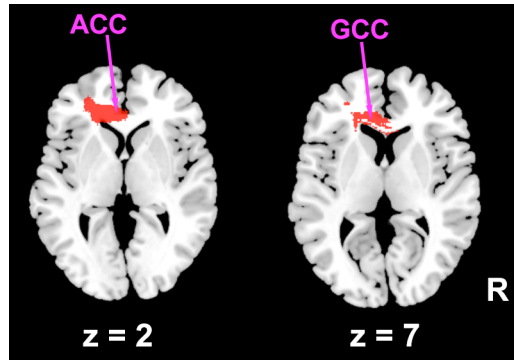


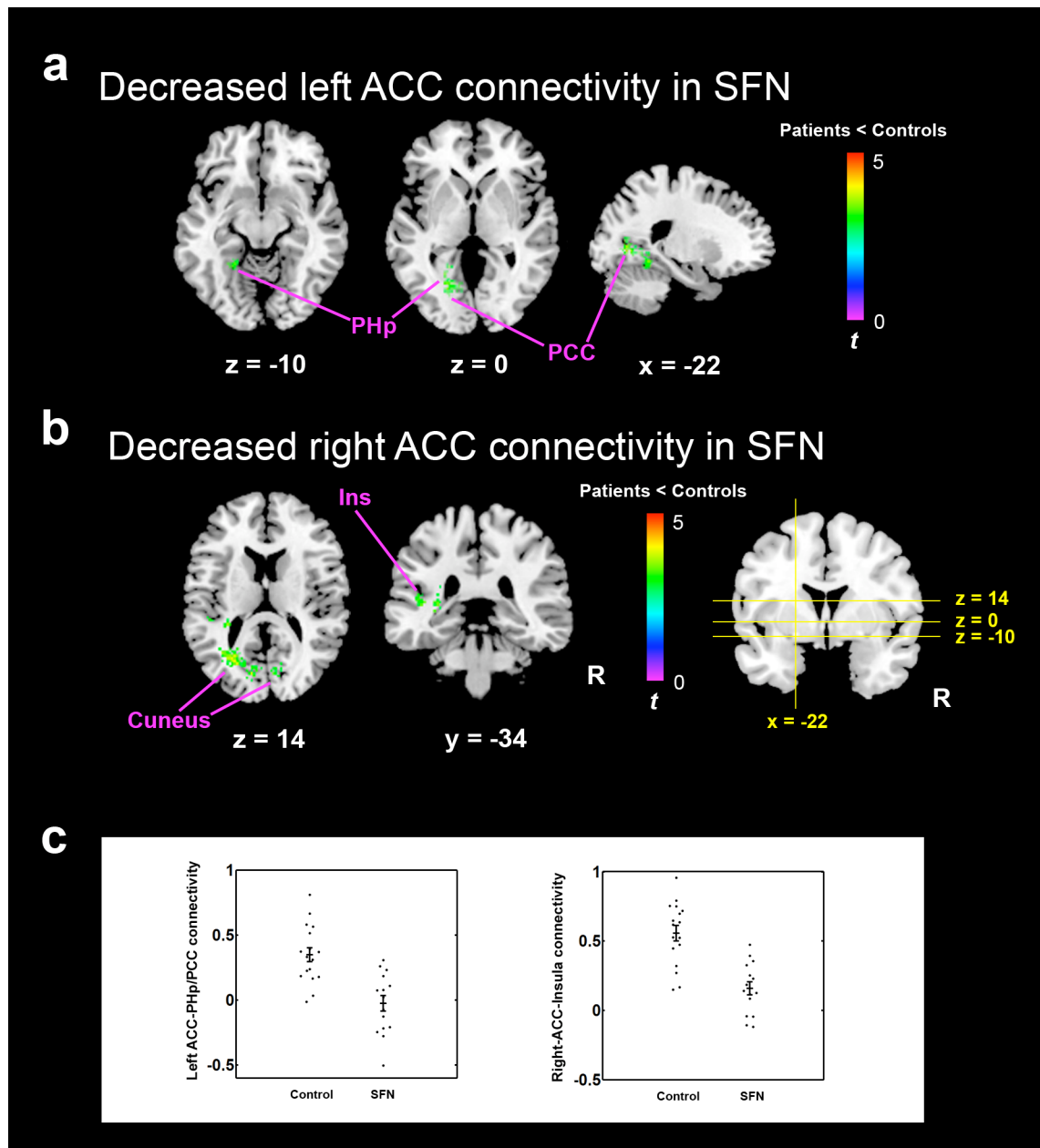
IMAGING SIGNATURES OF ALTERED BRAIN RESPONSES IN SMALL-FIBER NEUROPATHY: REDUCED FUNCTIONAL CONNECTIVITY OF THE LIMBIC SYSTEM AFTER PERIPHERAL NERVE DEGENERATION

