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Original Article

Proprioception deficits in chronic ankle instability associated with structural and functional alternations in cerebellar vermis

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ABSTRACT

Purpose: Ankle proprioception deficits have been widely reported in patients with chronic ankle instability (CAI), but their central neuropathological mechanisms have not been fully discussed. So, we aimed to figure out whether the structural and functional features of the cerebellar vermis differed between patients with CAI and healthy controls, and are associated with proprioception deficits in patients.

Methods: Twenty-two patients and 25 control individuals were enrolled in a cross-sectional investigation. All participants underwent structural and resting-state functional magnetic resonance imaging scanning to calculate voxel-based morphometry (VBM) and fractional amplitude of low-frequency fluctuation (fALFF) of the vermis. Between-group comparisons of the ankle instability-related subregions of the vermis were performed. Correlation analyses were performed between the outcomes of the surviving subregions and the proprioceptive scores of the ankle inversion discrimination apparatus for landing test.

Results: The subregion of vermis IV/V survived the multiple comparison correction to reveal a lower VBM value in patients than in healthy controls (Cohen's $d = -0.968$). The patients also showed significantly higher fALFF (Cohen's $d = 0.666$) in this subregion. After controlling the demographic features, the proprioceptive scores were significantly correlated with VBM ($r = 0.622$) and fALFF values ($r = -0.512$) in the group of patients.

Conclusions: Patients with CAI have lower gray matter volume and higher activity intensity in the cerebellar vermis than healthy control. The more severe proprioception deficits were significantly associated with the vermal volume and activity, which might be able to facilitate future diagnoses and treatments for CAI.

1. Introduction

Ankle sprain is one of the most common injuries during sports practices, especially those involving jumping and landing.[1] Furthermore, it is estimated that more than 40% of patients with a first-time ankle sprain would develop chronic ankle instability (CAI), manifesting as recurrent sprains, self-reported feelings of “instability,” and ankle “giving way”.[2] Until now, there have been no effective therapeutic strategies for CAI because sprained ankles might have mechanical instability and persistent sensorimotor deficits.[3,4] As a result, understanding the neuropathological mechanisms of CAI is clearly of interest to both practicing clinicians and researchers in sports medicine.

Among the sensorimotor factors in CAI, ankle proprioception is one of the most commonly discussed, initially defined as “the perceptions of the relative flexions and extensions of our limbs” by Charles Sherrington in 1906.[5,6] It is supported by a robust body of literature that the injured ankle would have impaired proprioception,[6,7] which might also be associated with lower postural balance, higher risk of re-injury, and worse sports performance.[8–10] Regarding the reasons for forming

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Abbreviations list

AMED	Aactive movement extent discrimination assessment
AIDAL	ankle inversion discrimination apparatus for landing
AUC	area under the curve
BMI	body mass index
CNS	central nervous system
CAI	chronic ankle instability
CIs	confidence intervals
CAIT	cumberland ankle instability Tool
fALFF	fractional amplitude of low-frequency-fluctuation
IQR	interquartile ranges
MRI	magnetic resonance imaging
ROI	region of interest
rs-fMRI	resting-state functional magneticresonance imaging
SD	standard deviations
VBM	voxel-based morphometry

proprioceptive deficits in CAI, the updated opinions indicated that the broken receptors, residual effusion, and inflammation would all induce ankle proprioceptive deafferentation during the pathological process of CAI, culminating in the neuroplasticity in the central nervous system (CNS) and leading to persistent functional deficits in CAI.[3,11]

The cerebellar vermis, which collects proprioceptive information originating from joints to distinguish the appropriate spatial positions of joints,[12,13] plays a critical role in proprioception. In CAI, Xue et al. first applied structural magnetic resonance imaging (MRI) and found a reduced volume of vermis in CAI patients.[14] Furthermore, the structural MRI of ankle instability mice models was longitudinally followed and found causal relationship between the ankle sprains and vermal difference, which supported that vermis atrophy is an ongoing part of the pathological process in CAI.[15,16] However, the direct association between the neuroplastic changes of the vermis and the established proprioception deficits in CAI still lacked evidentiary support.

