

Parallel cortical-brainstem pathways to attentional analgesia

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3 **Valeria Oliva¹, Rob Gregory^{1,2}, Wendy-Elizabeth Davies^{1,2}, Lee Harrison³, Rosalyn Moran⁴,**
4 **Anthony E. Pickering^{1,2}, Jonathan C.W. Brooks³.**

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6 1 School of Physiology, Pharmacology & Neuroscience, Biomedical Sciences Building, University
7 of Bristol, Bristol, BS8 1TD.

8 2 Anaesthesia, Pain & Critical Care Sciences, Bristol Medical School, University Hospitals Bristol,
9 Bristol, BS2 8HW.

10 3 School of Psychological Science, University of Bristol, Bristol, BS8 1TU.

11 4 Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College
12 London, SE5 8AF.

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13 **Abstract**

14 Pain perception is diminished when attention is diverted. Our previous human fMRI study, using a
15 2x2 factorial design with thermal stimuli and concurrent visual attention task, linked the brainstem
16 triad of locus coeruleus (LC), rostroventromedial medulla (RVM) and periaqueductal grey (PAG) to
17 attentional analgesia. This study was repeated with a larger cohort, replicating our earlier findings.
18 Pain intensity was encoded by the RVM, whilst activity in the contralateral LC correlated with the
19 magnitude of attentional analgesia. Psycho-Physiological Interaction analysis informed subsequent
20 Dynamic Causal Modelling and identified two parallel paths between forebrain and the brainstem
21 regions involved in analgesia. These cortico-brainstem connections were modulated by attentional
22 demand: a bidirectional anterior cingulate cortex (ACC) – right-LC loop, and a top-down influence
23 of task on ACC-PAG-RVM. Under conditions of competing attentional demands the ACC recruits
24 discrete brainstem circuits to modulate nociceptive input.

25

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26 **Introduction**

27 Attentional analgesia is a well-characterised phenomenon whereby increased cognitive load can
28 decrease pain perception (Peyron et al. 2000; Bantick et al. 2002; Brooks et al. 2002; Valet et al.
29 2004; Brooks et al. 2017; Sprenger et al. 2012). For example, this can be achieved by diverting
30 attention from a painful stimulus to a visual task or simply by active mind-wandering (Bushnell et
31 al., 2013; Kucyi et al., 2013). Central to attentional analgesia is the concept of divided attention,
32 whereby less cognitive resource is available to be allocated to nociception and pain. Since noxious
33 stimuli are inherently salient and therefore attention grabbing (Eccleston et al., 1999), then any
34 concurrent cognitive task must compete for ‘attentional’ resource. Attention is thus cast both as a key
35 component of pain behaviour (i.e. attending to pain (Crombez et al., 2004; Legrain et al., 2009;
36 Roelofs et al., 2002)) as well as a putative mechanism for pain relief. The processes regulating
37 attentional focus is of importance in the development, maintenance and potentially resolution of
38 chronic pain states.

39 The mechanisms that allow attention to regulate pain are currently not well understood and there has
40 been ongoing debate about whether attentional analgesia requires engagement of descending control
41 to attenuate nociception (Brooks et al., 2017; Bushnell et al., 2013; Lorenz, Minoshima, & Casey,
42 2003; Tracey et al., 2002; Valet et al., 2004). Several important regions have been linked to the
43 descending analgesic effects, including the anterior cingulate cortex (ACC), dorsolateral prefrontal
44 cortex (dlPFC) and components of the descending pain control system including periaqueductal grey
45 (PAG), rostroventromedial medulla (RVM) and locus coeruleus (LC). An interaction between
46 cortical and mid-brain structures during distraction from pain has been identified (Lorenz et al., 2003;
47 Valet et al., 2004) but these previous studies were unable to examine interactions in pontomedullary
48 regions that are known to be important for the descending control of nociception.

49 These brainstem regions are all candidates for mediating attentional analgesia given their known anti-
50 nociceptive roles (Millan, 2002). For example, multiple animal studies have demonstrated that

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51 interactions between the PAG and RVM produces endogenous analgesia, mediated by spinally
52 projecting neurons in the RVM (Basbaum et al., 1979; Fields et al., 1978; Heinricher et al., 2009).
53 Together with the ACC, these regions form one of the main pain modulatory pathways involved in
54 the bidirectional modulation (i.e. facilitation and inhibition) of nociception in the spinal cord dorsal
55 horn (De Felice et al., 2016; Ossipov et al., 2010; Quintero, 2013).

56 Similarly, the LC is another potential candidate region that could mediate the interaction between
57 attention and pain because of its projections to the spinal cord which release noradrenaline to produce
58 analgesia (Hirschberg et al., 2017; Llorca-Torrallba et al., 2016). Additionally, it has a known role in
59 salience signalling and attention mediated by ascending projections (Aston-Jones et al., 1999; Sales
60 et al., 2019; Sara et al., 2012). Despite it being challenging to resolve with fMRI (Astafiev et al.,
61 2010; Liu et al., 2017), the LC was recently identified as the only region whose activity reflected the
62 interaction between task and temperature in an attentional analgesia paradigm (Brooks et al., 2017).
63 The LC could therefore contribute to attentional analgesia as part of the PAG-RVM system, or as a
64 parallel descending modulatory pathway perhaps receiving inputs directly from ACC (Aston-Jones
65 et al., 1991; Bajic et al., 1999).

66 Within this framework the ACC is ideally placed to mediate between competing cognitive demands
67 (e.g. between a sustained visual attention task and pain) as it is active during conflict resolution
68 (Braver et al., 2001; Kerns, 2006; Kim et al., 2011), its activity is modulated by attention (Davis et
69 al., 2000) as well as being consistently activated by painful stimuli (Brooks et al., 2017; Garcia-Larrea
70 et al., 2013; Peyron et al., 2000; Wager et al., 2013). The ACC is known to code for pain intensity
71 (Büchel et al., 2002; Coghill et al., 2003) and unpleasantness (Rainville et al., 1997), furthermore,
72 sub-divisions (e.g. dorsal anterior ACC) are involved in high level cognitive appraisal of pain,
73 including attention (Büchel et al., 2002). Some have proposed a specific role for dorsal ACC (dACC)
74 in pain perception (Lieberman et al., 2015), though this is disputed with other studies suggesting that
75 activity within this structure reflects the multifaceted nature of pain (Wager et al., 2016). Connectivity

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76 between the ACC and structures involved in descending pain control e.g. the PAG, has been shown
77 to vary with pain perception due to both attentional modulation of pain and placebo analgesic
78 responses (Bantick et al., 2002; Eippert et al., 2009; Petrovic et al., 2000; Valet et al., 2004) suggestive
79 of a role in attentional analgesia. Indeed, cingulotomy has been shown to "disinhibit" noxious heat
80 and cold perception leading to hyperalgesia (Davis et al., 1994).

81 We hypothesised a top-down pathway mediating attentional analgesia where the PAG receives
82 attentional-shift signals from the ACC and/or LC and directs the RVM and/or LC to attenuate
83 nociceptive processing in the spinal cord. Given the multiplicity of possible pathways and interactions
84 by which activity in the brainstem can generate analgesia, we anticipated that effective connectivity
85 analyses could resolve the roles of these regions (identified in our previous investigation (Brooks et
86 al., 2017)) during attentional analgesia. To increase the statistical power to undertake this connectivity
87 analysis, two further fMRI datasets were acquired using the same paradigm as per Brooks et al.
88 (2017). Analysis of these additional datasets reproduced our previous regional activation results and
89 so the three datasets were pooled for the effective connectivity analyses and modelling. We tested for
90 psycho-physiological interactions (PPI, (Friston et al., 1997; McLaren et al., 2012; O'Reilly et al.,
91 2012) to explore whether the connectivity between the PAG, RVM, LC and ACC altered during the
92 experimental paradigm. Finally, we used dynamic causal modelling (DCM, Friston et al. 2003) to test
93 the directionality and strength of the connections.

94

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95 **Methods**

96 *Participants*

97 Subjects were recruited using poster and email adverts at the University of Bristol for three different
98 pain imaging studies at the Clinical Research and Imaging Centre (CRiCBristol) that used the same
99 experimental paradigm: an initial study on attentional analgesia (Brooks et al., 2017), a study on sleep
100 disruption and a study on fibromyalgia. The first two studies were approved by the University Bristol,
101 Faculty of Science, Human Research Ethics Committee (reference 280612567 and 291112606
102 respectively) and the fibromyalgia study was approved by NHS South Central Oxford B Research
103 Ethics Committee (reference 13/SC/0617).

104 All subjects gave written informed consent after application of standard inclusion/exclusion criteria
105 for participation in MRI studies. The presence of significant medical/psychiatric disorders (including
106 depression) or pregnancy precluded participation. Subjects with a chronic pain condition, or those
107 who were regularly taking analgesics or psychoactive medications were also excluded. All subjects
108 were right-handed, verified with the Edinburgh handedness inventory (Oldfield, 1971).

