SUPPLEMENTARY DATA

Thermal Stimulation and Pain Rating:

We used an adaptive staircase procedure to derive the individual subject's dose-response curve for the relationship between applied thermal stimulation and reported pain [1]. Thermal stimulation was delivered to the dorsal surface of the foot and anterior aspect of the thigh applied using a TSA-11 Neurosensory Analyser (PATHWAY, Medoc ltd. Chapel Hill, NC) with a 16mm Peltier thermode end-plate. Each stimulus lasted 30 seconds and always included a period of time during which the stimulus ramped up (1.5s) from baseline temperature (32^{o}) to the target temperature (27s) before ramping down (1.5s) to baseline temperature (Figure 1). The ramping was intended to help prevent head movement. We determined the temperature necessary to achieve a pain score of 7 out of 10 on a numeric rating scale (NRS, 0 = no sensation and 10 = maximum tolerable pain). We used a forced choice algorithm and testing begun at an intermediate temperature level (40.0^{o}C). The stimulus would be increased (if NRS<7) or decreased (if NRS>7) by 6 ^{o}C to the point of turnaround (NRS>7 at the higher level when <7 at a lower level or NRS<7 at the lower level when it had been NRS>7 at the higher level). After the first turnaround, stepping was in steps of 4 ^{o}C. After the second turnaround, stepping was by steps of 2 ^{o}C. Maximum temperature applied was 47.9 ^{o}C to prevent scalding. If three consecutive failures at 47.9 ^{o}C (i.e. NRS<7) the subject was classified as insensate. This procedure was performed on the dorsum of the right foot and repeated on the anterior aspect of the right thigh. Once the temperature level was established, subjects were positioned in the MRI scanner to begin MR imaging. Results of thermal psychophysics of the experiment is presented in Table 1.