In addition, the functional features of vermis in CAI also need further exploration. Resting-state functional magnetic resonance imaging (rs-fMRI) is a noninvasive technology for measuring intrinsic brain activity, which could reflect disease progression and predict behavior deficits in numerous diseases.[11,17] Coherence and intensity are the most commonly evaluated local neural features using rs-fMRI.[18] Since the difference of coherence in the vermis was not observed in a previous study when comparing patients with CAI and healthy controls,[19] the intensity features would be used in this study to explore the difference in vermal functions between patients with CAI and healthy controls and its association with proprioception deficits in patients.[18,20]

Given the above considerations, the aim of the current study was twofold: (i) replicating the observation of vermis atrophy and then exploring the functional difference of activity intensity in vermis between patients with CAI and healthy controls without a history of ankle injury, and (ii) determining the correlation between the ankle proprioception deficits in CAI and the structural/functional features of the vermis. We hypothesized that patients with CAI would have worse structural and functional features in the vermis than in control individuals, which would also be positively correlated with ankle proprioception in the group of patients.

2. Methods

2.1. Study design

This cross-sectional laboratory investigation was performed at Zhangjiang International Brain Imaging Center of Fudan University. All procedures were conducted adequate understanding and written informed consent from the subjects. All research protocols were approved by the institutional research ethics committee of Huashan Hospital (No. 2016-314). The report of this study followed the Strengthened Reporting of Observational Studies in Epidemiology Statement.

2.2. Recruitment of participants

The prior sample size calculation was performed according to the previously reported worse scores of the AIDAL test in the injured ankles of CAI patients compared to healthy controls (effect size = 0.76).[21] A total of 46 participants was needed for two groups with about a 1:1 allocation ratio to achieve a power of 0.8 and an α of 0.05.

To our knowledge, no previous studies have directly examined proprioception-related neuroplasticity in CAI and healthy controls using MRI. Therefore, we relied on indirect data from a previous study by Han et al. that evaluated proprioception deficits in CAI using the same method as our study to calculate the sample size.[21] Based on their outcomes, an effect size of 0.76 for the between-group difference indicated that a total of 46 participants was needed across two groups with a 1:1 allocation ratio to achieve a power of 0.8 and an α of 0.05 to detect proprioception deficits between the groups.[21] Given the potential for dropout or unusable data due to factors such as head motion during MRI scans, we planned for a final enrollment of 50 participants.

Fifty participants were finally enrolled in the local college between August 2022 and December 2022, considering potential losses after recruiting and data analysis. The inclusion criteria for individuals with CAI followed the International Ankle Consortium: (i) a history of at least one "significant" ankle sprain, which resulted in pain, swelling, and at least one interrupted day of normal physical activity, (ii) the first "significant" ankle sprain occurring at least 12 months before enrollment, and (iii) persistent symptoms of self-reported unilateral ankle instability measured by a score of < 24 on the Cumberland ankle instability Tool (CAIT) questionnaire for the injured ankle.[2] The inclusion criterion for healthy controls was no history of "significant" ankle injury in their lifetime. All participants were right footed, defined by the preferred limb when kicking a ball. Exclusion criteria for all participants included no (i) history of previous surgeries to the musculoskeletal structures or fractures requiring realignment in either lower extremity, (ii) "significant" acute injury in lower extremity in the previous three months, (iii) history of major medical illnesses, and (iv) current usage of medications.

2.3. Data acquisition

2.3.1. Demographic and clinical features

A single orthopedist obtained demographic and clinical features during the subject interview, including age, sex, height, weight, body mass index (BMI), injured side, Tegner scale for activity level, CAIT questionnaire for the feeling of instability intensity, the self-reported duration of CAI (from the significant initial sprain to scanning), and injured side.[2] The ankle tested for the healthy controls was selected using a random sequence.