109 The *discovery cohort* were 20 right-handed healthy subjects (median age 25 years, range 18–51 years,
110 10 females). Subjects attended for two sessions. During the screening visit, written consent was
111 obtained and both task difficulty and temperature of the thermal stimulation were individually
112 calibrated. Subsequently the subjects returned for the test session where they completed the
113 experiment in the MRI scanner (For full details on the *discovery cohort* see Brooks et al., 2017).

114 The *validation cohort* composed of control subjects from two separate studies:

115 Twenty healthy volunteers (median age 23, range 20-33, 10 females) were recruited for a study
116 investigating the effects of sleep disturbance on attentional analgesia. Subjects completed the same
117 experiment protocol on two occasions; after a habitual and a disturbed night's sleep (at the sleep

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118 laboratory at CRiCBristol). For the present study, only data obtained from the control condition was
119 used, wherein subjects experienced their habitual sleep regime the night prior to their scan.

120 A second group of 20 healthy participants (median age 31.5, range 20-59, 18 females) was recruited
121 from the control group of a study analysing attentional analgesia in fibromyalgia patients.

122

123 *Experiment*

124 Thermal stimuli were delivered to the left volar forearm (approximately C6 dermatome) using a
125 circular contact thermode (CHEPS Pathway, MEDOC) and each lasted 30 seconds. The noxious
126 thermal stimulus was individually titrated to obtain a 6 out of 10 pain rating (42-45°C plateau). The
127 innocuous stimulus plateau was set at 36°C. In both cases brief heat spikes of 2, 3 and 4°C above the
128 plateau temperature were added in a random sequence at a frequency of 1Hz. This heating profile
129 was used to maintain painful perception, whilst avoiding skin sensitisation. The baseline thermode
130 temperature was 32°C.

131 For the Rapid Serial Visual Presentation task (RSVP, Potter et al. 1969), subjects identified a visual
132 target (the number “5”) among distractors (other letters and numbers), presented using back-
133 projection to a screen, responding with a button box (Lumina LP-400, Cedrus). The speed of character
134 presentation for the hard RSVP task was individually calibrated to obtain a 70% correct detection rate
135 using d' , and ranged from 32 to 96 ms. The speed of presentation for the easy RSVP task was either
136 192 or 256 ms, depending on performance in the hard task (if the “hard” task interval for the subject
137 was <80 ms or >80 ms, respectively).

138 *Data acquisition*

139 In the scanner, participants received noxious or innocuous thermal stimuli (high/low) while
140 simultaneously performing the RSVP task with two levels of difficulty (easy/hard). Thus, there were
141 four experimental conditions (in a 2x2 factorial experimental design): *easy/low*, *easy/high*, *hard/low*,
142 *hard/high*. Each condition was repeated 4 times. Each experimental epoch started with instructions

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143 (5s), followed by the 30s experimental condition, followed by a 10s rest period before an 8s rating
144 period where subjects rated the perceived pain intensity from 0 to 10 on a visual analogue scale (VAS)
145 (See Fig 1 in Brooks et al. 2017). The post-stimulus interval, between the rating period and subsequent
146 instructions, was 17s.

147 The experiment for the *validation cohort* (n=38) was essentially identical to that of the *discovery*
148 *cohort*. The titrated mean high temperature for the *discovery cohort* was 44.2°C and for the *validation*
149 *cohort* it was 43°C (range 42–45 °C). The whole imaging session lasted 26 minutes for the *discovery*
150 *cohort* and sleep-disruption cohort and was 22 minutes for the fibromyalgia cohort (as a redundant
151 control condition, with no distraction during high temperature, was omitted).

152 Imaging was performed with a 3T Skyra MR system (Siemens Medical Solutions, Erlangen,
153 Germany) and 32-channel receive only-head coil. In addition to blood oxygenation level dependent
154 (BOLD) functional data, T1 weighted structural scans were acquired with an MPRAGE sequence to
155 allow image registration. Functional imaging data were acquired with TE/TR=30/3000 ms, GRAPPA
156 acceleration factor = 2, resolution = 1.5 x 1.5 x 3.5 mm. The slices were angulated perpendicularly to
157 the base of the 4th ventricle to improve the acquisition of brainstem nuclei. This slice orientation
158 optimised the ability to discriminate between the small brainstem structures in the transverse plane
159 and while allowing the capture of whole brain activity within 3 seconds. Fieldmap data were acquired
160 with a gradient echo sequence (TE1/TE2/TR = 4.92 / 7.38 / 520 ms, flip angle 60°, resolution 3 x 3 x
161 3 mm). During scanning, a pulse oximeter and a respiratory bellows (Expression MRI Monitoring
162 System, InVivo, Gainesville, FL) were used to monitor cardiac pulse waveform and respiratory
163 movement for subsequent physiological noise correction (Brooks et al., 2013).

164 *Behavioural Data analysis*

165 Pain VAS ratings were converted to a 0-100 scale for a repeated measures ANOVA in SPSS software
166 (after Brooks et al. 2017). Following estimation of main effects (task, temperature) and interactions,
167 post-hoc paired t-tests were performed. The presence of attentional analgesia was pre-defined as a

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168 significant interaction between task difficulty and high temperature on pain rating on post-hoc paired
169 t-testing ($p < 0.05$). To test for differences between the *discovery* and *validation* cohorts; group
170 membership was added as a between subject factor to the two within subject factors (task and
171 temperature). Subsequent analysis is reported on the *pooled* cohort.

172

173 *Imaging Data analysis*

174 *Image Pre-processing*

175 Functional images were corrected for motion using MCFLIRT (Jenkinson et al., 2012) and co-
176 registered to each subject's structural scan using brain boundary-based registration (Greve et al.,
177 2009) and then to the 2mm template ("MNI152") brain using a combination of fieldmap based
178 unwarping using FUGUE (Jenkinson, 2003), linear transformation using FLIRT (Jenkinson et al.,
179 2001) and non-linear registration using FNIRT (Andersson et al., 2007) with 5mm warp spacing.
180 Functional data were spatially smoothed with a kernel size of 3mm (FWHM) and high pass
181 temporally filtered with a 90s cut-off. Two subjects in the *validation* cohort and one from the
182 *discovery cohort* were excluded from the analyses at this stage because of signal dropout in the EPI
183 data (leaving 57 subjects).

184 *First level analyses*

185 Local autocorrelation correction was performed using FILM (Woolrich et al., 2001) as part of model
186 estimation, which also attempted to correct for physiologically driven signals (originating from
187 cardiac/respiratory processes) using slice-dependent regressors (Brooks et al., 2008; Harvey et al.,
188 2008). The four conditions (*easy/high*, *hard/high*, *easy/low*, *hard/low*) and tasks of no interest (cues
189 and rating periods) were modelled using a hemodynamic response function (gamma basis function,
190 $\sigma = 3s$, mean lag = 6s) alongside the physiological regressors within the general linear model in FEAT
191 (Jenkinson et al., 2012). A separate analysis tested for an intra-subject parametric relationship
192 between pain ratings (one per block) and BOLD signal (Büchel et al., 1998). In addition to tasks of

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193 no interest and physiological signal regressors, a constant regressor for all blocks (weighting = 1) and
194 a regressor weighting the individual pain ratings for each block were included. None of the regressors
195 were orthogonalised with respect to any other.

196 *Second level analyses*

197 Main effects were specified as positive and negative main effect of attention (hard versus easy task,
198 and vice versa) and positive and negative main effect of temperature (high versus low thermal
199 stimulus, and vice versa). A task x temperature interaction contrast was also specified. The parametric
200 data was assessed using a simple group average – to examine whether the linear relationship between
201 pain ratings and brain activity was consistent across the group. Lastly, a paired analysis compared
202 activity during the *easy|high* and *hard|high* conditions - to examine whether the inter-subject
203 difference in average pain ratings (i.e. *easy|high* minus *hard|high*) was linearly related to the
204 corresponding difference in BOLD signal (similar to Tracey et al. 2002 and Brooks et al. 2017). To
205 test for differences between the *discovery cohort* and the *validation cohort*, we used an unpaired t test
206 with FLAME (height threshold $z > 3.09$, corrected cluster extent threshold $p < 0.05$), in line with
207 guidelines on corrections for familywise error (FWE) (Eklund et al., 2016). Subsequent analyses of
208 the *pooled* cohort (i.e. all 57 subjects) used the same threshold.

