Biomarkers of Neuropathic Pain in Skin Nerve Degeneration Neuropathy: Contact Heat-Evoked Potentials as a Physiological Signature

Pain. 2017 Mar;158(3):516-525.(Taipei, Taiwan)

Contact heat-evoked potentials (CHEPs) have become an established method of assessing small-fiber sensory nerves; however, their potential as a physiological signature of neuropathic pain symptoms has not been fully explored. To investigate the diagnostic efficacy in examining small-fiber sensory nerve degeneration, the relationship with skin innervations, and clinical correlates with sensory symptoms, we recruited 188 patients (115 men) with length-dependent sensory symptoms and reduced intraepidermal nerve fiber (IENF) density at the distal leg to perform CHEP, quantitative sensory testing, and nerve conduction study. Fifty-seven age- and sex-matched controls were enrolled for comparison of CHEP and skin innervation. Among patients with neuropathy, 144 patients had neuropathic pain and 64 cases had evoked pain. Compared with quantitative sensory testing and nerve conduction study parameters, CHEP amplitudes showed the highest sensitivity for diagnosing small-fiber sensory nerve degeneration and exhibited the strongest correlation with IENF density in multiple linear regression. Contact heat-evoked potential amplitudes were strongly correlated with the degree of skin innervation in both patients with neuropathy and controls, and the slope of the regression line between CHEP amplitude and IENF density was higher in patients with neuropathy than in controls. Patients with evoked pain had higher CHEP amplitude than those without evoked pain, independent of IENF density. Receiver operating characteristic analysis showed that CHEP had better performance in diagnosing small-fiber sensory nerve degeneration than thermal thresholds. Furthermore, CHEPs showed superior classification accuracy with respect to evoked pain. In conclusion, CHEP is a sensitive tool to evaluate pathophysiology of small-fiber sensory nerve and serves as a physiological signature of neuropathic pain symptoms.

Cold-Evoked Potentials – Ready for Clinical Use?

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Eur J Pain. 2016 Nov;20(10):1730-1740 (Kiel, Germany)

BACKGROUND: Cold-evoked potentials (CEPs) are known to assess the integrity of A-delta fibres and the spinothalamic tract. Nevertheless, the clinical value was not investigated previously. The aim of this study was to measure CEPs in 16 healthy subjects from the face, hand and foot sole and to investigate whether CEPs reliably detect A-delta fibre abnormalities.

METHODS: Swift cold stimuli were applied to the skin with a commercially available thermode, which cooled down from 30 to 25 °C in approximately 0.5 s. CEP latencies (N1, N2 and P2) and amplitudes (N1, N2/P2) were recorded with EEG. Reversible A-fibre function loss was induced by applying a selective A-fibre block at the superficial radial nerve.

RESULTS: In all 16 subjects CEPs could be recorded from all locations; N2, P2 mean latencies were 276.4 ± 38.9 and 389.8 ± 52.5 (face), 318.6 ± 31.6 ms and 477.7 ± 43.6 (hand), and 627.6 ± 84.4 and 774.2 ± 94.0 (foot sole). N2/P2 amplitudes were 10.7 ± 4.1, 11.3 ± 4.1 and 7.5 ± 4.1 μV. During A-fibre block no CEPs were detectable in the grand average, which restored 10 min after block removal.

CONCLUSIONS: CEPs were reliably recorded in healthy subjects at the hand, face and foot. Experimentally induced reversible A-delta fibre function loss was detected by CEPs. Functional recovery was assessed as well. This study is basis for further CEP evaluation studies and might be the first step for implementing CEPs in clinical routine for the early diagnosis of small-fibre disease. WHAT DOES THIS STUDY ADD?: Cold-evoked potentials are capable of reliably measuring A-delta fibre integrity, loss of function and functional recovery in healthy subjects, which is an essential prerequisite for diagnostic use in patients with small-fibre disease.

