The thalamus and primary somatosensory cortex functional connectivity makes the difference in diabetic peripheral neuropathy

Aims: Central nervous system (CNS) alterations have been recently demonstrated in patients with both painful and painless diabetic peripheral neuropathy (DPN). The first objective of this study was to investigate functional connectivity alterations in sensory and pain-related brain regions in subjects with type 1 diabetes (DM1) with and without painful or painless DPN and in healthy control subjects. The second objective was to evaluate the association between alterations in brain connectivity and both peripheral nerve function and pain intensity.
Methods: In a cross-sectional study, 19 DM1 subjects with painful DPN, 19 with confirmed painless DPN, 18 without DPN, and 20 healthy subjects underwent resting-state functional MRI (fMRI) to investigate functional brain connectivity of bilateral thalamus, postcentral gyrus and insula using seed-based analysis and obtaining a connectivity maps of brain regions. The connectivity z-scores were correlated with peripheral nerve function and pain scores.
Results: DM1 subjects without DPN showed higher functional connectivity of thalamus to bilateral motor cortex with associated superior frontal gyrus compared with healthy control subjects ($p \leq 0.001$). The connectivity between the left thalamus and supplementary motor cortex/superior frontal gyrus was lower in the painful DPN group compared to the group without DPN ($p=0.011$). The postcentral gyrus had lower connectivity to the precentral gyrus and within and to their respective opposite postcentral gyrus in those with painful DPN compared to the group without DPN (all $p \leq 0.029$). In the participants with T1DM, lower connectivity z scores of the thalamus and postcentral gyrus were associated with lower peripheral nerve conduction measurements (all $p<0.043$) and with higher pain scores (all $p<0.035$). No connectivity differences were found in insula.
Conclusions: An increased connectivity of thalamus and the postcentral gyrus to motor areas in subjects with DM1 without DPN was observed. The increased connectivity was attenuated along with the DPN severity. Thalamic/postcentral gyral connectivity measures were associated with peripheral nerve function.

Comments. This study, part of the MEDON study, contributes to further understanding of the functional alterations of brain regions involved in sensory processing in DPN. Higher functional connectivity of thalamus and postcentral gyrus appeared only in diabetes without DPN, while a lower connectivity was observed in the painful DPN group. These results are in contrast with recent findings showing a higher connectivity to the insula and primary somatosensory cortex in subjects with DM1 and painful DPN (Teh K et al *Diabetologia 2021;64:1412-1421*), and an increased neuronal activity in the thalamus related to the painful DPN (Selvarajah D et al *Diabetes Care 2011;34:718-720*). The Authors suggest as a possible explanation of this discrepancy a severe degree of DPN in the participants with painful DPN and that the significant neuronal damage could contribute to a decreased transmission of pain signals to the thalamus. Also, the use of pain drugs, mainly duloxetine, in the painful DPN group might have exerted an interference in neuronal activity. The increased connectivity in DM1 subjects without DPN is instead explained as a potential compensatory neuroplastic mechanism to maintain normal sensory input/processing despite subclinical nerve dysfunction. The association of thalamic and gyral connectivity parameters with both poorer peripheral nerve functions and increased pain intensity ratings, indicate a strong link between peripheral nerve changes and brain functions. In conclusion, assessments of functional connectivity with fMRI may be essential to obtain potential early biomarkers capable of characterizing the different phenotypes of DPN.

Fabiana Picconi

Reference. Croosu SS, Røikjer J, Mørch CD, Ejskjaer N, Frøkjær JB, Hansen TM. Alterations in Functional Connectivity of Thalamus and Primary Somatosensory Cortex in Painful and Painless Diabetic Peripheral Neuropathy. Diabetes Care. 2023 Jan 1;46(1):173-182. doi: 10.2337/dc22-0587. PMID: 36469731. https://diabetesjournals.org/care/article/46/1/173/148020/Alterations-in-Functional-Connectivity-of-Thalamus