rTMS modulates precuneus-hippocampal subregion circuit in subjective cognitive decline

Jiu Chen (✉ ericcst@aliyun.com)

Nanjing Medical University

Guanjie Hu

Affiliated Brain Hospital of Nanjing Medical University

Chen Xue

Affiliated Brain Hospital of Nanjing Medical University

Wenzhang Qi

Affiliated Brain Hospital of Nanjing Medical University

Wenwen Xu

Affiliated Brain Hospital of Nanjing Medical University

Shanshan Chen

Affiliated Brain Hospital of Nanjing Medical University

Jiang Rao

Affiliated Brain Hospital of Nanjing Medical University

Wan Liu

Affiliated Brain Hospital of Nanjing Medical University

Fuquan Zhang

Affiliated Brain Hospital of Nanjing Medical University

Xiangrong Zhang (✉ dxrz@hotmail.com)

Affiliated Brain Hospital of Nanjing Medical University

Research

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Abstract

Background: Hippocampal subregions (HIPsub) and their network connectivities are considered to be abnormal in subjective cognitive decline (SCD). This study aimed to identify whether repetitive transcranial magnetic stimulation (rTMS) could ameliorate the HIPsub network connectivity by modulating one node of HIPsub network in SCD subjects.

Methods: In the first cohort (38 SCD and 55 healthy controls), we analyzed three HIPsub (i.e., hippocampal emotional, cognitive, and perceptual regions: HIPe, HIPc, and HIPp) functional connectivity to identify HIPsub network connectivity alterations that relate to SCD. And we further applied a support vector machine (SVM) approach using the alterations to identify how well this could distinguish SCD from CN. In the second cohort (13 SCD), rTMS with 5-day of once-daily for 2 weeks was used to modulate the altered HIPsub network connectivity in a sham-controlled design.

Results: SCD subjects showed differently altered patterns of HIPsub network connectivity compared to controls. The SVM classifier showed that the abnormalities had a high power to discriminate SCD from CN, with an ACC of 86.0%, an AUC of 92.9%, 83.8% sensitivity, and 89.1% specificity. Restoration of HIPc connectivity with left parahippocampal gyrus and HIPp connectivity with left middle temporal gyrus corresponded to amelioration of episodic memory in SCD patients after 2 weeks of rTMS.

Conclusion: rTMS can restore the posterior hippocampus connectivity by modulating the precuneus in SCD subjects. Correction of breakdown in HIPc and HIPp related to cognitive and perceptual processing can simultaneously ameliorate episodic memory in SCD subjects. Thus, these findings suggest that rTMS manipulation of precuneus-hippocampal circuit may prevent the disease progression by improving memory as the earliest at-risk state of AD in clinical trials.

Trial registration: CCTR, ChiCTR2000034533. Registered 9 July 2020 - Retrospectively registered, <http://www.chictr.org.cn>

Background

Subjective cognitive decline (SCD), who has self-reported persistent memory decline while cognitive performance remains within the normal range, is well-known considered as the earliest at-risk state of Alzheimer's disease (AD) even before amnesic mild cognitive impairment (MCI) [1-6]. Hippocampus, a hallmark of AD [7-9], is thought as one of the earliest brain regions to present with pathology that causes memory decline. A great number of studies have consistently reported hippocampal atrophy in SCD subjects [3, 10-12]. However, little is known about whether hippocampal network connectivity is also dysfunctional in SCD subjects, especially the hippocampal subregions networks. Therefore, our lack of understanding of their pathophysiology hampers the development of new interventions to prevent the clinical progression of SCD to MCI/AD.

