Test-Retest Reproducibility Of Cerebral And Subjective Responses To Painful And Non-Painful Contact-Heat Evoked Potential Stimulation (CHEPS)

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Background/Aims

Establishing biomarkers for pain research requires responses that are reproducible across individuals and repeatable over time. Ideally these methodologies should be translatable between preclinical and human studies. Contact-Heat Evoked Potential Stimulation (CHEPS) [Medoc, Israel] provides a means of examining responses to painful and non-painful heat stimulation[1]. Here we assess reproducibility of cerebral and subjective responses to CHEPS heat stimulation, using functional magnetic resonance imaging and psychophysical scaling techniques. We had two major aims; first, to discriminate reliably between differing classes of painful and non-painful heat stimulation within a session, and second, to assess reproducibility of response within a stimulus class over multiple sessions.

Methods

Design: 16 healthy right-handed male volunteers participated in a 4-session study. Session 1 was performed in a simulated 'mock scanner' environment, and sessions 2 3 and 4 in a 3 tesla whole body MR imaging system with proprietary quadrature head coil (General Electric, USA). Heat stimulation was provided by a 3 x 3 cm CHEPS thermode attached to the ventral surface of the right forearm. For each volunteer, thresholds were derived for 3 classes of stimulation; non-painful sensory detection (SDT), pain detection (PDT) and pain toleration thresholds (PTT). Thresholds were derived in sessions 1 and 2; thresholds from session 2 were used for fMRI sessions 2, 3 and 4. Following thresholding, in each session volunteers participated in two identical 20-minute event-related fMRI experimental runs. During fMRI, stimuli of 1s duration at SDT, PDT or PTT were presented approximately every 36s in a pseudo-randomised order. There were 20 repeats of each stimulation class, and 20 NULL stimulations. Ratings of perceived intensity were obtained after each stimulus using a computerised visual analogue scale (VAS) held in the left hand.

Imaging Parameters: 43 $T2^*$-weighted axial slices were acquired throughout the brain using a gradient echo-planar imaging sequence with the following parameters (slice thickness 3mm, inter-slice gap 0.3mm, field of view 240 x 240mm, acquisition matrix 64 x 64, TR = 3000ms, TE = 20ms, $\theta = 90°$). 400 volumes were collected during a 20-minute experimental run. A high-resolution T1-weighted 3D-FSPGR sequence (slice thickness 1.1mm, field of view 280 x 280mm, acquisition matrix 256 x 256, TR= 8.18ms, TE = 3ms, TI = 450ms, $\theta = 20°$) was additionally acquired for inter-subject registration and anatomical visualisation.

Statistical Analysis: [fMRI] Data were pre-processed, transformed to MNI space and spatially smoothed with an isotropic Gaussian kernel (5mm FWHM) prior to statistical analysis in FEAT v5.63 [http://www.fmrib.ox.ac.uk/fsl/feat5/index.html]. For each volunteer in each session, a single contrast-of-parameter-estimate [COPE] image was derived for each stimulus class (SDT, PDT, PTT), compared to a NULL event. COPE images served as inputs to higher-level mixed effects analyses. Within-session-between-class comparisons were computed to assess differences in brain activity between differing classes of stimulation. Within-class analyses of variance (ANOVA) were performed, with Session [2,3,4] as a repeated measure to examine differences in brain activity between sessions. Resulting gaussianised T-statistics were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $\alpha_p = 0.05$. In addition, to examine differences in signal intensity related to stimulus class, peri-stimulus time histograms were extracted from the forearm region of primary somatosensory cortex [S1][2] using PEATE [http://www.jonaskaplan.com/peate/peate.htm]

[Subjective Responses] VAS data were collated by stimulus class and analysed using SPSS (SPSS Inc, USA). Within-session differences in VAS score between stimulus classes (SDT, PDT, PTT) were examined using non-parametric Friedman-K tests and post-hoc Wilcoxon tests. Differences in within-class VAS score across sessions [1,2,3,4] were examined using linear regression analysis; for each class, gradients of lines of best fit were compared between visits using Fisher's r Test (modified for 3 related samples).

Results

Cerebral responses: Responses to PTTvNULL and PDTvNULL classes produced activation of a 'pain matrix'[3] including anterior/mid-cingulate cortex and brainstem, bilateral SII, insula & thalamus, and contralateral SI. Magnitude of response was qualitatively increased for PTTvNULL, compared to PDTvNULL. Thalamic activation was not present in responses to SDT [Figure 1, left]. Time course extraction from the forearm region of S1 indicated that in S1 magnitude of brain response was related to stimulus intensity [Figure 1, right]. ANOVA analyses in each stimulus class did not produce any significant clusters, indicating that brain activity in response to SDT, PDT or PTT did not differ between scanning sessions.

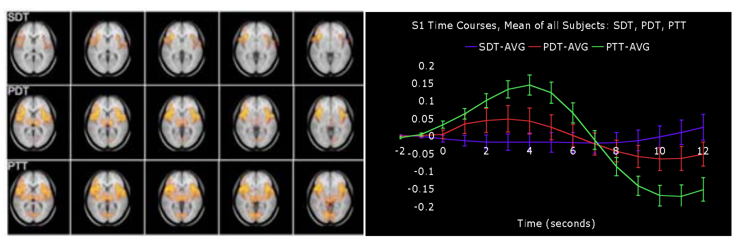

Figure 1

Subjective responses: Significant differences between subjective ratings of each stimulus class (SDT, PDT, PTT) were observed [Friedman-K related samples test: $\chi^2 = 47.72$, df =3, p<0.001; Post-hoc Wilcoxon test [n =16]: PTT-SDT, Z = -3.52, p<0.001; PTT-PDT, Z = -3.52, p<0.001; PDT-SDT, Z = -3.52, p<0.001] [Figure 2, left]. Regression analyses indicated that subjective responses to individual stimulus classes did not differ between visits [Fisher's r-test (modified for 3-samples): SDT, p = 0.867; PDT, p = 0.982; PTT, p = 0.930] [PTT illustrated in Figure 2, right].

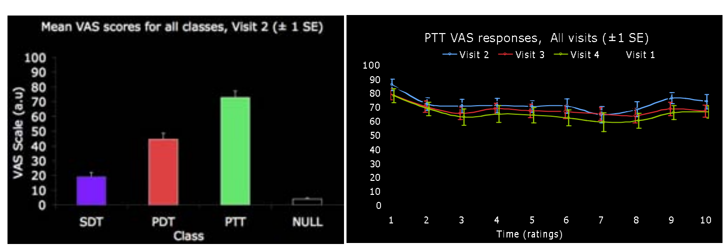

Figure 2

Conclusions

We have demonstrated that responses to varying intensities of painful and non-painful CHEPS heat stimulation can be reliably differentiated using both fMRI and visual analogue scales. Importantly, tests seeking effects of serial 'scanning' did not yield significant results; VAS scores and brain regions responsive to each class of stimulation did not differ across multiple sessions. The methodology aids the development of biomarkers for examining new strategies for treatment in acute and chronic pain states and provides a robust framework upon which existing and novel pharmaceutical compounds can be examined.

References

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