Cold-sensitive and nociceptive neural pathways interact to shape the quality and intensity of thermal and pain perception. Yet the central processing of cold thermosensation in the human brain has not been extensively studied. Here, we used magnetoencephalography and EEG in healthy volunteers to investigate the time course (evoked fields and potentials) and oscillatory activity associated with the perception of cold temperature changes. Nonnoxious cold stimuli consisting of Δ3°C and Δ5°C decrements from an adapting temperature of 35°C were delivered on the dorsum of the left hand via a contact thermode. Cold-evoked fields peaked at around 240 and 500 ms, at peak latencies similar to the N1 and P2 cold-evoked potentials. Importantly, cold-related changes in oscillatory power indicated that innocuous thermosensation is mediated by oscillatory activity in the range of delta (1-4 Hz) and gamma (55-90 Hz) rhythms, originating in operculo-insular cortical regions. We suggest that delta rhythms coordinate functional integration between operculo-insular and frontoparietal regions, while gamma rhythms reflect local sensory processing in operculo-insular areas. NEW & NOTEWORTHY Using magnetoencephalography, we identified spatiotemporal features of central cold processing, with respect to the time course, oscillatory profile, and neural generators of cold-evoked responses in healthy human volunteers. Cold thermosensation was associated with low- and high-frequency oscillatory rhythms, both originating in operculo-insular regions. These results support further investigations of central cold processing using magnetoencephalography or EEG and the clinical utility of cold-evoked potentials for neurophysiological assessment of cold-related small-fiber function and damage.

Normative Data for the Segmental Acquisition of Contact Heat Evoked Potentials in Cervical Dermatomes

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Sci Rep. 2016 Oct 6;6:34660 (Zurich, Switzerland; Vancouver, Canada)

Contact heat evoked potentials (CHEPs) represent a neurophysiological approach to assess conduction in the spinothalamic tract. The aim of this study was to establish normative values of CHEPs acquired from cervical dermatomes (C4, C6, C8) and examine the potential confounds of age, sex, and height. 101 (49 male) healthy subjects of three different age groups (18-40, 41-60, and 61-80 years) were recruited. Normal (NB, 35-52 °C) followed by increased (IB, 42-52 °C) baseline stimulation protocols were employed to record CHEPs. Multi-variate linear models were used to investigate the effect of age, sex, and height on the CHEPs parameters (i.e., N2 latency, N2P2 amplitude, rating of perceived intensity). Compared to NB, IB stimulation reduced latency jitter within subjects, yielding larger N2P2 amplitudes, and decreased inter-subject N2 latency variability. Age was associated with reduced N2P2 amplitude and prolonged N2 latency. After controlling for height, male subjects had significantly longer N2 latencies than females during IB stimulation. The study provides normative CHEPs data in a large cohort of healthy subjects from segmentally examined cervical dermatomes. Age and sex were identified as important factors contributing to N2 latency and N2P2 amplitude. The normative data will improve the diagnosis of spinal cord pathologies.

Improved Diagnosis of Cervical Spondylotic Myelopathy with Contact Heat Evoked Potentials

*J Neurotrauma. 2017 Apr 7. (Vancouver, Canada; Zurich, Switzerland)*

The aim of this study was to reveal the sensitivity and responsiveness of contact heat evoked potentials (CHEPs) to assess cervical spondylotic myelopathy (CSM). A total of 81 patients with clinically and radiologically confirmed spinal cord compression were reviewed. All patients underwent full clinical examinations with combined recordings of segmental CHEPs and somatosensory evoked potentials (dSSEPs) compared with healthy controls. Cross-sectional area, maximal canal compression, and maximal spinal cord compression were determined based on T2-weighted MRI. CHEPs exhibited the highest sensitivity (~ 95%) to disclose at-level impairments in CSM patients. Normally appearing rostral segments above the level of lesion were impaired in 17% of patients. Comparatively, dSSEPs were less affected (24%) and predominantly impaired at and below the level of CSM. Longitudinal evaluation revealed that CHEPs became progressively impaired in parallel with clinical deterioration. CHEPs were sensitive to CSM, revealing evidence of impaired neurophysiology at and below the radiographic level of stenosis. The changes observed above the level of CSM suggest neurophysiological deficits beyond the focally damaged area. Deteriorating CHEPs were observed in a cohort of patients with worsening neurological symptoms, indicating their responsiveness to track CSM. The present study highlights the value of incorporating CHEPs into the diagnosis and prognosis of CSM.

