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Thin and Plain Supplementary Motor Area in Chronic Ankle Instability: A Volume- and Surface-Based Morphometric Study

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Context: The supplementary motor area (SMA) is involved in the functional deficits of chronic ankle instability (CAI), but the structural basis of its abnormalities remains unclear.

Objectives: To determine the differences in volume- and surface-based morphologic features of the SMA between patients with CAI and healthy controls and the relationship between these features and the clinical features of CAI.

Design: Cross-sectional study.

Setting: Sports medicine laboratory.

Patients or Other Participants: A total of 32 patients with CAI (10 women, 22 men; age = 32.46 ± 7.51 years) and 31 healthy controls (12 women, 19 men; age = 29.70 ± 8.07 years) participated.

Main Outcome Measure(s): We performed T1-weighted structural magnetic resonance imaging of participants and calculated volume- and surface-based morphologic features of SMA subregions. These subregions included anterior and posterior subdivisions of the medial portion of Brodmann area 6 (6 ma and 6 mp, respectively) and supplementary and cingulate eye fields. Between-group comparisons and correlation analysis with clinical features of CAI were performed.

Results: Moderately thinner 6 mp (motor-output site; Cohen $d = -0.61$; 95% CI = −1.11, −0.10; $P = .02$) and moderately plainer 6 ma (motor-planning site; Cohen $d = -0.70$; 95% CI = −1.20, −0.19; $P = .01$) were observed in the CAI than the control group. A thinner 6 mp was correlated with lower Foot and Ankle Ability Measure Activities of Daily Living subscale scores before ($r = 0.400$, $P = .02$) and after ($r = 0.449$, $P = .01$) controlling for covariates.

Conclusions: Patients with CAI had a thinner 6 mp and a plainer 6 ma in the SMA compared with controls. The thin motor-output site of the SMA was associated with ankle dysfunction in patients. This morphologic evidence of maladaptive neuroplasticity in the SMA might promote more targeted rehabilitation of CAI.

Key Words: ankle injuries, neuronal plasticity, sensorimotor cortex, magnetic resonance imaging

Key Points

- Patients with chronic ankle instability showed altered supplementary motor area structures, with reduced thickness in motor-output regions and fewer complexities in motor-planning areas.
- These neural changes were correlated with diminished ankle function, suggesting neurologic adaptations in these patients.
- These findings should be considered in rehabilitation strategies to target neurologic changes and improve ankle stability.

Ankle sprains represent the most frequent musculoskeletal injury in sports, with a rate of 4.61 cases of overall ankle sprain per 10 000 sport sessions in the National Collegiate Athletic Association.[1] First-time ankle sprains are often erroneously considered innocuous injuries, but up to 74% of them will eventually progress to a debilitating condition termed *chronic ankle instability* (CAI).[2]

Patients with CAI typically experience persistent symptoms, such as regular occurrences of uncontrolled excessive ankle inversion (ie, "giving way") and repeated ankle sprains, and have an increased risk of articular degeneration and posttraumatic osteoarthritis.[2] The theory of Freeman et al, published in 1965, marked a significant milestone for understanding the progression of CAI.[3] The authors proposed that trauma-induced damage to afferent nerve fibers surrounding the ligaments results in residual functional instability after an ankle sprain.[3] This theory laid the foundation for subsequent research, suggesting that CAI might influence sensorimotor neuroplasticity of the central nervous system (CNS) because of prolonged disruption of proprioceptors and inflammation within injured joints.[4] Currently, it is understood that *sensorimotor insufficiencies*, which refers to deficits in the body's ability to process sensory information and respond with appropriate motor actions, are believed to substantially

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contribute to CAI, alongside issues such as the loss of ligament integrity.[5]

Unfortunately, current therapeutic efforts are often inadequate to fully restore the sensorimotor insufficiencies of CAI, and one reason could be the lack of knowledge of their mechanisms.[6] Hence, delving deeper into these mechanisms could pave the way for more effective interventions, benefiting both clinicians and patients. In a groundbreaking study, Rosen et al provided insights into this by exploring cortical alterations during single-legged stances in patients with CAI compared with uninjured and recovered controls.[7] Notably, no difference in brain activations measured using oxyhemoglobin levels was observed in the primary sensorimotor cortex, whereas the supplementary motor area (SMA) exhibited pronounced variability, as evidenced by high SDs in these activations (ie, unstable activity).[7] The SMA, located in the medial portion of Brodmann area 6, plays a crucial role in feed-forward adjustments, preparing muscles for activity beyond just the primary functions.[8] Its role becomes particularly pivotal when considering the coordination and planning of complex motor tasks, such as maintaining ankle stability.[8] Given these findings and the vital function of the SMA, it is plausible to surmise that functional abnormalities within the SMA could be intricately linked to the persistent ankle instability observed in patients with CAI. Thus, a deeper exploration of the properties and potential alterations of the SMA in CAI becomes essential, offering a window into the neural mechanism of persistent functional deficits in CAI.