209 *Brainstem-specific analyses*

210 Detecting activation in the brainstem is non-trivial due to its susceptibility to physiological noise and
211 artefacts (Brooks et al., 2013), small size of structures of interest and relative distance from signal
212 detectors in the head coil. Consequently, a brainstem focussed analysis was performed at the group
213 level using a series of anatomical masks and statistical inference using permutation testing in
214 RANDOMISE (Nichols et al., 2002). Analyses utilised pre-defined regions of interest based on (i) a
215 whole brainstem mask derived from the probabilistic Harvard-Oxford subcortical structural atlas
216 (Desikan et al., 2006) and thresholded at 50% and (ii) previously defined probabilistic masks of the
217 *a priori* specified brainstem nuclei (RVM, LC, PAG) from Brooks *et al.* (2017). The number of

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218 permutations were set to 10,000 in line with guidelines (Eklund et al. 2016) and results reported using
219 threshold free cluster enhancement (TFCE) corrected $p < 0.05$ (Smith et al., 2009).

220 *Psycho-Physiological Interactions (PPI)*

221 Effective connectivity analyses were performed on the *pooled cohort*. We used generalised PPI
222 (gPPI) to detect changes in interactions between regions during specific experimental conditions
223 (O'Reilly et al. 2012; McLaren et al. 2012; Friston et al. 1997). In this technique a physiological
224 signal (e.g. the time-course extracted from a seed region) is convolved with a modelled psychological
225 variable (i.e. each one of the experimental conditions) to build an interaction regressor. All interaction
226 regressors were added to a general linear model (GLM) that also included the non-convolved
227 experimental conditions and tasks of no interest (e.g. the rating period). Contrasts were built to test
228 for connectivity differences that could be explained by the main effects of task and temperature and
229 the task * temperature interaction.

230 Four regions identified in the main effect analyses (temperature and/or attention) in the *pooled cohort*,
231 were selected as seed-regions for the gPPI analysis: PAG, right LC and ACC in the main effect of
232 task and RVM in the main effect of temperature. For each subject, the physiological BOLD time
233 course was extracted from the peak voxel of the pre-processed images (as described in the previous
234 section) within each functional mask, and gPPI performed at the first level. Subsequently, group
235 responses were estimated with permutation testing within the same functional masks e.g. effective
236 connectivity between PAG seed region and the other three regions (RVM, right LC, ACC). For a post
237 hoc investigation of significant results in the task * temperature interaction contrast, we focussed on
238 the conditions of interest (i.e. *easy/high* and *hard/high*). Parameter estimates were extracted by first
239 defining a sphere of radius 2mm at the voxel of greatest significance in the group gPPI result, then
240 back-transforming this mask to subject space and extracting the signal from the voxel with highest Z-
241 score.

242 In summary, the procedure for gPPI analysis was:

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- 243 • Time series extraction from functional masks in pre-processed data
- 244 • Convolution of time-series with experimental condition
- 245 • Building statistical contrasts in a GLM
- 246 • First level (single subject) analysis
- 247 • Group analysis permutation testing with functional masks
- 248 • Extraction of parameter estimates from the conditions of interest.

249

250 *Dynamic Causal Modelling (DCM)*

251 Given the inability of gPPI to resolve the directionality of connections, we sought to extend our
252 findings by using DCM (Friston et al., 2003). This technique allows the specification of a hypothetical
253 network model (based on equation 1) fitted to the fMRI data to resolve connection strengths.

254 The change in activity of each region in a model with j inputs and n brain regions is formalized as
255 follows:

256 (1)

$$257 \quad \frac{dx}{dt} = (aA + \sum_{j=1}^n u_j b B^j) x + cCu + \omega$$

258 Where:

259 x - neuronal state of a region (i.e. BOLD signal convolved with haemodynamic response function)

260 A - binary vector that defines the connectivity of x is to each of the other regions in the model,

261 a - vector of parameters that define the strengths of such connections,

262 u - external input to the model,

263 B - binary vector that defines whether model connections are modulated by external input,

264 b - vector of parameters that defines the strength of such modulation,

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265 C - binary vector that defines whether x directly receives the external input,

266 c - contains parameters that regulate the strength of the received input,

267 ω - random neuronal noise.

268 Note since the model is estimated in a Bayesian framework, parameters are not single values but are
269 posterior densities.

270 Given the results of the PPI analysis, we specified bi-linear, one state, stochastic, input centred DCMs
271 (Daunizeau et al., 2009; Daunizeau et al., 2012) in SPM 12 (Wellcome Trust Centre for
272 Neuroimaging, London, UK). The models were estimated on a computer cluster (BlueCrystal) in the
273 Advanced Computing Research Centre, University of Bristol – <http://www.bristol.ac.uk/acrc/>.
274 Random effects Bayesian Model Selection (BMS) was used to compare the models and Protected
275 Exceedance Probability, the likelihood of a given model in respect to the others tested, was calculated.
276 Bayesian Omnibus Risk, a measure of the risk of all models having the same frequency within the
277 population, was also computed (Rigoux et al., 2014). Bayesian model averaging (Penny et al., 2010)
278 was used to extract the parameter estimates of interest.

279

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280 **Results**

281 *Comparison of the discovery cohort and validation cohort*

282 We initially analysed pain scores and main effects of task and temperature on brain activation maps
283 in the *validation cohort* (n=38) independently to qualitatively compare against the results previously
284 obtained in the *discovery cohort* (n=19, Brooks et al., 2017). A two-way repeated measures ANOVA
285 on the pain ratings in the *validation cohort* revealed a main effect of temperature ($F(1, 37) = 137.5$,
286 $P < 0.0001$) and a task x temperature interaction ($F(1, 37) = 24.6$, $P < 0.0001$, Fig. S1), and no main
287 effect of task ($F(1, 37) = 2.1$, $P = 0.15$). A post-hoc paired t-test showed performance of the hard task
288 produced a decrease in pain scores in the high temperature condition (mean *hard/high* =39.3, SD 18.9
289 vs *easy/high* =43.6, SD 18.3, $P < 0.001$, Bonferroni corrected), consistent with an attentional analgesic
290 effect (Fig S1).

291 Analysis of the fMRI activation maps in the *validation cohort* showed a main effect of temperature
292 (*high* versus *low* temperature) in a range of regions including the primary somatosensory cortex,
293 dorsal posterior insula and opercular cortex, with more prominent clusters contralateral to the side of
294 stimulation (applied to the left forearm, Fig S2). In the brainstem, permutation testing with PAG, LC
295 and RVM masks showed activation in all of these nuclei (Fig S2). No cluster reached significance in
296 the negative main effect of temperature (low temperature versus high temperature).

297 Analysis of the main effect of task (*hard* versus *easy* task) showed bilateral activation in the occipital
298 cortex (Fig S3). The anterior cingulate, anterior insula and paracingulate cortices also showed
299 extensive activation, consistent with the visual attention network (Wager et al., 2004). Activation in
300 the dorsolateral PAG was observed in this whole brain analysis without the need for brainstem-
301 specific masking (Fig S3), presumably because of the increased statistical power afforded by the
302 higher number of subjects compared to Brooks et al. (2017). A permutation test with PAG, LC and
303 RVM masks showed activation in all nuclei (Fig S3). In the reverse contrast (negative main effect of

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304 task, *easy* versus *hard*) main activation clusters were located in the posterior cingulate cortex, frontal
305 medial cortex and in the lateral occipital cortex.

306 Activation clusters from these main effects analyses are reported in table S1 and, as indicated, were
307 closely consistent with our previous results (Brooks et al, 2017). This qualitative comparison was
308 also assessed quantitatively as follows:

309 A three-way repeated measures ANOVA on the pain scores using task and temperature as within
310 subject factors and the group (*discovery* vs *validation cohort*) as between subject factor showed no
311 effect of group on the effects of temperature ($P = 0.481$), nor task ($P = 0.833$), nor on the
312 task*temperature interaction ($P = 0.481$).

313 An unpaired t-test on the functional image contrasts did not show any statistically significant
314 differences between the *discovery* and *validation cohorts* for the main effect of temperature (positive
315 and negative), main effect of task (positive and negative) and interaction contrast (positive and
316 negative).

317 Given the qualitative similarities and lack of demonstrable statistical differences we went ahead with
318 our planned intention to combine the three datasets and all subsequent results relate to the *pooled*
319 *cohort* comprising 57 subjects. We also note that the use of strict cluster thresholds for the brain, and
320 of permutation testing for ROI-based analyses in ‘noisy’ brainstem regions, can produce robust and
321 reproducible results even with a sample size of 20 (Brooks et al, 2017).