Demographic Predictors of Pain Sensitivity: Results from the OPPERA Study

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The demographic factors of sex, age, and race/ethnicity are well recognized as relevant to pain sensitivity and clinical pain expression. Of these, sex differences have been the most frequently studied, and most of the literature describes greater pain sensitivity for women. The other 2 factors have been less frequently evaluated, and current literature is not definitive. Taking advantage of the large Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study cohort, we evaluated the association of sex, age, and self-reported race with 34 measures of pressure, mechanical, and thermal pain sensitivity encompassing threshold and suprathreshold perception. Women were significantly more pain-sensitive than men for 29 of 34 measures. Age effects were small, and only significant for 7 of 34 measures, however, the age range was limited (18-44 years of age). Race/ethnicity differences varied across groups and pain assessment type. Non-Hispanic white individuals were less pain-sensitive than African-American (for 21 of 34 measures), Hispanic (19 of 34), and Asian (6 of 34) individuals. No pain threshold measure showed significant racial differences, whereas several suprathreshold pain measures did. This suggests that racial differences are not related to tissue characteristics or inherent nociceptor sensitivity. Rather, the differences observed for suprathreshold pain ratings or tolerance are more likely related to differences in central nociceptive processing, including modulation imposed by cognitive, psychological, and/or affective factors.

**PERSPECTIVE:** The influence of sex, age, and race/ethnicity on various aspects of pain sensitivity, encompassing threshold and suprathreshold measures and multiple stimulus modalities, allows for a more complete evaluation of the relevance of these demographic factors to acute pain perception.

Pathway Model ATS – Recently Published Papers

Structural Alterations of the Brainstem in Migraine

Chong CD, Plasencia JD, Frakes DH, Schwedt TJ.


Atypical brainstem modulation of pain might contribute to changes in sensory processing typical of migraine. The study objective was to investigate whether migraine is associated with brainstem structural alterations that correlate with this altered pain processing. MRI T1-weighted images of 55 migraine patients and 58 healthy controls were used to: (1) create deformable mesh models of the brainstem that allow for shape analyses; (2) calculate volumes of the midbrain, pons, medulla and the superior cerebellar peduncles; (3) interrogate correlations between regional brainstem volumes, cutaneous heat pain thresholds, and allodynia symptoms. Migraineurs had smaller midbrain volumes (healthy controls = 61.28 mm³, SD = 5.89; migraineurs = 58.80 mm³, SD = 6.64; p = 0.038), and significant (p < 0.05) inward deformations in the ventral midbrain and pons, and outward deformations in the lateral medulla and dorsolateral pons relative to healthy controls. Migraineurs had a negative correlation between ASC-12 allodynia symptom severity with midbrain volume (r = - 0.32; p = 0.019) and a positive correlation between cutaneous heat pain thresholds with medulla (r = 0.337; p = 0.012) and cerebellar peduncle volumes (r = 0.435; p = 0.001). Migraineurs with greater symptoms of allodynia have smaller midbrain volumes and migraineurs with lower heat pain thresholds have smaller medulla and cerebellar peduncles. The brainstem likely plays a role in altered sensory processing in migraine and brainstem structure might reflect severity of allodynia and hypersensitivity to pain in migraine.

