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Structural and Functional Brain Adaptation in Chronic Ankle Instability: Evidence from Structural and Functional Neuroimaging — A Systematic Review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The systematic review had been completed and submitted for publication. During peer review, the search strategy and eligibility criteria were revised in response to reviewer comments, and an updated literature search was conducted. The review is currently undergoing updated study screening and revision. This protocol is therefore being registered retrospectively during the revision process.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 September 2026 and was last updated on 3 September 2026.

INTRODUCTION

Review question / Objective The primary objective of this systematic review is to narratively summarize structural and functional brain differences in adults with chronic ankle instability (CAI) compared with healthy controls. The review will include evidence from structural and functional neuroimaging and neurophysiological methods, including magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion-weighted imaging (DWI), functional near-infrared spectroscopy (fNIRS), electroencephalography (EEG), and others, where applicable.

A secondary objective is to summarize reported associations between brain-related measures and clinical, sensorimotor, behavioral, or biomechanical characteristics of CAI. Given the anticipated heterogeneity in study designs, neuroimaging and neurophysiological methods, and reported outcomes, the evidence will be narratively synthesized without making causal inferences.

Condition being studied Chronic ankle instability (CAI) is a condition that may develop following lateral ankle sprain and is characterized by recurrent ankle sprains, repeated episodes of giving way, and/or persistent perceptions of ankle instability. In addition to peripheral sensorimotor impairments, growing evidence suggests that CAI is associated with alterations in central nervous system function and brain structure. Neuroimaging and neurophysiological studies have reported differences in cortical activity, cortical excitability, functional brain responses, gray matter

morphology, and white matter microstructure in individuals with CAI. This systematic review focuses on structural and functional brain differences associated with CAI in adults.

METHODS

Participant or population Adults aged 18 years or older with chronic ankle instability (CAI), functional ankle instability, mechanical ankle instability, or recurrent lateral ankle instability, as defined by the original study, will be eligible. Participants with a history of ankle sprain alone will be eligible only when the study clearly identifies a chronic or recurrent instability condition. Studies including mixed age groups or mixed clinical populations will be eligible only when data for the adult CAI subgroup can be separately extracted.
The primary comparison of interest is between adults with CAI and healthy adults without CAI.

Intervention No specific therapeutic intervention is required for inclusion. The exposure of interest is chronic ankle instability (CAI), including functional ankle instability, mechanical ankle instability, or recurrent lateral ankle instability, as defined by the original study. Studies conducted in the context of rehabilitation, other interventions, or surgery will not be excluded solely on that basis. Eligible baseline, pre-intervention, or preoperative brain-related data will be considered when separately extractable. Post-intervention data may also be considered when the intervention directly evaluates changes in eligible brain outcomes and will be interpreted separately.

Comparator The primary comparator will be healthy adults without chronic ankle instability or recurrent lateral ankle sprain. Studies including additional comparison groups, such as copers, may be eligible only when data for the CAI and healthy-control groups can be separately extracted. Data from coper groups will not be included in the synthesis.

Study designs to be included Eligible study designs will include cross-sectional, case-control, cohort, prospective longitudinal and experimental studies. Studies conducted in rehabilitation or surgical settings may be eligible when relevant brain-related data meeting the review criteria are separately extractable. Reviews, editorials, study protocols, case reports, conference abstracts without sufficient full-text information, and other non-peer-reviewed publications will be excluded.

Eligibility criteria Studies will be eligible if they: (1) include adults aged ≥18 years with chronic ankle instability (CAI), functional ankle instability, mechanical ankle instability, or recurrent lateral ankle instability, as defined by the original study; (2) include an eligible healthy-control comparison with separately extractable data; (3) report at least one direct measure of brain structure, brain function, cortical activity, or cortical/corticospinal excitability; and (4) are full-text, peer-reviewed articles published in English.
Eligible brain outcomes include structural measures such as gray matter volume, cortical thickness, surface area, cortical complexity/gyrification, regional brain volume, cerebral white matter microstructure, and white matter tract characteristics assessed using diffusion-weighted imaging or related methods. Functional and neurophysiological outcomes include task-based or resting-state fMRI, functional connectivity, fNIRS-derived cortical hemodynamic responses, EEG-derived cortical activity, TMS-derived cortical/corticospinal excitability, and other validated measures directly assessing brain function.

