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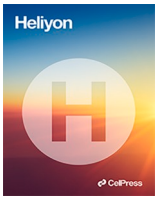

Research article

Functional dysconnectivity and microstructural impairment of the cortico-thalamo-cortical network in women with rheumatoid arthritis: A multimodal MRI study

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ABSTRACT

Background: Cognitive deficits are common in rheumatoid arthritis (RA) patients, but the mechanisms remain unclear. We investigated the effective connectivity and structural alterations of the core brain regions in RA patients with cognitive impairment.
Methods: Twenty-four female patients with RA and twenty-four healthy controls were enrolled. We analyzed abnormal brain activity patterns using functional MRI during the Iowa gambling task (IGT) and core regions effective connectivity using dynamic causal model (DCM). Structural alterations of white matter volume (WMV) and gray matter volume (GMV) were detected using voxel-based morphometry (VBM).
Results: RA patients showed altered activation patterns of the cortico-thalamo-cortical network, increased coupling strength from the left ventromedial prefrontal gyrus to the anterior cingulate cortex (ACC), the ACC to the right thalamus, and decreased connectivity from the thalamus to left hippocampus. VBM structural analysis showed increased GMV in the bilateral orbital frontal gyrus, bilateral hippocampus and right putamen, and reduced GMV and WMV in the bilateral thalamus in RA patients. Right thalamic GMV and WMV were positively correlated with the right thalamus-to-hippocampus connective strength. Additionally, the bold signal, GMV and WMV of the right thalamus were positively correlated with cognitive performance (IGT score) in RA patients.
Conclusion: Results suggest a structural and functional deficiency in the cortico-thalamo-cortical network, which is characterized by increased ACC-to-thalamus strength and reduced thalamus-to-hippocampus coupling in RA patients. The cognitive dysfunction may be the result of compensatory measures against imbalanced cortico-thalamic-cortical coupling.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease caused by an abnormal immune system and occurs more frequently in women. Approximately 0.5–1.1% of people worldwide suffer from rheumatoid arthritis [1]. Aside from joint pain, people with rheumatoid arthritis may experience symptoms of cognitive dysfunction, which significantly affects their quality of life [2,3]. Researchers have found that people with rheumatoid arthritis have a 61% increased risk of developing Alzheimer's, and the cohort study showed middle-aged RA patients have twice the risk of cognitive impairment after 20 years [4]. Currently, most studies have used neuropsychiatric scales to prove cognitive dysfunction in RA patients [2,5,6]. An fMRI investigation discovered higher brain connectivity between the medial prefrontal gyrus, inferior parietal lobule, and various brain networks, which predicted fatigue, pain and cognitive dysfunction [7]. The research showed alterations in the connection of the brain between the left insula and the inferior parietal lobule on the left side in RA patients who also have fibromyalgia [8]. These findings suggest changes occur in spontaneous brain activity and connectivity between brain regions in RA patients.

However, resting state fMRI can only detect the overall cognition and the functional connections can only indicate the strength of undirected connections between brain regions. At present, there has been no investigation about the effective connections between cognitively related brain regions and changes in brain networks induced by external stimuli in RA patients. A number of studies have indicated that RA patients have a heightened susceptibility to experiencing executive function impairment tested by neuropsychiatric scales [9,10]. In RA patients, the ability to make decisions under uncertain rules is crucial to their independence and overall cognitive function, so studying the neural mechanisms underlying impaired decision-making is important. In the Iowa gambling task (IGT), individuals acquire a rule of reward and punishment through a sequence of trials, replicating decision-making in real-life situations [11]. Currently, the utilization of model-based fMRI is extensively employed to examine the issue of how individuals can acquire the ability to make flexible choices when faced with uncertainty in order to optimize rewards [12]. Therefore, this study adopted IGT-based fMRI to detect the decision-making cognitive function in RA patients and the dynamic causal model (DCM) was used to test

