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• Clinical Research •

Altered brain network centrality in patients with retinal vein occlusion: a resting-state fMRI study

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Abstract

● **AIM:** To explore the intrinsic brain activity variations in retinal vein occlusion (RVO) subjects by using the voxel-wise degree centrality (DC) technique.

● **METHODS:** Twenty-one subjects with RVO and twenty-one healthy controls (HCs) were enlisted and underwent the resting-state functional magnetic resonance imaging (rs-fMRI) examination. The spontaneous cerebrum activity variations were inspected using the DC technology. The receiver operating characteristic (ROC) curve was implemented to distinguish the DC values of RVOs from HCs. The relationships between DC signal of definite regions of interest and the clinical characteristics in RVO group were evaluated by Pearson's correlation analysis.

● **RESULTS:** RVOs showed notably higher DC signals in right superior parietal lobule, middle frontal gyrus and left precuneus, but decreased DC signals in left middle temporal gyrus and bilateral anterior cingulated (BAC) when comparing with HCs. The mean DC value of RVOs in the BAC were negatively correlated with the anxiety and depression scale.

● **CONCLUSION:** RVO is associated aberrant intrinsic brain activity patterns in several brain areas including pain-related as well as visual-related regions, which might assist to reveal the latent neural mechanisms.

● **KEYWORDS:** retinal vein occlusion; functional magnetic resonance imaging; voxel-wise degree centrality; spontaneous brain activity
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INTRODUCTION

Retinal vein occlusion (RVO), sometimes referred to as "eye stroke", is a thrombosis obstruction in the retinal venous system, which might associate with the central or branch retinal vein[1], and characterized by intraretinal haemorrhages, various degrees of retinal vessel blockage and tortuosity, and cystoid macular edema[2]. The prevalence of epidemiological investigations varies from 0.1% to 0.5% among the middle-aged group and elderly group[3-5]. RVO becomes the 2nd common cause leading to vision deterioration among retinal vessels disorders following diabetic retinopathy. Regular ophthalmic examinations for RVO contain fundus fluorescein angiography and optical coherence tomography (OCT)[6], but there's few tests focus on the neuroimaging. The exploration of RVO-related cerebral progress using neuroimaging is a brand-new prospect in visual neuroscience which could promote to unveil the underlying mechanisms.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a broadly used noninvasive neuroimaging technology which is relied on cerebrum blood flow and metabolize analysis, and it has been improved progressively and enabled scientists to explore functional changes of specific cerebral regions at resting-state. The rs-fMRI has been applied to inspect the intrinsic alterations in several visual-related diseases on account of the blood-oxygen-level-dependent (BOLD) signal with several methods such as amplitude of low-frequency fluctuation (ALFF)[7], diffusion tensor imaging (DTI)[8] and regional homogeneity (ReHo)[9]. However, they cannot provide the data of functional connectivity in the whole-brain net system, and the underlying pathophysiological basis of the entire brain information processing remained unclear.

Voxel-wise degree centrality (DC) is an rs-fMRI analysis method that has been exploited to investigate the cerebrum functional connectome alterations[10]. The DC method detects the functional interrelationships between one cerebral area and the rest within the integral connectome at the voxel level, and a high DC value denotes a node with various direct connections to other nodes[11]. Thusly, DC is a superior network measurement than others for the reason that it calculates the sum of immediate connections in a meshwork for a given voxel and reveals the functional connectivity in cerebral network without a prior election. It has been effectively applied for exploring the concealed pathophysiological mechanisms of some other ocular disorders included glaucoma[12] and strabismus[13]. Hence, the DC is a reliable rs-fMRI technique that has not been utilized in RVO. This research designed to utilize the DC technology to further study the intrinsic cerebral activity of RVO comparing with healthy controls (HCs).

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University and complied with the Declaration of Helsinki. All participators were apprised the objective, content, potential risks, and signed informed consents.