The function of SMA is closely related to its neural structure. Although magnetic resonance imaging (MRI) advances have allowed for the identification of distinct brain features across various conditions, recent studies on CAI have presented an inconsistency.[9,10] Specifically, researchers have not identified structural changes in the SMA of patients with CAI when assessing overall gray-matter volume, despite observed functional abnormalities in these patients.[7,11,12] Such inconsistencies bear important implications, suggesting that our understanding of the effect of CAI on sensorimotor neuroplasticity might be incomplete or our current investigative tools may be missing subtle yet crucial details. The limitations of conventional volume-based MRI analysis, especially its potential to overlook nuanced changes in smaller regions such as the SMA within whole-brain scans, could be a contributing factor.[11–13] Furthermore, even though volume-based analyses present a broader picture, surface-based methodologies delve deeper by assessing cortical thickness and shape.[9,10] These advanced techniques could unveil finer structural nuances that may have been previously overlooked.[9,10] Given these inconsistencies and the potential insights offered by refined MRI techniques, the aim of our study was to bridge this knowledge gap. We used both volume- and surface-based MRI methods to comprehensively investigate the SMA, hoping to provide a more coherent understanding of the structural changes in patients with CAI.

The purpose of our study was 3-fold: to determine the differences in (1) volume-based and (2) surface-based morphologic features of the SMA between patients with CAI and healthy controls and (3) to determine their relationship with the clinical features of CAI. We hypothesized that patients with CAI would exhibit similar gray-matter volume but distinct cortical thickness and shape in the SMA compared with healthy controls and that these differences could be correlated with symptom severity and CAI chronicity.

METHODS

Study Design

We used a cross-sectional design. The study design and data analysis were aligned with the Strengthening the Reporting of Observational Studies in Epidemiology consensus.[14]

Participants

We used G*Power (version 3.1, Universität Düsseldorf) to perform the a priori sample size calculation based on the previously reported effect size (Cohen $d = 0.821$) of the different SMA activity between patients with CAI and healthy controls, with the expected power of 80%.[7] A total of 25 participants were needed for each group to meet the 2-tailed α value of 5%. We recruited 32 volunteers per group from a local college between August 2022 and February 2023 to cover a potential loss of 20%.

Patients with CAI were included based on the International Ankle Consortium guideline: (1) a history of at least 1 significant ankle sprain occurring at least 1 year before the study, resulting in inflammatory symptoms and causing at least 1 interrupted day of desired physical activity, and (2) self-reported ankle instability confirmed by the Cumberland Ankle Instability Tool (CAIT) questionnaire (a score of <24).[2,15] The healthy controls had no significant ankle sprain history in their lifetime. The exclusion criteria for both groups were (1) a history of other musculoskeletal injuries or surgeries in the lower limbs (except CAI in the CAI group); (2) acute significant ankle sprain in the previous 3 months; (3) a major medical illness or current use of medications that may affect sensorimotor or cognitive ability; and (4) left foot dominant, with the *dominant limb* defined as the preferred limb for kicking a ball. The rationale for excluding left-footed individuals stemmed from considerations of brain lateralization. Given that the dominant hemisphere of the brain often exhibits heightened activity related to the control of the dominant foot, excluding left-footed individuals ensured a more homogeneous sample and reduced potential variability in brain morphology. We did not set the ankle dysfunctions measured by the Foot and Ankle Ability Measure (FAAM; $<90\%$ as recommended by International Ankle Consortium) as a criterion for the correlation analysis between the neural features and full range of functional measurements.[2,16]

All participants provided written informed consent, and the Institutional Review Committee of Huashan Hospital (No. 2016-314) approved the study.

Data Acquisition

A single investigator (Q.L.) collected the demographic and clinical data before scanning using a customized checklist, including sex, age, body mass index (BMI), injured side, time since initial ankle sprain, Tegner Activity Rating Scale for activity level, the CAIT for the self-reported intensity of ankle instability (for both ankles), and the FAAM for the self-reported ankle function during activities of daily living (ADL) or sports.[2,15,16] If patients had bilateral CAI, the features of the side with lower CAIT scores were used for further analyses. A single radiologist (Y.Z.) who was blinded to group assignment performed the scanning and visual inspection for artifacts. Head motion was minimized with tight but comfortable head padding during the scanning. A 3.0-T Siemens Prisma scanner