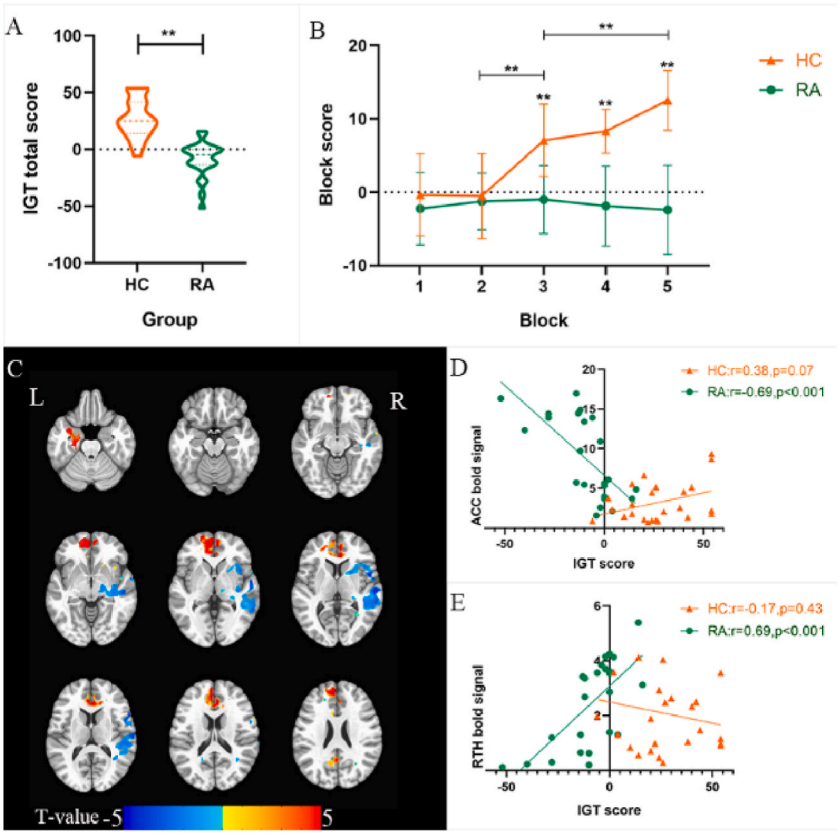

Fig. 1. Iowa Gambling Task (IGT) performance and activated brain regions in RA and HC groups. A. The total net IGT score was higher in healthy controls than in RA patients. B. There was no difference in the net score of blocks 1 and 2 between RA patients and healthy controls. The net score of blocks 3, 4, and 5 in healthy controls was higher than those of blocks 1 and 2, the score of block 5 was higher than that of block 3. RA patients did not show this learning trend. C. Enhanced activation in the left medial frontal gyrus, bilateral anterior cingulate, bilateral posterior cingulate, and left hippocampus and deactivation in right thalamus, right insula, right putamen and right middle temporal gyrus in RA patients compared to controls. D-E. In RA patients, the IGT net score was negatively correlated with the bold signal of the anterior cingulate (ACC) and positively correlated with the bold signal of the right thalamus (RTH).

the effective functional connectivity of decision-making cognition related brain regions and infer the causal relationship between brain regions [13]. What is more, the structural damage has been found in RA patients [14]. To calculate the brain volume of all participants, we utilized Voxel-based morphometry (VBM), a common technique for measuring gray matter volume (GMV). The relationship between brain volume and the structure-function association of intrinsic brain activity was strongly observed in healthy individuals [15], but the evidence of abnormal brain structure and intrinsic and functional activities in RA patients has not yet been shown. Therefore, in this study, we used multimodal MRI techniques based on IGT-task-state fMRI, DCM, and VBM to investigated the effective connectivity and structural alterations in the core brain regions of female RA patients with cognitive impairment.

We hypothesize that cognitive-related brain active pattern and effective connections are altered in RA patients, and we expect a significant association between altered effective functional connection and microstructure of brain regions in RA patients. The study was expected to find some neuroimaging markers to improve the early diagnosis rate of RA cognitive dysfunction.

2. Results

2.1. IGT performance

As Fig. 1A shown, the RA group's overall net score in the IGT was lower than that of healthy control group ($t = -7.545$, $p < 0.001$). Fig. 1B showed the curve of net scores for each block in RA patients and controls. Two-way mixed ANOVA for IGT performance revealed a significant main effect of the block ($F = 49.522$, $p < 0.001$, $\eta^2 = 0.518$) and the group ($F = 56.928$, $p < 0.001$, $\eta^2 = 0.553$), along with an interaction effect between group and block ($F = 55.328$, $p < 0.001$, $\eta^2 = 0.546$). Variations were observed between two groups in the third block ($F = 34.421$, $p < 0.001$, $\eta^2 = 0.428$), fourth block ($F = 64.929$, $p < 0.001$, $\eta^2 = 0.585$), and fifth block ($F = 99.783$, $p < 0.001$, $\eta^2 = 0.684$).

