

Neural networks involved in painful diabetic neuropathy: A systematic review

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Introduction

Distal symmetric polyneuropathy (DSPN) affects up to 50% of individuals with diabetes and is frequently accompanied by neuropathic pain that substantially reduces daily functioning and quality of life. Current pharmacological treatments provide limited pain relief and are often associated with adverse effects, highlighting the need for alternative therapeutic approaches.

Neuromodulation techniques, including non-invasive brain stimulation and neurofeedback, aims to reduce pain by targering central nervous system mechanisms involved in pain processing. However, the neural networks underlying painful DSPN (P-DPN) remain insufficiently understood.

This systematic review synthesizes evidence on central nervous system alterations in P-DPN to help identify potential targets for future neuromodulation-based interventions.

Method

This systematic review was conducted in accordance with PRISMA guidelines and preregistered in PROSPERO (CRD42022376505). A comprehensive search of MEDLINE, Embase, and PsycINFO identified relevant studies published between 2010 and May 2024. Titles, abstracts, and full texts were screened independently by multiple reviewers using Covidence (fig. 1).

Table 1: Study characteristics				
Population	Neuroimaging	Study design	Outcomes	Exclusions
 Adults with painful diabetic polyneuropathy	 MRI, fMRI, PET, EEG, SPECT	 Experimental and observational studies	 fMRI/Task-based connectivity, EEG frequency band power, source localization and/or connectivity analyses	 Pregnancy, animal studies, other neuropathic pain

Clinical neuroimaging studies involving adults with P-DPN were included, covering modalities such as MRI, fMRI, PET, EEG, and SPECT. Both observational and experimental study designs were eligible (table 1). Risk of bias was assessed using the NIH Quality Assessment Tools.



Fig. 1. Flow chart

Results

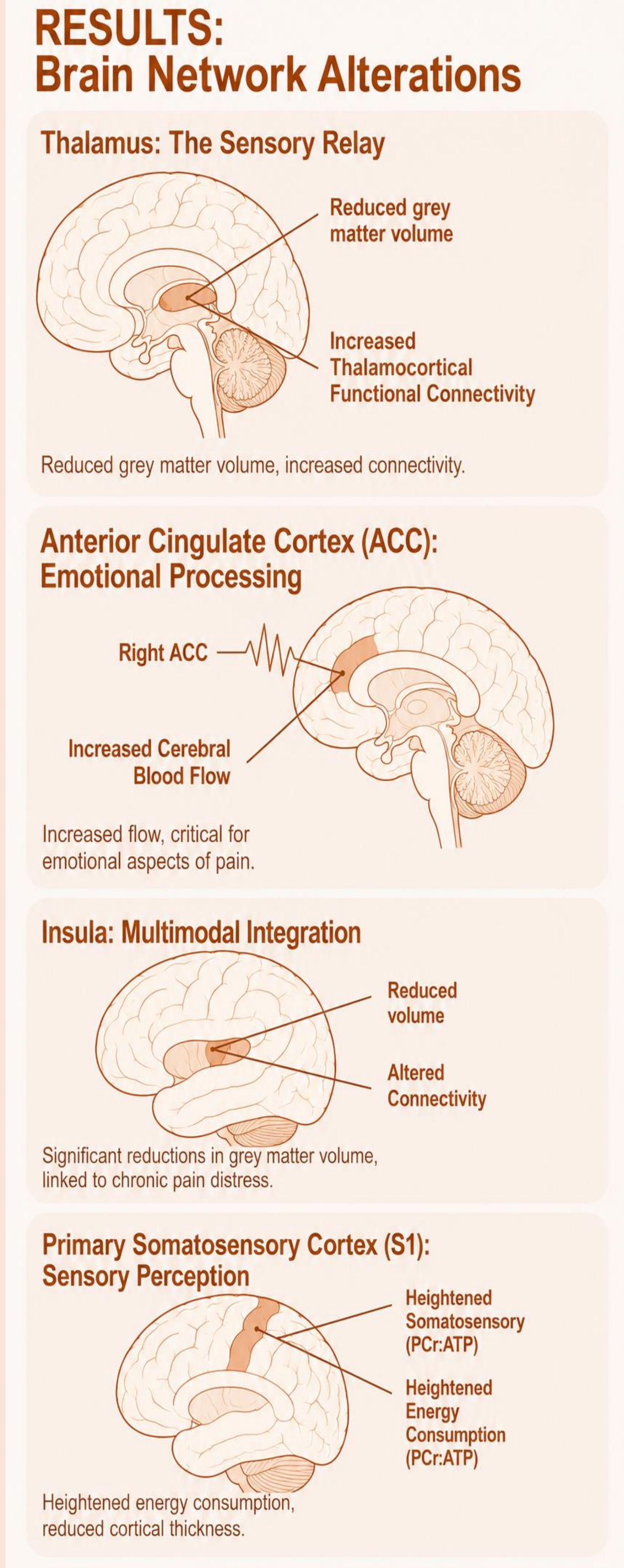


Fig. 2. Results. Image generated using Illustrate (OpenAI), 2026.

All of the 18 studies had a cross-sectional design. 15 studies used structural MRI or fMRI, 2 used EEG and 1 used SPECT.

Consistent changes were observed in the thalamus and primary somatosensory cortex (S1), suggesting disrupted sensory integration and altered thalamo-cortical signaling.

In addition, regions such as the anterior cingulate cortex and insula demonstrated altered activity and connectivity, reflecting affective and integrative components of pain.

At the network level, increased functional connectivity was identified within limbic and prefrontal regions, indicating enhanced emotional and cognitive engagement in pain processing. EEG findings further support these results, showing increased connectivity in theta and beta frequent bands.

P-DPN is best understood as distributed network dysfunction rather than isolated peripheral damage, implicating the thalamus, ACC, insula, and S1 as candidate targets for neuromodulations (fig. 2).

Conclusion

This review supports a central-peripheral model of neuropathic pain, with consistent structural and functional changes extending beyond traditional pain centers.

The results involve brain regions associated with both affective, cognitive, and sensory discriminative aspects of pain, emphasizing the multifactorial nature of P-DPN.

Clinical implications

Neuromodulation potential

Techniques like rTMS, tDCS, and EEG-based neurofeedback can target the identified brain regions to alleviate chronic neuropathic pain.

Precision pain management

Targeting the S1, ACC and thalamus with electrical or magnetic stimulation offers a promising path for personalized P-DPN treatment

Future research directions

Larger, prospective trials are needed to refine these neuroimaging biomarkes and translate them into effectice clinical interventions.

Ongoing randomized, sham-controlled RCT: Source-localized EEG Neurofeedback for P-DPN: This systematic review provided the scientific rationale for the targeted brain regions and neurofeedback approach. Results are pending.

