient groups to the NC group. b Significant when comparing the PCA and AD groups.

* Lowest/worst value for the assessment; ** Time limit for the test. Values in parentheses not marked with an asterisk indicate the highest/best value for the assessment.

AD, Alzheimer's disease; BNT, Boston Naming Test; CDR, Clinical Dementia Rating; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal control; PCA, posterior cortical atrophy; ROCFT, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test

	PCA group (n = 18)	AD group (n = 29)	NC group (n = 20)	F/χ 2	P
Reading test (s) Face agnosia(10)	84.25 ± 33.28 6.50 ± 3.11	43.52 ± 27.35 8.17 ± 2.66	20.59 ± 3.94 10.00 ± 0.00	21.26 10.28	< 0.01[a,b] < 0.01[a,b]
a Significant when comparing both patient groups to the NC group. b Significant when comparing the PCA and AD groups.					
* Lowest/worst value for the assessment; ** Time limit for the test. Values in parentheses not marked with an asterisk indicate the highest/best value for the assessment.					
AD, Alzheimer's disease; BNT, Boston Naming Test; CDR, Clinical Dementia Rating; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal control; PCA, posterior cortical atrophy; ROCFT, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test					

Simultanagnosia test results

The score of picture test and computer-based global shape test was statistically different among the three groups (F = 62.33, p < 0.01; F = 79.82, p < 0.01), in which PCA group were significantly lower than AD group (t=-7.63, P < 0.01; t=-9.20, P < 0.01), while there were no obvious difference in computer local shape test score (F = 1.91, p = 0.16). In addition, the time of the computer-based local shape test in PCA group was significantly longer than that of AD group (F = 20.83, p < 0.01), while the time of the computer-based global shape test was not different (F = 9.81, p□0.01).(Table 2)

Table 2

simultanagnosia test score of three groups

	PCA group (n = 18)	AD group (n = 29)	NC group (n = 20)	F	P
Picture test score (4)	1.11 ± 0.68	3.10 ± 1.11	4.00 ± 0.00	62.33	< 0.01 [a,b]
Computer test score (global) (1)	0.43 ± 0.20	0.93 ± 0.17	0.99 ± 0.01	79.82	< 0.01 [a,b]
Computer test score (local) (1)	0.91 ± 0.10	0.94 ± 0.02	0.94 ± 0.02	1.91	0.16
Computer test response time (global) (s)	425.09 ± 218.13	360.11 ± 383.41	62.04 ± 13.94	9.81	< 0.01 [a,]
Computer test response time (local) (s)	269.24 ± 146.93	159.55 ± 102.79	55.36 ± 12.77	20.83	< 0.01 [a,b]
a Significant when comparing both patient groups to the NC group. b Significant when comparing the PCA and AD groups.					

Grey matter volume in cerebral cortex

As shown in Fig. 1B and Fig. 1C, VBM analysis revealed typical spatial map of lower grey matter volumes in both AD and PCA patients compared to NC participants, covering the bilateral middle temporal lobe, precuneus, posterior cingulate cortex, as well as left temporoparietal cortices, and this spatial map extended to posterior occipital cortex in PCA patients (details on cluster coordinates in Additional file 2). It's worth to note that brain regions surviving the FWE correction when comparing PCA to AD located in left middle occipital gyrus (Cluster size = 1376, T = 5.980), left lingual gyrus (Cluster size = 162, T = 5.848), right fusiform gyrus (Cluster size = 116, T = 5.743), right middle occipital gyrus (Cluster size = 114, T = 5.328) and left inferior occipital gyrus (Cluster size = 99, T = 5.927), especially in left middle occipital gyrus along with ventral occipital areas (Fig. 1D, Additional file 3).

Functional disconnection

In order to figure out how reduced gray matter volume impacted cortical functional coupling, regions where significant lower gray matter volume were identified in PCA compared to AD group were selected (Additional file 3), and 5-mm radius sphere centered on each regions was used to extract the time series as the seed data, to calculate the iFC based on rs-fMRI. Comparing the iFC maps, we found functional disconnection in PCA compared to AD appeared only in three seed-ROI based maps: left middle occipital gyrus, left lingua gyrus and right middle occipital gyrus respectively. Smaller iFCs were observed in 7 regions with left middle occipital gyrus as the seed-ROI, as weel as some regions with the other seed ROIs (Fig. 2, Additional file 4).