Studies will be excluded if they involve only participants younger than 18 years without separately extractable adult data; animal, cadaveric, or in vitro models; acute ankle sprain without evidence of chronic or recurrent instability; mixed musculoskeletal populations without separately extractable CAI data; or outcomes limited to peripheral nerves, spinal reflexes, muscles, balance, gait, or other clinical measures without an eligible direct brain-related outcome. Reviews, editorials, protocols, case reports, conference abstracts without sufficient full-text information, and non-peer-reviewed publications will also be excluded.
Studies will not be excluded solely because they involve surgery, rehabilitation, or another intervention. Eligibility will be determined according to whether relevant brain-related data meeting the predefined criteria are available.

Information sources Electronic literature searches will be conducted in PubMed, Web of Science Core Collection, Scopus, CINAHL Plus (EBSCOhost), and the Cochrane Central Register of Controlled Trials (CENTRAL).
The electronic searches will be supplemented by backward reference checking of included studies, examination of the reference lists of relevant previous systematic reviews, and forward citation tracking of eligible studies. Studies specifically identified during the peer-review process will also be checked for eligibility. Only published, peer-reviewed, full-text articles in English will be eligible. Grey literature and conference abstracts without sufficient full-text information will not be included.

Main outcome(s) The main outcomes will be structural and functional brain measures in adults with chronic ankle instability compared with healthy controls.
Structural brain outcomes will include gray matter volume, cortical thickness, cortical surface area, cortical complexity or gyrification, regional brain volume, cerebral white matter microstructure, and white matter tract characteristics, including measures derived from diffusion-weighted imaging (DWI) and related diffusion imaging methods.

Functional and neurophysiological brain outcomes will include task-based and resting-state fMRI measures, functional connectivity, cortical hemodynamic responses measured using functional near-infrared spectroscopy (fNIRS), cortical activity measured using electroencephalography (EEG), and cortical or corticospinal excitability assessed using transcranial magnetic stimulation (TMS), as well as other validated measures that directly assess brain function.
Where reported, between-group differences between CAI and healthy-control participants will be summarized. Owing to anticipated methodological and outcome heterogeneity, findings will be narratively synthesized rather than pooled quantitatively when meta-analysis is not appropriate.

Quality assessment / Risk of bias analysis The methodological quality of included studies will be assessed using the Newcastle–Ottawa Scale (NOS), with the version appropriate to the study design. The assessment will consider the selection of study groups, comparability between groups, and ascertainment of the exposure or outcome, as applicable. Two reviewers will independently assess study quality. Any disagreements will be resolved through discussion and consensus, with consultation of a third reviewer if necessary. Quality assessment results will be summarized and considered when interpreting the overall evidence; studies will not be excluded solely on the basis of their quality score.

Strategy of data synthesis A narrative synthesis will be conducted because substantial heterogeneity is anticipated across study designs, neuroimaging and neurophysiological modalities, experimental tasks, brain regions, and outcome measures. Study characteristics and findings will first be summarized in structured tables.

Findings will then be organized according to the type of brain assessment and outcome. Structural findings will include gray matter morphology, cortical morphology, regional brain volume, and cerebral white matter microstructure or tract characteristics. Functional and neurophysiological findings will include task-based and resting-state fMRI, functional connectivity, fNIRS-derived cortical hemodynamic responses, EEG-derived cortical activity, and TMS-derived cortical or corticospinal excitability.

Where possible, the direction and pattern of differences between participants with chronic ankle instability and healthy controls will be summarized across studies. Associations between brain-related measures and clinical, sensorimotor, behavioral, or biomechanical characteristics will be summarized separately as secondary findings. Given the anticipated heterogeneity and limited comparability of outcome measures, quantitative pooling is not planned. Findings will be interpreted as differences or associations, and causal inferences will not be made.

Subgroup analysis No formal subgroup analysis is planned because a quantitative meta-analysis is not anticipated. Where sufficient evidence is available, findings may be narratively grouped according to neuroimaging or neurophysiological modality (e.g., structural MRI/DWI, fMRI, fNIRS, or EEG) and type of brain outcome. These groupings will be used to facilitate narrative interpretation and will not constitute formal statistical subgroup analyses.

Sensitivity analysis No formal sensitivity analysis is planned because quantitative meta-analysis is not anticipated. The methodological quality of included studies will be considered when interpreting the robustness and consistency of the narratively synthesized findings.

Country(ies) involved Japan.

Keywords Chronic ankle instability; Brain; Neuroimaging; Functional magnetic resonance imaging; Functional near-infrared spectroscopy; Electroencephalography; Transcranial magnetic stimulation; Gray matter; White matter.

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