2.3.2. MRI data acquisition and analysis

MRI images were quality controlled by an experienced technologist blinded to the group assignment and acquired by one 3.0 T Prisma scanner (Siemens, Erlangen, Germany). The T1 structural imaging and the blood oxygen level-dependent signals functional imaging were used. Then, to facilitate the multimethod analysis, the region of interest (ROI) analysis was performed by estimating the averaged values of each structural or functional outcome map within all included voxels. Regarding the selection of ROI, first, although the ankle instability-related subregions of the vermis (i.e., vermis IV/V) have been reported in a previous study, the total eight subregions of the cerebellar vermis in the automated anatomical labeling template were still used to replicate the previously published structural voxel-based morphometry (VBM) outcomes with multiple comparisons in our dataset.[14,22] The subregions that survived in the between-group comparison would be used to extract the functional outcomes for further comparisons and correlation analyses. The intensity features of fractional amplitude of low-frequency-fluctuation (fALFF) was then applied, which is defined as the ratio of the power spectrum of the low-frequency range to that of the whole frequency range and reveals the metabolic states of neurons.[20] More details of MRI data acquisition and analysis were given in Supplementary Appendix 1. The previously published coherence-related outcomes were also performed in Supplementary Appendix 2.

2.3.3. Ankle proprioception estimation

The ankle inversion discrimination apparatus for landing (AIDAL) test was used to measure the ankle joint position sense in inversion after MRI data collection. It has been proven to be more sensitive in detecting deficits in CAI than traditional proprioception measurements.[21,23] AIDAL tests were measured by two blinded kinesiologists with 10-cm high landing platforms and four ankle inversion platforms of 10°, 12°, 14°, and 16° slopes.[21] The participants were instructed in each trial to step down and land on both feet simultaneously (leading with the testing foot; Fig. 1 A). Three rounds of familiarization sessions (12 trials) and 40 formal trials (10 for each slope) were performed, and the proprioceptive scores were calculated by area under the curve (AUC). An overall AUC score of 1.0 means perfect ability to discriminate among the four inversion angles, while 0.5 means that the participant completely failed to discriminate between them (only chance responding). According to the data from Han et al., the intraclass correlation coefficient for the AIDAL test was 0.763, with no significant differences observed between test–retest sessions. This indicates that the AIDAL test is a reliable and valid method for assessing ankle inversion proprioception in CAI.[21] More details of AIDAL tests and data analysis were given in Supplementary Appendix 3.

2.4. Statistical analysis

GraphPad Prism version 9.0. (GraphPad Software, San Diego, California, USA) was used to perform the statistical analyses. Descriptive statistics are presented as numbers, means with standard deviations (*SD*), or medians with interquartile ranges (*IQR*) when appropriate. χ^2 tests, Mann-Whitney *U*-tests, and independent two-sample *t*-tests were used to check the between-group equivalence of demographic variables. For the MRI features, independent two-sample *t*-tests were first used to replicate the difference in structural outcomes (i.e., VBM) with Bonferroni corrections for eight subregions and to explore the difference in the functional outcomes for the survived subregion. For the AUC scores of the AIDAL test, independent two-sample *t*-tests were used to estimate the proprioception deficits of the patients compared with the healthy controls. Cohen's d is a measure of the standardized difference between two means, commonly used to quantify the effect size in studies. We further calculated the Cohen's *d* to express the magnitude of the difference in key outcomes between the CAI group and the control group.[24] Specifically, a Cohen's *d* value of 0.2 is generally considered a small effect, 0.5 a medium effect, and 0.8 or higher a large effect. Finally, the simple and partial Pearson correlation (with age, sex, and BMI as covariates) were used to explore the relationship between the structural/functional outcomes of the survived vermis subregion and ankle proprioception in the CAI group, with the absolute values of the coefficients classified as weak (0.0–0.3), moderate (0.3–0.5), or strong (> 0.5) correlation. A *p*-value < 0.05 was considered significant.

Table 1
The demographics and ankle injury features of all participants.