Participants A total of 21 RVO patients (11 males, 10 females) were enrolled in the First Affiliated Hospital of Nanchang University with the following inclusion criteria: 1) ophthalmoscopy showed ischemic RVO (Figure 1); 2) OCT showed mixed type of macular oedema within subretinal fluid; 3) fundus fluorescein angiography showed occlusion of retinal vein. Ischemic central retinal vein occlusion (CRVO) ≥10-disc areas of retinal capillary non-perfusion. Ischemic branch retinal vein occlusion (BRVO) ≥5-disc areas of retinal capillary non-perfusion. The exclusion criteria of RVO were: 1) any preceding ocular surgery history; 2) any proof of other ocular diseases; 3) any other systematic diseases.

Twenty-one HCs of comparable age and sex matched up with RVOs were recruited. Inclusion criteria were: 1) no history of ophthalmic diseases; 2) no psychiatric diseases, cerebral infarction diseases and other system diseases; 3) competent of magnetic resonance imaging (MRI) examination.

Magnetic Resonance Imaging Parameters and Data Processing MRI examination was scanned with a 3-Tesla MR scanner (Trio, Siemens, Munich, Germany). The whole-brain T1-weights were acquired with spoiled gradient-recalled echo sequence by utilizing these parameters in Table 1.

Pre-filter all the data with MRIcro (www.MRIcro.com) and preprocess them with SPM8, DPARSFA and the Resting-state

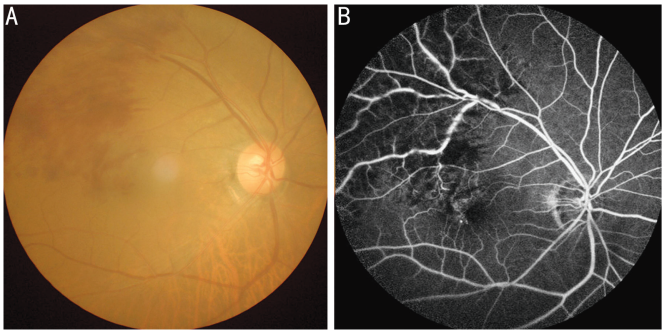

Figure 1 Fundus photography (A) and fundus angiography (B) in RVO patients.

Table 1 MRI scan parameters

Date acquisition	Echo planar imaging sequence	Brain volume sequence
Repetition time/echo time	2000/30ms	1900/2.26ms
Thickness/gap	4/1.2 mm	1/0.5 mm
Matrix	64×64	256×256
Field of view	220×220 mm^2	250×250 mm^2
Flip angle	90°	9°

Data Analysis Toolkit. Gathering the residual 230 volumes after deleting the beginning 10 time points. Volumes with the x, y, or z directions >2 were eliminated.

Degree Centrality DC based on the individual voxel-wise functional network, was computed by calculating the number of significant threshold correlations between the subjects. The conversion of DC map of each subject has been described in our previous study[13].

Brain-behavior Correlation Analysis DC values in diverse cerebrum areas between RVOs and HCs were categorized as region of interest (ROI). The correlationship analysis was implemented in RVO patients to inspect the interrelation between the DC signal of respective ROI and clinical features. $P<0.05$ was assumed to be statistically significant.

Statistical Analysis The clinical features between RVOs and HCs were analyzed utilizing SPSS20.0 software (SPSS, Chicago, IL, USA) with independent sample t test, $P<0.05$ was considered to be statistically significant.

To categorize the mean DC values in diverse cerebral regions of RVOs from HCs, the receiver operating characteristic (ROC) curve method was utilized. The correlationship between the DC signal of diverse cerebral regions and the clinical variables in RVOs were investigated with the Pearson's correlation analysis.

RESULTS

Demographics There were 12 CRVO and 9 BRVO patients in RVO group, and 11 left eyes and 10 right eyes. The average duration was 115.24±45.65d.

There were no differences in age (P=0.481) and handiness (P>0.99) between the RVO and HC group. The hospital anxiety and depression scale (HADS) score were significantly