Placebo and Nocebo Effects:
The Advantage of Measuring Expectations and Psychological Factors

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Front Psychol. 2017; 8: 308 (Maryland, USA)

Several studies have explored the predictability of placebo and nocebo individual responses by investigating personality factors and expectations of pain decreases and increases. Psychological factors such as optimism, suggestibility, empathy and neuroticism have been linked to placebo effects, while pessimism, anxiety and catastrophizing have been associated to nocebo effects. We aimed to investigate the interplay between psychological factors, expectations of low and high pain and placebo hypoalgesia and nocebo hyperalgesia. We studied 46 healthy participants using a well-validated conditioning paradigm with contact heat thermal stimulations. Visual cues were presented to alert participants about the level of intensity of an upcoming thermal pain. We delivered high, medium and low levels of pain associated with red, yellow and green cues, respectively, during the conditioning phase. During the testing phase, the level of painful stimulations was surreptitiously set at the medium control level with all the three cues to measure placebo and nocebo effects. We found both robust placebo hypolagesic and nocebo hyperalgesic responses that were highly correlated with expectancy of low and high pain. Simple linear regression analyses showed that placebo responses were negatively correlated with anxiety severity and different aspects of fear of pain (e.g., medical pain, severe pain). Nocebo responses were positively correlated with anxiety sensitivity and physiological suggestibility with a trend toward catastrophizing. Step-wise regression analyses indicated that an aggregate score of motivation (value/utility and pressure/tense subscales) and suggestibility (physiological reactivity and persuadability subscales), accounted for the 51% of the variance in the placebo responsiveness. When considered together, anxiety severity, NEO openness-extraversion and depression accounted for the 49.1% of the variance of the nocebo responses. Psychological factors per se did not influence expectations. In fact, mediation analyses including expectations, personality factors and placebo and nocebo responses, revealed that expectations were not influenced by personality factors. These findings highlight the potential advantage of considering batteries of personality factors and measurements of expectation in predicting placebo and nocebo effects related to experimental acute pain.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5337503/
Endogenous Analgesic Effect of Pregabalin: a Double-Blind and Randomized Controlled Trial

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Eur J Pain. 2017 Feb 7. (Maebashi, Japan)

BACKGROUND: Conditioned pain modulation (CPM) is widely used to measure endogenous analgesia, and a recent study indicated that drugs that act on endogenous analgesia are more effective in individuals with lower CPM. Recent animal studies have indicated that pregabalin activates endogenous analgesia by stimulating the descending pain inhibitory system. The present study examined whether the analgesic effect of pregabalin is greater in individuals with lower original endogenous analgesia using CPM.

METHODS: Fifty-nine healthy subjects were randomly assigned to either a pregabalin group or a placebo group, and 50 of them completed the study. CPM was measured before and after pregabalin or placebo administration. The correlation of initial CPM to change in CPM was compared between the pregabalin and placebo groups.

RESULTS: Initial CPM was significantly correlated with the change in CPM in the pregabalin group (r = -0.73, p < 0.0001) but not in the placebo group (p = 0.56) (difference in correlation coefficients between groups; p = 0.004). Furthermore, the initial CPM significantly affected the change in CPM in the pregabalin group but not in the placebo group (pregabalin group: adj R2 = 0.51, p < 0.001, y = -0.54x + 2.98; placebo group: p = 0.56, significant difference in regression slopes; p = 0.015). These results indicate that pregabalin has a higher endogenous analgesic effect in individuals with lower original endogenous analgesia.

SIGNIFICANCE: The analgesic effect of pregabalin depends on the original endogenous analgesia status. Its effect on conditioned pain modulation (CPM) was stronger for subjects with lower original endogenous analgesia, suggesting that the mechanism of pregabalin involves the improvement of endogenous analgesia.

