1   **A 5-day course of rTMS before pain onset ameliorates future pain and increases**

2   **sensorimotor peak alpha frequency**

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31   Abstract

32   Repetitive transcranial magnetic stimulation (rTMS) has shown promise as an intervention

33   for pain. An unexplored research question is whether the delivery of rTMS *prior to pain*

34   *onset* might protect against a future episode of prolonged pain. The present study aimed to

35   determine i) whether 5 consecutive days of rTMS delivered prior to experimentally-induced

36   prolonged jaw pain could reduce future pain intensity and ii) whether any effects of rTMS on

37   pain were mediated by changes in corticomotor excitability (CME) and/or sensorimotor peak

38   alpha frequency (PAF). On each day from Day 0-4, forty healthy individuals received a

39   single session of active (n = 21) or sham (n = 19) rTMS over the left primary motor cortex.

40   PAF and CME were assessed on Day 0 (before rTMS) and Day 4 (after rTMS). Prolonged

41   pain was induced via intramuscular injection of nerve growth factor (NGF) in the right

42   masseter muscle after the final rTMS session. From Days 5-25, participants completed twice-

43   daily electronic dairies including pain on chewing and yawning (primary outcomes), as well

44   as pain during other activities (e.g. talking), functional limitation in jaw function and muscle

45   soreness (secondary outcomes). Compared to sham, individuals who received active rTMS

46   subsequently experienced lower pain on chewing and yawning. Although active rTMS

47   increased PAF, the effects of rTMS on pain were not mediated by changes in PAF or CME.

48   This study is the first to show that rTMS delivered *prior* to pain onset can protect against

49   future pain and associated functional impairment. Thus, rTMS may hold promise as a

50   prophylactic intervention for persistent pain.

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62   Chronic pain is a global health concern, impacting patient quality of life and

63   healthcare systems [46;53;118]. Unfortunately, current interventions (e.g. surgery,

64   pharmacological, psychological, exercise) demonstrate at best, modest improvements in pain

65   and function [11;98;115;116]. A critical limitation of most treatments is that they are applied

66   once pain has already become chronic and maladaptive nervous system plasticity is

67   entrenched [30;52]. Treatments that target features of cortical activity associated with chronic

68   pain susceptibility *before pain begins* have potential to interrupt the transition to chronic pain

69   and improve clinical outcomes.

70   High frequency (>5Hz) repetitive transcranial magnetic stimulation (rTMS) is a

71   promising intervention for pain [43;111]. Single and multi-session 10Hz rTMS delivered to

72   the primary motor cortex (M1) after the onset of experimental pain and in patients with

73   chronic pain has been shown to reduce pain severity compared to sham [7;14;58;59;100].

74   Despite this, little research has investigated the prophylactic effect of rTMS applied prior to

75   pain onset on future pain severity. Several studies demonstrated that a single session of high

76   frequency rTMS [9;61;69;70;117] delivered within an hour before transient pain led to

77   reduced pain sensitivity and severity in pain-free individuals. However, no study has explored

78   these effects using a prolonged pain model, such as pain induced by intramuscular injections

79   of nerve growth factor (NGF) [45;89]. This is a critical question, as interventions that can

80   ameliorate future prolonged pain might also be effective in hindering the transition from

81   acute to chronic pain. NGF injections induce prolonged musculoskeletal pain [17] that

82   mimics the duration, time course, functional limitation and hyperalgesia associated with

83   chronic pain conditions [8;89]. This makes the NGF model a highly standardised and

84   clinically relevant model for exploring the prophylactic effects of rTMS on a future

85   prolonged pain episode.

86   The prophylactic effects of rTMS on pain might be mediated by two features of

87   cortical activity shown to predict an individual's pain sensitivity - peak alpha frequency

88   (PAF), which refers to the dominant oscillatory frequency in the 8-12Hz range [16] and

89   corticomotor excitability (CME), which is indexed via the magnitude of motor responses to

90   single-pulse TMS to M1 [112]. Several studies have shown that slower sensorimotor PAF

91   and lower CME predicts higher future pain severity [32-34;49;50]. This would suggest that

92   interventions that can increase PAF and CME might protect against future pain. 10Hz rTMS

93   to M1 is thought to directly increase the excitability of motor cortical neurons through long-

94   term potentiation mechanisms [3;24], or via entrainment of intrinsic alpha oscillators as a

95   result of synchronization with external stimulation [74;106]. Consistent with these

96   explanations, studies have reported increases in CME and PAF following single and multi-

97   session high frequency rTMS [2;29;64;67;73]. Thus, it is plausible that the prophylactic

98   effects of rTMS on pain is mediated by increases in PAF and CME.

99   The present study aimed to determine whether 5 consecutive days of rTMS delivered

100   *prior* to the onset of NGF-induced temporomandibular pain could subsequently reduce pain

101   severity compared to sham rTMS. A secondary aim was to determine whether the

102   prophylactic effects of rTMS were mediated by changes in PAF and CME. It was

103   hypothesised that active rTMS would lead to lower pain severity compared to sham, and that

104   reductions in pain would be mediated by increases in PAF and CME.