Neuroimaging evidences have consistently indicated a functional heterogeneity in hippocampus subregions (HIPsub) [13-15]. A recent neuroimaging meta-analytic study has defined the left hippocampus as consisting of the anterior emotional region (HIPe), the middle cognitive region (HIPc), and the posterior perceptual region (HIPp) based on its neurofunctional topography [13]. Furthermore, several studies have indicated that HIPsub have a selective topography of pathological involvement in preclinical AD [12, 15, 16]. Recently, several studies have reported that SCD present the structural and functional alterations of hippocampus [3, 10-12, 16]. Converging evidences suggest that SCD may present differently altered patterns of HIPsub network connectivity. Consequently, there is growing interest in answering the question how the dysfunctions in HIPsub network connectivity can be restored.

Neuromodulation techniques, including repetitive transcranial magnetic stimulation (rTMS), afford an opportunity to address this challenge by modulating intrinsic connectivity networks. Recently, rTMS has been broadly applied to study the changes across cortical networks [17-20]. Local stimulation of an accessible network node can be transmitted across synapses means to remote interconnected nodes with high spatial specificity [18, 21, 22]. Therefore, this approach can allow to establish a causal link between the applied stimulation and the observed changes in HIPsub network connectivity.

Recently, a neuromodulation study has verified that rTMS targeting the parietal cortex can improve hippocampal connectivity networks, and simultaneously improve associative memory performance in healthy individuals [20]. A recent MCI neuromodulation study applies rTMS to promote the improvement of episodic memory by targeting the precuneus [23]. The precuneus is well-known thought as a remote interconnected node of hippocampal intrinsic connectivity networks [20, 24] and a critical vulnerability area for the episodic memory deficit observed in early AD [25, 26]. Based on above-mentioned evidences, it is reasonable to speculate that the altered HIPsub network connectivity can be causally effected by rTMS modulation upon the precuneus in the HIPsub network in SCD subjects.

In this study, we propose a strategy to empirically discover a HIPsub pathological circuit related to SCD using a pattern classification approach (SVM: support vector machine), and subsequently, in a targeted manner, this circuit was experimentally manipulated to assess causal links in a separate cohort. We hypothesized that SCD subjects would display differently altered patterns of HIPsub network connectivity. And we further hypothesized that breakdown in HIPsub circuit related to episodic memory processing could be restored by rTMS modulation upon the precuneus in the HIPsub network in SCD subjects. **Figure S1** shows the data analysis pipeline conducted in this study.

Materials And Methods

Participants

Data used in this study were obtained from our in-home database: Nanjing Brain Hospital-Alzheimer's Disease Spectrum Neuroimaging Project (NBH-ADsnp) (Nanjing, China), which is constantly being updated. Relevant information of NBH-ADsnp is summarized in *SI Methods S.2*.

Network discovery of altered HIPsub related to SCD

A total of 99 elderly individuals participated in this study. Of the subjects, we excluded 2 healthy controls (CN) and 4 SCD subjects due to excessive head movement (see quality assurance section below), and incomplete or missing MRI data. The final analyses included 55 CN and 38 SCD eligible subjects. *SI Methods S.2* shows detailed inclusion and exclusion criteria.

Network validation of altered HIPsub related to SCD with rTMS

A total of 20 SCD subjects participated in the clinical trial (No. ChiCTR2000034533) in this study from the NBH-ADsnp database.

We used rTMS (or sham) with 5-day of once-daily to modulate the precuneus of SCD subjects for 2 weeks in a sham-controlled design. Clinical measures, neuropsychological assessments, and MRI data were collected at baseline (pre-rTMS or sham intervention) and at the end of 2 weeks of rTMS or sham. A total of 20 SCD subjects were enrolled in the study, of which 16 SCD subjects were randomly divided into real rTMS (8 SCD) or sham (8 SCD), and 13 SCD subjects (8 SCD for real rTMS, 5 SCD for sham rTMS) completed the trial of 2 weeks of rTMS.

Neuropsychological assessment

Neuropsychological assessments are summarized in *SI MethodsS.3*. This study performed a standardized clinical interview and comprehensive neuropsychological assessment to evaluate general cognitive function, executive function, information processing speed, episodic memory, and visuo-spatial function.