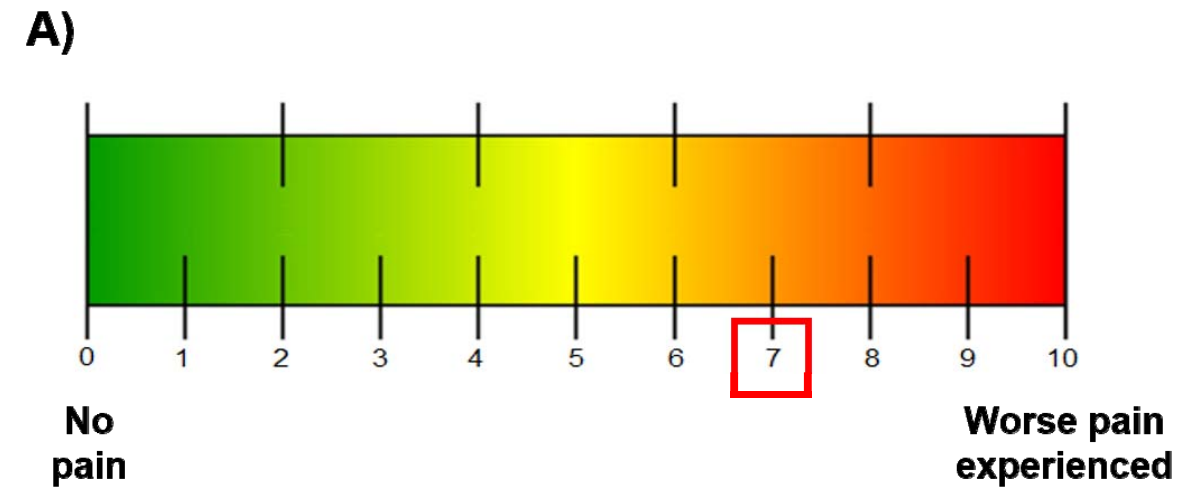
MRI Analysis

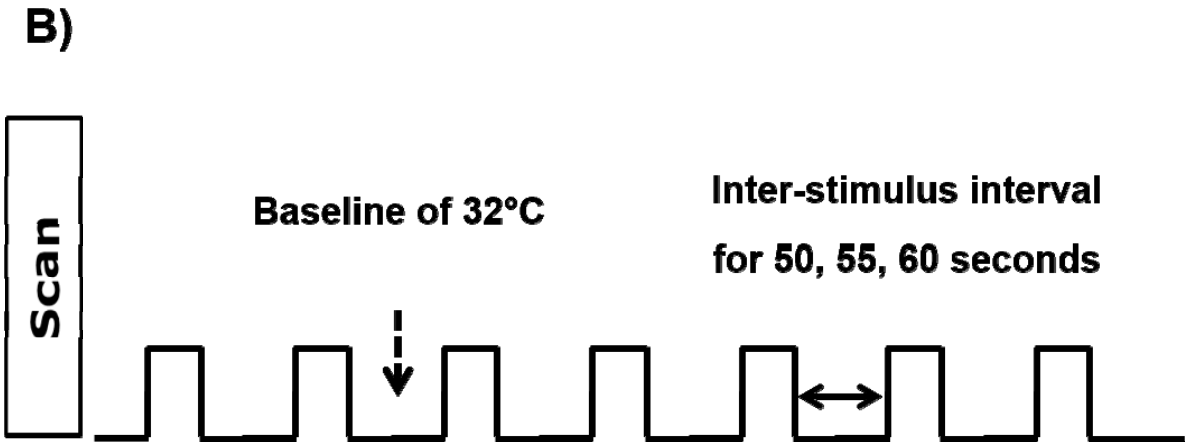
Functional MRI analysis:

Preprocessing. The following pre-statistics processing was applied to each individual run: slice timing and motion correction using FMRIB's Linear Image Registration Tool [2]; brain extraction using [3]; mean-based intensity normalization; spatial smoothing using a Gaussian kernel of FWHM (full width at half maximum) 5 mm and highpass temporal filtering of 300. In each subject, the fMRI image sets were aligned and coregistered with to their own spatially normalised T1-weighted anatomical image set initially using linear registration (FMRIB's Linear Image Registration Tool, FLIRT) [4,5], then optimized using Boundary-Based Registration. Structural images were transformed to standard MNI space using a nonlinear registration tool [6], and the resulting warp fields applied to the functional statistical summary images.

SUPPLEMENTARY DATA

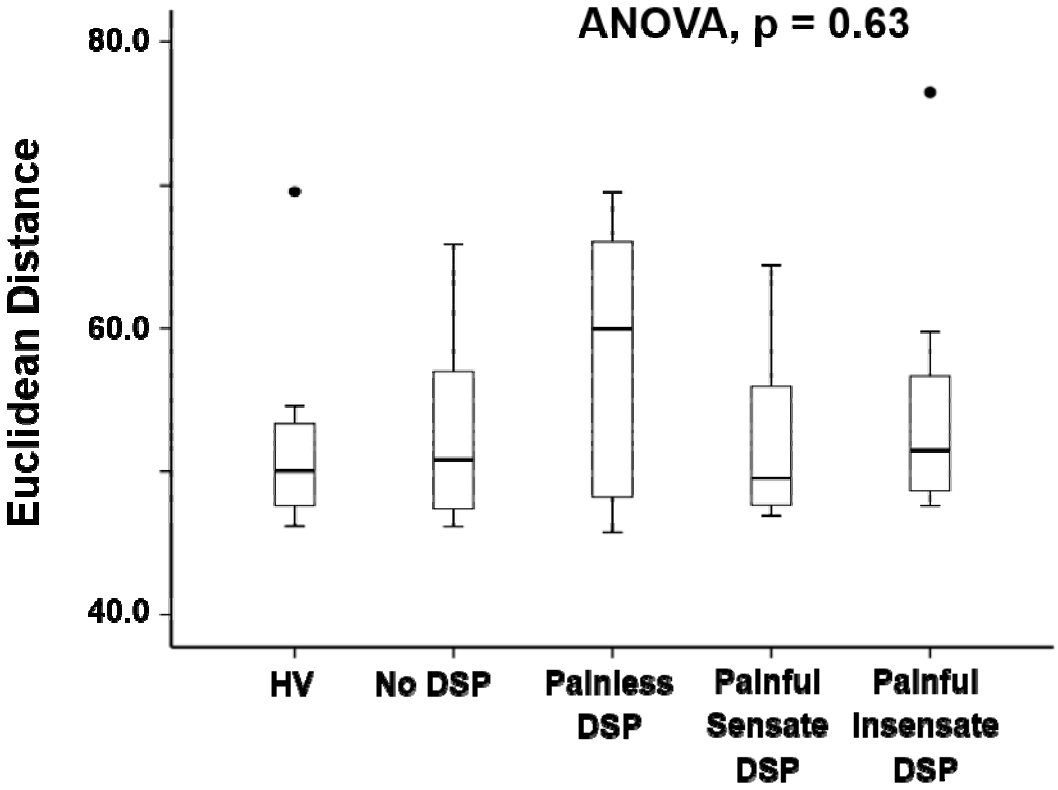
Supplementary Figure 1. A) Numeric rating scale used to for the pain calibration procedure B) Alternating sequence of nociceptive heat pain and baseline temperature stimulation applied to the foot and thigh during functional magnetic resonance imaging.





