Brain fMRI correlates of pain in Diabetes

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Introduction: Diabetes Mellitus is having and will have a major impact on world health. It is a multi-system disease that can affect many organs including the heart, brain, kidneys and limbs. One complication is that of diabetic peripheral neuropathy (DPN) which is common, affecting 40 percent of diabetic patients, leading to significant associated morbidity and mortality. Both hyper- and hypo-sensitivity to pain are prominent features, as is disablement bought about by limb amputation. Despite its abundance, the pathogenesis of DPN remains poorly understood and there are no effective treatments. It is commonly thought of as a disease of the peripheral nerves and much work has been reported regarding abnormalities in peripheral nerve physiology. However, recent MR studies have highlighted central nervous system involvement, showing lower spinal cord volumes (1) and proton-spectroscopic thalamic abnormalities in those with DPN (2). An understanding of CNS involvement may change the emphasis of treatment development which has hitherto been unsuccessful and, as part of this, we seek to understand the brain's response to pain stimulation in patients with DPN. This study reports our initial findings in this area using BOLD fMRI to monitor the functional neuroanatomical correlates to heat-pain stimuli applied to a group of subjects with diabetes.

Methods: Twelve male diabetics have been studied to date (mean age=54±12yrs). A detailed neurological evaluation that included neurophysiological tests (quantitative sensory testing, autonominc function tests and nerve conduction studies) was performed to diagnose and stage the severity of DPN (Dyck's neuropathy staging criteria) (3). Of the 12 subjects, 4 did not have neuropathy and the remaining 8 did. Of those 8 with DPN, 4 had painful-DPN and 4 had painless-DPN.
All patients and volunteers underwent MR imaging at 3T (Acheiva 3.0T, Philips Medical Systems, Best, Netherlands). Heat-pain stimulation was provided by an MR-compatible peltier-type device (Medoc TSA-II, Haifa, Israel). Pain perception was recorded prior to imaging using an visual analogue score (VAS) feedback-device. Whole-brain, susceptibility weighted datasets were acquired using a single-shot, gradient-recalled, echo-planar technique (TE=35ms; TR=3000ms; SENSE factor 1.5). One functional run was performed for each subject consisting 190 dynamics. At each of 190 'time points', thirty-five, 4mm thick contiguous slices were acquired in the transaxial plane. Automated, higher-order shimming maximised B_0 homogeneity over a localised volume angled to exclude the fromtal sinuses. A boxcar stimulus paradigm comprised 3 epochs each including 30 seconds at baseline temparature (35^0C), 30 seconds of warm stimulus (40-43^0C) and 30 seconds of heat-pain stimulus (47-49^0C), The epochs were separated by 150 seconds of rest at the baseline temperature.
Images were post-processed offline using Statistical Parametric Mapping (SPM2, IoN, UCL, London). After timing and movement correction, spatial normalisation and smoothing (5mm FWHM Gaussian), the difference between blood oxygen-level response between baseline and heat-pain conditions was estimated at each voxel across the whole brain, for each subject using the General Linear Model, generating t-statistic maps (corrected for multiple comparisons , thresholded at $p<0.05$).

Results: Analysis thus far has indicated significant differences in the brain's BOLD haemodynamic response to heat-pain between diabetic subject groups ($P<0.05$). Those without neuropathy (n=4) showed greater response than those with DPN (n=8) for the condition that hot stimulation returned greater signal than that returned at baseline temperature. For those with DPN, subjects who had symptoms of painful neuropathy (painful-DPN, n=4) showed significantly greater response than those who had a painless neuropathy (painless-DPN, n=4), again for the condition that hot stimulation returned higher signal than that returned at baseline temperature [figure 1]. The neuro-anatomical areas involved include the primary somatosensory cortex, lateral frontal and cerebellar regions.

Discussion:
This preliminary dataset analysis indicates that the brain's response to externally applied heat-pain stimulation is different at different stages of DPN. These differences occur within the frontal lobe, often associated with high-level perception and cognitive function, the cerebellum which may implicate processing speed action as well as the sensory cortex. Further correlative analyses is required to assess whether BOLD response outcome is coupled with measures of acute and chronic pain, and other physiological and clinical measures.

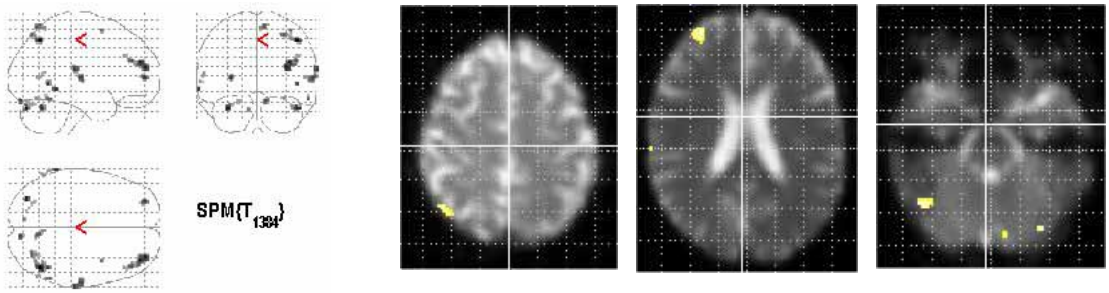

Figure 1. Statistical Parametric projection Maps (neurological coordinates) and anatomical overlays (radiological coordinates) depicting significantly greater BOLD response to heat-pain in diabetics with painful-DPN compared to diabetics with painless-DPN.

References:
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