MRI data acquisition

Detailed MRI data acquisition parameters in NBH-ADsnp are summarized in *SI MethodsS.4*.

fMRI data preprocessing

In this study, MATLAB2015b and DPABI software [27] were used to preprocess all fMRI data. The image processing procedure was performed as described in a previous study [28] and is summarized in *SI Methods S.5*.

Quality assurance (QA)

Brain atrophy effect

Given that significant hippocampal GM atrophies in SCD subjects have been reported [12, 29], the anatomical differences between groups may affect these differences on the FCs of HIPsub. To clarify this issue, we computed global intracranial volumes (ITV) based on native GM, WM, and CSF in CN and SCD subjects by using in-home MATLAB codes. Furthermore, we used ITV as an additional covariate when general linear model (GLM) analysis is used to investigate the differences on the network connectivity of HIPsub between CN and SCD subjects.

Head motion effect

In this study, we used three approaches to control the head motion effect both at the individual and at group levels. Firstly, we excluded SCD subjects with excessive head motion (cumulative translation or rotation > 3.0 mm or 3.0°). Then we used a Friston 24-parameter model to regress out head motion effects from the realigned data [30]. Secondly, we performed a ‘scrubbing’ procedure to scrub frames (volumes) with an excessively high whole-brain root mean square (RMS) signal change over time in the preprocessed fMRI data for each individual [31–33]. Furthermore, we regressed out all volumes with a framewise displacement (FD) greater than 0.2 mm as nuisance covariates, and discarded any scan with 50% of volumes removed as described in a previous study [34]. Overall, we excluded 1 CN because of excessive head movement. No significant differences were observed in the head motion parameters between qualified CN and SCD subjects (Table 1).

Strict multiple comparison correction strategy

To ensure the reproducibility, test–retest reliability, and replicability on the fMRI metrics, we performed a strict multiple comparison correction [35], that is, statistical maps were thresholded using the permutation test with Threshold-Free Cluster Enhancement (TFCE) [36] and the false discovery rate (FDR), as implemented in DPABI [27]. For cluster-extent permutation tests, voxel thresholds of two-tailed $p < 0.02$ ($Z > 2.3$) were set. Finally, we set a two-tailed $p < 0.05$ threshold (1,000 permutations in FDR evaluation).

Definition of hippocampal subregions

Our definition of HIPsub referred to recent studies from Robinson et al. [13] and Bai et al.[37], who used coactivation-based parcellation to reveal a subspecialization in the hippocampus by a data-driven method. We only selected the left HIPsub as regions of interest (ROI) (Fig. S2) based on the recent study published by Bai and colleagues [37]. The left hippocampus was defined as three subregions (HIPe, HIPc, and HIPp).

Functional connectivity analyses

First, we extracted the average time courses for all voxels within each HIPsub as the reference time course. Second, we performed voxelwise cross-correlation analysis between the averaged time courses of all voxels within the seed HIPsub region and each voxel in the remainder of the whole brain within the group-specific GM mask. Finally, we performed a Fisher's z-transform analysis to enhance the normality of the correlation coefficients.

rTMS protocol

rTMS was used to stimulate the precuneus of all aMCI participants using a Magstim Rapid2 magnetic stimulator with a 70-mm figure-8-shaped coil. We used the Pz site of the 10–20 electroencephalogram system to locate the precuneus, and the tip of the intersection of the two coil loops was placed at the Pz site to stimulate the precuneus [23].

rTMS was applied, using trains of 1000 stimuli at a frequency of 20 Hz and at an intensity of 100% of the motor threshold (MT). We defined the MT as the lowest intensity producing motor evoked potentials of greater than 50 μ V in at least 5 out of 10 trials in the relaxed first dorsal interosseous (FDI) muscle of the contralateral (right) hand [38]. Participants received 25 sessions of either rTMS or sham stimulation over the precuneus. Each daily stimulation session consisted of a stimulation of 42 s duration with an interval of 28 s. The entire session lasted approximately 30 minutes each daily. We performed the sham rTMS blocks with the coil held close to the precuneus, but angled away.