2.2. fMRI results

Comparing the brain activation between RA patients and controls revealed increased activation in the medial frontal gyrus on the left side, as well as in the anterior cingulate cortex (ACC) on both sides, posterior cingulate on both sides, and the hippocampus on the left side among RA patients. In RA patients compared to controls, various areas, including the right thalamus, right insula, right putamen, and right middle temporal gyrus, exhibited deactivation (Fig. 1C–Table 1). The net score of IGT in RA patients showed a negative correlation with the bold signal of the ACC and a positive correlation with the bold signal of the right thalamus (RTH), as depicted in Fig. 1D–E. Controls did not show any noticeable correlation between the IGT net score and bold signal of brain regions.

2.3. VBM results

Compared to controls, the main GMV increase in RA patients was found in the bilateral orbital frontal cortex, bilateral hippocampus, and right putamen, while clusters of decreased GMV was found in the bilateral thalamus and left middle temporal gyrus (Fig. 2A, Table 2). At the same time, decreased WMV was detected in the bilateral thalamus (Fig. 2B). We also found that the IGT score was positively correlated with both GMV and WMV in the RTH of patients with RA, and the RTH activation was positively associated with the RTH GMV and WMV (Fig. 2C–F).

2.4. DCM results

The DCM models of patients, controls and the different connections between RA patients and controls were shown in Fig. 3B–D. RA patients exhibited reduced connective strength in the projection from the RTH to LTH ($M_{RA}\pm SD_{RA} = 0.36 \pm 0.28$, $M_{HC}\pm SD_{HC} = 0.60 \pm 0.61$, $t = -1.77$, $p < 0.05$, Bonferroni correlated), LTH to HIP ($M_{RA}\pm SD_{RA} = 0.36 \pm 0.34$, $M_{HC}\pm SD_{HC} = 0.69 \pm 0.45$, $t = -3.175$, $p < 0.05$, Bonferroni correlated), and HIP to LTH ($M_{RA}\pm SD_{RA} = 0.34 \pm 0.24$, $M_{HC}\pm SD_{HC} = 0.64 \pm 0.43$, $t = -2.946$, $p < 0.05$, Bonferroni correlated), and stronger connective strength from the left PFC to ACC ($M_{RA}\pm SD_{RA} = 0.88 \pm 0.58$, $M_{HC}\pm SD_{HC} = 0.38 \pm 0.21$, $t = 4.65$, $p < 0.05$, Bonferroni correlated), and the ACC to RTH ($M_{RA}\pm SD_{RA} = 0.25 \pm 0.12$, $M_{HC}\pm SD_{HC} = 0.07 \pm 0.06$, $t = 6.41$, $p < 0.05$,

Table 1
fMRI brain activation differences between RA and HC groups in the Iowa Gambling task.

Condition	Region of activation	Right/Left	Cluster size	MNI coordinate			BA	T-value
				X	Y	Z		
RA > HC	Medial frontal gyrus	L	412	−8	59	−2	BA11	4.06
	Anterior cingulate	L/R	98	0	31	13	BA24	2.81
	Posterior cingulate	L/R	49	−1	−57	25	BA31	2.74
	Hippocampus	L	86	−25	18	−24	–	3.21
RA < HC	Thalamus	R	86	18	−11	4	–	−3.25
	Insula	R	65	41	6	0	BA13	−2.31
	Putamen	R	42	26	12	0	–	−2.22
	Middle temporal gyrus	R	76	49	−34	8	BA22	−2.34

MNI coordinate: Montreal Neurologic Institute coordinate; BA: brodmann's area.

