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TRAINEE EVENT

DATABLITZ

DAY 2
Asia/Australia/NZ

August 11, 2020
6:30 pm EST

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Centre for Multimodal Sensorimotor and Pain Research

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Investigating a causal relationship between acute stage sensorimotor cortex activity and development of chronic low back pain

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Conflict of Interest: None declared.

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Ethical permissions: All participants provided written informed consent to participate in the study. Ethical approval was obtained from Western Sydney University Human Research Ethics Committee (H10465) and from Neuroscience Research Australia (SSA: 16/002).

ABSTRACT:

Background: Several authors have highlighted the lack of robust, causal explanations for low back pain (LBP) persistence. Increasing evidence suggests that LBP is characterised by alterations in brain structure and function. We tested the hypothesis that sensorimotor cortex activity exerts a causal effect on transition to chronic LBP.

Methods: We performed a prospective cohort study in 120 participants. Somatosensory evoked potentials (SEP) were recorded using gold plated cup electrodes. The N_{80} component of the SEP is thought to represent primary somatosensory cortex, while N_{150} is thought to arise from secondary somatosensory cortex. Primary motor cortex activity was assessed with transcranial magnetic stimulation and recordings were obtained from L3 and L5 spinal level. Variables confounding the exposure-outcome relationship were identified using causal directed acyclic graphs and adjusted within multivariable regression models.

Results: Following adjustment for confounding and false discovery rate correction, smaller map volume at L3 recording site during acute LBP increased six-month pain intensity while smaller N_{80} and N_{150} area of the SEP increased transition to chronic LBP.

Conclusion: This study provides evidence for a relationship between "acute-stage" sensorimotor cortex activity and six-month outcome. Smaller sensorimotor cortex activity during acute LBP increases transition to chronic LBP.

Title Page

The Dorsomedial Prefrontal Cortex as a Flexible Hub Mediating Behavioral as well as Local and Distributed Neural Effects of Social Support Context on Pain: a Theta Burst Stimulation and TMS-EEG Study

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Abstract

Increasing evidence points to an analgesic influence of social support context, in which the dorsomedial prefrontal cortex (dmPFC) may play a key role. Transcranial Magnetic Stimulation (TMS) has the capacity to causally modulate brain activity. This study was designed to investigate the potential role of dmPFC in orchestrating the behavioral and neural effects of social context during pain. Twenty-three healthy participants underwent a three-session cross-over, single-blinded, sham-controlled protocol in which they received Theta Burst Stimulation (TBS) (facilitatory intermittent TBS, suppressive continuous TBS, or Sham) delivered to the dmPFC. In each session, participants underwent cold pain while viewing an image of a romantic partner or a stranger. Effects of TBS to the dmPFC were assessed using a measure of pain perception, neural activity and network connectivity using electroencephalography (EEG) and TMS-EEG. In the stranger condition, pain experience increased following iTBS. This was associated with increased connectivity between central regions and fronto-parietal regions. In contrast, in the romantic partner condition, iTBS increased connectivity only between frontal and occipital regions and did not modulate pain experience. In line with recent studies, neither cTBS nor Sham stimulation elicited neural or behavioral changes. Together these findings suggest that the dmPFC has the capacity to causally modulate pain-related information integration and network configuration in a context-dependent manner.

Keywords: social support; pain; theta burst stimulation; TMS-EEG; connectivity

Title: Modulation of attentional control in a prolonged heat pain model: Brain-Behaviour Differentiation.

Authors: Skippen, P[1]., Millard, S[1,2]., Furman, A[3,4]., Chowdhury, N[1,2]., Mazaheri, A[5,6]., Schabrun, S[1]., & Seminowicz, D[1,3,4].

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Abstract:

Pain is a complex experience involving sensory, affective, and cognitive dimensions. Within the cognitive dimension, there is a growing understanding of the importance of attentional processes in the experience and management of pain. Here, we use a cross-modal attention task with concurrent electroencephalogram (EEG) to explore the modulation of cognitive processes during acute, prolonged pain. Participants (*N* = 39) were tasked with identifying the location of either an auditory or visual target, which could be predictively or ambiguously cued. Distractors in one modality were presented alongside targets in the opposing modality on some trials. Manipulations of the paradigm to increase attentional control were evident, with increased reaction times and error rates to ambiguously cued targets, as well as to those presented alongside distractors. However, the influence of pain on these behavioural markers of attentional control was not supported, but instead Bayesian analysis showed evidence in favour of the null. Nevertheless, pain was shown to modulate EEG activity in the pre-target period, especially alpha activity. Facilitatory effects of alpha activity on attention were reduced in the presence of pain. This suggests a modulation of cognitive processes occurs during acute pain, yet the effects may not be detectable in behaviour alone. (199/200 words).