TMS protocol adverse events

The participants did not report any adverse events during the rTMS trial.

Statistical Analysis

Demographics and neuropsychological data

We performed two-sample t-test and chi-square tests to assess differences in demographic data, clinical, cognitive performance, ITV, and head rotation parameters between SCD and CN subjects ($p < 0.05$).

Network discovery of altered HIPsub related to SCD

To characterize the HIPsub network FC patterns at a group level, we performed a random-effect analysis using one-sample t -tests in the spatial maps of FC in CN and SCD subjects with a stringently threshold of $p < 0.001$ using the permutation test with TFCE and the family-wise error (FWE) correction together with a cluster extent $k > 100$ voxels (2700 mm³).

We performed GLM analysis to investigate the differences in the FCs of HIPsub between SCD subjects and CN before rTMS treatment after controlling for age, sex, education, ITV, and mean FD (TFCE-FDR-

corrected $p < 0.05$ and cluster size $> 405 \text{ mm}^3$). Then we made masks based on brain regions showing differences in the FCs of HIPsub in SCD compared to CN. These masks were used for the analysis of pre- v.s. post-rTMS (pre-sham- v.s. post-sham-rTMS) fMRI data from study #2 (i.e., network validation of altered HIPsub related to SCD). These findings identified network connectivity of altered HIPsub related to SCD, which can explain the changes that are related to SCD during rTMS treatment.

Pattern classification based on the altered HIPsub GM and FC

To further identify GM and network connectivity of altered HIPsub as closely related to SCD patients, we applied a support vector machine (SVM) approach using the alterations in the identified ROIs as a biomarker to test how well this could distinguish SCD patients from CN subjects. A leave-one-out cross-validation (LOOCV) strategy was used to assess the generalization of this SVM classifier and to assess its accuracy, sensitivity, and specificity. These findings identified GM and network connectivity of altered HIPsub related to SCD patients, which can explain the changes that are related to SCD during rTMS treatment.

Network validation of altered HIPsub related to SCD with rTMS

To empirically validate altered HIPsub network connectivity related to SCD, we used paired t-tests to calculate the changes in network FC of HIPsub pre- v.s. post-rTMS (or pre-sham- v.s. post-sham-rTMS) in SCD subjects after controlling for age, sex, education, and GM.

Sham v.s. real rTMS comparison

Of the 13 SCD subjects with full clinical assessments, usable sMRI, and fMRI scan data at baseline and 2 weeks of post-rTMS (or sham), 8 subjects had been randomized to real rTMS and 5 subjects received the sham rTMS. We performed a two-sample t-test to investigate the differences in the changes in FC of HIPsub between pre-post real rTMS and pre-post sham rTMS. Pre-real-rTMS (or sham-rTMS) maps were subtracted from post-real-rTMS (or sham-rTMS) maps to generate maps of FC changes for each subject.

Non-parametric statistics

To improve the statistical power with a low sample size, we performed a re-sampling method of stationary 10,000 bootstrap samplings to obtain significance in demographic data, clinical characteristics, cognitive performance, and FC of HIPsub between baseline assessment and at 2 weeks of post-rTMS (sham rTMS) for all statistical analyses (i.e., chi-square test, two-sample t-test, Pearson correlation, and paired-sample t-test).

Study approval

This study was approved by the responsible Human Participants Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (No. 2018-KY010-01 and No. 2020-KY010-02) (Nanjing, China).

Written informed consent was received from participants prior to inclusion in the study.

Results

Demographics, and clinical and cognitive function characteristics

As shown in **Table 1**, compared with CN, SCD subjects did not show no any significant differences in age, gender, education, general cognitive function (i.e., MMSE, MoCA, MDRS scores), and multimodal cognitive function (i.e., episodic memory, information processing speed, executive function, visuospatial function) (all $p > 0.05$, 10000 bootstraps) when showed higher HAMD and SCD-Q (all $p < 0.05$, 10000 bootstraps).