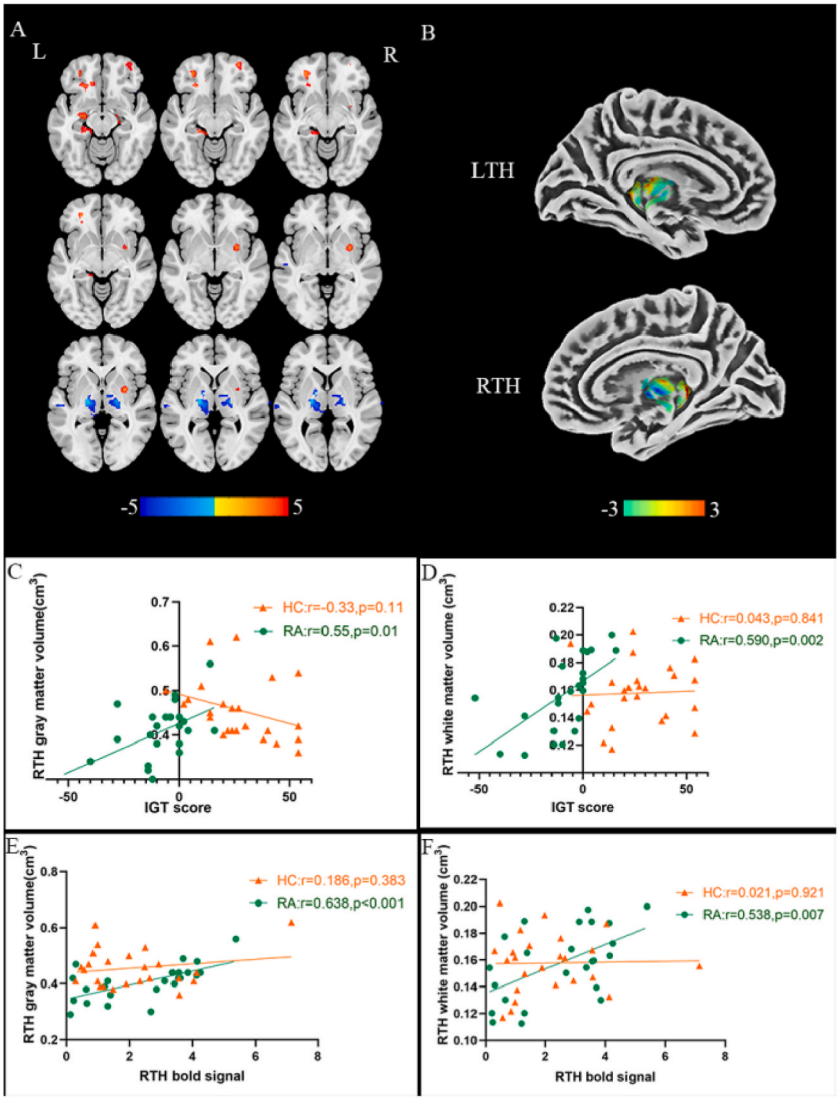

Fig. 2. Differences in gray matter volume (GMV) and white matter volume (WMV) between the RA and HC groups. A. Compared to controls, the main GMV increases in RA patients were found in the bilateral orbital frontal cortex, bilateral hippocampus, and right putamen, whereas clusters of decreased GMV were found in the bilateral thalamus and left middle temporal gyrus. B. Decreased WMV was detected in the bilateral thalamus of RA patients. C-F. Total IGT net score was positively correlated with both GMV and WMV of right thalamus (RTH) in patients with RA, and the bold signal of the right thalamus was positively associated with GMV and WMV of the right thalamus.

Table 2
Differences in gray matter volume between RA and HC groups.

Condiction	Brain region	Right/Left	Cluster size	MNI coordinate			BA	T-value
				X	Y	Z		
RA > HC	Orbital frontal cortex	L	256	−21	30	−16	BA11	3.19
		R	56	11	49	−6	BA10	2.16
	Hippocampal	L	460	−26	−26	−16	BA20	4.21
		R	235	26	−20	−16	BA20	3.31
	Putamen	R	124	30	4	−6	BA48	2.44
RA < HC	Thalamus	L	583	−16	−19	4	–	−4.68
		R	546	18	−11	4	–	−4.33
	Middle temporal gyrus	L	86	−54	−19	−2	BA22	−2.68

MNI coordinate: Montreal Neurologic Institute coordinate; BA: brodmann's area.