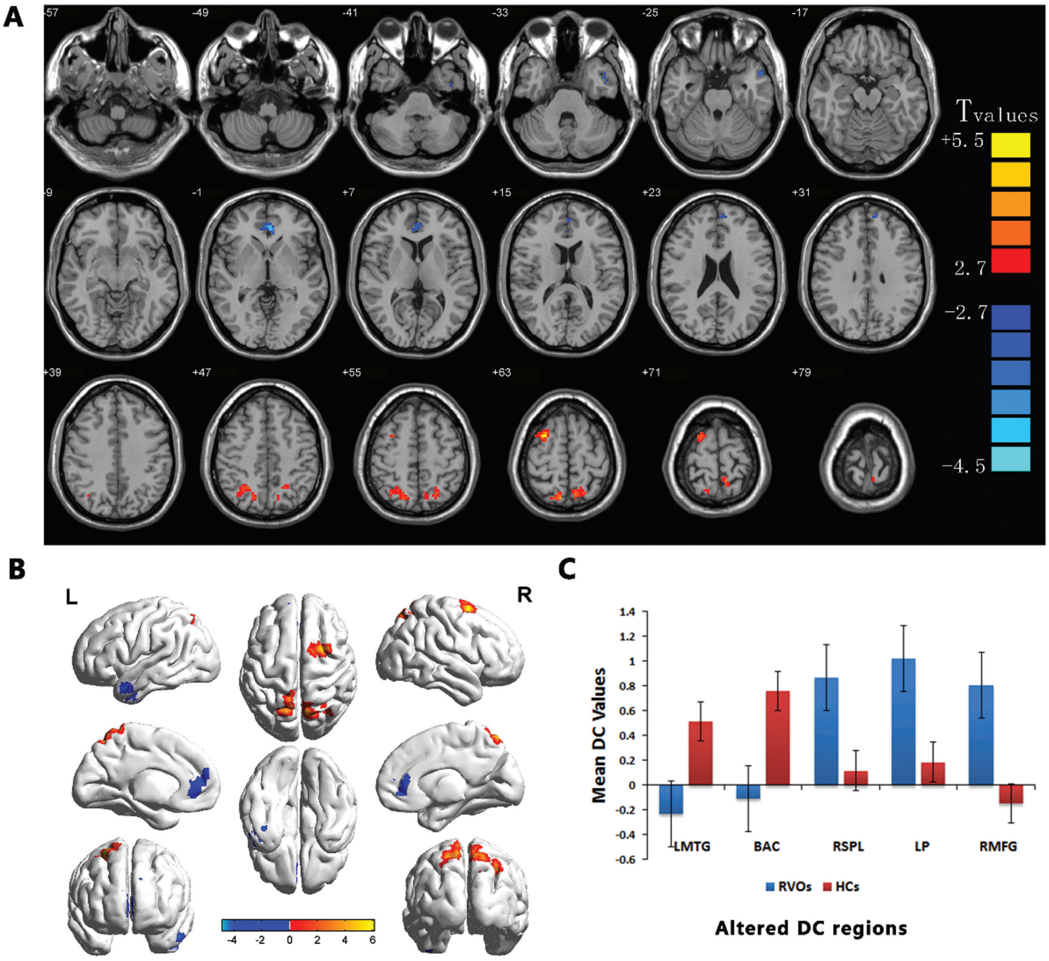

Figure 2 Comparison of DC values in the RVO and HC group A, B: There were significant differences of DC between two groups. The red parts show increased DC values, the blue regions show decreased DC values; C: The mean DC values in specific areas between RVOs and HCs.

Table 2 Brain areas showed statistical differences in DC between RVO patients and HCs

Conditions	Brain regions	Brodmann area	MNI coordinates			Peak voxels	*t*-value
			X	*Y*	*Z*		
RVOs>HCs							
1	RSPL	7	51	-57	-36	162	4.4701
2	LP		-12	-66	60	127	4.2945
3	RMFG	6	30	6	63	80	6.1133
RVOs<HCs							
4	LMTG	21	-54	9	-27	58	-4.8749
5	BAC	32	-3	42	0	108	-4.4668

DC: Degree centrality; RVO: Retinal vein occlusion; HC: Healthy control; MNI: Montreal Neurological Institute; RSPL: Right superior parietal lobule; LP: Left precuneus; RMFG: Right middle frontal gyrus; LMTG: Left middle temporal gyrus; BAC: Bilateral anterior cingulate.

increased in RVOs (13.76±3.67) when compare with HCs (5.52±1.14, P<0.011).