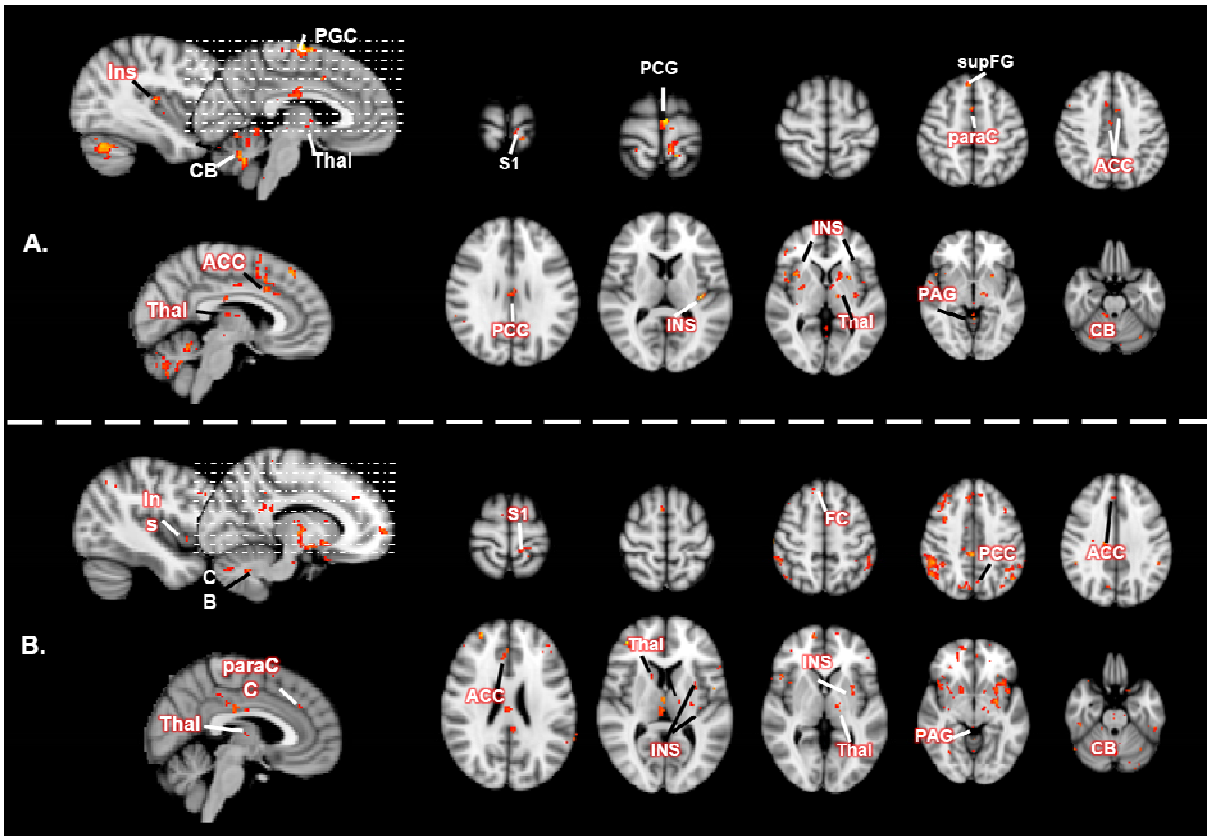
SUPPLEMENTARY DATA

Supplementary Figure 2. Task specific Euclidean distance (ED, mm) of study cohorts. There was no significant difference in ED for nociceptive heat stimulation of the right foot. The region of interest selected was the S1 cortex. HV, Healthy volunteers; DSP, Diabetic peripheral neuropathy.