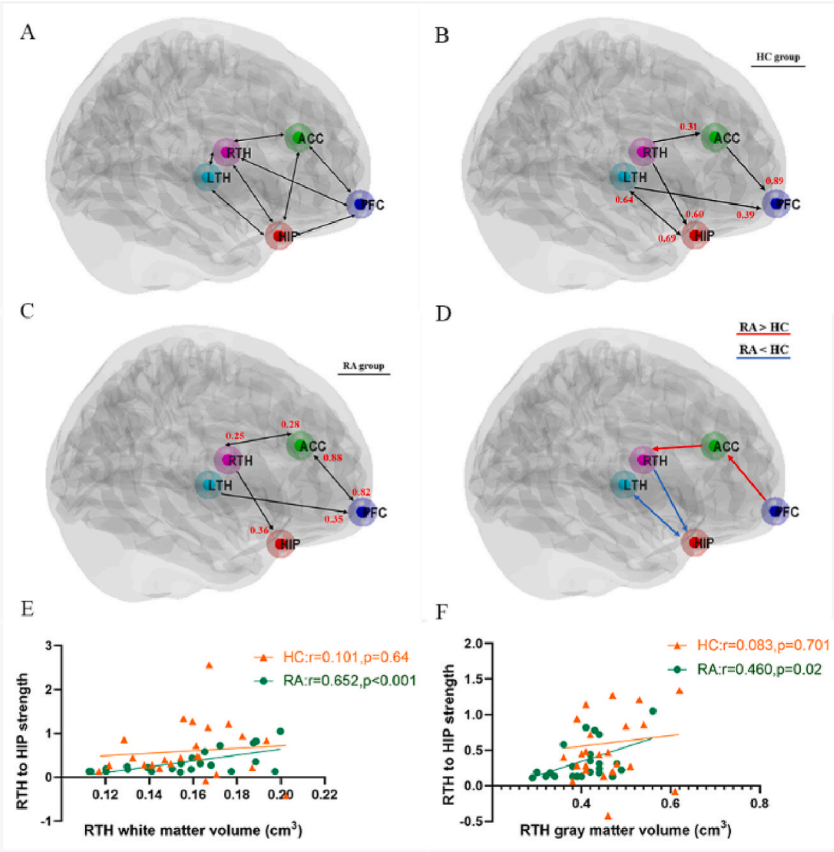

Fig. 3. Effective connectivity between the right thalamus (RTH), left hippocampus (HIP), left thalamus (LTH), left ventromedial prefrontal gyrus (PFC) and anterior cingulate cortex (ACC). A. 20 models in which the brain regions in each model had bidirectional connections, and the decision-masking effect stimulation acted on effective connection in each of the two brain regions. B. DCM of healthy controls. C. DCM of RA patients. D. RA patients showed an abnormal effective connectivity between the right thalamus, left hippocampus, left thalamus, left PFC and ACC. E-F. In RA patients, both GMV and WMV of the right thalamus were positively correlated with the connective strength from the right thalamus to the hippocampus.

Bonferroni correlated). In RA patients, both GMV and WMV of the RTH were positively correlated with the connective strength from RTH to HIP (Fig. 3E–F).

3. Discussion

In this multimodal study, structure and effective connective dysfunction in the cortico-thalamo-cortical network was found in RA patients. We found the correlation between activation intensity, gray matter volume (GMV) and white matter volume (WMV) of the RTH in patients. Furthermore, The GMV and WMV of the RTH was positively correlated to the connective strength from the RTH to HIP in RA patients. Thus, we demonstrate that the cortico-thalamo-cortical network could potentially serve as a crucial circuit in cognitive decline observed in individuals with RA, with the thalamus acting as the pivotal hub within this loop.

In this study, RA patients had abnormal activation in the ventromedial PFC, ACC, posterior cingulate, hippocampus, thalamus, insula and putamen under uncertain decision-making conditions. These brain regions have been identified as playing a role in neural circuits related to decision-making in healthy people [16]. There are neural alterations in frontal areas during decision events and in sub-cortical areas (e.g. striatum and insula) when rewards are achieved [17], which is consist with our study results. Considering that these brain regions form part of the cortico-thalamo-cortical circuit, abnormal activation patterns of this network may contribute to cognitive impairment. Neuro-related factors of decision-making under risk have been used as brain-based biomarkers of treatment outcomes [18].

A study revealed that, in comparison to healthy controls, RA patients exhibited a greater average white matter volume, a higher average cortical infarction, and a greater number of cerebrovascular pathological abnormalities on neuroimaging [14]. The present study identifies structural anomalies in the orbitofrontal cortex, hippocampus, putamen, thalamus, and middle temporal regions of RA patients, with a noteworthy decrease of gray and white matter volume in the bilateral thalamus. We evaluated the intersection between structural and functional modifications and observed a spatial convergence in the left hippocampus, right putamen, and bilateral