Degree Centrality Differences In RVO group, the DC signals were significantly elevated in the brain areas including the right superior parietal lobule (RSPL), left precuneus (LP) and right middle frontal gyrus (RMFG), and declined in the left middle temporal gyrus (LMTG) and bilateral anterior cingulated (BAC; Figure 2, Table 2). However, there is no significant differences between CRVO and BRVO (Table 3).

Correlation Analysis In RVO patients, the average DC value in BAC were negatively correlated with the HADS score (r=-0.858, P<0.001; Figure 3).

Receiver Operating Characteristic Curve We contemplated that the variations of DC signal might be potential valuable diagnostic markers for clarifying the RVOs from HCs. The ROC curve analysis was applied to substantiate this hypothesis, the average DC values of specific cerebral regions were calculated. The respective area under the curve (AUC)

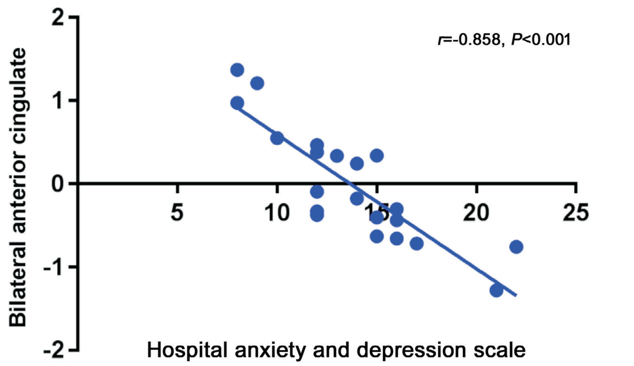

Figure 3 Correlationship between DC values in specific areas and the HADS score in RVO group The mean DC value of BAC was negatively correlated with the HADS score.

Table 3 DC differences of specific brain areas between CRVOs and BRVOs

Brain regions	BRVO	CRVO	*P*
RSPL	0.767±0.424	0.931±0.358	0.419
LP	1.156±0.351	0.921±0.441	0.242
RMFG	0.581±0.497	0.962±0.349	0.111
LMTG	-0.122±0.325	-0.313±0.277	0.230
BAC	-0.155±0.694	-0.074±0.648	0.812

DC: Degree centrality; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; RSPL: Right superior parietal lobule; LP: Left precuneus; RMFG: Right middle frontal gyrus; LMTG: Left middle temporal gyrus; BAC: Bilateral anterior cingulate.

of DC signal in different brain regions were as follow: RSPL (0.896, $P<0.001$), LP (0.900, $P<0.001$), RMFG (0.931, $P<0.001$; Figure 4A, RVOs>HCs); LMTG (0.962, $P<0.001$), BAC (0.855, $P<0.001$; Figure 4B, RVOs<HCs).

DISCUSSION

Rs-fMRI can exhibit spatial patterns of temporal interrelationship efficiently beyond the extent of the data's point spread function. DC is an innovative and dependable rs-fMRI technique to explore the changes of cerebral functional connectivity, detecting and quantitating sites of activation in the brain. The DC technique has been profitably utilized in a few ophthalmological diseases[12-15] (Table 4). To the best of our knowledge, this investigation is the first study to discover the cerebrum functional connectivity referred to RVO patients. In this current research, we proved that the intrinsic cerebral activity patterns of various areas in RVOs were changed when compared with HCs. The RVO group revealed significant incremental DC signal values in RSPL, LP and RMFG, but decreased in the with LMTG and BAC with impaired visual function (Figure 5).

Analysis of Higher Degree Centrality Signal in the Retinal Vein Occlusion Patients The parietal lobe is situated behind the frontal lobe and above the temporal lobe, where superior parietal lobule lies on top, and the precuneus is a segment of the superior parietal lobule on the medial surface of hemicerebrum. A pile of evidence about functional neuroimaging researches have consistently disclosed that the superior parietal lobule is associated with many sensory and cognitive process, including visuospatial attention[16-17], visuomotor integration[18], spatial perception[19] and memory[20]. Previous study has detected the activity in the superior parietal lobule and precuneus during visual stimulation[21]. Khan *et al*[22] reported that RSPL damaged in left optic ataxia patient, indicating the relationship with visual-motor transformation in this region. Chen *et al*[23] has demonstrated that the gray matter volume exhibited a prominent escalation in superior parietal lobe and precuneus of patients with primary open-angle glaucoma. In addition, research of the patients with stroke, a kind of vascular occlusive disorder as well, displayed damage in the superior parietal lobule while visual extinction[24]. In agreement with those previous reports, the elevated DC values in right parietal lobule and LP found in our investigation reflected a significant visual-related activation in this region, which may have been affected by the impaired visual function.