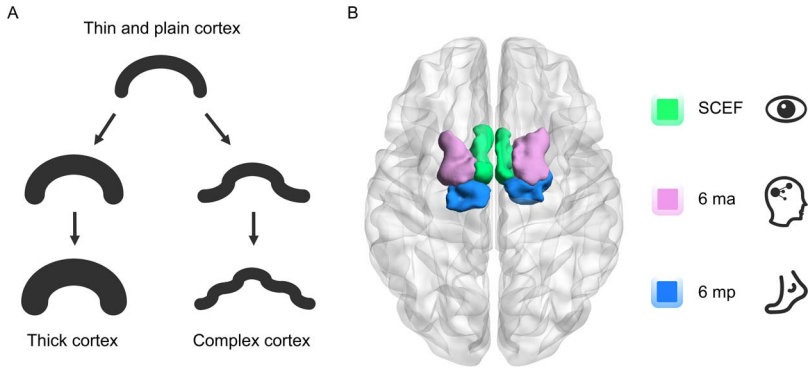

Figure 1. Diagrams of the cortical thickness and A, complexity and B, the 3 subregions of the supplementary motor area. Abbreviations: 6 ma, anterior subdivision of the medial portion of Brodmann area 6; 6 mp, posterior subdivision of the medial portion of Brodmann area 6; SCEF, supplementary and cingulate eye fields.

with 32-channel head coils was used to perform the T1-weighted structural MRI. Detailed data-acquisition variables are provided in Supplemental Material A (available online at https://dx.doi.org/10.4085/1062-6050-0257.23.S1). Preprocessing procedures of volume- and surface-based morphometric outcomes were performed using the Computational Anatomy Toolbox (https://neuro-jena.github.io/cat12-help/) package that was implemented in Statistical Parametric Mapping (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software.[9,10] The magnetic field inhomogeneities and noise were removed, and the image intensities were globally normalized for all images. To guarantee the integrity and precision of our MRI analyses, we used an objective image quality assurance test on all MRI scans. This test encompassed the noise contrast ratio, inhomogeneity contrast, and image resolution metrics. Participants with scans that fell below a C+ rating were excluded to maintain the robustness and consistency of our data set, aligning with the criteria for excellent/good quality as stipulated by the Computational Anatomy Toolbox manual.

To evaluate the volume-based outcomes, we separated the images into gray-matter, white-matter, and cerebrospinal-fluid components according to the tissue probability maps and integrated them into Montreal Neurological Institute-Hospital–normalized space using the Dartel algorithm. The modulated gray-matter maps were used for region-of-interest (ROI) extraction. For the surface-based outcomes, we performed topologic correction, spherical mapping, and spherical registration.[9] Cortical thickness was measured as the distance between the inner boundary (white and gray matter) and outer boundary (gray matter and cerebrospinal fluid) using projection-based methods.[9] The complexity of the cortical shape was quantified as the fractional dimension calculated using the spatial frequency of cortical-shape details through spherical harmonic reconstruction. A higher complexity indicated a more irregular cortical shape (Figure 1A).[9] The estimated cortical-thickness and -complexity maps were used for the ROI extraction.

Subsequently, the ROI-wise analysis was performed based on the Human Connectome Project multimodal parcellation atlas of the human cortex, which defines each cortical region by combining myelin content, cortical thickness, topographic organization, resting-state functional connectivity, and task-based activation.[17,18] Regarding the motor-related tasks, participants performed the active movements (foot, hand, or tongue) initiated by a visual cue.[17] More details of the tasks used to define the Human Connectome Project atlas are provided in Supplemental Material B. The SMA was divided into 3 subregions: supplementary and cingulate eye fields (SCEF) and the anterior and posterior subdivisions of Brodmann area 6 (6 ma and 6 mp, respectively; Figure 1B).[17] The SCEF is involved in eye movements and thus was activated when receiving the visual motor cue (about which movements were needed to perform) onscreen. The 6 ma, also known as the pre-SMA, manages the motor planning and guidance of ongoing movements during the motor cue. The 6 mp, the only subregion of the SMA that has reciprocal connections with the primary motor cortex, was directly related to motor output during foot and hand movements, with substantially stronger activation in foot movements.[17] Given that all of them were activated bilaterally during the motor cue and ipsilateral movement tasks, the average volume- and surface-based outcomes of each SMA subregion were extracted bilaterally for further analyses.

Statistical Analysis

For data normality, $P > .1$ using the Kolmogorov-Smirnov Z test indicated normally distributed data. Age, BMI, and morphologic outcomes of the SMA were described as the mean ± SD and compared between groups using parametric tests, and the duration and clinical questionnaire scores that violated the normality assumptions were described using the median (interquartile range [IQR]) and compared between groups using nonparametric tests. Demographic equivalence was examined using a 2-tailed χ^2 test, a Mann-Whitney U test, and a 2-tailed independent-samples t test at first.