Network discovery of altered HIPsub related to SCD

As shown in **Figure 1-3** and **Figure S3**, SCD subjects displayed distinctly differently altered patterns of HIPsub network connectivity compared to controls.

As shown in **Figure 4A** and **Table S3**, in the HIPE network, compared with CN, SCD subjects displayed reduced FC in right CERpos, increased FC in FusG.L, Insula.L and PHG.L ($P_{TFCE-FDR} < 0.05$, cluster size $> 405 \text{ mm}^3$). As shown in **Figure 4B** and **Table S3**, in the HIPc network, compared with CN, SCD displayed reduced FC in IFGorb.R, increased FC in PHG.L ($P_{TFCE-FDR} < 0.05$, cluster size $> 405 \text{ mm}^3$). As shown in **Figure 4C** and **Table S3**, in the HIPp network, compared with CN, SCD displayed reduced FC in MFG.L, increased FC in Insula.L, bilateral MTG, PreCUN.L ($P_{TFCE-FDR} < 0.05$, cluster size $> 405 \text{ mm}^3$). All results were controlled for age, sex, education, ITV, and FD.

Classification of aMCI patients based on the altered HIPsub GM volumes and functional connectivities in SCD patients

The SVM classifier's classification accuracy was 86.0%. As shown in **Figure 5**, the SVM classifier's receiver operating characteristic (ROC) curve shows a high power to discriminate SCD patients from CN on an individual subject basis, with an AUC of 92.9%, 83.8% sensitivity, and 89.1% specificity.

Network validation of altered HIPsub related to SCD with rTMS

Changes of HIPsub FC pre- v.s. post-rTMS (or sham rTMS)

As shown in **Figure 6A**, in the HIPc network, compared with pre-rTMS, SCD subjects showed significantly reduced FC in PHG.L at 2 weeks of post-rTMS ($p < 0.05$, 10000 bootstraps). As shown in **Figure 6B**, in the

HIPp network, compared with pre-rTMS, SCD subjects showed significantly reduced FC FC in MTG.L at 2 weeks of post-rTMS ($p < 0.05$, 10000 bootstraps). No differences were found in the HIPe, HIPc and HIPp connectivity pre- v.s. post-sham rTMS.

Changes of episodic memory pre- v.s. post-rTMS (or sham rTMS)

As shown in **Figure 7**, SCD subjects showed improvement of episodic memory (AVLT) after 2 weeks of real rTMS treatment ($p < 0.001$, 10000 bootstraps) while no differences were observed after 2 weeks of sham TMS treatment ($p > 0.05$, 10000 bootstraps).

Discussion

To our knowledge, this study was the first to answer questions that the dysfunctions in posterior hippocampus (i.e., HIPc and HIPp) network connectivity could be causally restored by rTMS modulation upon the precuneus in SCD subjects. It further suggests that the precuneus-HIPsub circuit may be a potential target circuit to prevent the clinical progression of SCD to MCI/AD in therapeutic trials.

This study showed that SCD subjects presented differently altered patterns of HIPsub network connectivity compared to controls, which supports the notion that HIPsub involves in functional heterogeneity [13-15]. The SVM classifier showed that the abnormalities in brain memory networks had a high power to discriminate SCD from CN on an individual subject basis, with an ACC of 86.0%, an AUC of 92.9%, 83.8% sensitivity, and 89.1% specificity, which suggests that this study identifies a HIPsub pathological circuit related to SCD. The HIPe network connectivity in SCD subjects is predominantly abnormal in the brain regions involved in many aspects of emotional processing, including the cerebellum [39, 40], anterior insula [39, 41], parahippocampa gyrus [39, 42], and fusiform gyrus [43]. Indeed, SCD subjects are characterized by self-reported concerns regarding their memory decline [44], which significantly increases the risk of AD [5]. Based on above-mentioned evidence, it suggests that SCD subjects exist the abnormal network connectivity associated with emotional processing. In particular, SCD subjects showed altered HIPc and HIPp network connectivity in these brain regions involved in memory processing: the input and integration of sensory perception spatial information, visual object recognition memory, and the formation of episodic memory [15, 45-47]. Based on the processing theory of memory system, memory formation requires two neruopathways: occipito-temporal visual object processing pathway (the “what” stream) [47, 48] and parieto-temporal visuospatial pathway (the “where” stream) [49, 50]. Therefore, our results suggest that although SCD self-reported memory declines within the normal range, there are abnormalities in the networks associated with memory processing. That is, abnormalities in brain memory networks may precede the onset of clinical symptoms in SCD subjects.

