

fMRI of pain processing in diabetic neuropathy

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Aims: Painful diabetic neuropathy (DN) is a distressing and disabling complication seen in between 16 and 26% of diabetic patients⁽¹⁾. Pharmacological treatment is often ineffective and a large proportion of patients report diminished quality of life and mood disorders⁽²⁾. The exact pathophysiology underpinning painful DN remains elusive although several mechanisms have been postulated⁽³⁾. Recent studies have implicated the role of central pathways in painful DN⁽⁴⁾. Investigating the brain's response to acute painful stimuli in diabetic patients with DN along with healthy volunteers (HV) may allow insight into the central nociceptive processing and supraspinal mechanisms involved in this chronic pain condition.

Methods: A total of 30 subjects were studied. 20 subjects (10 painful-DN and 10 painless-DN) underwent neurophysiological assessment (quantitative sensory, autonomic function and nerve conduction tests). Painful-DN subjects had severe neuropathic pain below the knees. All diabetic patients plus 10 HV underwent fMRI whilst enduring noxious heat pain to their right foot (potential neuropathic site) and then to their thigh (non-neuropathic site). Stimulation thresholds were acquired prior to fMRI for each participant and stimuli were delivered using a compatible Contact Heat Evoked Potentials (CHEPS) device. Data were acquired at 3.0T (Acheiva, Philips). A single shot, gradient-recalled, EPI technique was used to obtain T2*-weighted fMRI datasets (TE=35ms; TR=3s; SENSE encoding factor= 1.5; 35 slices; 4mm thickness; in-lane resolution of 1.8mm x 1.8mm). Each functional run lasted 600s and acquired images during rest (baseline) and during application of thermal stimuli to either the foot (run 1) or thigh (run 2) in a boxcar design (7 pain-off for 55, 60 or 65s, 7 pain-on for 30s). Images were analysed using SPM5: standard pre-processing then Gaussian probabilistic analysis via a General Linear Model. A 1st-level analysis identified voxels where significant BOLD response was greater in the foot than the thigh. A 2nd-level multivariate analysis then compared the identified 1st-level significant-response regions between cohort groups.

Results: For functional anatomical areas that showed greater significant BOLD response in subjects with heat-pain stimuli delivered to the foot site compared to the thigh, significant differences were present in:

- i) Prefrontal Cortex (PFC) [fig 1], anterior cingulate gyrus (ACC) and primary somatosensory cortex when comparing subjects with painful-DN to HV ($p < 0.01$, uncorrected);
- ii) PFC when comparing Painful-DN with Painless-DN ($p < 0.01$, uncorrected).

Discussion: The PFC, ACC and somatosensory cortex have been implicated in the processing of acute pain, forming part of the central "pain matrix" previously identified in experimental pain models. The PFC is involved in emotion, mood and cognitive aspects of pain processing and the cingulate gyrus has been associated with the 'suffering' component of pain. Enhanced activation in these areas suggests an increased role for the emotional-affective dimension of acute pain processing in painful-DN sufferers which may reflect the high prevalence of mood disorders associated with this condition. Differential cortical activation seen in response to an acute pain stimulus in neuropathic and symptom-free sites may reflect abnormalities in central pain processing unique to painful DN and allow a more targeted approach to future treatment of this complex condition.

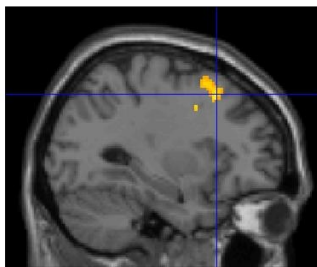


Fig 1. Functional overlay highlighting greater prefrontal cortical difference between [(foot > thigh) BOLD response to thermal stimulation] from subjects with painful-DN compared to HV's.

References:

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