We used the 2-tailed independent-samples t test for between-groups comparisons. As mentioned, our hypothesis was divided into 2 sections: (1) no volume-based differences would be observed and (2) surface-based differences between the subregions of the SMA would be observed. For surface-based outcome comparisons, multiple comparison corrections were performed using false-discovery-rate methods.[19] The effect sizes with 95% CIs of between-groups differences were calculated as Cohen d effect sizes, with the absolute values interpreted as *small* (0.2–0.5), *moderate* (0.5–0.8), or *large* (>0.80) differences.[20] Univariable and multivariable linear regressions were also performed as sensitivity analyses to control the residual biases of between-groups comparisons caused by age, sex, BMI, and total intracranial volume. To investigate the relationships between the morphologic outcomes that were different (normally distributed) and the clinical features

Table 1. Participant Baseline Characteristics

Characteristic	Chronic Ankle Instability Group (n = 32)	Control Group (n = 31)	*P* Value
Sex, female/male, No.	10/22	12/19	.72
Age, mean ± SD, y	32.46 ± 7.51	29.70 ± 8.07	.16
Body mass index, mean ± SD, kg/m^2	23.36 ± 2.79	23.01 ± 3.10	.64
Tegner score, median (IQR)	4.00 (3.75–5.25)	4.00 (4.00–5.50)	.90
Cumberland Ankle Instability Tool, median (IQR)	20.50 (15.75–22.00)	30.00 (28.00–30.00)	<.001
Foot and Ankle Ability Measure, median (IQR)			
Activities of Daily Living	97.62 (95.24–98.81)	100.00 (100.00–100.00)	<.001
Sports	93.75 (84.38–100.00)	100.00 (100.00–100.00)	<.001
Duration of chronic ankle instability, median (IQR), y	10.00 (4.75–13.00)	0.00 (0.00–0.00)	<.001
Injured side, %			<.001
None	0	31	
Left	15	0	
Right	15	0	
Both	2	0	

Abbreviation: IQR, interquartile range.

of CAI (not normally distributed, namely the FAAM, the CAIT, and duration), we used Spearman correlation coefficients. Both simple and partial correlation coefficients were computed within the patient group, considering age, sex, and BMI, which are known to influence brain morphology and function as confounders, as covariates. The absolute values of these coefficients were interpreted as *weak* (0.0–0.3), *moderate* (0.3–0.5), and *strong* (>0.5) correlations.[20] The correlation analyses were conducted only in individuals with CAI because most healthy controls scored the maximum points on the clinical scale, leading to a lack of variability. The α level was set at .05 for all statistical tests. Statistical analyses were performed using GraphPad Prism (version 9.0; GraphPad Software).

RESULTS

Demographic and Clinical Features

A total of 32 patients with CAI (10 women, 22 men; age = 32.46 ± 7.51 years) and 31 controls (12 women, 19 men; age = 29.70 ± 8.07 years) were enrolled in the analysis, with poor image quality found in 1 control (classified as *F*). No differences were found for sex, age, or BMI ($P > .05$). Lower scores in the CAI than in the control group were observed for the CAIT and FAAM ($P < .001$). Regarding the Tegner scores, the control and CAI groups had similar activity levels ($P = .90$). The median duration of CAI was 10.00 years (IQR, 4.75–13.00 years; Table 1).

Volume- and Surface-Based Outcomes of the SMA

The volume-based outcomes were compared first, and no differences in gray-matter volume were observed in SMA subregions (*P* range, .36–.90). Regarding the surface-based outcomes, a moderately thinner 6 mp (Cohen $d = -0.61$; 95% CI = −1.11, −0.10) and moderately plainer 6 ma (Cohen $d = -0.70$; 95% CI = −1.20, −0.19) were observed in the CAI than in the control group (Table 2). The relationships between the 95% CIs of β values and the zero lines were stable before and after controlling for covariates for the outcomes (Figure 2). The SCEF exhibited thinner cortical thickness in patients on univariable

Table 2. Between-Group Comparisons of the Volume- and Surface-Based Morphometric Outcomes

