The Brain's fMRI response to heat-pain stimulation in diabetic neuropathy

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Introduction: Recent evidence suggests that the CNS, along with many other organ systems, is involved in Diabetes Melitus (DM). Not only is there a high incidence of stroke due to cerebrovascular disease, but spinal cord atrophy (1) and thalamic spectroscopic abnormalities (2) have been shown to be linked with the presence of peripheral Diabetic Neuropathy (DN). Diabetic neuropathy is disabling with only a third of patients receiving 50% relief from medical therapy. The presence of chronic pain and allodynia (hypersensitivity) as well an insensate state can be devastating. Intervention is limited, due to a lack of knowledge regarding the underlying pathological mechanisms. The aim of this work is to investigate the brain's BOLD-fMRI correlates associated with acute heat-pain in subjects with type-1 DM.

Methods: Twenty –three male subjects were studied (table 1). Of the 23, 5 did not have DM, 6 had DM but no neuropathy, 6 had DM and a painful neuropathy whilst the raining 6 had DM and a painless neuropathy. 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 DN (Dyck's neuropathy staging criteria) (3).

	Non-diabetics (n=5)	Diabetics, no DN (n=6)	Diabetics, painful DN (n=6)	Diabetics painless DN (n=6)
Age (yrs)	47.7 (±13.8)	40.5 (±9.5)	47.3 (±7.3)	49.2 (±9.2
Body Mass Index (kg/m^2)	27.3 (±5.1)	26.2 (±5.9)	29.9 (±5.6)	28.5 (±5.5)
Duration of Diabetes (yrs)	-	16 (±13.4)	20 (±12.4)	29 (±8.8)
HbA1c (%)	-	8.3 (±1.6)	8.2 (±1.3)	7.9 (±1.7)
Dyck's neuropathy score	0	1	21	20

Table 1. Cohort details.

All participants had MR imaging at 3T (Acheiva 3.0T, Philips Medical Systems, Netherlands). Heat-pain stimulation was provided by an MR-compatible, PC-controlled, foot-thermode device (Medoc TSA-II, Haifa, Israel). Whole-brain, T2*-weighted datasets were acquired using a single-shot, gradient-recalled, echo-planar technique (TE=35ms; TR=3000ms; SENSE factor 1.5, 35 axial 4mm thick slices). One functional run was performed for each subject consisting 190 dynamics. A boxcar stimulus paradigm comprised 3 epochs each including 30 seconds at baseline temparature (35^{0}C), 30 seconds of warm stimulus (40-43^{0}C) and 30 seconds of heat-pain stimulus (47-49^{0}C), 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.

Results: There were no significant differences in BOLD haemodynamic response to heat-pain compared to baseline temperature between the non-diabetic control group and the group with DM with no neuropathy (P>0.05). Those with DM but without neuropathy showed greater response than those with DN (n=12). For those with DN, subjects who had symptoms of painful neuropathy (n=6) showed significantly greater response than those who had a painless neuropathy (n=6). The primary somatosensory cortex, lateral frontal and cerebellar regions demonstrated involvement. There was a significant negative correlation between BOLD fMRI response and overall neuropathy score in both the thalamus and left parietal lobe (T=4.14, P<0.001, uncorrected).

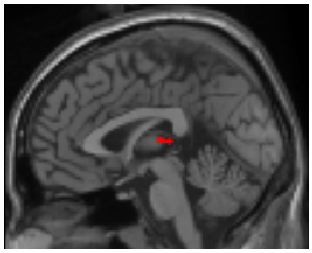

Figure 1. Area within the thalamus having significant -ve correlation between Dyck's neuropathy staging score and BOLD-fMRI response to hot compared to baseline temperature.

Discussion:

The brain's response to externally applied heat-pain stimulation varies at different stages of DN and demonstrates a negative correlation with neuropathy score. The latter occurs within the thalamus, which is often considered as the 'sensory gateway' to the brain. Group differences occur within the frontal lobe (high-level perception / cognitive function), the cerebellum (processing speed action) as well as in the sensory cortex. These differences occur despite there being a mix of neuropathic symptoms (such as hyper- and hypo-algesia) within groups and across Dyck's score, suggesting that reduction in BOLD response is complex, not simply reflecting the diminution of nerve input to the brain following peripheral nerve damage.

References:

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3. Dyck, JL et al. Neurology 1997; 49:229-239.