Age Differences in the Time-Course and Magnitude of Changes in Circulating Neuropeptides Following Pain Evocation in Humans


This study tested the hypothesis that older adults would have a stronger response for substance P (facilitatory) but weaker response to β-endorphin (inhibitory), both in magnitude and time-course. Eight younger and 9 older adults underwent 3 experimental sessions using well-validated laboratory pain models: cold pressor task (CPT), contact heat pain (HP), and a non-painful control. Blood was collected through an indwelling catheter at baseline and 3, 15, 30, 45, and 60-minutes post-stimuli administration. Older adults had higher baseline levels of both neuropeptides suggesting increased peripheral activity compared to younger adults. Following CPT, older adults demonstrated a quick and strong release of substance P with dramatic recovery, whereas young adults maintained a constant low-grade response. Unlike substance P, β-endorphin increased between 3 and 15 minutes for both groups with the upsurge substantially higher for older adults. Following HP, younger adults had an immediate surge in circulating substance P and β-endorphin that was more pronounced than among older adults. However, levels of substance P for younger adults slowly tapered whereas they continued to climb for the older adults through 30 minutes. β-endorphin peaked at 30 minutes for both groups and returned to baseline. No changes were observed during the non-painful control.

The Disruptive Effects Of Pain on Multitasking in a Virtual Errands Task

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Scandinavian Journal of Pain, Volume 16, July 2017 (Liverpool, UK)

BACKGROUND AND AIMS: Pain is known to have a disruptive effect on cognitive performance, but prior studies have used highly constrained laboratory tasks that lack ecological validity. In everyday life people are required to complete more complex sets of tasks, prioritising task completion and recalling lists of tasks which need to be completed, and these tasks continue to be attempted during episodes or states of pain. The present study therefore examined the impact of thermal induced pain on a simulated errand task.

METHODS: Fifty-five healthy adults (36 female) performed the Edinburgh Virtual Errands Task (EVET) either during a painful thermal sensation or with no concurrent pain. Participants also completed the Experience of Cognitive Intrusion of Pain (ECIP) questionnaire to measure their self-reported cognitive impact of pain in general life.

RESULTS: Participants who completed the EVET task in pain and who self-reported high intrusion of pain made significantly more errors than those who reported lower intrusion on the ECIP.

CONCLUSIONS: Findings here support the growing literature that suggests that pain has a significant impact on cognitive performance. Furthermore, these findings support the developing literature suggesting that this relationship is complex when considering real world cognition, and that self-report on the ECIP relates well to performance on a task designed to reflect the complexities of everyday living.

IMPLICATIONS: If extrapolated to chronic pain populations, these data suggest that pain during complex multitasking performance may have a significant impact on the number of errors made. For people highly vulnerable to cognitive intrusion by pain, this may result in errors such as selecting the wrong location or item to perform tasks, or forgetting to perform these tasks at the correct time. If these findings are shown to extend to chronic pain populations then occupational support to manage complex task performance, using for example diaries/electronic reminders, may help to improve everyday abilities.

Different Effects of Cold Stimulation on Reflex and Non-Reflex Components of Poststroke Spastic Hypertonia

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Front Neurol. 2017; 8: 169. (Houston, USA)

OBJECTIVE: To use an established biomechanical approach to quantify reflex and non-reflex responses from spastic–paretic elbow flexors in response to controlled cold and heat stimulation.

METHODS: Thirteen spastic–hemiplegic stroke subjects were tested in the experiment. The spastic elbow joint was stretched into extension for 50° at two speeds (5°/s and 100°/s) in a customized apparatus. Thermal stimulation (HEAT at heat pain threshold, COLD at 0°C, or BASELINE at room temperature) was applied to the thenar eminence of the contralateral hand immediately prior to stretching for at least 30 s.

RESULTS: Total torque was greater at 100°/s than at 5°/s. Total torque was significantly increased after COLD, but not HEAT as compared to BASELINE. When normalized to total torque at baseline, HEAT decreased total torque by 6.3%, while COLD increased total torque by 11.0%. There was no significant difference in the reflex torque among three thermal conditions.

CONCLUSIONS: The findings demonstrate differentiated effects of cold stimulation on the total resistance from spastic muscles. They provide objective evidence for anecdotal clinical observations of increased muscle spasticity by cold exposure.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5408071/