Section of Hypothesis[a]	Supplementary Motor Area Subregion	Group, Mean ± SD		Cohen *d* Effect Size (95% CI)	*P* Value	
		Chronic Ankle Instability (n = 31)	Control (n = 32)		Uncorrected	False-Discovery-Rate Corrected
Section 1						
Volume[b]	6 mp	0.46 ± 0.06	0.46 ± 0.07	0.00 (−0.49, 0.49)	.90	NA
	6 ma	0.42 ± 0.06	0.42 ± 0.05	0.00 (−0.49, 0.49)	.76	NA
	SCEF	0.53 ± 0.06	0.51 ± 0.06	0.33 (−0.16, 0.83)	.36	NA
Section 2						
Thickness, mm	6 mp	2.89 ± 0.17	2.99 ± 0.16	−0.61 (−1.11, −0.10)	.02	.046[c]
	6 ma	3.23 ± 0.14	3.29 ± 0.16	−0.40 (−0.90, 0.10)	.14	.21
	SCEF	3.23 ± 0.17	3.34 ± 0.20	−0.59 (−1.10, −0.09)	.03	.051
Complexity[b]	6 mp	2.22 ± 0.09	2.24 ± 0.11	−0.20 (−0.69, 0.30)	.47	.47
	6 ma	2.38 ± 0.11	2.46 ± 0.12	−0.70 (−1.20, −0.19)	.01	.046[c]
	SCEF	2.19 ± 0.09	2.22 ± 0.14	−0.25 (−0.75, 0.24)	.38	.46

Abbreviations: 6 ma, anterior subdivision of the medial portion of the Brodmann 6 area; 6 mp, posterior subdivision of medial portion of the Brodmann 6 area; NA, not applicable; SCEF, supplementary and cingulate eye fields.

[a] Two sections of hypothesis: (1) there were no volume-based differences and (2) there were surface-based differences between the subregions of the supplementary motor area.

[b] Measure is unitless.

[c] Indicates difference ($P < .05$).

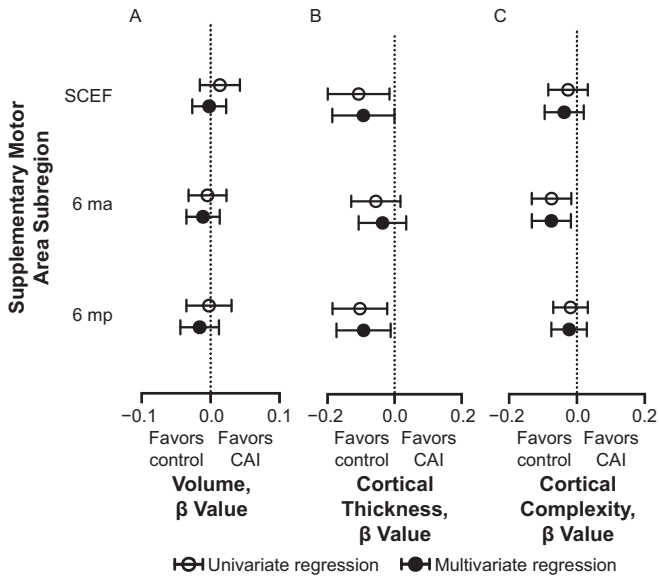

Figure 2. Forest plots of the linear regressions for the relationship between chronic ankle instability (CAI) and morphologic outcomes of the supplementary motor area. A, Volume. B, Cortical thickness. C, Cortical complexity. Covariates of multivariable regressions included sex, age, and body mass index (for volume, additionally, total intracranial volume). The results with 95% CIs that do not cross zero indicate a significant group-morphology relationship. A positive β value indicates higher morphologic outcomes in the CAI than in the control group. Abbreviations: 6 ma, anterior subdivision of the medial portion of Brodmann area 6; 6 mp, posterior subdivision of the medial portion of Brodmann area 6; SCEF, supplementary and cingulate eye fields.

analysis but was not different after false-discovery-rate correction or covariate regression. The numeric results of the univariable and multivariable regression are given in the Supplemental Table.

Relationships Between SMA Morphology and Clinical Features

Among the exploratory correlation analyses within the CAI group, the cortical thickness of 6 mp had a moderate positive correlation with FAAM-ADL scores ($r = 0.400$, $P = .02$). After further controlling the demographic data, a thinner 6 mp was still correlated with lower FAAM-ADL scores ($r = 0.449$, $P = .01$). No correlations were observed between the cortical thickness of 6 mp and the FAAM-Sports and CAIT scores (Figure 3). In addition, none of the clinical features were correlated with the cortical complexity of 6 ma (P range, .26–.87; Supplemental Figure).

DISCUSSION

Our study produced 2 key findings that offer deeper insights into the morphologic adaptations of the CNS in patients with CAI. Primarily, we found that the abnormality of the SMA in patients with CAI may not be characterized by gray-matter volume but by the thinner cortex in the 6 mp subregion and plainer cortex in the 6 ma subregion compared with those of the control group. Secondarily, a thin 6 mp was correlated with ankle dysfunction in daily activity.