322

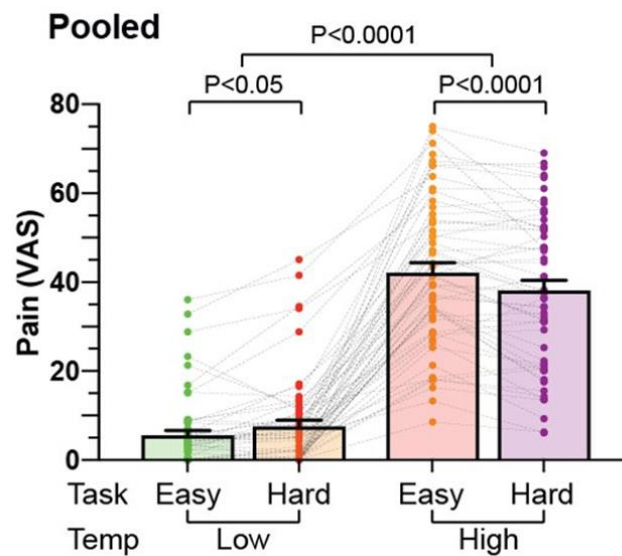
323 *Behavioural analysis (Pooled cohort)*

324 The average high (noxious) temperature in the *pooled cohort* was 43.4°C (range 42°C - 45°C).
325 Analysis of the pain ratings showed the expected main effect of temperature ($F(1, 56) = 252.799$, P
326 < 0.0001 , repeated measures ANOVA) and a task x temperature interaction ($F(1, 56) = 31.969$, $P <$
327 0.0001 , Fig. 1). The main effect of task was not statistically significant ($F(1,56) = 2.935$, $P = 0.092$).

328 A post-hoc paired t-test showed performance of the hard task produced a decrease in pain scores in

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329 the high temperature condition (mean *hard/high* = 38.1, SD 17.0 vs *easy/high* = 42.1, SD 16.5, $P <$
330 0.0001, Bonferroni corrected), consistent with an attentional analgesic effect (Fig 1).



331

332 **Figure 1.** Pain ratings across experimental conditions (means with error bars representing the standard error of the mean)
333 for the pooled cohort. A 2-way repeated measures ANOVA on the pain ratings showed the expected main effect of
334 temperature ($P < 0.0001$) and a task x temperature interaction ($P < 0.0001$). A post-hoc paired t-test showed a decrease in
335 pain scores in the high temperature condition during the hard task compared to the easy task ($P < 0.0001$), showing an
336 analgesic effect caused by the increased cognitive load, as well as an increase in pain scores in the low temperature
337 condition during the hard task compared to the easy task ($P < 0.05$). The main effect of task was not significant ($P = 0.92$).
338 Error bars represent the standard error of the mean.

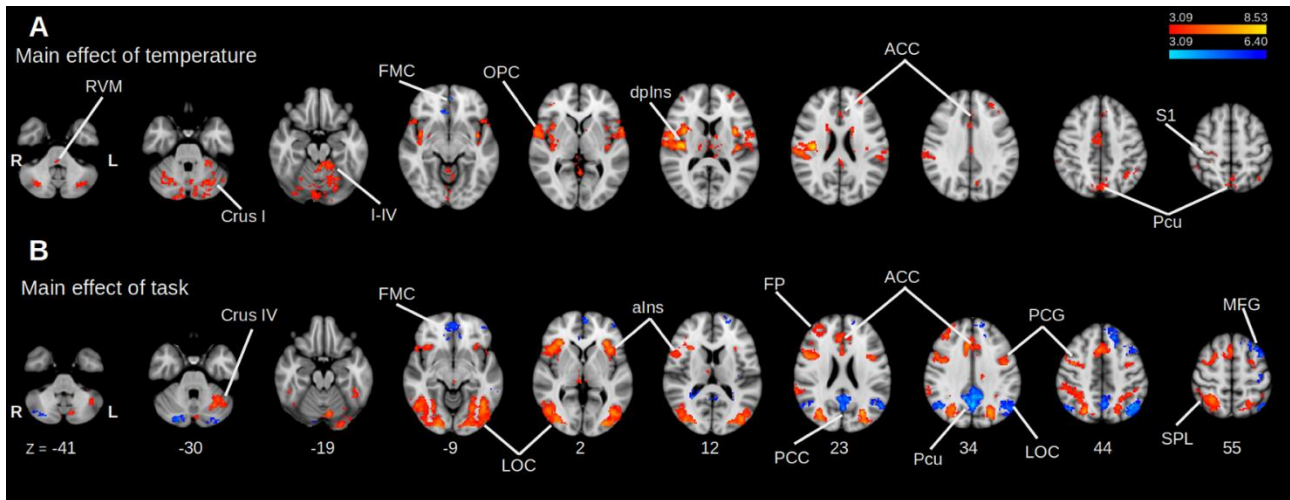
339

340 *Whole Brain & Brainstem-focussed analysis (Pooled cohort)*

341 Activations were found for the positive main effect of temperature in a range of regions including the
342 anterior and posterior cingulate cortices, precuneus, cerebellum, post-central gyrus (S1), dorsal
343 posterior insula and opercular cortex, in the latter three cases with more prominent clusters
344 contralateral to the side of thermal stimulation (Fig. 2A). In the negative main effect of temperature,
345 significant clusters were found in the frontal medial cortex and in the subcallosal cortex (Fig 2A). At
346 this whole brain level, no clusters of activity were found in the brainstem. To improve our ability to
347 resolve activity in hindbrain structures, we undertook permutation testing using a *whole brainstem*

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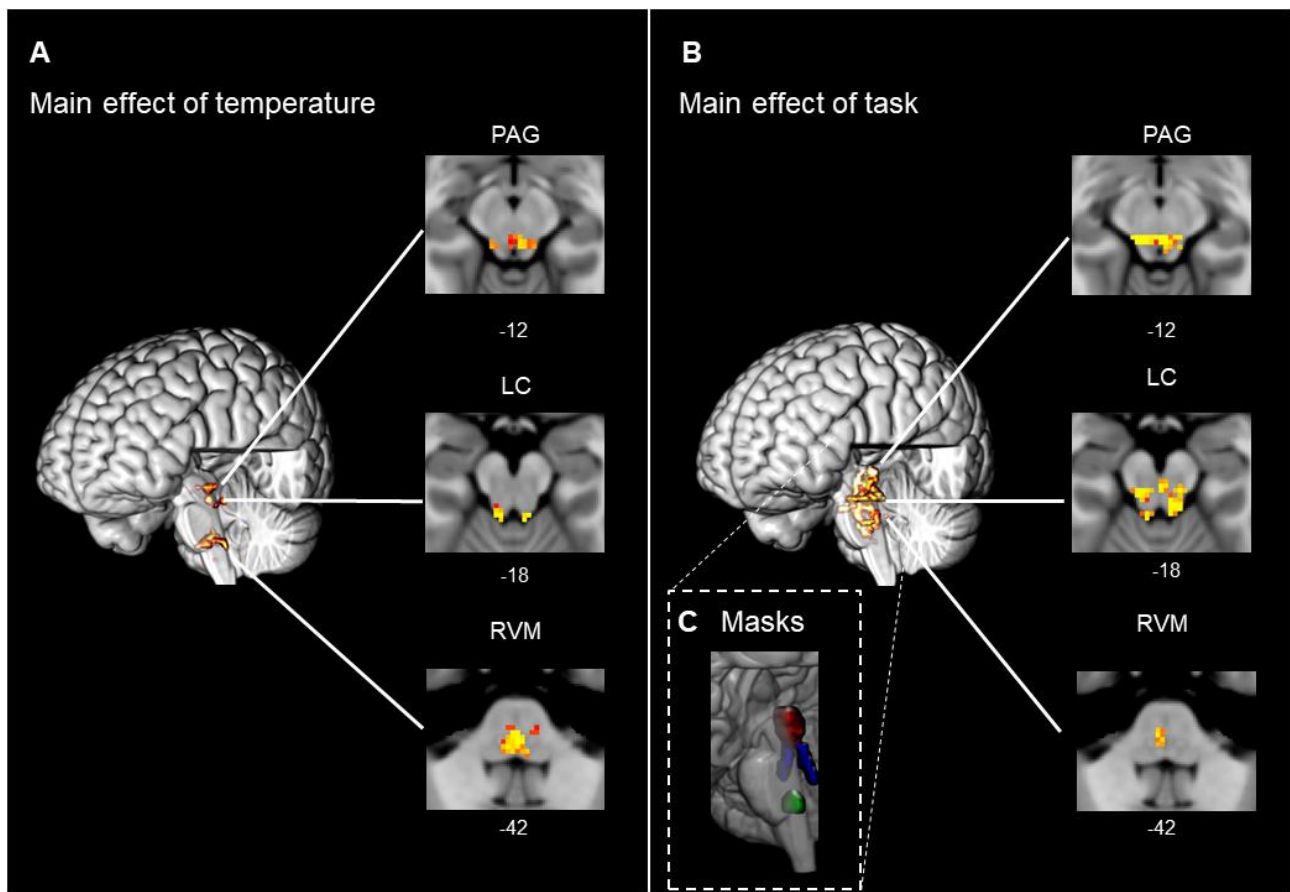
348 mask which revealed clusters of activation in the positive main effect of temperature in the ventral
349 PAG, LC bilaterally as well as the RVM (Fig 3A, $p < 0.05$, TFCE corrected).