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Supplementary materials



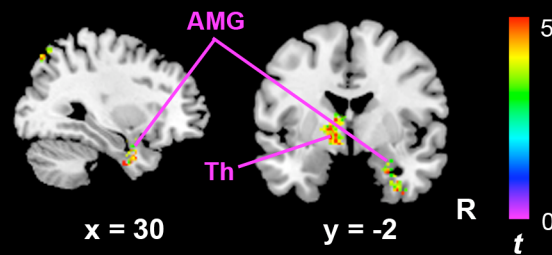
Supplementary Fig. 1. Brain volume reduction detected in small-fiber neuropathy (SFN) when Diagnosis (patient versus control) was the only explanatory factor. By comparing the regional brain volume (measured by the Jacobian determinant of brain mapping) at every point of the brain between the patients with small-fiber neuropathy and controls, volume reduction in the patients was significant when Diagnosis (patient versus control) was the only explanatory factor. These significant regions, corrected for multiple comparisons, are in the gray matter and the adjacent white matter of the left anterior cingulate cortex ($z = 2$ mm), and the genu of the corpus callosum ($z = 7$ mm), displayed as red-colored clusters. Nevertheless, the differences in brain volume between the patients and controls became insignificant after age and gender effects were adjusted for. ‘R’ indicates the right hemisphere. The MNI coordinate (mm) is shown at the bottom of each slice. Abbreviations: ACC, anterior cingulate cortex; GCC, the genu of the corpus callosum.



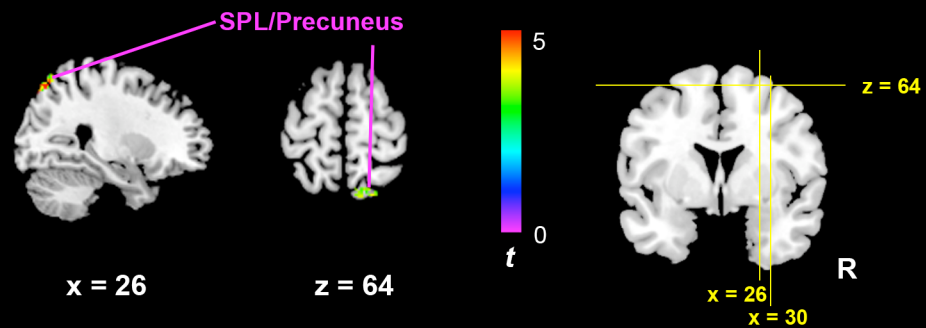
Supplementary Fig. 2. Brain maps showing reduction in functional connectivity across pain-processing regions in small-fiber neuropathy, derived by excluding participants without heat-evoked pain. Functional connectivity under noxious thermal stimulation between the seed region, the left anterior cingulate cortex (ACC; in (a)) and the right ACC in (b) respectively, and every point of the brain (excluding the seed region) was assessed using PPI analysis. Brain maps show regions where functional connectivity between these regions and the