These findings enrich our understanding of the maladaptation of the CNS to CAI. Building on the foundational insights, our research is pioneering in its comparative analysis of both volume- and surface-based brain morphometry in patients with CAI. One key aspect of our research is that we looked at both volume- and surface-based brain measurements in patients with CAI. This dual approach is crucial as it provides a more comprehensive view of the structural nuances of the SMA, which might have been overlooked in previous studies using single-method analyses.[11,12] Based on earlier studies that showed functional changes in the SMA,[7] we adopted a focused ROI-based approach, specifically targeting the subregions of the SMA, and provided the structural basis for the deficits. We hope our study provides a starting point for others to further investigate and understand the mechanism of CAI.

Neuroplasticity of the SMA in CAI

The motor responses of the musculoskeletal system are directly generated by the CNS. Recent evidence has shown that reorganization of the CNS after peripheral ligamentous injuries involves multiple brain areas.[4] Neuroanatomically, regarding the sensory-to-motor loop, our findings on the SMA abnormalities align with the well-documented evidence of neurophysiological reorganization in CAI: (1) for sensory input, the SMA receives projections from the basal ganglia and cerebellum, and proprioceptive deafferentation-related cerebellar abnormalities have also been observed in structural and functional MRI studies on CAI and (2) for motor output, the blocked corticospinal pathway was the most commonly reported feature of maladaptive neuroplastic changes after ankle sprains, and about 10% of corticospinal tracts comprise neurons from the SMA.[4,5,11,21–25] Therefore, we suggest that the SMA might be a key node in the network of central adaptation after ankle injury.

Regarding the morphologic differences of the SMA in CAI, our preliminary outcomes showed that the difference between groups was not explained by the gray-matter volume, which was consistent with findings of previous studies of whole-brain exploration.[11,12] Surface-based measures, focusing on cortical thickness and shape, provide a nuanced view of cortical morphology. This view allows for a more detailed understanding of subtle changes, especially in regions such as the SMA that might be overlooked in volume-based analyses. Our findings suggest that surface-based measures are more sensitive in detecting abnormalities in CAI, potentially because of their ability to capture morphologic nuances. According to our results, the surface-based outcomes seemed to have better sensitivity in relation to CAI, and a regionally lesser thickness of 6 mp and lower complexity of 6 ma were observed initially.

Physiologically, the SMA contributes to many essential sensorimotor abilities in humans, including modulation of proprioception, control of postural stability, and programming of variable feed-forward muscular contraction.[25] Impairments of these abilities have been well documented in patients with CAI.[5,26–28]

Regarding the subregions, the thinner cortex observed in the 6 mp might indicate reduced active neurons, which could compromise motor-output capabilities vital for tasks such as single-legged stance.[7,9,29] This potential reduction in motor-output capability aligns with functional impairments observed in patients with CAI.[7] Similarly, the plainer cortex in the 6 ma may suggest fewer foldings for efficient neural processing in motor planning, another crucial aspect compromised in