More especially, the most fascinating finding was that rTMS modulation upon the precuneus for 2 weeks could restore HIPc connectivity with left parahippocampa gyrus and HIPp connectivity with left middle temporal gyrus accompanied by improvement of episodic memory. Indeed, numerous studies have consistently indicated that the precuneus is a node belonging to hippocampal intrinsic connectivity networks [15, 20, 24], a key node for episodic memory deficits observed in early AD [25, 26], and a

vulnerable region for the progress of MCI to AD [23]. Local rTMS stimulating accessible network nodes can be transmitted across synapses to distant but highly spatially specific interconnected nodes [18, 21, 22]. Therefore, it is reasonable to speculate that the effects of rTMS may propagate in the hippocampus through synaptic transmission in the precuneus-HIPsub pathway. Furthermore, this study only showed that rTMS modulation could restore the dysfunctions in posterior hippocampus (i.e., HIPc and HIPp) network connectivity related to memory processing but did not the dysfunctions in anterior hippocampus (i.e., HIPe) network connectivity related to emotional processing. It suggests that the precuneus-HIPsub pathway is an ideal target circuit for tailored rTMS intervention to improve episodic memory decline in SCD.

Limitations

First, a relatively small sample size was used to validate the effects of rTMS on the HIPsub pathological circuit related to SCD in this study. According to the general rTMS clinical trials, a single clinical symptom indicator was used as the clinical efficacy criteria. In this case, our sample size is indeed relatively small. However, this study combined clinical response with functional connectivity as the efficacy criteria, so it can be speculated that our conclusions are still reliable. Second, our findings suggested a potential target circuit the restoring the dysfunctions in HIPc and HIPp network connectivity, but this study did not find a target circuit for the restoration of HIPe network connectivity. In the future, a large sample size is needed to explore the therapeutic pathways of anterior hippocampus network connectivity.

Conclusions

This study provides a novel experimental evidence on correction of breakdown in posterior hippocampus (HIPc and HIPp) related to cognitive and perceptual processing by modulating the precuneus in SCD subjects. Furthermore, rTMS manipulation may prevent the disease progression by improving memory as the earliest at-risk state of AD in clinical treatment trials. It further suggests that the precuneus-HIPsub circuit may be used as a useful target circuit for SCD subjects to design rationale strategies for therapeutic trials.

Abbreviations

HIPsub: hippocampal subregions; SCD: subjective cognitive decline; rTMS: repetitive transcranial magnetic stimulation; HIPe: hippocampal emotional region; HIPc: hippocampal cognitive region; HIPp: hippocampal perceptual region; AD: Alzheimer's disease; MCI: amnesic mild cognitive impairment; NBH-ADsnp: Nanjing Brain Hospital-Alzheimer's Disease Spectrum Neuroimaging Project; CN: healthy controls; ITV: intracranial volumes; GLM: general linear model; RMS: root mean square; FD: framewise displacement; TFCE: threshold-free cluster enhancement; FDR: false discovery rate; ROI: regions of interest; MT: motor threshold; FWE: family-wise error; CEREPoS.R: right cerebellum posterior lobe; FusG.L: left fusiform gyrus; PHG.L: left parahippocampal gyrus; IFGorb.R: right inferior frontal gyrus, orbital part;

MTG.R: right middle temporal gyrus; MTG.L: left middle temporal gyrus; MFG.L: left medial frontal gyrus; PreCUN.L: left Precuneus.