The Influence of Experimental Pain on Primary Motor Cortex Function: A Systematic Review and Meta-analysis

Nahian S Chowdhury[1,2], Wei-Ju Chang[1], Samantha K Millard[1,2], Patrick Skippen[1], Katarzyna Bilska[1,2], David A Seminowicz[3,4], Siobhan M Schabrun[1]

Nahian Chowdhury – Postdoctoral Fellow

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The primary motor cortex (M1) is a key brain region implicated in pain processing. Here, a systematic review/meta-analysis is presented which aimed to assess the effects of experimental pain on M1 function in healthy individuals. For eligible studies, we assessed group level changes in corticomotor excitability (CME), as well as the individual level relationships between CME change during pain and pain severity ratings. The meta-analysis considered factors such as pain duration and whether effects were localised to the painful tissue. Preliminary results show that paradigms which deliver brief (transient) pain in the milliseconds range have generalised effects on CME, whereas paradigms which deliver tonic pain which lasts minutes/hours had effects that were localised to the painful tissue. While studies which delivered delayed-onset pain sustained over several days showed no group level effects for CME, higher pain severity was correlated with stronger CME suppression during pain. This suggests that while transient and tonic pain paradigms may reveal information about adaptive corticomotor responses to pain at a group level, paradigms which deliver sustained pain over several days may be useful in explaining why some people develop more severe pain than others.

Ethics Approval and Consent to Participate: Not Applicable
Consent for Publication: Not Applicable
Availability of Data and Materials: Not Applicable
Competing Interests: The authors declare they have no competing interests
Funding: SMS receives salary support from the National Health and Medical Research Council of Australia (1105040)

Title: Individual variability in brain representations of pain

Submitting author: Lada Kohoutová

Abstract

Brain systems for pain processing are distributed across the whole brain, and it is unlikely that all the related brain regions play the same roles across individuals; each person may feel pain with different underlying neural causes or through different pathways. Here, we identified candidate brain regions that could explain this individual variability of pain processing. We used a functional Magnetic Resonance Imaging (fMRI) dataset (N = 404) from multiple previous thermal pain studies to build individualised predictive models. Across the individual predictive maps, we identified 21 brain regions important for pain processing and examined the regional pattern variability in both univariate and multivariate fashions. Regions such as ventromedial and ventrolateral prefrontal cortices showed larger variability, while, for example, posterior midcingulate cortex, somatosensory cortex and supplementary motor area were more stable. We also identified 10 region clusters that shared a similar pattern of inter-subject variability. As a proof-of-concept demonstration we clustered subjects within three selected region groups. Low similarities between the subject clusterings suggested there may exist different biotypes in pain processing within these areas. In summary, our study proposes brain targets for further subtyping of individuals in pain processing and creates a path towards personalised brain mapping of pain.

Ethics statement: The institutional review board of Columbia University and the University of Colorado Boulder and the Ethics committee of the Medical Chamber Hamburg approved all the studies. All subjects provided written informed consent. The author declares no conflict of interest.

UNDERSTANDING THE NEURAL MECHANISM OF TEMPORAL DYNAMICS OF INTEGRATING PREDICTION INTO PAIN PERCEPTION

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ABSTRACT

Pain is not a mere reflection of sensory inputs but constructed experience through the dynamic integration of prior and contextual information into incoming sensations. While previous studies have examined the neural mechanisms related to these integration processes, its temporal feature remain unclear. Here, we used task-based fMRI to explore these temporal dynamics of pain integration processes. We found that the trajectory regarding participants' real-time prediction toward pain experience reflected their prior information and its integrating processes with sensory inputs, demonstrating different time-varying effects on experimental conditions. In addition, the temporal mediation analysis framework showed that there exist distinctive temporal patterns associated with brain networks in mediating the cue and stimulus intensity effects on prediction rating. Specifically, brain regions within the dorsal attention and fronto-parietal networks mediated the cue effects at the early stage of pain experience, whereas the stimulus intensity was mediated by the somatosensory and dorsal attention/fronto-parietal network regions. Additional analysis revealed that these cue-mediating brain networks were closely related to the transmodal area, and stimulus intensity-mediating brain networks were associated with the unimodal area. Through these novel tools and analysis methods, this study helps us better understand how different brain systems integrate prior predictive information into pain perception.