Correlation between simultanagnosia and MRI results

In order to explore how structural and functional cortical alterations linked to simultanagnosia, we analyzed the relationship of neuroimage indices (GMV or iFC) and simultanagnosia within the PCA group. After adjusting age, gender, years of education and disease course, it was revealed that only GMV of left middle occipital gyrus was associated with picture test ($r = 0.670$, $p = 0.002$), while only GMV of left inferior occipital gyrus was correlated to the accuracy rate of the computer global shape test ($r = 0.778$, $p < 0.001$; Fig. 3). iFC between left middle occipital gyrus and right superior occipital gyrus, as well as between right middle occipital gyrus and left superior parietal gyrus, was associated with the computer global shape test score ($r=-0.517$, $p = 0.028$; $r = 0.605$, $p = 0.008$; Fig. 3).

Discussion

In this study, PCA patients were selected as the experimental group to research the imaging abnormalities of simultanagnosia in not only brain structure but also brain iFC. The AD group was included in this study aimed to specifically eliminate the impact of cognitive decline. To the best of our knowledge, this is the first study that examined both structural and functional abnormalities in PCA.

Our results showed that compared with AD group, reduced grey matter volume in PCA group occurred in five different brain regions, mainly in the left middle occipital gyrus and ventral occipital area, which were

positively correlated with the scores of picture-based test or computer global shape test. Among these atrophic brain regions, only the left middle occipital gyrus, left lingua gyrus and right middle occipital gyrus had decreased functional connections. Furthermore, we found correlations between bilateral middle occipital gyrus and the computer global shape test scores. Overall, our findings suggested that the occurrence of simultanagosia was related to left middle occipital gyrus and left inferior occipital gyrus.

The reduced grey matter volume and iFC related to simultanagnosia in PCA patients

In our study, picture-based test and computer-based global shape test scores were adopted as the principal standards of evaluating simultanagnosia, on the basis of which the severity of symptom was distinguished. It was showed that both AD and PCA patients had simultanagnosia, but its degree of PCA patients was more severe. Most previous imaging studies on PCA patients did not correlate the imaging results with their clinical manifestations, or only explored the relationship between the MRI results and visual perception disorders in general, without focusing on a complex and characteristic symptom.[29–31] In the present study, according to the structural and rs-fMRI measures which significant differences between PCA and AD were observed, not only the grey matter volume but also its decreased iFC associated with simultanagnosia with PCA patients.

Our result showed that the brain regions with significantlhy reduced grey matter volume in PCA patients were left middle occipital gyrus, whose iFC to right superior occipital gyrus, bilateral postcentral gyrus, left precentral gyrus, right inferior parietal gyrus, left superior parietal gyrus and left superior temporal gyrus also decreased distinctly, and ventral occipital areas including left lingual gyrus, left inferior occipital gyrus, right fusiform gyrus and right middle occipital gyrus. Moreover, both reductions were each positively correlated with simultanagnosia, providing evidence that simultanagnosia is related to the atrophy of the left middle occipital gyrus and the left inferior occipital gyrus. Another interesting finding of our current study was the negative correlation of simultanagnosia with the iFC between left middle occipital gyrus and right superior occipital gyrus. With the lack of other possible interpretations and need for additional studies, we postulate that this might suggest the presence of compensation mechanism. The increased connectivity between right middle occipital gyrus and left superior parietal gyrus of PCA patient reinforced our conclusion. Simultanagnosia was more dependent on the malfunction of iFC between occipital cortex and the higher visual processing cortex, meanwhile negatively correlated with the functional connectivity within the occipital lobe. Besides, right middle occipital gyrus was atrophic and in PCA group, as well as with decreased iFC to left superior parietal gyrus, consistent with the observed positive correlation with simultanagnosia. Again, because of the limited number of samples and the need for direct hypothesis based evidence, additional studies are needed to confirm our findings especially the role of right middle occipital gyrus in simultanagnosia.