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110 **Methods**

111 **Design**

112   This study used a longitudinal, randomised, sham-controlled, parallel design to follow

113   healthy individuals over the course 26 days. Figure 1 shows the experimental protocol.

114   Participants attended five lab sessions (Day 0-4). On the Day 0 visit, PAF and CME were

115   assessed, followed by delivery of either active or sham rTMS. On Days 1, 2 and 3, participants

116   received the rTMS intervention only. On Day 4, participants received the final session of rTMS,

117   followed immediately by a repeat assessment of PAF and CME. Intramuscular injection of

118   NGF was given into the right masseter muscle at the end of the Day 4 session to induce

119   prolonged pain and dysfunction mimicking temporomandibular disorder (TMD) [89]. From

120   Days 5-25, participants completed twice daily electronic dairies comprising measures of pain

121   and function. Written, informed consent was obtained prior to study commencement. The

122   study was approved by the UNSW ethics committee (HREC reference number: HC220602).

123   Data collection was conducted at Neuroscience Research Australia (NeuRA).

124 **Participants**

125   Participants were recruited through notices posted online, at universities across

126   Sydney, Australia or by contacting participants held on a database at NeuRA. Forty-one

127   healthy individuals (23 female and 18 male; age 23 ± 4 [mean $\pm$SD]; range 18-35) were

128   recruited. Participants were included if they were aged between 18-44. This was justified

129   based on data from the OPPERA prospective cohort study that demonstrated an incidence

130   rate of first onset TMD of 2.5% per annum among 18 to 24-year olds and 4.5% per annum

131   among 35 to 44-year olds [99]. Participants were excluded if they presented with any acute

132   pain, had a previous history of chronic pain, major medical complaints, psychiatric or

133   salivary gland conditions, were pregnant and/or lactating, or were contraindicated for TMS

134   (e.g., metal implants in the skull, epilepsy) as assessed using the Transcranial Magnetic

135   Stimulation Adult Safety Screen Questionnaire [85]. A sample size calculation was

136   conducted (G*Power 3.1.9.7) based on effect sizes, which varied between 1.08 and 2.17,

137   from previous studies examining the influence of active vs. sham rTMS on NGF-induced

138   pain[13;26], producing a sample size between 5-15 per group to achieve 80% power at .05

139   significance. Given that no previous study has applied rTMS before prolonged pain onset, we

140   conservatively selected a sample size of 20 individuals in each group.

Randomization/Blinding Procedure

142   Prior to the study, participants were randomly assigned to either the active or sham

143   condition using a random number list generator (https://www.random.org/lists/). The

144   allocations were revealed to the experimenter (KT, AC or WC) delivering rTMS on Day 0 via

145   an automated email notification. The allocations were not known by the experimenter (NC)

146   that collected PAF and CME data, administered the injection of NGF, performed data pre-

147   processing and prepared the analysis plan. Group allocations were revealed to experimenter

148   NC when the data collection, pre-processing and analysis plan was complete. Participants were

149   not informed of the existence of two conditions at any time throughout the study (Day 0-25).

150   Participants were debriefed (experimenter KT) after completing the study (contacted by phone

151   or email) to explain that they were randomly assigned to either an active or sham intervention

152   and were asked which condition they believed they received. Subsequently, participants' group

153   allocation was notified by a follow-up email.

Data Collection Procedures

155   **Baseline Questionnaires.** On Day 0, prior to rTMS, participants completed a series of

156   questionnaires including the (1) Pain Catastrophizing Scale [101], (2) Perceived Stress Scale

157   [104], (3) Sleep Scale, (4) Patient health questionnaire [57], (5) Pennebaker Inventory of

158   Limbic Languidness Questionnaire [78], (6) Short-Form-8 Health Questionnaire [109] and (7)

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159   The Brief Pain Inventory Pain Severity and 7-item Interference subscales [55;103]. These

160   questionnaires would help characterize the physical and mental health profile of the active and

161   sham groups.

162   **Peak Alpha Frequency**: Resting state EEG was collected in line with previous

163   methods [33]. Participants were seated in a comfortable chair. Scalp EEG was recorded using

164   the Brain Products platform (BrainVision Recorder, Vers. 1.22.0101 with actiCHamp Plus,

165   Brain Products GmbH, Gilching, Germany). Recording was done at a sampling rate of 5000

166   Hz. Signals were recorded from 63 active electrodes (actiCAP slim, Brain Products GmbH,

167   Germany), embedded in an elastic cap (EASYCAP, EASYCAP GmbH) in line with the 10–10

168   system. Recordings were referenced online to 'FCz' and the ground electrode placed on 'Fpz'.

169   Electrode impedances were maintained below 25 kOhms. Based on previous research [28;54]

170   and the actiCHamp manual, we anticipated negligible signal loss with this impedance cut-off.