[Word counts: 200 words]

No more nocebo: Nocebo hyperalgesia can be attenuated by classical extinction

Libo Zhang[1,2], Xuejing Lu[1,2], Li Hu[1,2]

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Abstract

Clinical trials have shown that negative expectations and prior experience considerably exacerbate pain, leading to nocebo hyperalgesia. An important question is thus whether such an effect can be attenuated or extinguished. In this study, we aim to test exactly whether this is possible using the classical extinction paradigm. We recruited 79 healthy participants and induced nocebo hyperalgesia using a classical conditioning task with an 90% partial reinforcement schedule. Participants who successfully established nocebo effects in a first test session were randomly assigned to undergo an extinction procedure or simply take a rest, and then went through a second test session. We collected pain intensity, unpleasantness, and expectation ratings, and recorded electroencephalography (EEG) signals. We found that the extinction procedure successfully attenuated nocebo hyperalgesia in terms of pain intensity and unpleasantness ratings. Mediation analysis showed that expectations served as a mediator in the effect of extinction. Spectral analysis of EEG signals indicated that the extinction effect and changes of expectation ratings were related to a power increase of α oscillations in the prefrontal and parieto-occipital regions. These findings demonstrate that nocebo hyperalgesia can be attenuated using the classical extinction paradigm, and provide insights into minimizing nocebo effects in clinical settings.

Key Words: Nocebo Hyperalgesia, Classical Extinction, Expectation, Mediation, α oscillations

Ethics Statement:

The local ethics committee at the Institute of Psychology, Chinese Academy of Sciences approved the procedures. Written informed consent was obtained from all participants.

Deficits in ascending and descending pain modulation pathways in patients with postherpetic neuralgia

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Abstract

Postherpetic Neuralgia (PHN), develops after the resolution of the herpes zoster mucocutaneous eruption, is a debilitating chronic pain. However, there is a lack of knowledge regarding the underlying mechanisms associated with ascending and descending pain modulations in PHN patients. Here, we combined psychophysics with structural and functional MRI techniques to investigate the brain alternations in PHN patients. Psychophysical tests showed that compared with healthy controls, PHN patients had increased state and trait anxiety and depression. Structural MRI data indicated that PHN patients had significantly smaller gray matter volumes of the thalamus and amygdala than healthy controls, and the thalamus volume was negatively correlated with pain intensity in PHN patients. When the thalamus and periaqueductal gray matter (PAG) were used as the seeds, resting-state functional MRI data revealed abnormal patterns of functional connectivity (FC) within pain pathways in PHN patients. In addition, subjective ratings of both Present Pain Index (PPI) and Beck-Depression Inventory (BDI) were negatively correlated with the strength of FC between the PAG and S1, and importantly, the effect of BDI on PPI was mediated by the PAG-S1 FC. Overall, our results provided evidence suggesting deficits in ascending and descending pain modulation pathways, which were highly associated with the intensity of chronic pain and its emotional comorbidities in PHN patients. Therefore, our study deepened our understanding of the pathogenesis of PHN, which would be helpful in determining the optimized treatment for the patients.

Pain-processing abnormalities in schizophrenia:

Evidence from EEG and fMRI studies

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Abstract

Clinical observations demonstrated that schizophrenia patients had reduced or absent pain responses when suffering from painful conditions, leading to high mortality and morbidity. However, the underlying mechanism of this phenomenon has been poorly understood. Here, we adopted a stimulus-response paradigm with brief stimuli of different sensory modalities (i.e., nociceptive, non-nociceptive somatosensory, and auditory) to test whether pain insensitivity in schizophrenia is supra-modal or modality-specific, and used electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) techniques to clarify its neural mechanisms. Compared to healthy controls, schizophrenia patients showed significantly lower ratings to nociceptive stimuli, but similar ratings to non-nociceptive somatosensory and auditory stimuli. These behavioral results were confirmed by stimulus-evoked brain responses sampled by EEG (Figure 1) and fMRI techniques (Figure 2A), thus verifying the modality-specific nature of pain modulation in schizophrenia patients. Moreover, there were significant group differences in the spectral power of alpha oscillations in prestimulus EEG and the seed-based functional connectivity in resting-state fMRI (Figure 2B), indicating that the phenomenon could be resulted from a potential cortical-subcortical dysfunction. Taken together, our study provides insight into the neural mechanisms of pain-processing abnormalities in schizophrenia and calls attention to systematic assessments of their pain-related diseases.