	CAI ($n = 22$)	Control ($n = 25$)	p value
Sex (male/female)	15/7	15/10	0.781
Age (years, mean ± *SD*)	34.04 ± 6.22	31.97 ± 9.11	0.375
Height (m, mean ± *SD*)	171.86 ± 9.55	169.68 ± 7.81	0.393
Weight (kg, mean ± *SD*)	70.59 ± 8.97	65.70 ± 11.63	0.117
BMI (kg/m^2, mean ± *SD*)	23.89 ± 2.33)	22.68 ± 2.64	0.104
Tegner (median [*IQR*])	4.00 [4.00, 5.00]	4.00 [4.00, 6.00]	0.790
CAIT (median [*IQR*])	21.00 [16.50, 21.75]	30.00 [30.00, 30.00]	< 0.001
Duration (years, median [*IQR*])	10.00 [6.00, 19.25]	–	–
Injured side (Left/Right)	12/10	–	–

BMI, body mass index; ADL, activities of daily living; CAIT, Cumberland Ankle Instability Tool; *SD*, standard deviations; *IQR*, interquartile range; n.s., not significant.

3. Results

3.1. Demographic and clinical features

Twenty-four individuals with unilateral CAI and 26 healthy controls were enrolled for inclusion from the local community. Two patients and one control were removed due to the head motion of the functional images. A total of 22 patients and 25 controls were analyzed. Twelve patients injured their left ankle, and 10 injured their right ankle. Thirteen controls tested the left ankle, and 12 tested the right ankle. The two groups did not differ significantly in demographic features. Significantly lower CAIT scores were found in patients than in controls ($p < 0.05$) (Table 1).

3.2. Structural and functional MRI feature comparisons

Among the eight pairs of comparisons on VBM, only the subregion of Vermis IV/V survived the Bonferroni correction to reveal a lower VBM value in patients (Cohen's $d = -0.968$, 95% *CIs* −1.575 to −0.361; *p*-corrected = 0.015) (Supplementary Appendix 4), which replicated ankle instability-related location in the previous reports. Thus, it was used in the following analyses.[14] Regarding the functional estimations in vermis IV/V, the CAI patients showed significantly higher fALFF than the healthy controls (Cohen's $d = 0.666$, 95% *CIs* 0.172 to 1.161; $p = 0.027$)

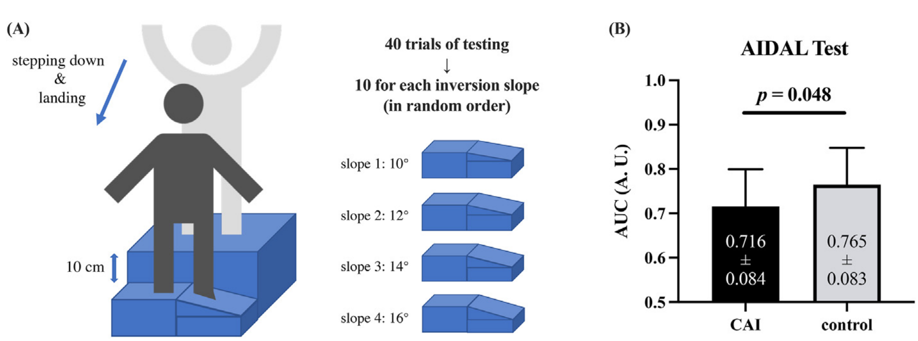

Fig. 1. **(A)** Schematic diagram of the AIDAL test; (B) the comparison of AUC scores in the AIDAL test between the two groups. AIDAL: ankle inversion discrimination apparatus for landing; AUC: area under the curve; CAI: chronic ankle instability.