Declarations

Author contributions

JC and XZ: designed the study. GH,CX, WQ, WM, WX, SC, JR, and WL: collected the data. FZ and JC: analyzed the data and prepared the manuscript.

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Availability of data and materials

The dataset generated and analyzed in the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the responsible Human Participants Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (No. 2018-KY010-01 and No. 2020-KY010-02) (Nanjing, China). Written informed consent was received from participants prior to inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no conflict of interest exists

Supplementary material

Please see the supplementary material.

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Tables

Table 1. Demographics, clinical measures, and head rotation parameters of SCD subjects and CN

Items		CN	SCD
		n=55	n=38
Age (years)		62.91(5.94)	65.84(7.73)
Gender (male/female)		23/32	8/30
Education level (years)		12.51(2.51)	12.22(2.72)
MMSE		28.58(1.43)	28.32(2.63)
MoCA		25.05(2.42)	24.92(1.79)
MDRS		141.46(2.33)	140.37(3.05)
HAMD		1.82(2.26)	3.92(3.17) ^a
SCD-Q		3.55(1.50)	6.51(0.90) ^a
ITV		1130.24(114.65)	1083.55 (109.21) ^a
Episodic memory tests			
AVLT-IR	raw score	19.15(4.36)	18.66(4.22)
	Z score	0.35(0.94)	0.25(0.91)
AVLT-5min-DR	raw score	6.35(2.20)	6.26(1.90)
	Z score	0.34(0.93)	0.31(0.80)
AVLT-20min-DR	raw score	6.30(1.94)	6.32(2.12)
	Z score	0.40(0.73)	0.41(0.80)
AVLT-total	raw score	31.79(7.61)	31.24(7.39)
Composite Z scores of each cognitive domain			
Episodic memory		0.27(0.53)	0.34(0.59)
Information processing speed		0.27(0.67)	0.18(0.71)
Executive function		0.27(0.48)	0.30(0.57)
Visuospatial function		0.17(0.66)	0.26(0.50)
Head rotation parameters			
FD_VanDijk		0.05(0.03)	0.04(0.03)
FD_Power		0.18(0.08)	0.16(0.09)
FD_Jenkinson		0.09(0.04)	0.09(0.05)

Data are presented as the mean (standard deviation, SD). Abbreviations: CN, healthy controls; SCD, subjective cognitive decline; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MDRS, Mattis Dementia Rating Scale; HAMD, Hamilton Depression Scale; SCD-Q, Subjective Cognitive Decline-Questionnaire; ITV, intracranial volume; AVLT-IR, Auditory Verbal Learning Test – immediate recall; AVLT-5min-DR, Auditory Verbal Learning Test – 5-minute delayed recall; AVLT-20min-DR, Auditory Verbal Learning Test – 20-minute delayed recall; FD, framewise displacement. ^a Significant differences were found between CN and SCD subjects. MMSE, MoCA, and MDRS are displayed as raw scores. This study used the composite Z scores to indicate the level of each cognitive domain. Note, to improve the statistical power, this study used a re-sampling method of stationary bootstrap (10,000 bootstrap samplings) to obtain significance.

Figures

Figure 1

Schematic polar plot and bar chart depicting distinct functional connectivity patterns of HIPE seeds with target regions of interest (ROI) distributed across the whole brain among CN and SCD subjects. The concentric circles depict parameter estimates representing the connectivity strength. Note that the functional connectivity data are only extracted from the brain regions corresponding to Fig. S3. Abbreviations: CN, healthy controls; SCD, subjective cognitive decline; HIPE, hippocampal emotional region; ROI, region of interest.

Figure 2

Schematic polar plot and bar chart depicting distinct functional connectivity patterns of HIPc seeds with target regions of interest (ROI) distributed across the whole brain among CN and SCD subjects. The concentric circles depict parameter estimates representing the connectivity strength. Note that the functional connectivity data are only extracted from the brain regions corresponding to Fig. S3. Abbreviations: CN, healthy controls; SCD, subjective cognitive decline; HIPc, hippocampal cognitive region; ROI, region of interest.