Keyword: electroencephalogram; functional magnetic resonance imaging; pain sensitivity; schizophrenia; sensory processing.

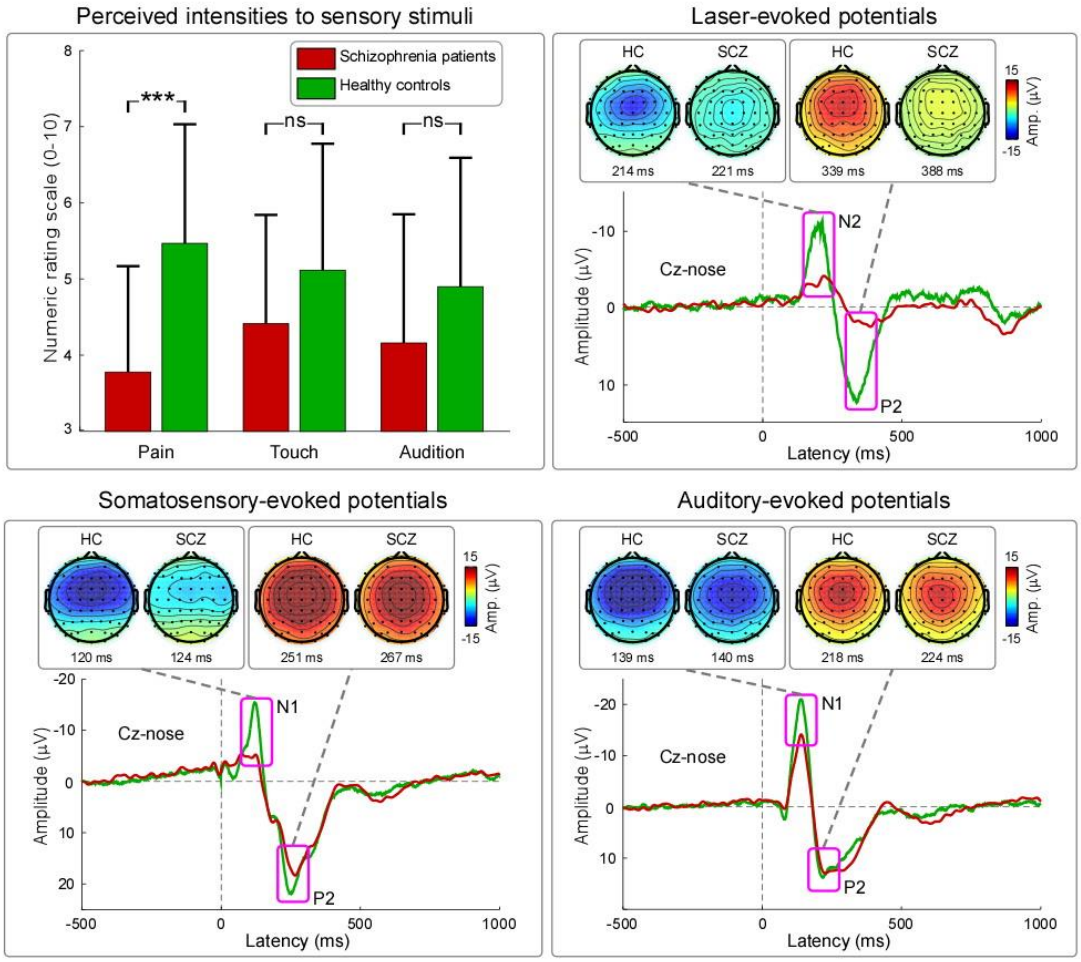

Figure 1. Comparisons of behavioural variables and electrophysiologic features between SCZ and HC.