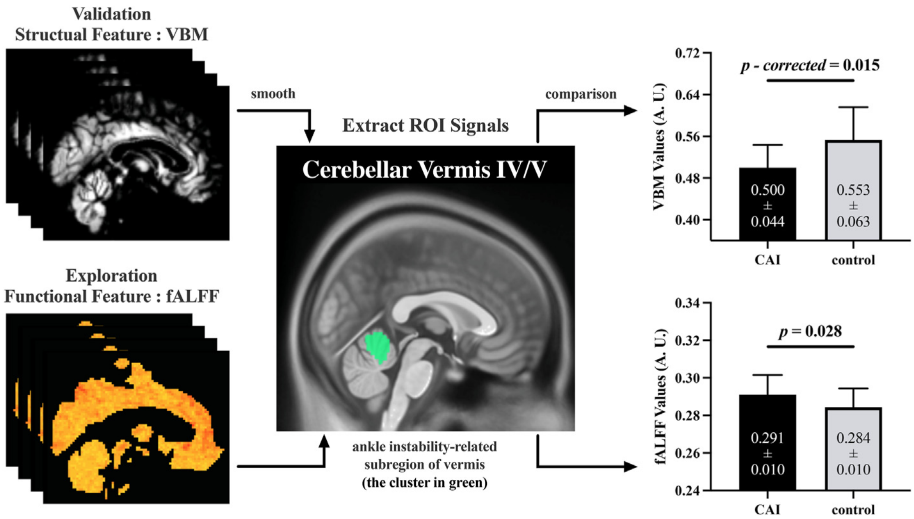

Fig. 2. Visualization of the VBM and fALFF maps, the analyzed ankle instability-related cerebellar subregion (the cluster in green), and the comparison of VBM and fALFF values between the two groups. VBM, voxel-based morphometry; fALFF, fractional amplitude of low-frequency fluctuations; CAI, chronic ankle instability.

(Fig. 2), while the coherence did not differ significantly in the two groups ($p = 0.289$) (Supplementary Appendix 2).

3.3. AIDAL score and its correlations with MRI features

The CAI patients showed significantly lower AUC scores than the healthy control individuals in the AIDAL test (Cohen's $d = -0.594$, 95% *CIs* −1.180 to −0.008; $p = 0.048$). This result also tended to be correlated with the lower VBM values ($r = 0.408$, $p = 0.059$) and was moderately correlated with the higher fALFF values ($r = -0.463$, $p = 0.030$) within the subregion of vermis 4/5 in the CAI group (Fig. 3A–C). After controlling for age, sex, and BMI, a significant strong relationship between AUC scores and VBM values ($r = 0.622$, $p = 0.002$) and fALFF values ($r = -0.512$, $p = 0.015$) was also observed (Fig. 3B–D).

4. Discussion

The most important findings of this study were that we replicated the lower volume and observed the higher intrinsic activity intensity in subregions of Cerebellar Vermis IV/V of patients with CAI compared with healthy controls without a history of significant ankle sprains. Additionally, we found that the deficits in ankle inversion proprioception in CAI were significantly correlated with the structural and functional features of the vermis.

4.1. Proprioception deficits in CAI

Since the ankle-foot complex is the only part of our body contacting the ground, its proprioception is essential for humans to interact with the