171   Once setup was complete, the lights were switched off with ambient noise reduced to a

172   minimum. Participants were instructed to relax and keep their eyes closed while remaining

173   awake. The resting-state EEG signal was then recorded for 5 minutes.

174   **Corticomotor Excitability**. TMS was used to map the corticomotor representation of

175   the right masseter muscle, in line with previously described techniques [20;88;90]. Participants

176   wore a swim cap with a grid of 1cm x 1cm resolution. Single-pulse, monophasic stimuli were

177   delivered to the left hemisphere using a Magstim stimulator and a figure-of-eight coil. Bipolar

178   surface electrodes were used to record electromyographic (EMG) activity from the masseter

179   muscle, with active (muscle belly) and reference (tendon) electrodes placed along the

180   mandibular angle, and the ground electrode was placed on the right acromion process. EMG

181   signals were amplified (x2000), with a high pass (16Hz) and low pass (1000 Hz) filter applied,

182   and digitally sampled at 5kHz.

183   It is common to assess CME from the masseter muscle during active contraction that is

184   at a certain percentage of the maximum voluntary contraction (MVC) [23;83], as it is

185   challenging to obtain reliable MEPs from the masseter muscle at rest [10;113]. Participants

186   were instructed to contract at 20% MVC which provided a balance between obtaining

187   sufficiently large MEPs for analyses [65] and minimizing fatigue. To measure MVC,

188   participants were verbally encouraged to clench their jaw as hard as possible for 3 seconds on

189   3 separate trials, with a 1-minute rest break in between trials. The MVC was computed based

190   on the average of the 3 trials, and 20% MVC was computed based on this average. Participants

191   practiced maintaining a masseter contraction of 20% MVC by receiving live visual feedback

192   from the EMG signal prior to TMS recording.

193   Consistent with previous studies investigating optimal coil orientation for inducing

194   masseter MEPs, an angle of 90 degrees between the anterior-posterior line and the coil handle

195   was used [39]. This orientation induced current in the lateral-to-medial direction. The scalp site

196   evoking the largest MEP (i.e., the "hotspot") during active contraction was then determined.

197   The active motor threshold (AMT) was determined using the ML-PEST (maximum likelihood

198   strategy using parametric estimation by sequential testing) algorithm [6] which estimates the

199   minimum TMS intensity required to induce a reliable MEP with a 50% probability . A reliable

200   MEP was identified if the EMG waveform between ~5-15ms [63;77] after the TMS pulse was

201   visually larger in amplitude relative to background contraction. The TMS intensity for mapping

202   was set at 120% AMT.

203   The procedure for mapping has been described in detail previously [87;90]. While

204   participants maintained contraction of the masseter muscle, three stimuli were delivered at each

205   location around the grid, starting at the hotspot. The number of stimulation sites was

206   pseudorandomly increased until an MEP was no longer observed (i.e., no reliable MEP in all

207   3 trials at all border sites). In line with the approach used in previous studies [25;95;102], the

208   hotspot location and test stimulus intensity determined on Day 0 was used for subsequent

209   mapping procedures on Day 4. This approach ensures that any changes in motor cortical maps

210   occurring as a result of rTMS can be observed. To confirm that the AMT did not change, we

211   re-assessed AMT on Day 4.

212   **rTMS**. We employed a rTMS protocol used in previous studies investigating the

213   analgesic effects of rTMS [13;93]. High-frequency 10Hz, biphasic active rTMS was applied

214   over the left primary motor cortex using a Magstim Super Rapid2 stimulator and a figure-of-

215   eight coil. The location and intensity of rTMS was calibrated based on resting motor threshold

216   (RMT) of the first dorsal interosseous (FDI) muscle rather than the targeted masseter muscle.

217   This is due to the difficulty involved in obtaining reliable masseter responses to TMS at rest

218   [10;113] and given previous studies have demonstrated non-somatotopic effects of rTMS on

219   pain [4;51;56]. Surface bipolar EMG electrodes were placed over the FDI to record MEPs. The

220   coil was orientated at 45° to the midline. The motor hotspot for the FDI was determined, which

221   corresponded to the scalp site which generated the largest MEP at the targeted FDI. The RMT

222   was determined using ML-PEST [6], which estimated the minimum TMS intensity required to

223   induce a MEP of 50 microvolts with a 50% probability. This was reassessed at each session to

224   account for potential changes in CME in response to rTMS [76;94]. During rTMS, the coil was

225   held at 90° to the midline [60]. 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-second

226   intertrain interval) were delivered at 90% of RMT. For sham rTMS, a sham coil that looked

227   identical to the active rTMS coil but produced only audible clicks was used to deliver the

228   stimulation protocol identical to the one used for active rTMS.

229   **NGF Injection.** The NGF injections were provided at the end of the Day 4 session. To

230   prepare the masseter muscle for injection, the surface was cleaned using alcohol wipes. A

231   sterile solution of recombinant human NGF (dose of 5 μg [0.2 ml]) was then administered as a

232   bolus injection into the muscle belly of the right masseter using a 1-ml syringe with a disposable

233   needle (27-G). The needle was inserted perpendicular to the masseter body until bony contact

234   was reached, retracted ∼2 mm, and NGF injected. Any adverse events (e.g. excessive bleeding,

235   swelling) were monitored.