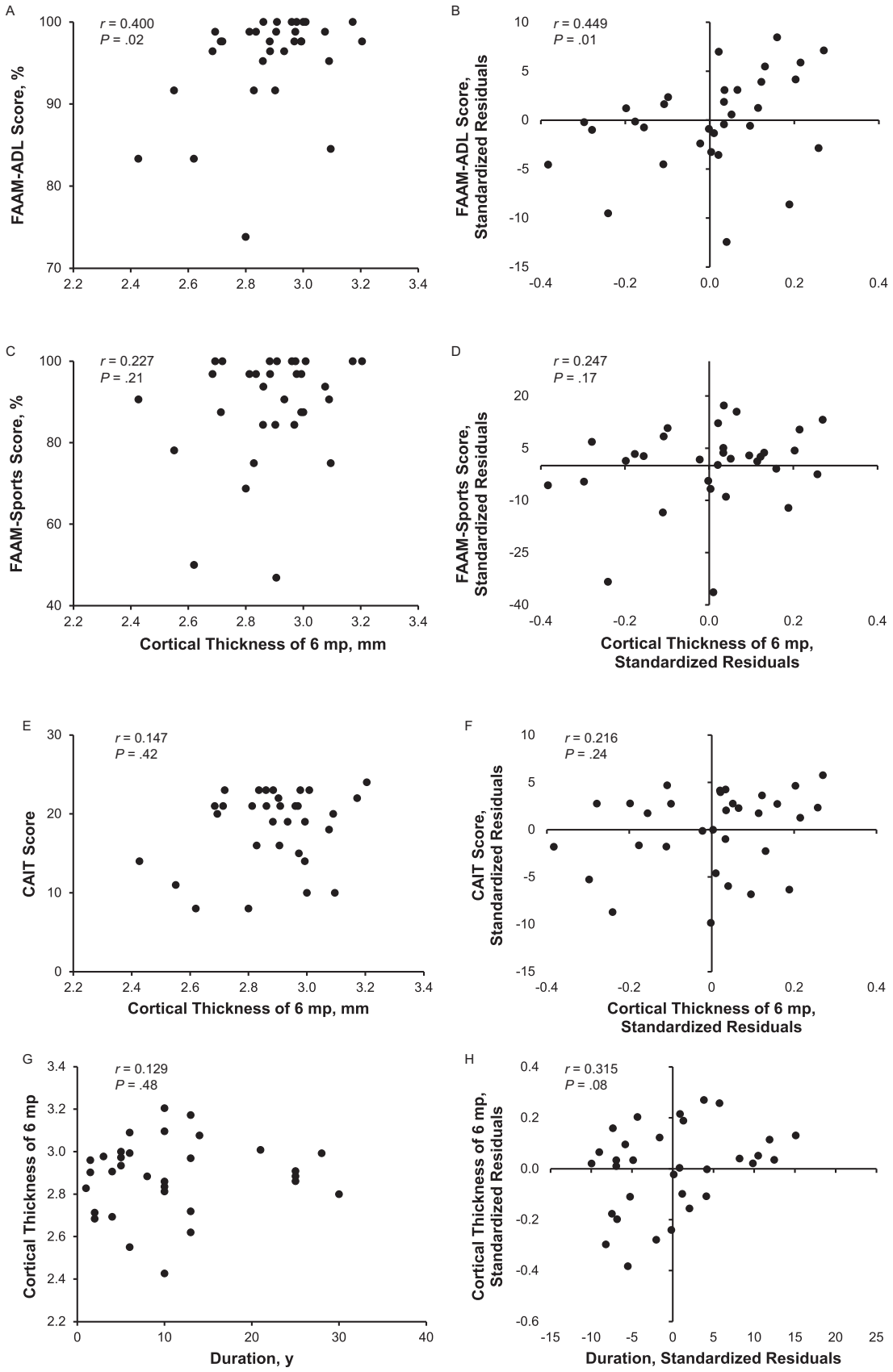

Figure 3. Scatter plot of the simple and partial correlations between the cortical thickness of posterior subdivision of the medial portion of Brodmann area 6 (6 mp) and A and B, the Foot and Ankle Ability Measure–Activities of Daily Living (FAAM-ADL) score; C and D, the FAAM-Sports score; E and F, the Cumberland Ankle Instability Tool (CAIT) score; and G and H, the duration of ankle instability. A, C, E, and G indicate simple correlations accounting for covariates including sex, age, and body mass index. B, D, F, and H indicate partial correlations without adjusting for these covariates.

patients with CAI.[9,26,29] This aligns with previous studies highlighting motor-planning deficits in CAI.[26] Although SCEF-related outcomes were not different between groups in this study, we suggest that further investigations of the SCEF are still needed to explore the role of visual-motor centers in the compensatory visual reliance of CAI. The SCEF has been implicated in visual-motor integration, which plays a role in compensatory strategies in patients with CAI. Given that patients with CAI may rely more on visual input to compensate for proprioceptive deficits, understanding the role of SCEF becomes pivotal.[30] A deeper exploration of SCEF may provide valuable insights into the neural strategies adopted by patients with CAI to manage their condition.

Although our findings provide valuable insights, understanding the chronologic order of these SMA adaptations is imperative. Longitudinal studies are pivotal in this regard, as they can offer clarity on causality and the progression of neuroplastic changes in response to CAI. Such studies can provide definitive evidence on whether the SMA changes are a consequence of CAI or if they predate its onset, thereby informing targeted interventions. In addition, our observations are preliminary, and the underlying causes for the distinct structural changes in the SMA subregions still require in-depth laboratory investigations.

Abnormal SMA and Ankle Dysfunctions in CAI

In our study, we observed a correlation between the thin 6 mp and ankle dysfunction as gauged by the FAAM-ADL subscale. This scale encompasses routine daily activities such as walking on flat ground and hills and ascending or descending stairs. The reduced thickness of the 6 mp region in the SMA suggests potential neuronal deficiencies that could hinder optimal motor output.[16,28] Consequently, the muscular reactions essential for these daily activities may be compromised, leading to ankle dysfunction. Although the FAAM-ADL subscale is centered on ADLs, the FAAM-Sports subscale and CAIT address more intricate movements such as running and jumping. The absence of a linear correlation in these challenging tasks insinuates the involvement of other brain regions such as the subcortical nucleus and cerebellum, underscoring the complexity of neural mechanisms in CAI.[15,16,23,26] In contrast, although the reduced complexity (ie, plainness) of 6 ma suggests a potential role in CAI, its exact clinical contribution requires further, targeted investigation through specific behavioral tests.