Primary visual cortex lesion is the main pathogenesis of simultanagnosia

The primary visual cortex of human being is located in Brodmann 17 area, which is the neural basis for the earliest processing of visual stimulus, processing visual features including directional movement, spatial frequency, parallax and color.[3] Totally overlapping with primary visual cortex, our findings with regard to the left middle occipital gyrus and left inferior occipital gyrus and their volumetric/iFC association with simultanagnosia suggested a reasonable hypothesis that the lesion of primary visual cortex is the main pathogenesis of simultanagnosia.

There were some researches attributed simultanagnosia to the lesion of unilateral region along the ventral visual pathway, some found an association between simultanagnosia and dorsal pathway [32–35] yet others suggested that the change of temporal parietal lobe, the terminal of visual dorsal pathway, was highly correlated with the development of simultanagnosia.[36, 37] Besides, the hypothesis that attention deficit results in simultanagnosia is still the most widely accepted viewpoint at present, but there are also some studies have confirmed that the attention network is largely affected by ventral visual pathway.[38–40] The key point all these mechanism studies ignored is that although the visual pathway of human being is divided into dorsal pathway and ventral pathway, they both starts from primary visual cortex.[41] Combining with our study results, we suggested that the generation of simultanagnosia is derived from the dysfunction of visual pathway with the origin at the primary visual cortex.

Clinical implications and limitations

We hope that the results of this study can help distinguish the visual functional impairment characterized by simultanagnosia and other ocular dysfunction, contributing to the early diagnosis of PCA. This conclusion can also provide a target cerebral region for further research for the treatment of patients with simultanagnosia.[42] On the whole, the biggest limitation in our study is the relatively small sample size. Moreover, although strict diagnostic criteria were applied to recruit PCA patients and AD patients, amyloidosis for them were not part of the diagnosis. In future research, we will increase the sample size, assess the amyloidosis and conduct longitudinal follow-up to further confirm our conclusion and hypothesis.

Conclusion

This study indicated that simultanagnosia which is independent of the cognitive impairment is associated with the lower structural GMV and lower iFC in the left middle occipital gyrus and the left inferior occipital gyrus in PCA.

Declarations

Ethics approval and consent to participate: This study was performed in accordance with the Declaration of Helsinki and approved by Ethics committee, Xuanwu Hospital. Informed consent to participate in the study have been obtained from participants and a statement to this effect appeared in the manuscript.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: YL, BKL, KWC and LYW were responsible for study concept and design. CLC, DLJ, ZGL, XXZ and DL were responsible for clinical data collection. CSY, YJC and ZJZ analyzed image results. YC and YL were the major contributors in writing the manuscript. JL, PRN, SG, ZJZ, KWC and LYW were responsible for critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Abbreviations

AD, Alzheimer’s disease; ANCOVA,analyses of covariance; AVLT:Auditory Verbal Learning Test; BNT:Boston Naming Test; CDR:Clinical Dementia Rating; FWE:family-wise error; GMV:grey matter volume; iFC:Intrinsic functional connectivity; MMSE:Mini Mental State Examination; MNI:Montreal Neurological Institute; MoCA:Montreal Cognitive Assessment; NC:normal control; PCA:posterior cortical atrophy; ROCFT:Rey-Osterrieth Complex Figure Test; ROI:regions of interest; rs-fMRI:resting-state functional MRI; sMRI:structural magnetic resonance imaging; TMT:Trail Making Test; VBM:voxel-based morphometry

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Additional Files

File name and file format: Additional file 1.png

Title of data: Additional Figure 1.

Description of data: A: picture-based test; B: computer-based test

File name and file format: Additional file 2.doc

Title of data: Additional Table 1. Atrophied foci characteristics that were found in clinical patients compared to NC group

Description of data: Atrophied foci characteristics that were found in clinical patients compared to NC group

File name and file format: Additional file 3.doc

Title of data: Additional Table 2. Atrophied foci characteristics that were found in the PCA group as compared to AD group

Description of data: Atrophied foci characteristics that were found in the PCA group as compared to AD group