Top left panel: Perceived intensities to different sensory stimuli. While the perceived intensities to nociceptive stimuli were significantly smaller for SCZ compared to HC, the perceived intensities of non-nociceptive somatosensory and auditory stimuli showed no significant differences between the two groups.

Top right panel: Group-level LEP waveforms and scalp topographies of N2 and P2 waves (Cz-nose). Data from SCZ and HC are displayed in red and green respectively. Scalp topographies are plotted at the peak latency of each wave.

Bottom left panel: Group-level SEP waveforms and scalp topographies of N1 and P2 waves (Cz-nose).

Bottom right panel: Group-level AEP waveforms and scalp topographies of N1 and P2 waves (Cz-nose).

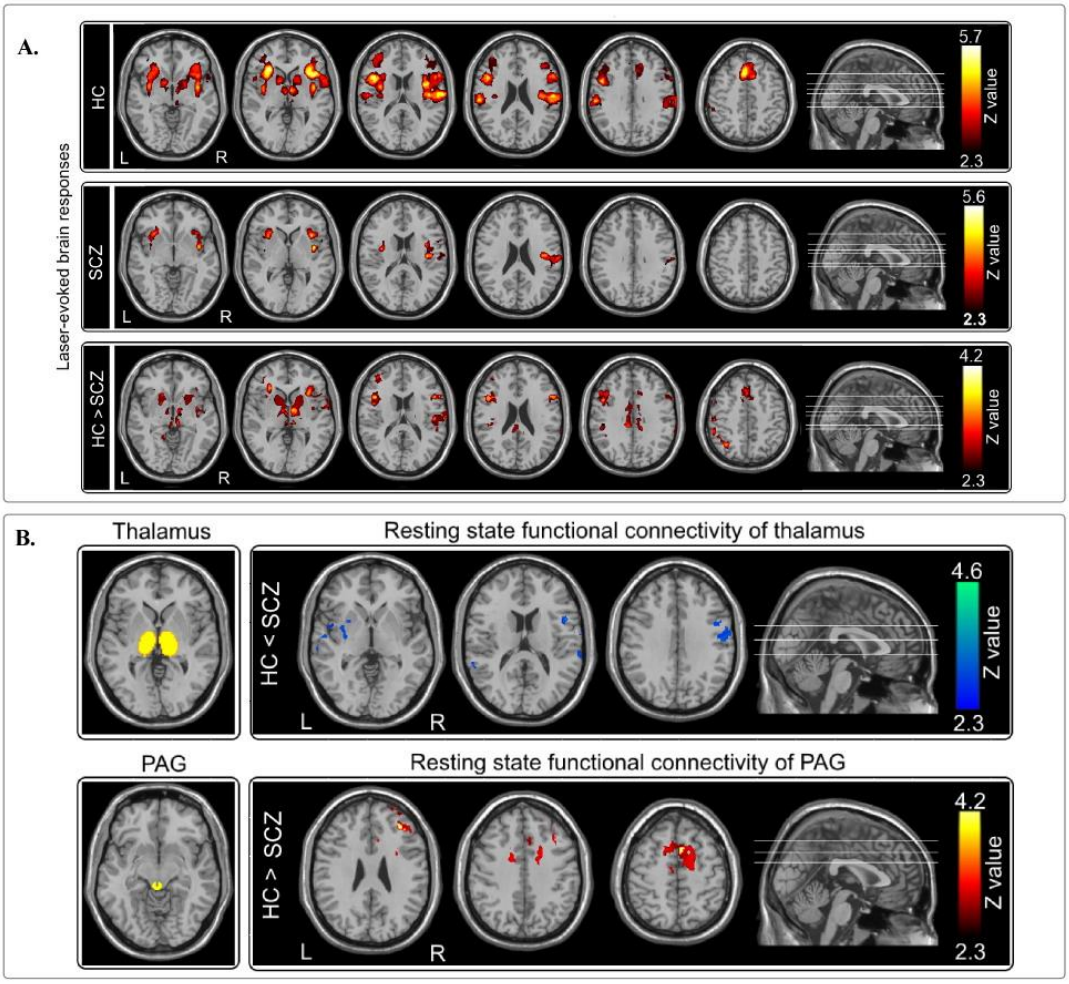

Figure 2A. Event-evoked BOLD responses to nociceptive stimuli.
Top panel: For HC, nociceptive stimuli elicited significant activations in PAG, thalamus, S1, S2, insula, and dACC.
Middle panel: For SCZ, nociceptive stimuli elicited significant activations in right S2 and bilateral insula.
Bottom panel: Brain activations were significantly smaller in SCZ than HC in almost all brain regions responsible for nociceptive information processing, including PAG, thalamus, left S1, S2, insula, and dACC.