The middle frontal gyrus is an expansive gyrus that locates between the inferior and superior frontal sulci, and the frontal eye field (FEF) lies on the back of middle frontal gyrus including a sizable oculomotor area[25], which is competent of initiate eye movement as well as influence the precision or latency[26]. Several researches illuminated that the middle frontal gyrus took a vital part in saccade associated with movement generation[27-28]. Dai *et al*[29] found that the functional connectivity of glaucoma was increased specifically in the primary visual cortex and middle frontal gyrus. And many retina-involved disorders were detected higher activation in FEF, including progressive retinitis pigmentosa[30], macular hole[31] and age-related macular degeneration[32]. In supporting of the precedent findings, we also discovered that individuals with RVO displayed conspicuous increasing DC values in the RMFG, suggesting activate of the visual processing. This kind of alterations might indicate the cerebral plasticity which recompense for RVO causing visual input deficiency.

Analysis of Lower Degree Centrality Signal in the Retinal Vein Occlusion Patients The middle temporal gyrus lies on the lateral exterior of the temporal lobe, abdominal to the superior temporal gyrus, connected with the multi-sensory integration[33] and semantic comprehension processing[34-35]. Previous investigation has displayed that the brain activity was obviously higher in the middle temporal gyrus during visual stimulation[36]. And similar activation of the middle temporal gyrus was also observed when fusion stimulus[37-38]. Studies on gaze perception have demonstrated the middle temporal gyrus showed sensitive to the gaze shift[39-40]. Moreover, Yu *et al*[41] and

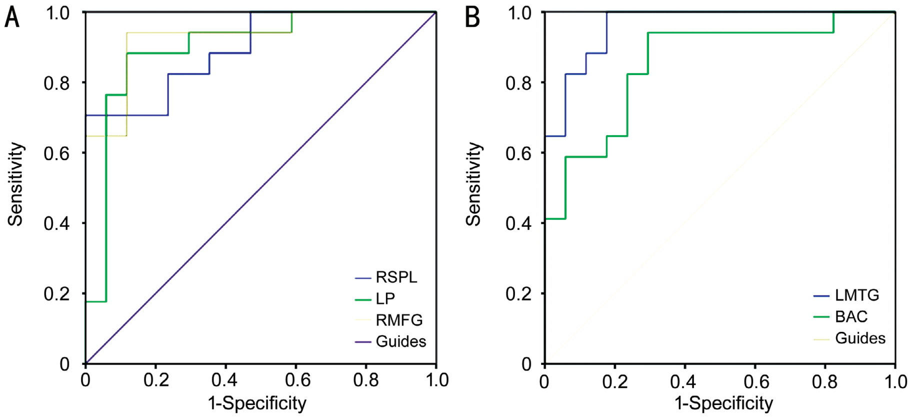

Figure 4 ROC curve analysis in specific brain areas A: The AUC of RSPL were 0.896 (95%CI: 0.793-0.999), LP 0.900 (95%CI: 0.786-1.000), RMFG 0.931 (95%CI: 0.844-1.000) (RVOs>HCs); B: The AUC of LMTG were 0.962 (95%CI: 0.906-1.000), BAC 0.855 (95%CI: 0. 725-0.984) (RVOs<HCs).

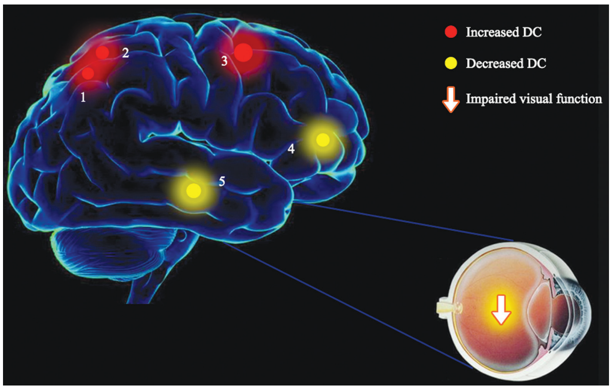

Figure 5 The altered brain regions in RVO group The DC values in RVOs of these areas were increased: 1-LP (t=4.2945), 2-RSPL (t=4.4701) and 3-RMFG (t=6.1133), and these areas decreased: 4-BAC (t=-4.4668) and 5-LMTG (t=-4.8749).