seed region was significantly stronger in the control participants than the patients with small-fiber neuropathy, displayed as clusters that passed the multiple comparisons threshold. 4 participants, all were patients, who did not feel painful (i.e., reported a verbal rating scale < 4) during thermal stimulation were excluded from analysis. Voxels in these regions were color-coded by their t -values. The patients with small-fiber neuropathy had reduced functional connectivity from the left ACC seed to the left parahippocampal gyrus (PHp; $z = -10$ and 0 mm) and the left posterior cingulate cortex (PCC; $z = 0$ and $x = -22$ mm), as shown in **(a)**. Reduced functional connectivity in small-fiber neuropathy was also found from the right ACC seed to the left posterior insula ($y = -34$ mm) and the bilateral cuneus ($z = 14$ mm), as shown in **(b)**. ‘R’ indicates the right hemisphere. The MNI coordinate (mm) is shown at the bottom of each slice. The beeswarm plots in **(c)** show the individual-level differences in the strength of functional connectivity (adjusted for age, gender, and VRS rating) between the patients and controls, for the left ACC to the left PHp and PCC (left), and for the right ACC to the left posterior insula (right). The error bars show the mean connectivity with variations between the subjects (the standard error of the group mean). Abbreviations: Ins, insula; PCC, posterior cingulate cortex; PHp, parahippocampal gyrus.

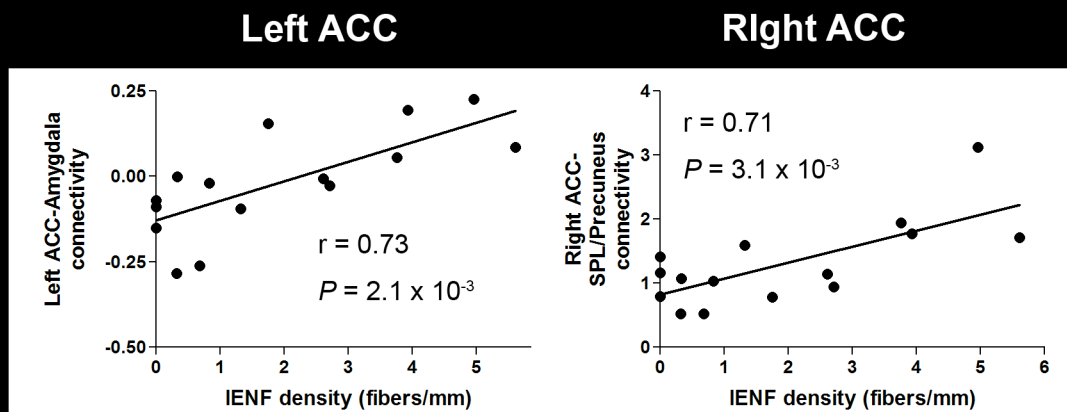
a Left ACC connectivity associated with IENF density



b Right ACC connectivity associated with IENF density



c



Supplementary Fig. 3. Brain maps showing the associations between depletion of skin sensory axons and reduction in functional connectivity across pain-processing regions in small-fiber neuropathy, derived by excluding participants without heat-evoked pain. The brain maps show regions where the strength of functional connectivity under noxious thermal

stimulation was associated with the IENF density in the patients with small-fiber neuropathy. The strength of functional connectivity at each voxel was defined as the partial regression coefficient with respect to the PPI interaction term at that voxel. 4 participants, all were patients, who did not feel painful (i.e., reported a verbal rating scale < 4) during thermal stimulation were excluded from analysis. Regions where the association between the functional connectivity strength and the IENF density was significant (adjusted for age, gender, and VRS rating) are displayed as clusters that passed the multiple comparisons threshold. Voxels in these clusters were color-coded by their *t*-values. The functional connectivity strength of the right amygdala and the left thalamus (with respect to the left ACC seed in **a**), and of the right superior parietal lobule (SPL) and precuneus (with respect to the right ACC seed in **b**), was correlated positively with the IENF density. This means that lower density in the cutaneous nerves in small-fiber neuropathy was associated with weaker functional connectivity strength in these two regions. ‘R’ indicates the right hemisphere. The MNI coordinate (mm) is shown at the bottom of each slice. The associations are also demonstrated in the scatter plots in **(c)** where the mean functional connectivity strength of the significant region (amygdala in **(a)** and SPL/precuneus in **(b)** respectively) is regressed against the IENF density in the distal leg, yielding (i) the Pearson correlation coefficient $r = 0.73$, $P = 2.1 \times 10^{-3}$ for the right amygdala **(a)**, and (ii) $r = 0.71$, $P = 3.1 \times 10^{-3}$ for the right SPL/precuneus **(b)**. Abbreviations: ACC, anterior cingulate cortex; AMG, amygdala; SPL, superior parietal lobule; Th, thalamus.