thalamus. In comparison to healthy controls, RA patients exhibited a reduction in both WMV and GMV of right thalamus, which corresponded to abnormal functional activation in the right thalamus during decision-making processing. Additionally, an anomalous effective connection was observed in the cortico-thalamus network, characterized by enhanced connectivity from the ventromedial prefrontal cortex to the ACC, from the ACC to the thalamus, and a decline in the bidirectional connections of the thalamus and hippocampus. The study on reward-guided learning in rhesus monkeys revealed notable modifications in functional connectivity within the ventromedial, orbitofrontal prefrontal, ACC and thalamic regions, alongside structural changes in the white matter of the ventral prefrontal tract, and these findings underscore the significance of diverse communication pathways within corticocortical and thalamocortical circuitry for the capacity to make decisions based on rewards [19]. By integrating the outcomes of both structural and functional connectivity analyses of the cortico-thalamo-cortical network, our study reveals a positive association between GMV and WMV in RA patients and the strength of the thalamus-hippocampus connection. This phenomenon may be attributed to the chronic inflammation in RA patients, which impairs the integrity of the blood-brain barrier. Consequently, pro-inflammatory factors infiltrate the brain parenchyma, exacerbating the damage to the cerebral vascular endothelium, disrupting cerebral blood supply, and significantly affecting the perfusion and fiber bundle integrity, ultimately leading to morphological changes in the WMV and GMV(7). This partly explains the structural damage and abnormal functional linkage of the cortico-thalamo-cortical network in this study. Our study suggests that damage to the cortico-thalamo-cortical system may serve as a possible neural mechanism for cognitive decline in RA patients, with the thalamic nucleus serving as the central component of this circuit. The cortico-thalamo-cortical network has garnered significant attention among investigators studying cognitive disorders [20–22]. Cognitive disorders have been shown to alter the structure and function of the corticothalamo-cortical loop [23,24]. A comprehensive investigation of this circuitry will facilitate comprehension of the neural mechanisms underlying cognitive disorders, thus making a significant contribution to the diagnosis and treatment of cognitive diseases or those associated with cognitive impairment.

Our findings indicated that cognitive decline in RA patients was correlated with the thalamus, and that the activation intensity, GMV, and WMV of the thalamus were all associated with decision-making performance in RA patients. Moreover, the structural changes in the thalamus may lead to an aberration of the functional interdependence between the thalamus and other cerebral areas. As a crucial structure located within the forebrain of mammals, the thalamus receives input from various cortical and subcortical structures and performs a wide range of functions [25]. In human investigations, impairments ensuing from thalamic injury are frequently linked to executive function disturbance [26]. Several animal model studies have commenced to comprehend the fundamental roles of the thalamus and cortex in collaboration during higher cognitive processes like decision-making [27–29]. Thalamic injury-induced systemic dysfunction can affect various brain regions, as well as the central and peripheral nervous systems. In patients, thalamic strokes typically cause harm to various thalamic nuclei and nearby tracts of white matter [30]. The association cortex is connected to higher order thalamic relays through the cortico-thalamo-cortical pathway, which allows for reciprocal communication with other cortical and subcortical sources [31]. The interconnectivity of the various subdivisions of the thalamus with distinct regions of the frontal lobes (medial PFC, orbital frontal cortex, anterior cingulate cortex) is demonstrated by cortico-thalamo-cortical connections [32–34]. Furthermore, the majority of cortical projections originating from the thalamus have a modulatory role in addition to driver inputs. The thalamus has the potential to impact cortico-cortical communication through bidirectional connections with the cortex in multiple ways [35]. Our findings are consistent with this theoretical framework.

It is important to consider the constraints of this research. Firstly, due to the limited sample size, there are no more detailed subgroups for control study in this study, which indicates that cognitive dysfunction is caused by RA. In the follow-up study, we will increase the sample size to investigate the impact factors of cognitive impairment in RA patients. Secondly, the treatment regimen of patients with RA may affect cognitive function. Thirdly, this study did not utilize other imaging methods. In future studies, sample size should be expanded and medication effects should be considered to better understand how medication affects cognitive function in patients with RA.

4. Conclusion

This study indicates that RA patients exhibit structural impairments and abnormal functional connectivity within the cortico-thalamo-cortical circuit, which may underlie cognitive dysfunction related to decision-making. The thalamus seems to have an important role in this neural network, and additional investigation into this circuitry could improve our comprehension of the neural mechanisms involved in cognitive disorders in RA. In the end, these findings could have significant consequences for identifying and managing cognitive impairment in individuals with RA.