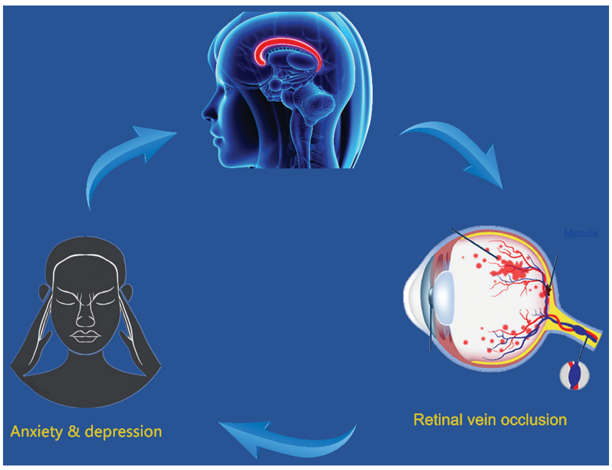

Figure 6 Relation between rs-fMRI imaging and clinical features and symptoms in RVO Retinal vein occlusion in RVO contributes to vision loss and anxiety, further leads to changes in anterior cingulate activity.

Li *et al*[42] detected that the volume of gray matter in middle temporal gyrus was found to be decreased in primary open-angle glaucoma. In the present investigation, the DC reduction in the LMTG of RVO group suggested functional damaged in this specific area. Hence, we ulteriorly assumed that the decline may be due to the visual deterioration in RVO patients.

The anterior cingulate is the front portion of the cingulate cortex which is like a "collar" encircling the anterior corpus callosum, comprises of a wide swath of neural territory along the frontal midline of the cerebrum. The anterior cingulate is broadly identified to play a role in the interaction between cognitive control[43-44] and emotional response[45-46]. The negative relationship between anterior cingulate and the HADS we found in the current study may due to the anxiety emotion caused by the vision loss (Figure 6). A recent study has reported that damage to the anterior cingulate cortex is involved in deficits in visual function[47]. And lower ReHo was identified at the BAC cortex in patients with optic neuritis[48]. The DC decline in the BAC exhibited in the present research may indicate functional impairment in RVO group, which offered additional proof that the RVO might contribute to the disfunction of the anterior cingulate.

Notwithstanding all this, the present investigation still has some limitations. First, the total number of enlisted patients and controls were relatively small, and the small sample size might influence the reliability. Moreover, different types of RVO were involved, which should be classified when analyzed. Nevertheless, no significant differences were discovered between CRVO and BRVO (Table 3), this could be a result of the sample size. Further investigation is required to study the cerebral functional alterations more precisely.

In conclusion, the current research illustrated that patients with RVO had aberrant intrinsic activities in distinct cerebral areas, which provided discernment into the neural alteration in RVO subjects, and aided to reveal the latent mechanisms of RVO.

Table 4 DC technique applied in ocular diseases

Diseases	Authors	Increased regions	Decreased regions
Open globe injury	Wang *et al*[14]	Bilateral V1 and LP	Bilateral insula, right inferior parietal lobule/ supramarginal gyrus, right supplementary motor area and right postcentral gyrus
Comitant exotropia strabismus	Tan *et al*[13]	Right superior temporal gyrus, BAC, and left inferior parietal lobule	Right cerebellum posterior lobe, inferior frontal gyrus, middle frontal gyrus and superior parietal lobule
Primary angle-closure glaucoma	Cai *et al*[12]	Left anterior cingulate cortex and cuneus	Bilateral visual cortices
Monocular blindness	Huang *et al*[15]	Left inferior temporal gyrus and bilateral medial frontal gyrus	Bilateral cuneus/V1/V2

DC: Degree centrality; LP: Left precuneus; BAC: Bilateral anterior cingulate.

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