File name and file format: Additional file 4.doc

Title of data: Additional Table 3. Functional disconnection in PCA versus AD

Description of data: Functional disconnection in PCA versus AD

Figures

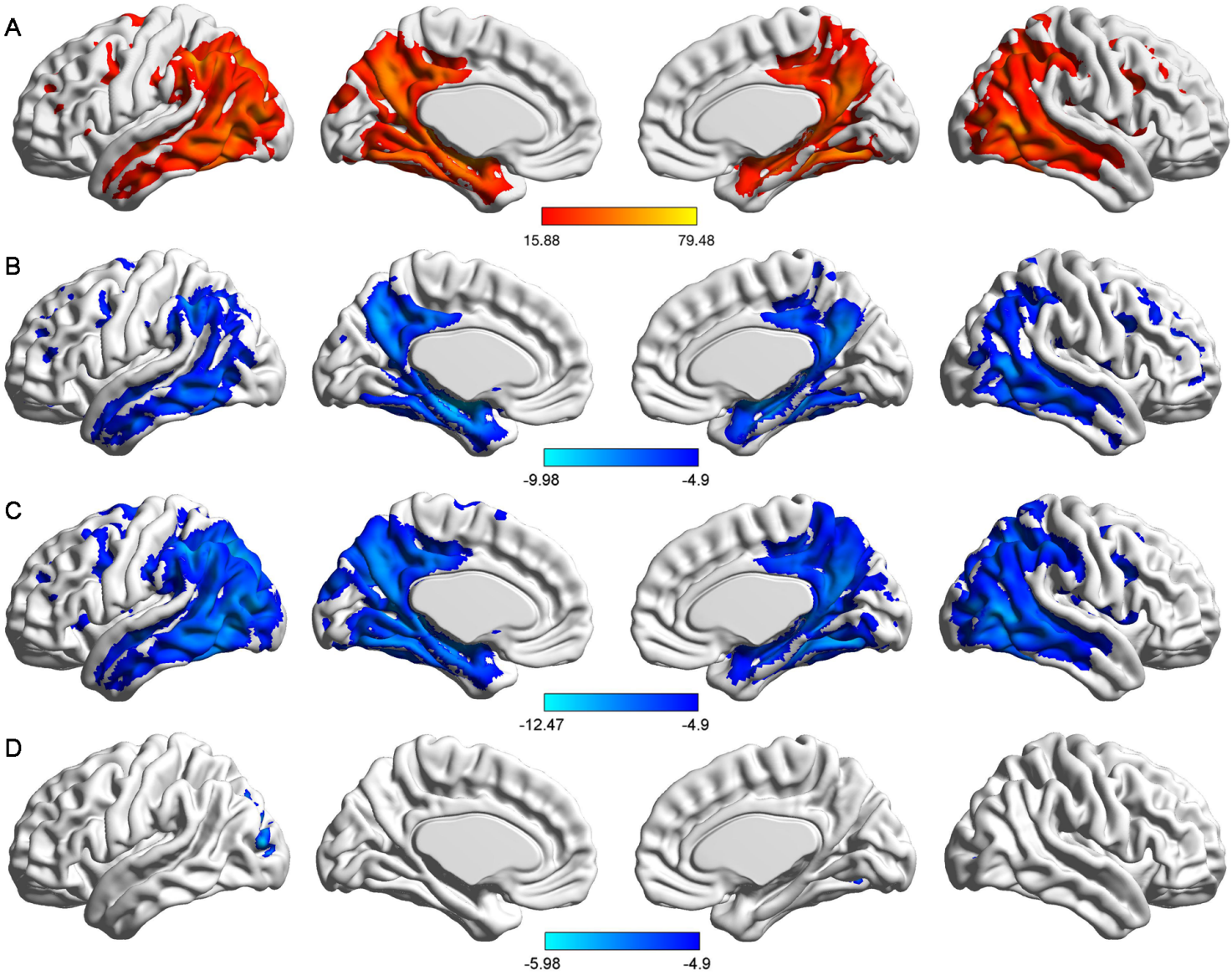

Figure 1

Group comparisons of whole brain grey matter volume. All results survived the FWE corrected $p < 0.05$. (A) Comparison in NC, AD and PCA groups using ANCOVA. (B) Reduced gray matter volume in the AD group, relative to the NC group. Reduction was mainly found in bilateral middle temporal lobe, precuneus, posterior cingulate cortex, and left temporoparietal cortices. (C) Reduced gray matter volume in the PCA group, relative to the NC group. Reduction was mainly found in left superior occipital lobe, right fusiform, left thalamus, left superior temporal lobe and right middle frontal lobe. (D) Reduced gray matter volume in the PCA group, relative to the AD group. Reduction was mainly found in left middle occipital gyrus, along with ventral occipital areas.