Figure 2B. Resting state functional connectivity.
Top panel: Thalamus showed weaker resting state functional connectivity with right S1, right S2, left posterior insula in HC than in SCZ.
Bottom panel: PAG showed stronger resting state functional connectivity with SMA, dACC, and DLPFC in HC than in SCZ.

Predicting Post-operative Pain in Lung Cancer Patients using Pre-operative Peak Alpha Frequency

Millard, S.K., Kerr, A., Furman, A., Seminowicz, D., Gao-Smith, F., Naidu, B., Mazaheri, A.

Context: Chronic post-thoracotomy pain is highly prevalent and currently unpredictable pre-operatively. However, experimental models of neuropathic pain suggest that individual peak alpha frequency (PAF), measured using electroencephalography (EEG), can predict future pain sensitivity.
Methods: The feasibility and efficacy of pre-operative PAF as a possible neuro-marker for post-operative pain sensitivity was assessed in 17 patients undergoing thoracic surgery for lung cancer (age = 67.53 ± 4.38 [SD]). Patients underwent a five minute cEEGrid recording pre-operatively, they also provided ratings of current, average, and worst pain pre-operatively, within three days post-operatively, and at six months.
Results: Chronic pain assessments are ongoing. However, pre-operative PAF was significantly higher for those reporting lower pain severity compared to those reporting higher pain severity in the immediate post-operative period. Furthermore, quantile regressions suggest lower pre-operative PAF was predictive of more severe post-operative pain.
Conclusions: PAF is a promising candidate neuro-marker to pre-operatively assess individual susceptibility to high pain severity in the immediate post-operative period. This would enable a shift towards pain prevention rather than treatment, such as more informed assessment of an individual's suitability for surgery by considering their risk of pain. Furthermore, assessment using cEEGrids was fast, comfortable for patients, and technically feasible. (198/200 words)

Ethics statement: Data were collected as part of a larger prospective research project examining rehabilitation for operated lung cancer (ROC). The ROC project was approved by the NHS ethics committee on 27th July 2010 (Reference: 10/H1208/41). Addition of the EEG sub-study discussed was approved on 18th February 2019.

Title: Brainstem mechanisms of placebo and nocebo pain modulation

Authors: Crawford, L[1]., Mills, E[1]., Macefield, V[2]., Henderson, L[1].

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[2]Baker Heart and Diabetes institute, Melbourne, Victoria, Australia

Due to technological limitations, the brainstem mechanisms underlying the placebo and nocebo pain response remain largely unexplored in humans. Utilizing ultra-high field 7-tesla functional magnetic resonance imaging (fMRI), we investigated the brainstem neural network responsible for placebo analgesia and nocebo hyperalgesia in 25 healthy control subjects.

Over subsequent days subjects were conditioned to believe that two deceptively labelled Vaseline creams: “Lidocaine” and “Capsaicin”, contained analgesic and hyperalgesic properties respectively through surreptitious application of differing intensity noxious thermal stimuli. During a test phase, identical stimuli were applied to both creams and subjective reports of pain perception were collected on-line to measure the intensity of the modulatory response.

Based on individual subjects change in perceived pain intensity, we divided them into placebo responder, placebo non-responder, nocebo responder and nocebo non-responder groups and compared brainstem signal intensity changes between groups. We found changes in activity in the PAG-RVM circuit associated with both the placebo and nocebo response, although largely in opposing directions. Furthermore, we observed differential recruitment of the substantia nigra and rostral ventrolateral medulla between placebo and nocebo responders. This data defines the brainstem neural circuitry responsible for the pain-modulatory placebo and nocebo phenomena in healthy humans.

Word count: 195

Ethics: The University of Sydney Human Research Ethics Committee approved all experimental procedures. Written consent was obtained from subjects at the beginning of each testing session. Subjects were provided with an emergency buzzer while inside the scanner so they could stop the experiment at any time. At the conclusion of testing, subjects were informed both verbally and through an information statement of the necessary deception and true methodology of the experiment.