Figure 4

Differences in HIPsub functional connectivity between SCD subjects and CN before rTMS treatment after controlling for age, sex, education, ITV, and FD ($p < 0.05$, TFCE-FDR correction, cluster size $> 405 \text{ mm}^3$). (A) HIPe-subregion and brain different regions of the HIPe functional connectivity between CN and SCD subjects. Bar chart showing the quantitative comparison of functional connectivity in these regions. (B) HIPc-subregion and brain different regions of the HIPc functional connectivity between CN and SCD

subjects. Bar chart showing the quantitative comparison of functional connectivity in these regions. (C) HIPp-subregion and brain different regions of the HIPp functional connectivity between CN and SCD subjects. Bar chart showing the quantitative comparison of functional connectivity in these regions. * PTFCE-FDR<0.05. Abbreviations: CN, healthy controls; SCD, subjective cognitive decline; HIPE, hippocampal emotional region; HIPc, hippocampal cognitive region; HIPp, hippocampal perceptual region; TFCE, threshold-free cluster enhancement; FDR, false discovery rate; ITV, Intracranial volume; FD, framewise displacement; CEREpos.R, right cerebellum posterior lobe; FusG.L, left fusiform gyrus; PHG.L, left parahippocampa gyrus; IFGorb.R, right inferior frontal gyrus, orbital part; MTG.R, right middle temporal gyrus; MTG.L, left middle temporal gyrus; MFG.L, left medial frontal gyrus; PreCUN.L, left Precuneus.

CN vs. SCD ROC Curve

Figure 5

Classification of individuals as SCD versus CN by MRI-based “classifier”. ROC curve showing the classification power in MRI-based “classifier” of SCD from CN. Note: the values of ACC, AUC, sensitivity, and specificity in lower right of the figure present the optimum values under the optimum combined index score (red piont). Abbreviations: SCD, subjective cognitive decline; CN, healthy controls; AUC, area under the ROC curve; ACC, accuracy; Opt, optimum; ROC, receiver operating characteristic; MRI, magnetic resonance imaging.

Figure 6

Changes in HIPsub network functional connectivity of SCD before and after 2 weeks of rTMS treatment controlling for age, sex, GM, and education. (A) HIPc seed, brain regions of HIPc functional connectivity changes, and quantitative changes on HIPc functional connectivity of SCD subjects after 2 weeks of rTMS treatment. (B) HIPp seed, brain regions of HIPp functional connectivity changes, and quantitative changes on HIPp functional connectivity of SCD subjects after 2 weeks of rTMS treatment. * $p < 0.05$. Abbreviations: bef-SCD, subjective cognitive decline before rTMS treatment; aft-SCD, subjective cognitive decline after rTMS treatment; HIPc, hippocampal cognitive region; HIPp, hippocampal perceptual region; PHG.L, left parahippocampal gyrus; MTG.L, left middle temporal gyrus.

Figure 7

Changes of episodic memory in SCD subjects after 2 weeks of rTMS treatment. Line chart showing the changes in episodic memory in SCD subjects before and after 2 weeks of rTMS treatment. Notably, to improve the statistical power, this study used a re-sampling method of stationary bootstrap (10,000 bootstrap samplings) to obtain significance between groups. * $p < 0.05$, ** $p < 0.01$. Abbreviations: CN, healthy controls; SCD, subjective cognitive decline; HIPc, hippocampal cognitive region; MTG.L, left middle temporal gyrus; FC, functional connectivity; 2w-rTMS, 2 weeks of rTMS. AVLT-IR, Auditory Verbal Learning Test - immediate recall; AVLT-5min-DR, Auditory Verbal Learning Test – 5-min delayed recall, AVLT-20min-DR, Auditory Verbal Learning Test – 20-min delayed recall.

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