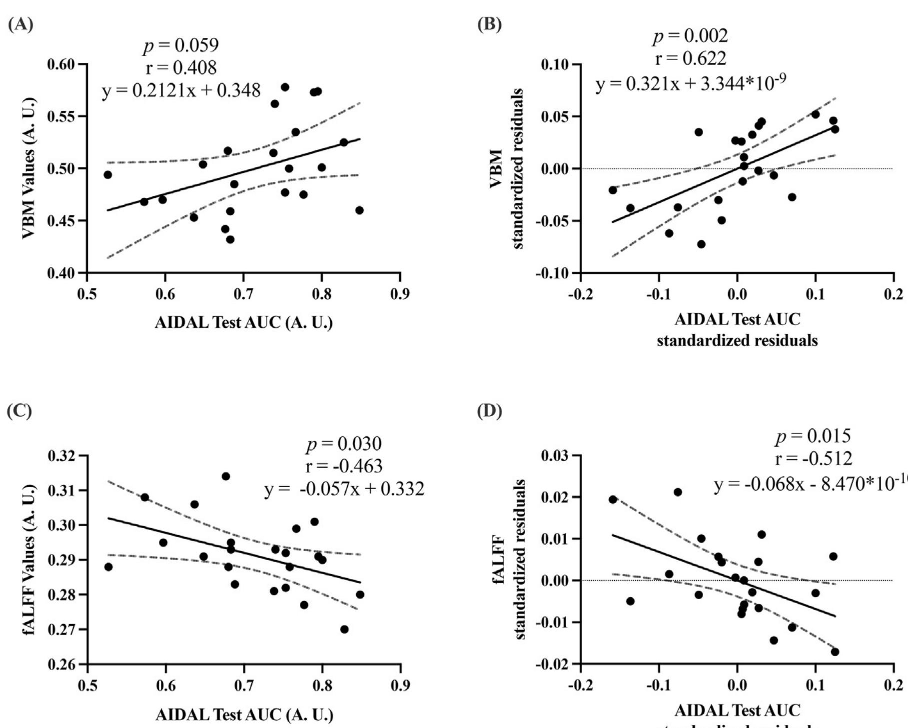

Fig. 3. Scatter plot of the linear relationship between the AUC scores in the AIDAL test and the VBM and fALFF values of vermis IV/V before (A, C) and after (B, D) controlling for age, sex, and body mass index in the patient group. AIDAL, ankle inversion discrimination apparatus for landing; AUC, area under the curve; CAI, chronic ankle instability; VBM, voxel-based morphometry; fALFF, fractional amplitude of low-frequency fluctuations.

environment and enable balance control.[4,12,25] The joint position reproduction test has traditionally been used in previous studies to assess joint position sense. Still, its ecological validity was questioned because they were measured in non-weight bearing conditions (lying or sitting on the isokinetic dynamometer).[21,23] An active movement extent discrimination assessment (AMEDA) test was used to assess the performance of the proprioceptive system in a more natural exercise condition. In such a test, the participants were asked to experience and judge inversion stepping displacements during normal gait was applied in CAI by Witchalls et al.[26] Recently, Han et al. further improved the sensitivity of the AMEDA test by changing simple walking into challenging actions that simulated "ankle action at injury" (i.e., landing in the AIDAL test).[21,23] In this study, we also observed that the unstable ankles had lower AIDAL scores than the healthy controls, again supporting that the deficits in determining the ankle inversion angles from 10° to 16° in CAI could be detected by this proprioception measurement.

If the unrehabilitated patients were landing on the ground, they might have failed to compare the actual ankle inversion sensation with the intended movements for a safe landing and subsequently placed the joints in a situation in which they were vulnerable to injury (e.g., landing with a more inversed or unprepared ankle).[3,12] Considering the peripheral morphological bases, the normal multidimensional proprioceptive sense is derived from the physical stimulation of a distinct class of ligamentous and musculus receptors (e.g., Pacinian corpuscles and muscle spindles).[12,13] After an ankle sprain, both the direct disruptions and the indirect influences (caused by local edema, pain, and inflammation) would be induced to the receptors and would lead to a prolonged lack of accurate proprioception and cumulates in neuroplastic changes to the CNS.[11] As a result, we attempted to supplement the existing pathological framework of CAI by evaluating proprioception deficit-related neuroplastic changes in both structural and functional views.

4.2. Neural correlates of proprioception deficits in CAI

As aforementioned, the cerebellar vermis played as the first supraspinal center to receive the proprioceptive projection from the lower limbs.[13] Beginning with structural research, it has been suggested in previous clinical and animal studies that reduced volumes after ankle injuries could be observed in the cerebellar vermis.[14,16] The reduced volume is associated with lower cell body density of neurons and is usually caused by prolonged dysfunction or disuse in the CNS.[27] We replicated the previous results in an independent CAI cohort and supplied evidence that atrophy was linearly associated with poor ankle inversion proprioception in this study. This result fits the hypothesis that maladaptive neuroplasticity causes the persistent loss of proprioceptive inputs in CAI. However, although we speculated that it was deafferentation that led to vermis atrophy because the sprained ankle is the source of this pathological process, it was also possible that the abnormal vermis might also be associated with poor performance in the AIDAL tests. The exact causal relationship between vermis atrophy and proprioceptive disability still needs further controlled laboratory research to confirm.