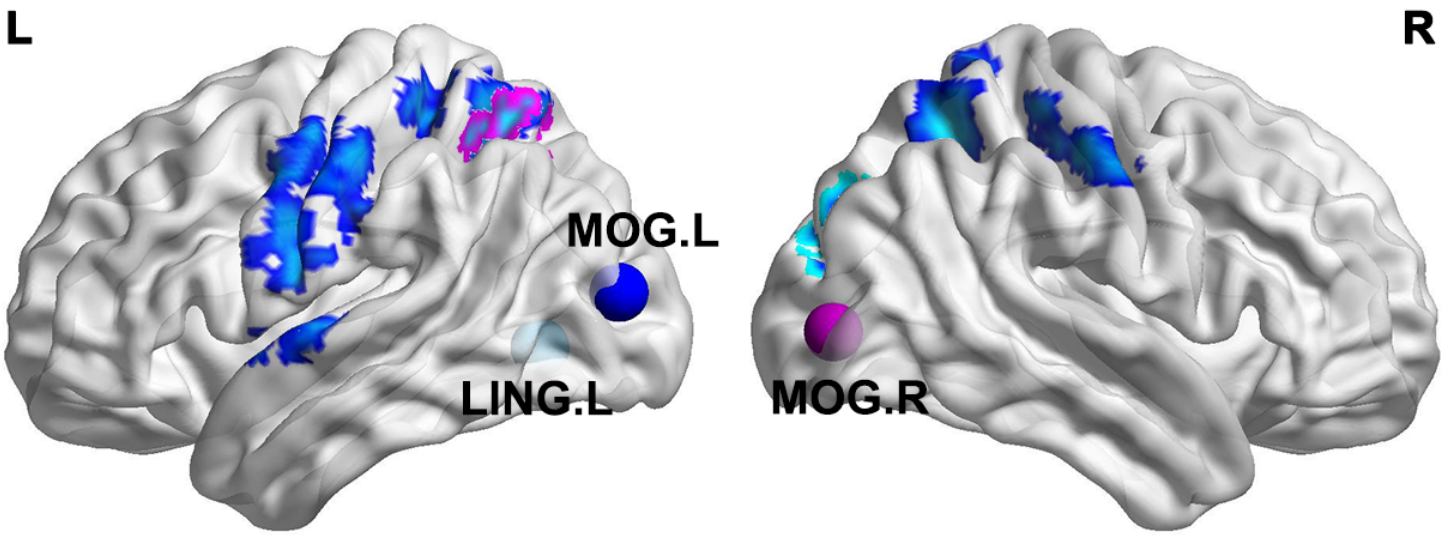

Figure 2

Reduced functional connectivity in PCA compared to AD. According to VBM analysis, five regions with significant atrophy in PCA patients compared with AD group, then 5-mm radius sphere centered on peak coordinates were drawn for calculating iFC. iFC from left middle occipital gyrus to right superior occipital gyrus, bilateral postcentral gyrus, left precentral gyrus, right inferior parietal gyrus, left superior parietal gyrus and left superior temporal gyrus was decreased significantly in PCA patients; meanwhile, iFCs from left lingua gyrus to right superior occipital gyrus, from right middle occipital gyrus to left superior parietal gyrus was also reduced in PCA. MOG.L, left middle occipital gyrus; LING.L, left lingua gyrus; MOG.R, right middle occipital gyrus.

