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Specific neuroimaging brain alterations are associated with pain phenotypes: can they drive mechanism-based treatments?

Aim: It is widely accepted that both positive and negative symptoms of diabetic peripheral neuropathy (DPN) are peripherally generated and maintained. However, there is mounting evidence anatomical alterations in brain regions associated with sensorimotor function and pain processing in people with DPN. This study aimed to identify group differences in seven brain regions of interest with associated sensorimotor functions in carefully phenotyped people with painful and painless DPN.
Methods: 66 healthy volunteers and 211 people with diabetes underwent clinical/neurophysiological assessment. Those with diabetes were dichotomised into no DPN (n=57), painless (n=77) and painful DPN (n=77) categories using signs/symptoms, nerve conduction studies and DN4 questionnaire (cut-off 4). The German Research Network on Neuropathic Pain quantitative sensory testing protocol was used to further subgroup participants with DPN into irritable (n=34) and non-irritable (n=43) nociceptor phenotype. All participants underwent high-resolution, three-dimensional, quantitative T1-weighted brain MRI (3T). A standard research protocol for reconstruction and volumetric segmentation and voxel based morphometric analysis was applied. Group differences were identified using univariate linear modelling controlling for age and sex with Bonferroni adjustment.
Results: Participants with diabetes had lower total, cortical and sub-cortical grey matter volume relative to healthy controls (p=0.012, p=0.018, and p=0.005 respectively). Participants with painful DPN had significantly lower bilateral postcentral (p=0.01), precentral (p= 0.001) and insular cortical thickness (p=0.002) relative to healthy controls. (p=0.01), Participants with painless DPN had lower bilateral postcentral (p<0.001 and p=0.002), precentral (p<0.001 and p=0.02), and insula (p<0.001 and p=0.002) cortical thickness relative to both healthy controls and participants with diabetes without DPN after multivariate adjustment. Both painful and painless DPN groups had lower pre-central (p=0.001 and p<0.001 respectively) and insula (both p=0.002) cortical thickness relative to healthy controls and participants with diabetes without DPN. Participants with the non-irritable nociceptor phenotype had lower posterior cingulate cortex (PCC) and bilateral thalami volumes relative to participants with the irritable nociceptor phenotype (PCC; p=0.02, left thalamus; p=0.03, right thalamus; p=0.03). Further, the irritable nociceptor phenotype group had a significantly lower anterior cingulate cortex thickness relative to the non-irritable nociceptor phenotype group (p<0.001). The irritable nociceptor phenotype group had higher mean primary somatosensory cortical area relative to participants with the non-irritable phenotype (p=0.02).
Conclusions: Anatomic differences in brain regions associated with sensorimotor and pain processing are present in participants with DPN. Moreover, painful, or painless presentations of DPN are associated with contrasting reductions in discrete MRI-derived metrics. Indeed, participants exhibiting distinct pain phenotypes show group differences in key somatosensory associated regions of interest. Anatomical brain alterations in these regions may have utility in predicting drug response and selecting first-line therapy.

Comments. This largest neuroimaging study highlights central nervous system involvement in the pathophysiology of DPN. Indeed, pain phenotypes appear to be associated with distinct neuroanatomical group differences in grey matter volume. Addressing the relative contributions of microvascular complications on the central and peripheral nervous systems longitudinally in participants with DPN is needed to holistically understand these adaptions along the length of the neuroaxis.

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