236   **Electronic Pain dairies.** Questionnaires assessing jaw pain, muscle soreness, and

237   functional limitation were completed on Day 0 and Day 4 (before and after rTMS) prior to the

238   NGF injection, twice daily from Day 5 to 25 (after NGF injection) via automated links to an

239   electronic dairy sent to participants at 10am and 7pm each day.

240   *Primary outcomes:* Pain upon functional jaw movement is a key criterion for the

241   diagnosis of TMD [91]. Moreover, previous research has shown that, after an NGF injection

242   to the masseter muscle, pain during chewing and yawning activities are higher compared to

243   other activities [23;89]. As such, our primary outcomes were pain upon chewing and yawning.

244   Pain intensity was rated on an 11-point numerical rating scale (NRS). The scale ranged from 0

245   = 'no pain' to 10 = 'worst pain imaginable'.

246   *Secondary outcomes:* At each timepoint, participants also rated pain at rest,

247   swallowing, drinking, talking, and smiling. They also completed a functional limitation scale

248   consisting of 20 activities to assess jaw functional impairment experienced in the previous 24

249   hours [72]. For each item, the participant rated the ease at which they could perform the

250   particular activity on an 11-point NRS, 0 = 'no limitation' and 10 = 'severe limitation'. If an

251   activity was not applicable, a rating was not provided or given as 'NA'. The mean score was

252   calculated for each participant across 3 subscales. Items 1-6 represented mastication, items 7-

253   10 jaw mobility, and items 11-20 verbal and emotional communication. Lastly participants

254   completed a muscle soreness scale on a modified 7-point Likert scale [45]: 0 = a complete

255   absence of soreness, 1 = a light soreness in the muscle felt only when touched/vague ache, 2 =

256   a moderate soreness felt only when touched/a slight persistent ache, 3 = a light muscle soreness

257   when opening the mouth fully or chewing hard food, 4 = a light muscle soreness, stiffness or

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258   weakness when opening the mouth or chewing soft food, 5 = a moderate muscle soreness,

259   stiffness or weakness when opening the mouth or chewing soft food, and 6 = a severe muscle

260   soreness, stiffness or weakness that limits the ability to open the mouth or chew.

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262   **Data Pre-processing**

263   **Sensorimotor Peak Alpha Frequency**. EEG data processing was conducted using

264   custom MATLAB (R2020b, The Mathworks, USA) scripts implementing the EEGLAB

265   (eeglab2019_1) [27] and Fieldtrip (v20200215) toolboxes [75]. The pre-processing pipeline

266   matched those used in previous studies investigating the relationship between PAF and pain

267   [20;32]: data downsampled to 500 Hz, re-referenced to common average, and band-pass

268   filtered between 2 and 100 Hz using an FIR filter. Channel data was visually inspected, and

269   overtly noisy channels were removed, and the signal re-referenced. Data were segmented into

270   5s epochs, and epochs containing marked muscular artefacts were manually rejected.

271   Independent component analysis (runica in fieldtrip) was applied to the data. We visually

272   inspected the frequency-spectra of the components, and identified components that had a clear

273   alpha peak (8–12 Hz) and a scalp topography suggestive of a source predominately over the

274   sensorimotor cortices [32]. The power spectral density of the chosen sensorimotor component

275   was derived in 0.2 Hz bins. The 2–50 Hz range was extracted using Fast Fourier Transform. A

276   Hanning taper was applied to the data to reduce edge artefacts. Sensorimotor alpha power was

277   calculated as the sum of all z-transformed spectral amplitudes in the 8-12Hz window.

278   Sensorimotor PAF was calculated using the Centre of Gravity method, using the following

279   equations:

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$$CoG = \frac{\sum_{i=1}^{n} f_i * a_i}{\sum_{i=1}^{n} a_i}$$

281   Where f_i is the ith frequency bin within 8-12Hz window, and a_i represents the spectral

282   amplitude at f_i.

283   **Corticomotor Excitability.** TMS data was processed using a custom MATLAB script.

284   The MEP onsets and offsets were fixed to 7.3 and 15.3 ms after the TMS pulse based on our

285   previous study [20] which showed that using a fixed MEP window produce similar map

286   outcomes to manually choosing the offsets and onsets. The root mean square (RMS) of

287   background EMG was determined using a fixed window between 55 and 5ms before the TMS

288   pulse [86]. Background RMS was subtracted from the RMS of the MEP window to determine

289   MEP amplitude. The mean MEP amplitude at each stimulation site was determined and

290   normalized (as percentage of the maximum site) [71]. CME was indexed as map volume, which

291   was calculated by adding the MEP amplitudes of all active sites. A stimulation was deemed

292   active if the MEP amplitude was >10% of the maximum MEP amplitude [107].