350
351 **Figure 2.** Main effect analyses in the *pooled cohort*, whole brain analysis. Positive (red/yellow) and negative (blue/light-
352 blue). Data was obtained from cluster-based thresholding using an initial threshold of $Z > 3.09$ and FWE corrected $p <$
353 0.05 , one-sample t-test. (A) Main effect of temperature. Positive activation in the high temperature conditions was found
354 in anterior cingulate cortex (ACC), thalamus (THAL), dorsal posterior insula (dpIns), precuneus (PCu), primary
355 somatosensory cortex (S1) and rostroventromedial medulla (RVM). Activation in the negative main effect of temperature
356 (low temperature vs high temperature) was observed only in the frontal medial cortex (FMC). (B) Main effect of **task**.
357 Activity in the positive main effect was found in the anterior insula (aIns), lateral occipital cortex (LOC), ACC, superior
358 parietal lobule (SPL). Activity in the negative main effect was found in the frontal pole (FP), posterior cingulate cortex
359 (PCC) and Pcu.

360 Analysis of the positive main effect of task, showed extensive areas of activation within the lateral
361 occipital cortex, superior parietal lobule, anterior cingulate cortex and anterior insula, as well as the
362 PAG (Fig 2B). In the negative main effect of task, clusters were located in the posterior cingulate
363 cortex, frontal medial cortex and in the lateral occipital cortex (Fig 2B). Permutation tests within the
364 *whole brainstem* mask showed multiple clusters of activation, including in the LC bilaterally, RVM
365 and PAG (Fig 3B, $p < 0.05$, TFCE corrected).

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366

367 **Figure 3.** Main effect analyses in the brainstem. Results obtained after permutation testing with a probabilistic *whole*
368 *brainstem* mask ($p < 0.05$, TFCE corrected). (A) Clusters of activation in the brainstem corresponding to the main effect
369 of **temperature** was found in the ventral periaqueductal grey (PAG), rostroventromedial medulla (RVM) and bilateral
370 locus coeruleus (LC). (B) Many areas in the superior brainstem show activity in the main effect of **task**, including the
371 PAG, RVM and bilateral LC. (C) Anatomical masks defined in (Brooks et al., 2017), identifying the PAG (red), LC
372 (blue), RVM (green).

373 In the interaction contrast between task and temperature no cluster reached significance either at the
374 whole brain level nor when using the whole brainstem masked analysis.

375 These findings from the *pooled cohort* showed close similarity to those of Brooks et al. (2017) with
376 the same areas found in the main effects analysis (Table 1 shows all significant clusters). The
377 additional findings at a whole brain level were that both the RVM and the precuneus now appear in
378 the main effect of temperature and the dorsolateral PAG in the main effect of task (the RVM and
379 PAG were only seen in a nucleus specific masked analysis in Brooks et al 2017). Similarly, activity
380 in the brainstem is now seen in more areas using a whole brainstem mask rather than only in the

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381 nucleus specific masks (e.g. main effect of temperature in RVM alone previously versus RVM, LC
382 and PAG in this *pooled* analysis).

383 **Table 1.**

Voxels	Z-MAX	X (mm)	Y (mm)	Z (mm)	Atlas labels
Main effect of temperature in the pooled cohort					
2680	8.53	40	-18	18	46% Central Opercular Cortex, 27% Parietal Operculum Cortex, 5% Insular Cortex
2072	5.08	6	-86	-24	3% Occipital Fusiform Gyrus
839	7.03	-36	4	12	61% Central Opercular Cortex, 10% Insular Cortex
386	4.87	0	-70	48	76% Precuneous Cortex
352	4.84	0	20	28	87% Cingulate Gyrus, anterior division
345	6.58	-38	-18	18	50% Central Opercular Cortex, 20% Insular Cortex, 5% Parietal Operculum Cortex
268	5.26	22	-46	72	54% Superior Parietal Lobule, 12% Postcentral Gyrus
265	5.23	32	-26	62	35% Precentral Gyrus, 28% Postcentral Gyrus
238	4.75	4	-26	8	28.2% Right Thalamus
223	4.87	-28	54	18	85% Frontal Pole
133	4.31	4	-26	30	81% Cingulate Gyrus, posterior division
97	4.09	12	-10	18	55.0% Right Thalamus
95	4.7	-34	-56	42	29% Superior Parietal Lobule, 18% Angular Gyrus, 13% Supramarginal Gyrus, posterior division, 12% Lateral Occipital Cortex, superior division
43	4.25	20	16	18	5.8% Right Caudate
42	4.47	36	46	8	47% Frontal Pole

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41	4.34	2	-90	-6	34% Lingual Gyrus, 23% Occipital Pole, 13% Intracalcarine Cortex
39	4.73	-26	-50	-50	57.0% Left VIIIa, 35.0% Left VIIIb
36	3.97	-34	32	40	66% Middle Frontal Gyrus, 7% Frontal Pole
34	4.54	-16	8	22	25.6% Left Caudate
34	4.11	-48	-54	46	44% Angular Gyrus, 25% Supramarginal Gyrus, posterior division, 9% Lateral Occipital Cortex, superior division
32	4.8	36	-82	-22	7% Lateral Occipital Cortex, inferior division
32	4.33	48	-44	50	46% Supramarginal Gyrus, posterior division, 17% Angular Gyrus
29	4.31	-4	-40	-44	100.0% Brain-Stem
26	4.3	-48	-64	-30	99.0% Left Crus I

Negative main effect of temperature in the pooled cohort

67	4.25	6	30	-6	21% Subcallosal Cortex, 13% Cingulate Gyrus, anterior division
28	4.06	-4	46	-12	63% Frontal Medial Cortex, 28% Paracingulate Gyrus

Main effect of task in the pooled cohort

4948	7.22	22	-90	-8	29.00% Occipital Fusiform Gyrus, 22.00% Occipital Pole, 10.00% Lateral Occipital Cortex, inferior division
4790	7.33	-28	-76	20	41.00% Lateral Occipital Cortex, superior division
3773	7.13	46	16	0	48.00% Frontal Operculum Cortex, 6.00% Insular Cortex
635	6.81	-34	26	0	38.00% Frontal Orbital Cortex, 20.00% Frontal Operculum Cortex, 13.00% Insular Cortex
540	5.26	36	38	36	56.00% Frontal Pole, 23.00% Middle Frontal Gyrus

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433	5.87	-42	6	26	27.00% Precentral Gyrus, 26.00% Inferior Frontal Gyrus, pars opercularis
241	6.33	-8	-74	-38	43.0% Left VIIb, 38.0% Left Crus II
205	5.43	4	-26	-2	12.8% Brain-Stem
58	4.68	-46	-38	38	25.00% Supramarginal Gyrus, anterior division, 10.00% Supramarginal Gyrus, posterior division
46	4.65	44	-8	-10	66.00% Planum Polare
45	4.14	-28	-2	58	28.00% Middle Frontal Gyrus, 16.00% Superior Frontal Gyrus, 6.00% Precentral Gyrus
41	5	-38	-52	-44	63.0% Left Crus II, 13.0% Left VIIb, 6.0% Left Crus I
38	5.71	10	-74	-38	57.0% Right Crus II, 18.0% Right VIIb
27	4.52	-14	-22	36	19.00% Cingulate Gyrus, posterior division

Negative main effect of task in the pooled cohort

1731	6.31	8	-56	30	38% Precuneous Cortex, 20% Cingulate Gyrus, posterior division
1126	6.6	-38	-72	48	68% Lateral Occipital Cortex, superior division
876	5.43	-34	18	56	63% Middle Frontal Gyrus, 2% Superior Frontal Gyrus
511	5.77	32	-70	-36	44.0% Right Crus I, 24.0% Right Crus II
461	5.95	50	-66	40	83% Lateral Occipital Cortex, superior division
346	4.66	6	28	-4	14% Subcallosal Cortex anterior division
257	5.06	-36	-24	70	32% Postcentral Gyrus, 24% Precentral Gyrus
125	4.97	-38	-72	-36	97.0% Left Crus I
94	5.33	-66	-42	-6	54% Middle Temporal Gyrus, posterior division, 29% Middle Temporal Gyrus, temporooccipital part
92	4.99	-16	64	18	82% Frontal Pole

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78	4.47	-42	52	2	88% Frontal Pole
41	4.07	-38	-18	18	50% Central Opercular Cortex, 20% Insular Cortex, 5% Parietal Operculum Cortex
38	4.38	-24	-50	18	1% Precuneous Cortex
34	4.16	-64	-8	-14	44% Middle Temporal Gyrus, anterior division, 24% Middle Temporal Gyrus, posterior division, 8% Superior Temporal Gyrus, posterior division

384

385 **Table 1.** Activation clusters from main effects of temperature and distraction in the pooled cohort obtained with cluster-
386 forming threshold $Z > 3.09$ and cluster-corrected $p < 0.05$. The tables were created with Autoaq (part of FSL), with atlas
387 labels based on the degree of overlap with probabilistic atlases (Harvard Oxford Cortical Structural Atlas, Harvard
388 Oxford Subcortical Structural Atlas, Cerebellar Atlas in MNI152 space after normalization with FNIRT). Only those
389 structures to which the cluster had a $> 5\%$ chance of belonging to are presented.