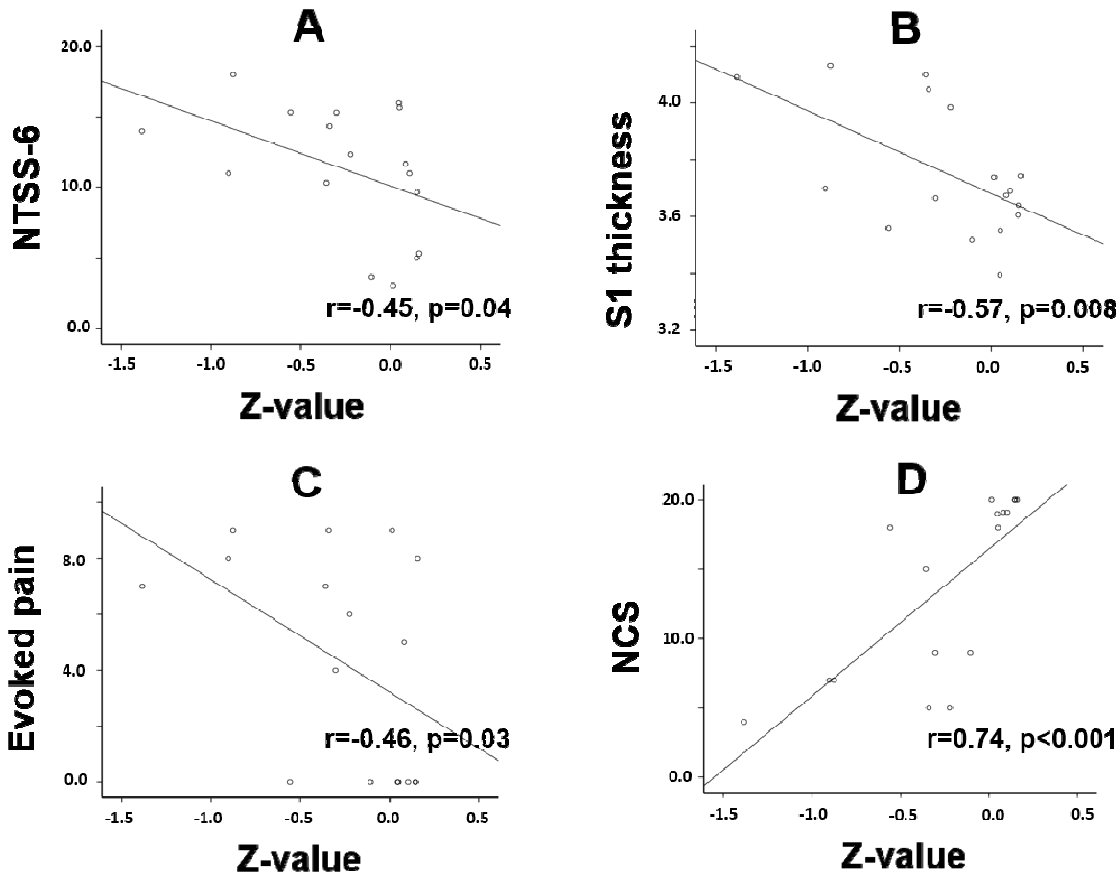
SUPPLEMENTARY DATA

Supplementary Figure 3. Group activation maps showing brain areas significantly activated in response to heat pain stimulation of the right foot (A) and thigh (B) in diabetic subjects with no neuropathy (No-DSP). The map shows activation that exceeds a threshold of Z >1.5  4.0 and a family-wise-error-corrected cluster significance threshold of P<0.05 (for display only). ACC denotes anterior cingulate cortex, CB cerebellum, INS insula, PAG, periaqueductal gray matter, ParaCC para cingulate cortex. PCC posterior cingulate cortex, PFC prefrontal cortex, PCG precentral gyrus, Thal thalmus, S1 postcentral gyrus.



SUPPLEMENTARY DATA

Supplementary Figure 4. Spearman rank correlation between Z-values of S1 signal intensity in the face/lips region with A) neuropathic total symptom score-6 (NTSS-6), B) primary somotosensory (S1) cortical thickness, C) evoked foot pain score and D) neuropathy composite score (NCS).



SUPPLEMENTARY DATA

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