293   **Electronic Pain Diaries**. We consolidated the morning and afternoon recordings into

294   a single table to maintain a chronological order of pain intensity records, spanning from Day 5

295   through Day 25.

296   **Statistical Analyses**

297   Means and Standard Deviations (SD) in pain outcomes, sensorimotor PAF and CME

298   were calculated for each group. Assumptions were assessed using Shapiro-Wilk Test (for

299   normality of pain, Sensorimotor PAF and CME data) and Mauchley's test (for equality of

300   variance between timepoints). Any normality assumption violations were addressed by

301   square-root transforming the data or using non-parametric tests where applicable. Statistical

302   significance was set to .05.

303   **Effect of rTMS on pain outcomes.** To determine the effect of active rTMS relative

304   to sham rTMS, a mixed-model ANOVA was conducted with factors time (Day 5-25) and

305   group (active vs. sham) and primary or secondary pain outcomes as the dependent measure.

306   The group main effect assessed whether, averaged across all days (Day 5-25), active and

307   sham groups differed on the dependent measures. The interaction effect assessed whether

308   group level effects differed across time.

309   **Effect of rTMS on Sensorimotor PAF and CME.** A mixed-model ANOVA with

310   factors: group (active vs. sham) and time (Day 0 vs. Day 4), was used to determine whether

311   active rTMS modulated CME and sensorimotor PAF compared with sham rTMS (i.e.,

312   whether there was a group x time interaction). A mixed-model ANOVA with factors: group

313   (active vs. sham) and time (Day 0 vs. Day 4), was also conducted to determine whether active

314   rTMS modulated alpha power (quantified as the sum of the power from all frequency bins

315   between 8-12Hz) compared to sham rTMS.

316   **Mediation Analysis**. Mediation analysis was conducted in R (version 4.2.1) using the

317   lavaan package [84]. For the primary pain outcomes, we determined whether the effects of

318   rTMS on pain (mean pain of first week [Days 5-11]) were mediated by changes in PAF or

319   CME (Day 4 – Day 0) using two separate mediation models. Figure 2 shows the mediation

320   models used, which assessed the direct effect of rTMS on PAF or CME (*a* path), the effect of

321   change in PAF/CME on pain (*b* path), the direct effect of rTMS on pain outcome (*c'* path),

322   and the indirect effect of rTMS on pain (*a + b* path). A significant indirect effect suggests the

323   effect of rTMS on pain was mediated by changes in PAF or CME.

324   **Relationship between PAF/CME prior to injection and subsequent pain**

325   **intensity.** To test the theoretical rationale that slower PAF/lower CME predicts higher future

326   pain intensity, we conducted a correlation analysis to determine whether slower sensorimotor

327   PAF and lower CME at Day 0 and Day 4 (regardless of group allocation) was associated with

328   and average pain upon yawning and chewing of the first week (Day 5 to Day 11).

Results

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330   All participants completed the 5 sessions as planned, with the exception of one

331   participant who withdrew on Day 2 due to an unwillingness to receive the subsequent NGF

332   injection, leaving 40 participants in the final sample (21 active, 19 sham). Demographics and

333   questionnaire data are summarised in Table 1. No adverse events were reported. Following

334   CONSORT recommendations [68], baseline statistics comparing participant characteristics

335   were not reported. Two participants could not be contacted at the conclusion of the study for

336   their group allocation. For the remaining 38 participants, the proportion of participants who

337   guessed the correct condition was not significant for both the active group (62%, χ^2 = 1.19, p

338   = .27) and sham group (53%, χ^2 = .05, p = .82), indicating that participant blinding was

339   successful.

rTMS did not alter RMT

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341   For the active and sham groups respectively, the mean resting motor threshold was

342   51.4 ± 10.9 and 59.9 ± 9.9 on Day 0, and 53 ± 11.1 and 56.4 ± 13.4 on Day 4. A two-way

343   ANOVA (time main effect: Day 0-4, group: active vs. sham) showed resting motor threshold

344   did not differ across Days 0-4, $F(4, 152)$ = .61 p = .66, or between groups (group main effect:

345     $F(1,38)$ = 2.59, p = 0.12, group x time interaction: $F(4,152)$ =1.67, p = .16).

Characteristics of the NGF model

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347   Diary completion rates were ~90% on average (95% for the first week after injection).