5. Participants and methods

5.1. Participants, experimental paradigm and MRI data acqusition

The study included 24 female participants who met the 2010 ACR/EULAR classification criteria for RA [36] and were recruited from the Department of Rheumatology, the First Affiliated Hospital of Shantou University Medical College. Additionally, 24 healthy controls (HC) were included, all females. There were not significantly different between two groups in age (RA: 43.08 ± 8.55 years old, HC: 41.08 ± 8.99 years old, $t = 0.79$, $p = 0.43$) and education (RA: 10.01 ± 4.02 years, HC: 10.88 ± 2.74 years, $t = -0.80$, $p = 0.40$). The cognitive abilities of the participants were evaluated using the Montreal Cognitive Assessment (MoCA), whereby individuals were categorized as possessing normal cognitive function if their score equaled or exceeded 26 points, exhibiting mild cognitive impairment if their score was less than 26 points, and demonstrating dementia if their score was 19 points or lower [37]. Two groups had different

MoCA scores (RA: 24.75 ± 2.05, HC: 27.71 ± 1.65, t = −5.50, $p < 0.001$). The mean score of RA patients were lower than 26, which indicated the RA patients exited cognitive impairment. There was no brain disorders, mental illness, drug and alcohol dependence and MRI contraindications in all participants.

All RA patients were treated with medication, including DMARDs (methotrexate/hydroxychloroquine/sulfasalazine), glucocorticoid (prednisone/methylprednisolone) and NSAIDS. The specific medication regimen for each RA patient was shown in Table S1. The subjects were provided with comprehensive information about the study and subsequently granted written informed consent. Approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (No.B-2021-237).

5.2. Experimental paradigm: Iowa gambling task

The design of Iowa gambling task (IGT) was described in detail in our previous paper [38]. In brief, the paradigm includes decision-making and control tasks, each task contains 5 blocks. In decision-making task, A and B decks present substantial immediate benefits, but are associated with high long-term penalties (disadvantageous decks). The C and D decks offer lower rewards but also lower long-term penalties (advantageous decks). The control task required participants to pick a specific deck every time. The control task necessitated participants to select a designated deck. The IGT net score for each block was determined by deducting the number of choices made for the disadvantageous decks (A + B) from the number of choices made for the advantageous decks (C + D). The cumulative net score was obtained by summing the net scores of the five task blocks. A higher IGT net score indicates superior decision-making proficiency [39].

The stimulus was administered utilizing the E-Prime software and stimulus presentation goggles system (SA-9939, Shenzhen Sinorad Medical Electronics Co., Ltd.). The IGT was conducted concurrently with MRI scan, and the selections of decks were logged by E-prime.

5.3. fMRI image and data acquisition

Radiology data were obtained utilizing a 1.5 T MR scanner (GE Medical Systems, Milwaukee, WI, USA) along with a standard GE head coil in the Department of Radiology, the First Affiliated Hospital of Shantou University Medical College. To block out background noise, headphones and earplugs were given. Using echo-planar imaging, the following settings were used for BOLD-fMRI acquisition: echo time (TE) of 45 ms, repetition time (TR) of 3000 ms, imaging matrix of 64 × 64, field of view (FOV) measuring 250 mm × 200 mm, flip angle (FA) of 90°, 20 slices and each slice thickness of 6.0 mm, along with no gap. To prevent interference between neighboring slices, the acquisition of slices was done using an alternating method. FSPGR (fast spoiled gradient recalled) 3DT1-weighted image parameters are: TE = 5.1 ms, TR = 1.6 ms, FOV = 256 × 256 mm^2, matrix = 256 × 256, FA = 20°, 244 slices with a thickness of 1.3 mm, and no gap between slices.

5.4. Iowa gambling task-based fMRI data analysis

The fMRI data underwent processing with Statistical Parametric Mapping12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm), which was executed in MATLAB2021a (MathWorks, Natick, MA, USA; http://www.mathworks.com). We excluded the first two time-points of the fMRI images. The preprocessing procedures encompassed the correction of slice timing, compensation for head motion, spatial smoothing with a 6 mm full width at half maximum (FWHM), and spatial normalization to the standard coordinates of the Montreal Neurologic Institute standard space (MNI152). Participants displaying conspicuous head movements (rotation >2° or motion >2 mm) during the scanning session were excluded from the study. For first-level analysis, six motion covariates were incorporated into a general linear model (GLM) to examine decision-making impact. The independent-samples *t*-test was utilized to conduct a comparison analysis at the between-subject level. An appropriate level of significance was set at a level of $p < 0.05$, after accounting for the false discovery rate (FDR). There was a cluster size correction of 20 voxels applied, with the voxel size in the analysis area being 3 × 3 × 3 mm^3.