390

391 *Linear pain encoding regions*

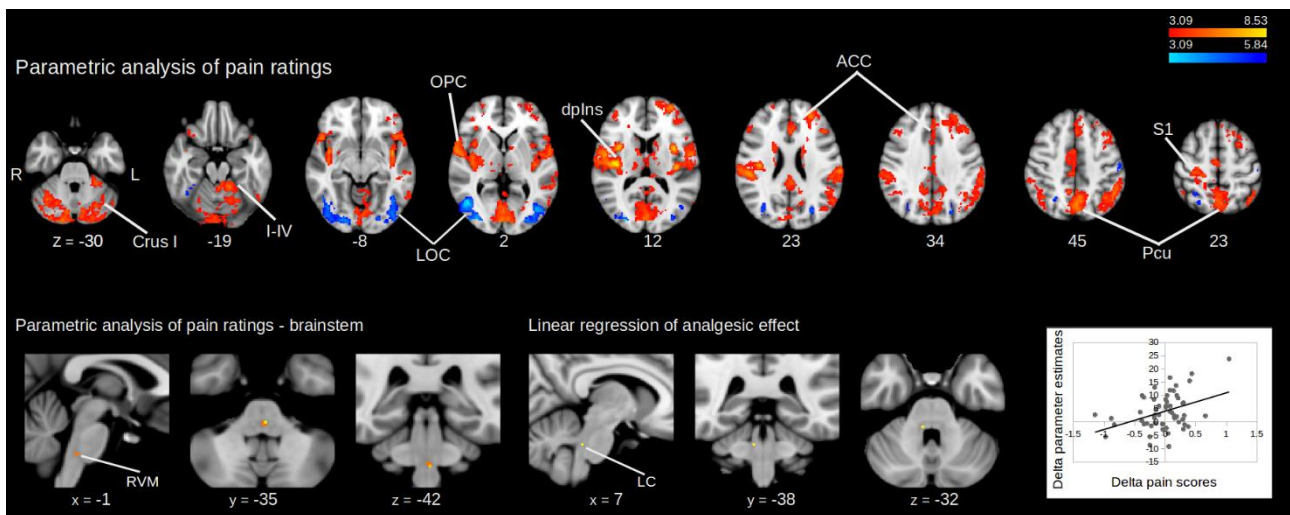
392 Brain regions whose activity was linearly related to perceived pain intensity were identified using an
393 *intra*-subject parametric regression. This revealed a network of positively correlated regions (similar
394 to those seen in the main effect of temperature) including primarily the right (contralateral) dorsal
395 posterior insula and S1, the anterior cingulate cortex, frontal lobe and the precuneus (Fig 4A). Regions
396 showing a linear decrease in activation with pain ratings were restricted to the occipital cortex
397 bilaterally and ipsilateral primary somatosensory cortex (Fig 4A). Permutation testing in the
398 brainstem (using RVM, PAG and LC masks) identified only the RVM as showing a positive
399 correlation with pain intensity (Fig 4B). No region showed a negative correlation with pain. All these
400 findings were consistent with Brooks *et al* (2017), with the addition of a cluster identified in the
401 thalamus (Table 2).

402 *Regions whose activity correlates with analgesic effect*

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403 An *inter*-subject whole-brain mixed effects comparison between the *hard/high* and *easy/high*
404 conditions did not identify any region whose activity linearly correlated with the differences in pain
405 ratings (i.e. analgesia). A parametric regression showed a linear relationship between activity and
406 analgesic effect only in the contralateral (right) LC (i.e. decreased pain ratings were associated with
407 increased BOLD), after permutation testing with LC, RVM and PAG masks (Fig. 4C). A positive
408 relationship was noted between the parameter estimates extracted from the rLC and the attentional
409 analgesic effect on pain scores (Fig 4C).

410



411

412 **Figure 4. A)** Intrasubject parametric regression with pain ratings across all the experimental conditions, in the whole
413 brain. In red-yellow are shown regions whose activity linearly increase with pain ratings, in blue-light blue regions whose
414 activity decreases with the pain ratings. (height threshold $Z > 3.09$, corrected cluster extent threshold $p < 0.05$) **B)**
415 Intrasubject parametric regression with pain ratings, using RVM, LC and PAG masks. Only the RVM shows linear
416 increase in activity with the pain scores ($p < 0.05$, TFCE corrected). **C)** Inter-subject parametric regression with the
417 analgesic effect (i.e. ratings of *easy/high* – *hard/high*), using a LC mask ($p < 0.05$, TFCE corrected).

418

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419 **Table 2.**

Voxels	Z-MAX	X (mm)	Y (mm)	Z (mm)	Atlas labels
Positive relationship with pain ratings					
9467	6.36	32	-28	64	40% Postcentral Gyrus, 26% Precentral Gyrus
3621	8.37	40	-18	18	46% Central Opercular Cortex, 27% Parietal Operculum Cortex, 5% Insular Cortex
3481	7.78	-56	-2	8	45% Central Opercular Cortex, 28% Precentral Gyrus, 5% Planum Polare
1693	5.93	-26	46	26	79% Frontal Pole
287	4.98	-62	-56	-10	54% Middle Temporal Gyrus, temporooccipital part, 21% Inferior Temporal Gyrus, temporooccipital part, 7% Lateral Occipital Cortex, inferior division
285	5.2	4	-26	8	28.2% Right Thalamus
120	4.42	20	-8	28	3.1% Right Caudate
95	4.18	42	48	8	80% Frontal Pole
86	4.71	16	-20	10	099.8% Right Thalamus
71	5.79	-26	-50	-50	57% Left VIIIa, 35% Left VIIIb
59	4.41	46	26	36	65% Middle Frontal Gyrus
46	3.82	-20	-28	68	39% Precentral Gyrus, 23% Postcentral Gyrus
38	4.17	-42	-72	24	72% Lateral Occipital Cortex, superior division
37	4.11	-18	-38	66	51% Postcentral Gyrus
36	3.84	2	-66	-38	69% Vermis VIIIa, 13% Vermis VIIIb
34	3.83	24	54	26	76% Frontal Pole
33	4.48	52	30	22	32% Middle Frontal Gyrus, 30% Inferior Frontal Gyrus, pars triangularis

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31	3.78	28	58	0	76% Frontal Pole
Negative relationship with pain ratings					
1637	6.16	46	-64	2	56% Lateral Occipital Cortex, inferior division, 10% Middle Temporal Gyrus, temporooccipital part
1184	5.36	-42	-74	0	63% Lateral Occipital Cortex, inferior division
176	5.38	-26	-76	30	67% Lateral Occipital Cortex, superior division
126	4.73	26	-52	50	34% Superior Parietal Lobule, 3% Lateral Occipital Cortex, superior division
51	4.32	-54	-16	52	57% Postcentral Gyrus, 8% Precentral Gyrus

420 **Table 2.** Results from intrasubject parametric regression with pain ratings in the *pooled cohort* obtained with cluster-
421 forming threshold $Z > 3.09$ and cluster-corrected $p < 0.05$. The tables were created with Autoaq (part of FSL), with atlas
422 labels based on the degree of overlap with probabilistic atlases (Harvard Oxford Cortical Structural Atlas, Harvard
423 Oxford Subcortical Structural Atlas, Cerebellar Atlas in MNI152 space after normalization with FNIRT). Only those
424 structures to which the cluster had a $> 5\%$ chance of belonging to are presented.