Beyond the structure, fALFF was also used to measure the activity intensity of the cerebellar vermis. Contrary to our hypothesis, the patients with CAI showed an increased fALFF compared to the controls, and the high fALLF is also associated with worse proprioception behaviors in patients. Unlike the same activity intensity measured in task-based fMRI, the resting-state fALFF is more likely to reflect the "baseline" activation intensity.[20] Since the activity level of our patients was similar to the controls, we speculated that CAI patients with impaired proprioceptive pathways might have to activate the rest of intact cerebellar neurons more heavily to meet the similar requirement of activity level in normal life.[11] After that, the "over-activated" vermis might theoretically leave fewer processing resources for further adaption to the challenging tasks and thus exhibit deficits in the behavior tests. However, these speculations still needed the validation of future task-based fMRI studies in which, in contrast, the possibility that CAI patients would exhibit reduced activation during proprioceptive tasks than the healthy controls would be examined.

4.3. Future implications

Both the clinical assessment and rehabilitation of proprioception deficits in CAI are complex.[6,28] On one hand, even the latest AIDAL test was still hard to be widely used in the clinic due to its difficult task learning and testing requirements.[21] Although it is not commonly affordable now, if the population and convenience of MRI scanning could be improved in the future, the measurements of cerebellar features might be a standardized and sensitive measurement for proprioception deficits in CAI. On the other hand, our results highlight the potential for a paradigm shift in rehabilitation strategies for CAI. Traditional rehabilitation methods often focus on biomechanical profiles, which may not fully address the underlying neuroplastic changes associated with proprioception deficits.[28–31] Our findings suggest that interventions aimed at enhancing the efficiency of the cerebellum in processing proprioceptive information could lead to more effective rehabilitation outcomes. For example, in older people with a high risk of falling, vermis stimulation was supposed to benefit sensory integration and improve postural balance in the short and long terms.[32,33] We hope similar strategies could be applied to modulate our observed compensatory overactivation of the vermis, make the cerebellum more efficient when handling the increased proprioceptive demands, and, finally, bring optimal clinical function to patients with CAI.

4.4. Limitations

This study has several limitations. First, the causal relationships between ankle injuries and vermal atrophy and the ones between proprioception deficits and structural/functional abnormality of the vermis still need further exploration due to our cross-sectional design. It might well be that patients with cerebellar changes or atrophy are prone to ankle sprains due to inherited proprioception deficits. Second, we did not include the individuals who suffered from significant sprains but recovered (i.e., Copers), which could be an essential supplement to the existing pathological framework of CAI. Future studies could consider to include this additional group to make the relationship between structural or functional abnormalities of the cerebellar vermis and chronic ankle instability more convincing. Third, the AIDAL test involved the contribution of plantar cutaneous sensation and high-level cognitive components (e.g., memory and learning) and was still not a direct measure of proprioception input from the ankle joint.[21] Although we found statistically significant correlations between the neural features and proprioception, the clinical significance of these relationships is difficult to establish, particularly in the context of our exploratory analysis. Further studies are needed to validate the behavioral associations with the cerebellar vermis. More updated assessments were needed to validate our behavioral associations with the cerebellar vermis. Last but not least, although more convenient and accessible than the task-based fMRI, the rs-fMRI is still lacking in exact physiological meaning and its mechanisms are ambiguous.

5. Conclusion

Patients with CAI have lower gray matter volume (VBM values) and higher intensity of intrinsic activity (fALFF values) in the cerebellar vermis IV/V subregion than healthy controls. The more severe proprioception deficits were significantly associated with vermal volume and activity of the vermis in patients.

CRediT authorship contribution statement

Xiao'ao Xue: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yuwen Zhang:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Le Yu:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Qianru Li:** Writing – review & editing, Software, Methodology. **Yiran Wang:** Writing – review & editing, Visualization, Software. **Zikun Wang:** Writing – review & editing, Methodology. **Shanshan Zheng:** Writing – review & editing, Formal analysis. **Yang Sun:** Writing – review & editing, Supervision, Resources. **He Wang:** Writing – review & editing, Supervision, Funding acquisition. **Yinghui Hua:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Ethical approval statement

All procedures were conducted adequate understanding and written informed consent from the subjects. All research protocols were approved by the institutional research ethics committee of Huashan Hospital (No. 2016-314).

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

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