5.5. VBM analysis

The CAT12 software (http://www.neuro.uni-jena.de/cat/) in SPM12 was utilized to perform voxel-based morphometry. T1 images underwent bias-field correction, registration with linear and nonlinear transformations, spatial normalization using the DARTEL algorithm, and the brain was segmented into gray matter, white matter, and cerebrospinal fluid. The total intracranial volume (TIV) was calculated by adding gray matter volumes (GMV), white matter volumes (WMV), and cerebrospinal fluid volumes. After segmentation, every tissue category was transformed to MNI space using a 1.5 mm isotropic adult template given by the CAT12 toolbox. To maintain the original volumes of the tissue classes, the tissue class images were adjusted during DARTEL normalization. Before conducting group level analysis, the segmentations of and white matter and gray matter were smoothed using Gaussian kernels with a 6 mm FWHM.

5.6. DCM analysis

Effective connectivity among the brain regions was determined using the DCM12 toolbox in SPM12. The standard DCM can infer

causal relationships between various regions of the brain and examine the impact of external stimuli on functional networks. In a given model, DCM estimates distinct sets of parameters: wherein endogenous parameters A delineate the fixed connections between brain regions, extrinsic parameters B quantify the direct effects of external stimuli on brain regions, and modulatory parameters C gauge alterations in effective connectivity influenced by the experimental task or the activity within brain regions [13].

Initially, the placement of ROIs relied on the outcomes of the univariate SPM analysis and the activation regions of the IGT-task-based fMRI. Subsequently, a dynamic causal model was constructed using five regions of interest (ROIs), namely the PFC (left medial prefrontal gyrus), ACC (anterior cingulate cortex), HIP (left hippocampus), LTH (left thalamus), and RTH (right thalamus). In each subject, 8 mm spherical volumes of interest (VOIs) were extracted in the PFC [−8, 59, −2], ACC [0, 31, 13], HIP [−25, 18, 13], LTH [−16, −19, 4] and RTH [18, −11, 4]. Second, based on the assumption that all brain regions are interconnected, we constructed 20 models in which external stimuli acted on one of the effective connections (Fig. 3A). Given there is only an external stimulus acting on the effective connection, only the effective connection matrix A between brain regions was considered. Thirdly, the expectation-maximum algorithm to estimate the model parameters and the random effect Bayesian model selection (RFX BMS) method were used to choose the best model of each participant. Then, a single sample *t*-test was used to obtain the model parameters A (effective connective strength) of the patients and controls. Finally, effective connectivity differences between two groups was compared using the independent two-sample *t*-test. The Bonferroni method was utilized to adjust for statistical significance.

5.7. Statistical analysis

The study employed the independent two-sample *t*-test to compare age, years of education, and neuropsychological data between groups. IGT net scores were calculated for each block and a two-way mixed ANOVA analysis of variance was conducted on the IGT net score [selections from decks (C + D) - decks (A + B)] to evaluate the cognitive disparities between two groups. For each group, the correlation of total IGT net score, IGT-based fMRI bold signal, GMVs WMVs and effective connective strength (parameters A) of the ROIs were evaluated using Pearson correlation analysis. SPSS 26 (Chicago, IL) was utilized for all statistical analyses. Mean ± standard deviation (M±SD) is used to report descriptive characteristics of participants. Statistically significant differences were deemed when $p < 0.05$ (two-tailed).

Ethics declarations

The Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (No.B-2021-237) thoroughly examined and granted approval for this study. Every individual involved in the research willingly agreed to participate by giving their informed consent. Consent was obtained from all participants for the publication of their anonymized case details and images.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Yanmin Zheng: Writing – original draft, Visualization, Formal analysis, Data curation. **Lei Xie:** Writing – review & editing, Funding acquisition. **Zikai Huang:** Data curation. **Jianhua Peng:** Data curation. **Shuxin Huang:** Data curation. **Ruiwei Guo:** Formal analysis. **Jinzhuang Huang:** Data curation. **Zhirong Lin:** Data curation. **Zelin Zhuang:** Data curation. **Jingjing Yin:** Formal analysis. **Zhiduo Hou:** Supervision, Resources. **Shuhua Ma:** Validation, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24725.

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