425

426 *gPPI analysis*

427 The analysis aimed to identify changes in effective connectivity associated with altered task
428 difficulty, temperature and the task x temperature interaction. The previous main effect analyses
429 provided us with functional activation masks that were used to extract time courses for these gPPI
430 analyses; in the RVM for the main effect of temperature, and in the PAG, rLC and ACC for the main
431 effect of task (see Methods). Permutation testing revealed increased connectivity with the following
432 contrasts (Fig 5):

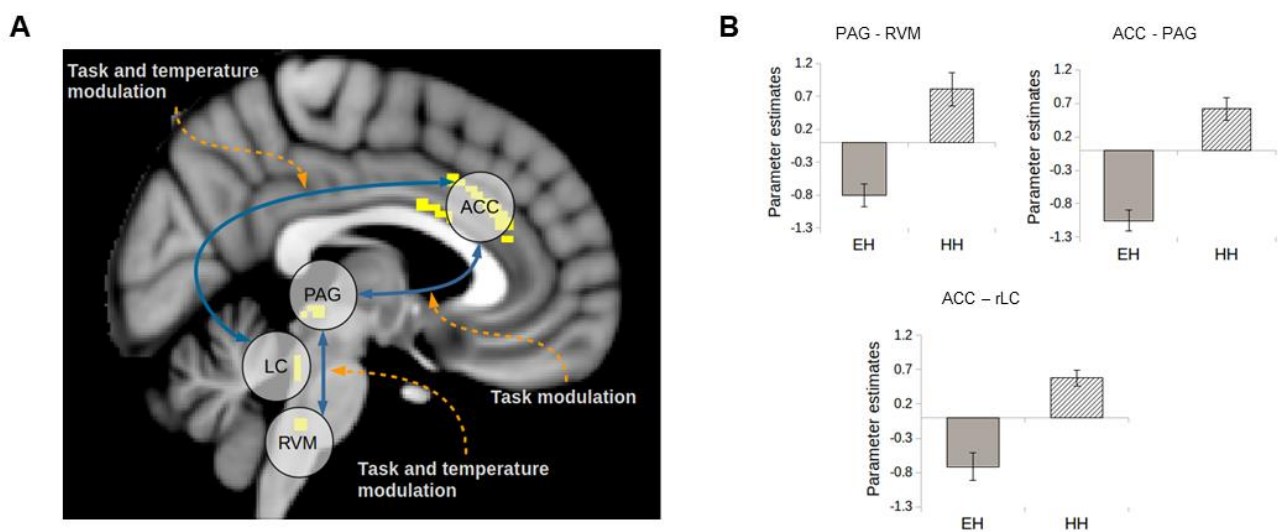
- 433 • RVM seed - increased connectivity to PAG for the interaction contrast
- 434 • ACC seed - increased connectivity with the right (contralateral) LC in the interaction contrast
435 and with the PAG in the main effect of task

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- 436 • PAG seed - did not show any significant change in effective connectivity
- 437 • rLC seed - did not show any significant change in effective connectivity.

438

439 For all gPPI results, parameter estimates were extracted from the voxel with greatest significance in
440 each individual to explore the nature of these interactions (Fig 5B). In all cases, the parameter
441 estimates were greater in the *hard/high* compared to the *easy/high* condition, indicating an increase
442 in coupling in the circumstances producing analgesia.



443

444 **Figure 5 (A)** Schematic representation of results of the PPI analysis. Results were obtained with single-nucleus functional
445 masks and permutation testing ($P < 0.05$, TFCE corrected). **(B)** Parameter estimates extracted from the peak destination
446 voxel from the PPI analysis (see text for details), in the *easy/high* and *hard/high* conditions.

447

448 DCM

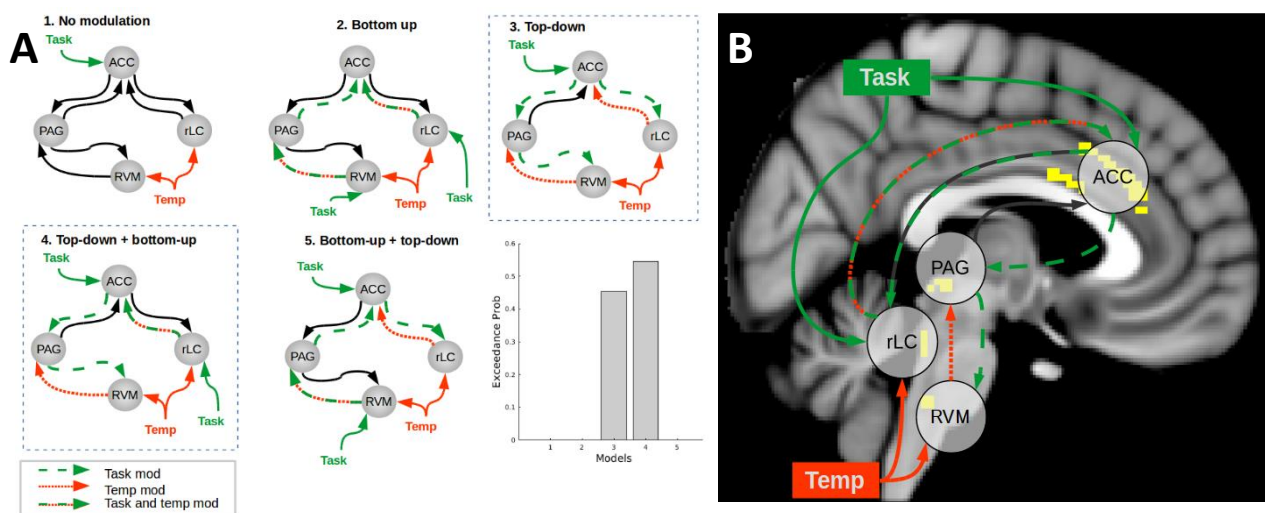
449 The connections resolved in the gPPI were further examined with DCM to resolve the directionality
450 of the task effect. We systematically varied the location of the task inputs and modulation, while the
451 temperature modulation was kept fixed in all models as a bottom-up effect. External inputs were both
452 hard/easy task and high/low temperature, while modulations were only hard task and high
453 temperature. Five models were specified (Fig 6A):

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- 454 1) No modulation of connections,
455 2) Task was bottom-up on the ACC-PAG-RVM and on the ACC-LC axis.
456 3) Task was top-down for both pathways.
457 4) Task was top-down in the ACC-PAG-RVM axis and bottom-up in the ACC-LC connection.
458 5) Task was bottom-up in ACC-PAG-RVM and top-down in ACC-LC.

459 Models 3 and 4 were found to best fit the data in BMS, with protected exceedance probability = 0.45
460 and 0.55 respectively (Fig 6B), and Bayesian omnibus risk of zero. In both, the task had a top-down
461 influence on ACC-PAG-RVM, while the ACC-LC connection was top-down modulated in one model
462 and bottom-up modulated in the other. Bayesian model averaging was used to extract parameter
463 estimates (Table 3).

464 All connections were also tested with an analgesic covariate, to find whether one or more consistently
465 differed in participants that showed an analgesic effect. No connection reached significance in this
466 test.



467
468 **Figure 6** (A) Specified models and result of Bayesian Model Selection. The effect of temperature is always bottom-up,
469 while the task could have a bottom-up or top-down effect. Model 3 and 4 have the strongest evidence of reproducing the
470 data, with slightly stronger evidence for model 4. (B) Schematic representation of interactions during attentional
471 analgesia, after PPI and DCM.

472 **Table 3.**

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Parameter	Parameter estimate mean (SD)	Task modulation mean (SD)
ACC-PAG connection	0.084 (0.0012)	0.029 (0.0052)
ACC-LC connection	0.058 (0.0011)	-0.019 (0.0054)
PAG-ACC connection	0.083 (0.0012)	-0.0058 (0.0026)
PAG-RVM connection	0.039 (0.0011)	-0.038 (0.0061)
LC-ACC connection	0.054 (0.0012)	-0.012 (0.0052)
RVM-PAG connection	0.034 (0.0012)	-0.0004 (0.0026)

473 **Table 3.** Summary of mean parameter estimates for connections and task modulation in DCM.

474

475

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476 **Discussion**

477 In the context of a reproducibility crisis that is afflicting neuroscience, especially in fMRI experiments
478 (Button et al., 2013; Eklund et al., 2016), we report results that have reproduced and extended the
479 generalisability of the key findings regarding the neural substrates of attentional analgesia that were
480 originally reported in Brooks et al., 2017. The same subset of brain regions was shown to be involved
481 in the performance of a visual attention task and in pain perception. Importantly, we replicated the
482 involvement in attentional analgesia of brainstem structures such as PAG, LC and RVM. This was
483 demonstrable without the need for region specific anatomical masks because we increased our
484 resolving power by analysing a larger cohort of subjects. By using gPPI and DCM analyses we
485 demonstrated changes in effective connectivity between these key brainstem regions and the ACC,
486 that are likely involved in the mediation of attentional analgesia.

487 The higher statistical power provided by 57 subjects, some 3-fold greater than in Brooks et al. (2017),
488 yielded stronger findings especially in the brainstem nuclei. For the main effect of temperature, we
489 were now able to see activation in the RVM at a whole brain analysis level. Additionally, using a full
490 brainstem mask (rather than region specific masks) we found activation not only in the RVM, as
491 previously (Brooks et al., 2017), but also in PAG and bilaterally in LC. While it has long been known
492 from animal studies that these brainstem regions receive nociceptive input from the spinal cord
493 (Blomqvist & Craig, 1991; Cedarbaum & Aghajanian, 1978; Keay et al., 1997) this has seldom been
494 clearly demonstrated in human imaging studies. The specificity of this pattern of nociceptive
495 information flow is striking with activations confined to discrete territories including ventral PAG,
496 LC and RVM as well as activations in the region of parabrachial nucleus, nucleus solitarius, sub
497 nucleus reticularis dorsalis and nucleus cuneiformis. The intra-subject linear regression analysis with
498 pain scores in regions such as the dorsal posterior insula and the anterior cingulate cortex, where the
499 BOLD signal linearly scales with perceived pain, was also consistent with previous results (Horing
500 et al., 2019). In the brainstem, the only region showing the same linear relationship is the RVM. This
501 clearly demonstrates that this brainstem territory is likely to be playing an important role in coding

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502 nociceptive intensity. To our knowledge, no other single study has been able to produce such a
503 complete activation map in the human brainstem in response to noxious stimulation (see review by
504 Henderson & Keay, 2018).