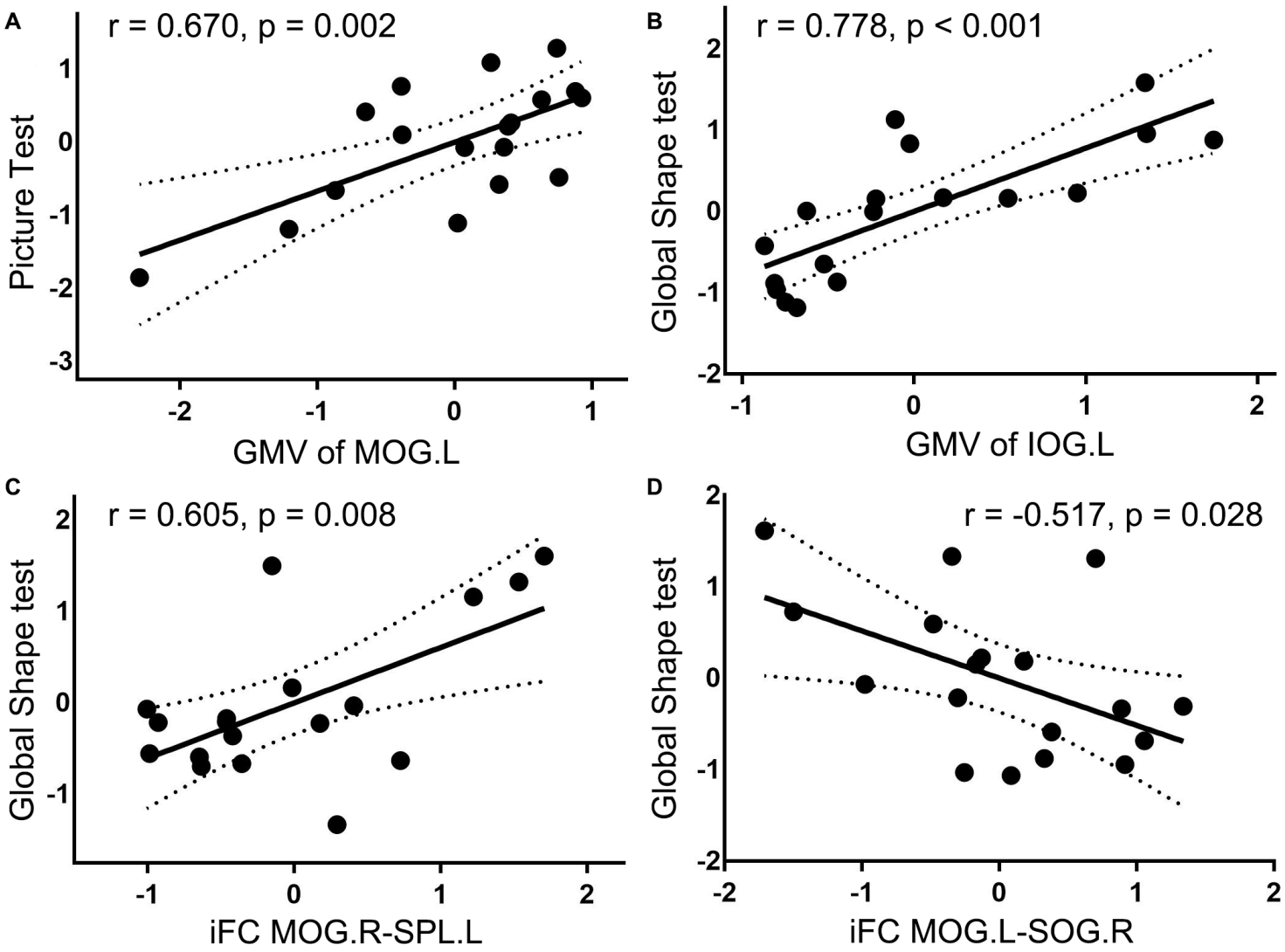

Figure 3

Relationships between simultanagnosia and GMV and iFC. (A-B) Simultanagnosia is positively correlated with the grey matter volume of left middle occipital gyrus and left inferior occipital gyrus. (C)Simultanagnosia is positively correlated with the iFC between right middle occipital gyrus and left superior parietal gyrus. (D)Simultanagnosia is negatively correlated with the iFC between left middle occipital gyrus and right superior occipital gyrus. All measurements were standardized to calculate the partial correlations. MOG.L, left middle occipital gyrus; IOG.L, left inferior occipital gyrus; MOG.R, right middle occipital gyrus; SPL.L, left superior parietal gyrus; SOG.R, right superior occipital gyrus.

Supplementary Files

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