Clinical Relevance

Our findings suggest a potential link between CAI and changes in the SMA, which plays a role in planning and controlling movement.[8] This understanding may be important for rehabilitation strategies aimed at patients with CAI. Although traditional rehabilitation methods focus on physical strength and mobility, understanding the role of the SMA suggests that we might need to look beyond just the physical aspects. Addressing the functions of the SMA may help patients with CAI achieve better neuromuscular control of their ankles. In light of this, conventional resistance training might not fully address the issue. Incorporating motor-learning exercises that gradually increase in difficulty could be beneficial, helping patients with CAI rebuild their neuromuscular control more effectively.[4] Emerging technologies, such as biofeedback using electromyography and virtual reality, have shown promise in other areas of musculoskeletal rehabilitation. These techniques might be adapted to target the SMA and help patients develop better control over their ankle movements.[4,31] In addition, some initial studies have indicated that techniques such as transcranial stimulation, which have been applied to the primary motor cortex and might also be effective for the SMA, might be beneficial for patients with CAI.[32] However, these ideas are still in the early stages. More research is needed to fully understand how best to apply these findings in clinical settings.

Limitations

This study had several limitations. First, it was difficult to fully determine whether the thin SMA cortex predated or resulted from CAI based on our cross-sectional design, although robust indirect evidence has demonstrated maladaptive neuroplastic changes caused by ankle sprains and CAI.[4,24] Future studies using longitudinal designs could be done to provide clarity on the temporal relationship between SMA abnormalities and CAI. Second, despite the previous functional evidence of an abnormal SMA, we did not perform a correlation analysis between its structure and function because of the objective difficulty of merging multimethod neural evolution in 1 study on CAI.[7] More laboratory brain-behavior correlation analyses could explain how the SMA dictated the dysfunction of CAI in daily activities.[4] Third, our segmentation of the SMA subregions was based on the previous atlas, and the functions of each subregion were based on foot, not ankle, movements.[17] Although the central activation might be similar for foot-and-ankle–complex movements, future researchers could consider using task-based functional MRI with ankle-specific movements (eg, inversion/eversion) to determine SMA activation patterns. This could be followed by a refined segmentation of the SMA based on these task-specific activations, potentially yielding more precise insights into CAI-related abnormalities. Fourth, participants were enrolled based on convenience. Stratified sampling should be adopted in future studies to ensure balanced representation and mitigate biases. Finally, ankle dysfunction was not set as a criterion for the correlation analysis between neural features and the full range of functional measurements, which was relatively subtle (>90% in FAAM subscales). The relationships between the thickness of the 6 mp and the severity of ankle dysfunction still warrant further research considering a broader range of CAI severities, potentially revealing more pronounced neural correlates in individuals with more severe dysfunction.[5]

CONCLUSIONS

Our study provides a deeper understanding of the structural abnormalities in the SMA associated with CAI. Specifically, we found that patients with CAI exhibit a thinner posterior subdivision (motor-output site) and a plainer anterior subdivision (motor-planning site) in the SMA compared with controls. Importantly, the thinness of the motor-output site was correlated with ankle dysfunction in these patients. These findings not only advance our knowledge of the neural underpinnings of CAI but also have potential clinical implications. Recognizing these maladaptive changes in the SMA could pave the way for more targeted and effective rehabilitation

strategies for patients with CAI. As we continue to explore this avenue, further research is needed to confirm these findings and to develop interventions that specifically address SMA abnormalities in CAI.

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DATA STATEMENT

The original imaging data used to support the findings of this study have not been made available because of the data security; the SMA features are available upon reasonable request corresponding to the senior authors (H.W., hewang@fudan.edu.cn; Y.H., hua_cosm@aliyun.com).

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SUPPLEMENTAL MATERIAL

Supplemental Material. Supplementary details of structural magnetic resonance imaging data acquisition and analysis.

Supplemental Table. Univariable and Multivariable Linear Regression of the Volume- and Surface-Based Morphometric Outcomes.

Supplemental Figure. Scatter plots of the simple and partial correlations between the cortical complexity of 6 ma and A and B, the Foot and Ankle Ability Measure–Activities of Daily Living (FAAM-ADL) score; C and D, the FAAM-Sports score; E and F, the Cumberland Ankle Instability Tool (CAIT) score; and G and H, the duration of ankle instability. A, C, E, and G, Simple correlations, accounting for covariates including sex, age, and body mass index. B, D, F, and H, Partial correlations without adjusting for these covariates. Abbreviation: 6 ma, anterior subdivision of the medial portion of Brodmann area 6. [a] Measure is unitless.

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