348   We used linear interpolation to impute missing pain data, as has been done previously in

349   situations where collection of pain outcomes yields missing data [31;108;110]. Figure 3

350   shows scores for the active and sham rTMS groups on the primary pain outcomes. For both

351   groups, pain upon chewing and yawning peaked the day after the injection, with 2.2 ± 1.4 and

352   2.6 ± 1.7 points out of 10 respectively in the active group, and 3.1 ± 2.4 and 4.2 ± 2.4 points

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353   out of 10 in the sham group for the 10AM timepoint. Figure 4 shows the scores for other pain

354   outcomes, functional limitation and muscle soreness across time. For both groups, functional

355   limitation during mastication, jaw mobility and verbal communication peaked the day after

356   the injection, with 2.5 ± 2.5, 2.1 ± 2.5 and 1.0 ± 1.5 points out of 10 respectively in the active

357   group and 2.5 ± 2.2, 2.3 ± 1.7 and 1.2 ± 1.5 points out of 10 in the sham group for the 10AM

358   timepoint. For both groups, muscle soreness peaked three days after the injection (Day 7),

359   with 2.6 ± 1.6 points out of 7 in the active group and 2.6 ± 1.6 points out of 7 in the sham

360   group, for the 10AM timepoint.

361   **rTMS applied before pain onset reduces future pain severity**

362   **Primary outcomes**: Compared to sham, those who received active rTMS experienced

363   lower pain upon chewing and yawning, with evidence that these effects were larger at earlier

364   timepoints (pain on chewing: time main effect, $F(41, 1558) = 81.12$, $p < .001$, group main

365   effect, $F(1, 38) = 5.24$, $p = .028$, group x time interaction, $F(41,1558) = 3.46$, $p < .001$, group

366   x time interaction linear trend: $F(1, 38) = 6.17$, $p = .017$; pain on yawning: time main effect,

367    $F(41,1558) = 74.47$, $p < .001$, group main effect, $F(41,1558) = 4.17$, $p < .001$, group x time

368   interaction, $F(41,1558) = 4.17$, $p < .001$, group x time interaction linear trend: $F(1, 38) =$

369   8.33, $p = .006$).

370   **Secondary Outcomes**: While active rTMS did not lead to lower pain upon talking or

371   lesser functional limitation of jaw mobility when averaged across the 3 week period, stronger

372   reductions in pain, and less functional limitation were present compared to sham at earlier

373   timepoints (pain upon talking: time main effect, $F(41,1558) = 21.83$, $p < .001$, group main

374   effect: $F(1,38) = 2.20$, $p = .15$, group x time interaction: $F(41, 1558) = 1.73$, $p = .003$;

375   functional jaw mobility: time main effect, $F(41,1558) = 55.96$, $p = .001$, group main effect,

376    $F(1,38) = 1.14$, $p = .29$, group x time interaction, $F(41, 1558) = 2.43$, $p < .001$). The rTMS

377   intervention did not alter the severity or time course of pain associated with swallowing,

378   smiling, drinking, or pain at rest, functional outcomes of mastication and communication, or

379   muscle soreness (p's > .05 for all group and group x time interaction effects, p's < .05 for all

380   time main effects).

381   **Five days of rTMS increases PAF, but does not alter CME**

382   Figure 5 shows the mean spectral and topographical data, and violin plots of

383   individual data of the identified sensorimotor alpha component for each rTMS group at Day 0

384   and Day 4. Figure 6 shows the mean masseter motor maps for each rTMS group at Day 0 and

385   Day 4. 5 days of active rTMS modulated PAF when compared to sham rTMS (time main

386   effect: $F(1, 38) = .46$, $p = .50$, group main effect: $F(1, 38) = .74$, $p = .40$, group x time

387   interaction: $F(1, 38) = 6.41$, $p = .016$), with an increase in PAF on Day 4 vs. Day 0 following

388   active rTMS ($t_{20} = 2.34$, $p = .029$). While observation of Figure 5 might suggest the increase

389   in PAF was accounted for by an increase in power in 10-12Hz alpha band, there were no

390   significant effects of active rTMS on alpha power when compared to sham (time main effect:

391    $F(1, 38) = .03$, $p = .88$, group main effect: $F(1, 38) = 1.05$, $p = .31$, group x time interaction:

392    $F(1, 38) = 1.52$, $p = .23$). rTMS did not alter CME (time main effect: $F(1, 38) = .06$, $p = .82$,

393   group main effect: $F(1, 38) = 1.90$, $p = .18$, group x time interaction: $F(1, 38) = 2.62$, $p =$

394   .11).

395   **The effects of rTMS on pain were not mediated by changes in PAF or CME**

396   While the mediation models showed significant effects of rTMS on pain upon

397   chewing and yawning and an effect of rTMS on PAF, there was no evidence that changes in

398   PAF mediated the effect of rTMS on pain upon chewing (total effect: $b = -.40$, $p = .006$,

399   direct effect of rTMS on pain: $b = -.36$, $p = .023$, effect of rTMS on PAF: $b = .21$, $p = .009$,

400   indirect effect: $b = -.05$, $p = .45$) or yawning (total effect: $b = -.56$, $p = .001$, direct effect of

401   rTMS on pain: $b = -54$, $p = .004$, effect of rTMS on PAF: $b = -.40$, $p = .006$, indirect effect: b

402   = -.01, p = .86). There was also no evidence that changes in CME mediated the effect of

403   rTMS on pain upon chewing (total effect: b = -.41, p = .006, direct effect of rTMS on pain: b

404   = -.39, p = .01, effect of rTMS on CME: b = .27, p = .097, indirect effect: b = - .02, p = .67)

405   or yawning (total effect: b = -.56, p = .001, direct effect of rTMS on pain: b = -0.52, p = 003,

406   effect of rTMS on CME: b = .27, p = .097, indirect effect: b = -.03, p = .54).