505 Considering the main effect of task, we were now able to identify activity in the PAG at the whole
506 brain level. By using a whole brainstem mask, we were able to detect activity in RVM and LC
507 bilaterally (as well as the dorsal PAG), while in our previous study using region specific masks we
508 could only find responses in the right LC and PAG (Brooks et al., 2017). It is interesting to note that
509 the attention task recruited the dorsal and ventral PAG whereas the noxious input produced activation
510 in the ventral region of the nucleus perhaps in line with the known behavioural specialisation of
511 columns within this crucial integrating nucleus (Linnman et al., 2012; Roy et al., 2014).

512 The magnitude of the analgesic effect showed a correlation with activity in the right LC (a finding
513 that we previously noted in Brooks et al. (2017) but was just below formal statistical significance).
514 This was the only location in the neuroaxis that showed this relationship. The LC is well positioned
515 both anatomically and functionally to mediate a component of attentional analgesia, not only because
516 it is responsive to attentional states and cognitive task performance (Aston-Jones & Cohen, 2005;
517 Sales et al., 2019; Sara, 2009; Yu & Dayan, 2005) and to nociceptive inputs (Cedarbaum &
518 Aghajanian, 1978; Howorth et al., 2009), but also particularly in being able to cause analgesia via its
519 direct spinal cord projections (Hirschberg et al., 2017; Jones et al., 1986). Intriguingly, the spinal
520 cord-projecting neurons are located in the caudal part of the LC in rodents (Hirschberg et al., 2017),
521 as is the LC region that we found to correlate with the analgesic effect. Previous analyses have
522 demonstrated linear relationships between the analgesic effect and activity located in the PAG in 9
523 subjects (Tracey et al., 2002) and RVM in 20 subjects (Brooks et al., 2017). We note that neither of
524 these findings were replicated our current study of 57 subjects. While all three findings are
525 biologically plausible, a large sample size seems necessary to produce robust results with inter-subject
526 regression (especially in small, noisy brainstem nuclei) and this is likely to be complicated by the
527 known interactions between these regions in nociceptive processing (discussed below).

Parallel cortical-brainstem pathways to attentional analgesia

528 To examine interplay between the cortical and brainstem structures we hypothesised to be involved
529 in attentional analgesia, we performed a generalised PPI, which determines how connectivity changes
530 as a result of experimental manipulation (i.e. effective connectivity). Our prior hypothesis for a role
531 of the ACC was supported by the observation that it showed overlapping areas of activation in both
532 conditions. We observed altered connectivity between the ACC and contralateral (right) LC during
533 the interaction between task and temperature. Parameter estimates extracted from voxels showing this
534 interaction revealed that coupling was enhanced during the hard task/high temperature condition.
535 Furthermore, coupling increased between ACC and PAG with task demand, and between PAG and
536 RVM, during the task x temperature interaction. Extraction of parameter estimates revealed that, as
537 for ACC-LC connection, this PAG-RVM interaction was enhanced in the hard task/high temperature
538 condition.

539 Effective connectivity changes in these pathways may therefore mediate the process of attentional
540 analgesia. This could be achieved through LC projections to the ACC increasing the signal-to-noise
541 (or salience) of one input over another (Manella et al., 2017; Muller et al., 2019; Sales et al., 2019;
542 Sara, 1985; Vazey et al., 2018) and/or ACC to spinally projecting LC neurons modulating the activity
543 of dorsal horn neurons (i.e. decreasing nociceptive transmission) both actions potentially giving
544 'precedence' to the task. One intriguing aspect of this interaction is the lateralised nature of
545 relationship between the right LC and the analgesic effect (i.e. contralateral to the stimulus) - a finding
546 that has previously been noted in rodent studies where noxious stimuli increase the activity in the
547 contralateral LC to a greater effect (Cedarbaum et al., 1978). Similarly, the reduction in perceived
548 pain could equally be via ACC recruiting the PAG and RVM to produce antinociception at a spinal
549 level during the demanding attentional task (Millan, 2002). This conceptually extends previous
550 studies that have identified the ACC-PAG connection as being involved in a distraction from pain
551 (attentional analgesia) paradigm (Valet et al., 2004), as well as in a placebo analgesia paradigm
552 (Petrovic, 2002). The PAG-RVM descending control system has also already been implicated in
553 placebo analgesia (Eippert et al., 2009; Grahl et al., 2018) via an opioid-dependent mechanism. The

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554 behavioural component of attentional analgesia has been reported to be impaired by opioid blockade,
555 possibly by disrupting connections between the ACC-PAG-RVM descending control system
556 (Sprenger et al., 2012).

557 We used dynamic causal modelling to resolve the directionality of the connection changes that were
558 shown in the gPPI, with the objective of better characterising the network mechanism generating
559 analgesia. We employed stochastic DCM, which allows for modelling of random neuronal noise in
560 the system, to improve network resolution in brainstem areas significantly affected by physiological
561 noise (Brooks et al., 2013). This routine was shown to improve the characterization of network
562 structure and parameter inference over deterministic DCM (Daunizeau et al., 2012; Osório et al.,
563 2015) and has been widely used in resting state and task-based fMRI studies since its release (Kahan
564 et al., 2014; Ma et al., 2015, 2014; Ray et al., 2016; Zhang et al., 2015). Bayesian Model selection
565 validated the results of the gPPI by excluding, for lack of evidence, a model where no connection was
566 modulated by task. We resolved a top-down influence of task on the ACC-PAG and PAG-RVM
567 connections, consistent with a descending pain modulatory system being involved in attentional
568 analgesia (Sprenger et al., 2012). The ACC-LC pathway was however not resolved as clearly, with
569 similar evidence in BMS for task modulation of the top-down and bottom-up connection. As
570 discussed above, both possibilities are supported by solid biological evidence and it is possible that
571 the two regions work in a feedback loop during attentional analgesia. On examination of the
572 parameter estimates, it was noted that the task modulation had a negative effect on all connections,
573 except for ACC-PAG. This is consistent with a reciprocal negative feedback loop between ACC and
574 LC (Breton-Provencher et al., 2019; Ramos et al., 2007), and with a disinhibition of the RVM “off-
575 cells” by the PAG (Lau et al., 2014). It is quite conceivable that the parallel ACC-LC and ACC-
576 PAG-RVM systems described here work in concert to cause analgesia. Previous animal studies show
577 that electrical stimulation of the PAG triggers noradrenaline release in the cerebrospinal fluid (Cui et
578 al., 1999; Hammond et al., 1985) and the analgesic effect of stimulation can be partially blocked with
579 intrathecal alpha2 antagonists.

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580 We propose that the ACC acts to resolve the conflict caused by an attention-grabbing painful stimulus
581 and the cognitive demands of a sustained visual attention task, by sending downstream signals to
582 brainstem structures to facilitate optimal behaviour. Intriguingly, inputting the coordinates of the peak
583 attentional activation of the ACC to Neurosynth (Yarkoni et al., 2011) identified three studies where
584 the same region was involved in response to conflict (Barch et al., 2001; Scholl et al., 2017; van Veen
585 et al., 2005; Wittfoth et al., 2008). In addition, voluntary control over the activation of this area was
586 shown to result in modulation of pain perception in a neurofeedback study (deCharms et al., 2005).
587 This network is also relevant for mindfulness-based techniques, where focus on an internal signal
588 (e.g. breathing), effectively distracts subjects from the painful stimulus. Interestingly, mindfulness
589 mediated pain relief is not mediated by endogenous opioids (Zeidan et al., 2016) but relies on the
590 rACC (Zeidan et al., 2012; Zeidan & Vago, 2016), perhaps through the ACC-LC pathway.

591 In this study we have been able to resolve parallel cortical – brainstem pathways that form a network
592 that is functionally engaged when pain perception is attenuated during attentional analgesia. We note
593 that the spinal cord BOLD response to nociception has previously been shown to be modulated by
594 attention (Sprenger et al., 2012). Whether this spinal modulation of nociception is the product of
595 activation of the ACC-PAG-RVM and/or the ACC-LC system still needs to be demonstrated in
596 humans. It is known that both pathways could involve opioids (Fields, 2004) and so previous studies
597 using naloxone do not discriminate between these possibilities. A connectivity analysis examining
598 the network activity between cortical territories, brainstem nuclei and dorsal horn *in toto* may help to
599 define the key pathway in attentional analgesia. We further postulate that this network may be of
600 importance in chronic conditions where disruption of attention and cognition (i.e. fibromyalgia) are
601 co-morbid alongside pain.

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