PAF and CME predict future pain severity

408   Slower PAF on Day 4 was associated with higher pain upon chewing (spearman's ρ =

409   -0.40, p = .01) and yawning (ρ = -0.32, p = .05) averaged across the first week (Days 5-11),

410   as shown in Figure 7. Moreover, lower CME on Day 4 was associated with higher pain on

411   yawning (ρ = -0.40, p = .01) but not chewing (ρ = -0.21, p = .18). There was no relationship

412   between Day 0 CME and chewing (ρ = -0.04, p = .8) and yawning (ρ = -.12, p = .45). There

413   was also no relationship between Day 0 PAF and pain during chewing (ρ = -0.24, p =0.14)

414   and yawning (ρ = -0.27, p =.10).

Discussion

416   The present study investigated whether 5 consecutive days of rTMS over left M1

417   prior to the onset of prolonged temporomandibular pain could reduce future pain severity. A

418   secondary aim was to determine whether any reduction in pain severity was mediated by

419   changes in CME or PAF. Relative to sham, active rTMS applied prior to pain onset led to

420   subsequently lower pain upon chewing and yawning. The neurophysiological results showed

421   that active rTMS increased PAF speed, but did not alter CME. There was no evidence that

422   reductions in pain upon chewing and yawning induced by active rTMS were mediated by

423   changes in PAF or CME. However, regardless of group, faster PAF and higher CME on Day

424   4 was associated with lower intensity of future pain.

425

rTMS delivered prior to a prolonged pain episode protects against future pain severity

426

427   Our study showed that 5 days of pre-pain rTMS led to a reduction in future pain upon

428 chewing and yawning within a model of prolonged temporomandibular pain lasting days to

429 weeks. Pain upon functional jaw movement is a key criterion for the diagnosis of clinical

430 TMD [91]. Moreover, previous research has shown that, after an NGF injection to the

431 masseter muscle, pain during chewing and yawning activities is greater compared to other

432 activities, [23;89] which was replicated in the present study. As such, we considered pain

433 upon chewing and yawning as primary outcomes. As anticipated, rTMS showed stronger

434 effects on these measures relative to other outcomes. Further consistent with the idea of jaw

435 movement being the most relevant to the NGF-TMD model, we found stronger reductions in

436 functional limitation of jaw mobility in the active vs. sham group at earlier timepoints. This

437 suggests rTMS delivered prior to the onset of pain can influence both pain itself and pain-

438 related functional impairment.

439   Taken together, our findings support existing evidence for the analgesic effects of

440 high-frequency rTMS delivered to M1 in clinical populations [1;36;37], and in healthy

441 participants during prolonged pain induced by NGF [13;25;93]. Further, this study is the first

442 to demonstrate a reduction in pain severity when the rTMS intervention is delivered prior to

443 the onset of prolonged pain. Previous studies have shown that single sessions of rTMS

444 delivered prior to pain can subsequently reduce pain sensitivity to transient noxious stimuli

445 relative to sham rTMS or a baseline timepoint prior to rTMS [9;61;69;70;117]. However, the

446 brief nature of these painful stimuli hinder the external validity to clinical pain, which

447 typically lasts for weeks or months [8] . In contrast, the NGF paradigm is one of few

448 experimental pain paradigms that can produce a prolonged pain experience in humans lasting

449 several weeks [8]. Several studies have shown that injecting NGF to the neck, forearm or

450 masseter muscles can mimic symptoms of clinical neck pain [21], lateral epicondylalgia

18

451   (tennis elbow) [8] and TMD [89] respectively, including the time course (gradual onset and

452   prolonged duration), movement-evoked pain, impaired joint movements, limited function and

453   hyperalgesia (lower pressure pain thresholds).

454   Given the clinical relevance of the NGF model, our findings have implications for the

455   use of rTMS as a prophylactic pain intervention. A critical limitation of most pain treatments

456   is that they are applied in the chronic stages when maladaptive nervous system plasticity has

457   already occurred and may be difficult to reverse [30;52]. As such, there is growing interest in

458   preventative approaches for the transition from acute to chronic pain. Here, we provide pre-

459   clinical evidence that rTMS delivered prior to a prolonged pain episode may protect against

460   future pain. One application of these findings could be surgical procedures that present a risk

461   of severe post-operative pain and future development of chronic pain [48]. For example, post-

462   operative jaw pain can occur following procedures such as dental implant, orthognathic and

463   maxillofacial surgery, with 5-13% of patients undergoing a dental surgery going on to

464   experience chronic jaw pain [22;79;80;92]. Given a strong predictor of the development of

465   chronic pain after surgery is high pain severity during the acute stage [42;105], the delivery

466   of rTMS prior to surgery could be an effective method to reduce post-operative pain. This

467   would interrupt the transition from acute to chronic pain, whilst also reducing reliance on

468   opioid based treatments that may put individuals at risk of long-term dependence [97] .

469   Future studies are needed to build on these preliminary findings.

470

471   **While the mechanisms of rTMS were unclear, PAF and CME predicted future pain**

472   As hypothesised, our findings showed that 5 days of rTMS led to an increase in PAF.

473   This is consistent with previous studies showing an increase in PAF following single sessions

474   of high frequency rTMS [2;67;73], though ours is the first study to demonstrate these effects

475 following a multi-session protocol. Thus, our results suggest that, along with other methods

476 such as exercise [40], visual stimulation [114] and nicotine [66], rTMS can be used as an

477 experimental method of increasing PAF. This has implications for understanding the role of

478 PAF in various other cognitive/sensory processes such as working memory and attention

479 [15;16;41;82]

480 We did not find an increase in CME following rTMS, which is inconsistent with

481 previous work [25;35]. One possible explanation is that rTMS intensity and location was

482 calibrated relative to the activation of the FDI muscle rather than the masseter muscle.

483 However, a previous study which based the rTMS intensity on the activation of masseter

484 muscle did not show a significant increase in MEP amplitudes following 10Hz rTMS [47].

485 Another possibility is that effects of rTMS on CME lack reproducibility, as recent research

486 has shown low to moderate reliability of an increases or decreases in CME following high or

487 low frequency rTMS [81]. As such, current rTMS protocols may need further refining to

488 improve the reliability of CME changes following rTMS.

489 The mediating mechanisms behind the analgesic effects of rTMS remain poorly

490 understood and are seldom investigated [62]. While our study is novel in this regard, we did

491 not find evidence that changes in PAF/CME mediated the effects of rTMS on future pain.

492 This suggests rTMS may have acted on other cortical mechanisms that attenuated future pain.

493 One possibility is other cortical regions (e.g. dlPFC, insular, cingulate cortices) which are

494 *also* activated by M1 rTMS, mediated the prophylactic effects [5;38;44]. Indeed, connectivity

495 between dlPFC and subcortical regions involved in descending pain inhibition has been

496 shown to predict future response to pain interventions [96]. Another possible mechanism is

497 alterations in sensorimotor inhibitory/excitatory processes that cannot be captured by TMS-

498 MEP methodologies, but which can only be captured using combined TMS-EEG

499 methodologies. TMS-EEG allows activity to be measured directly from the cortex rather than

500   from peripheral muscles [18]. We have preliminary evidence showing that GABAergic

501   processes within the sensorimotor cortex (indexed using TMS-EEG) partially mediated the

502   analgesic effects of rTMS during pain [19]. As such, we encourage future studies to

503   determine whether such mechanisms are also involved in the prophylactic effects of rTMS

504   from future pain.

505   While the present study showed that PAF and CME did not mediate the effect of

506   rTMS on pain, we showed that an individual's CME or PAF on Day 4, regardless of group

507   allocation, was correlated with future pain intensity. Specifically, lower PAF and CME on

508   Day 4 were associated with higher future pain. This is consistent with previous research

509   showing lower CME during the acute stage of non-specific low back pain predicts higher

510   pain intensity at 6 months follow-up [49], and studies showing that slower PAF prior to

511   experimental pain onset predicts higher future pain [32-34]. Note a relationship between

512   PAF/CME on Day 0 and future pain was not observed. This is likely due to fluctuations in

513   PAF/CME introduced by the rTMS intervention and/or the longer time interval between Day

514   0 PAF/CME and pain measurements on Day 5-25. Overall, our results suggest that while

515   changes in PAF or CME did not drive the analgesic effects of rTMS, these measures are

516   relevant predictors of future pain sensitivity.

517   **Strengths and Limitations**

518   This study used a thorough experimental approach with successful blinding of

519   participants to group allocation, roughly equal split of males and females in each group and

520   blinding of the experimenter involved in data collection, pain induction, pre-processing and

521   the statistical analysis plan. One potential limitation of the study is the use of the marked

522   hotspot method for the five sessions of rTMS rather than neuronavigation. The latter has been

523   shown to improve the consistency of coil positioning and orientation across sessions [12]. As

21

524   such, the use navigation-guided rTMS in the present study may have increased the magnitude

525   of the prophylactic pain effects. Another limitation is that pain catastrophizing and other

526   mood-related measures were not collected following rTMS. This may have provided further

527   information regarding the mediating mechanisms for the protective effect of rTMS, such as

528   changes in affective-emotional dimensions of pain [52].

529   **Conclusion**

530   Five consecutive days of high frequency rTMS delivered *prior* to pain onset can

531   reduce the intensity of a future episode of prolonged pain, suggesting rTMS may be useful as

532   a prophylactic intervention in some clinical settings, including as an adjunct intervention to a

533   pre-surgical optimisation program aiming to reduce post-surgical pain. Future studies are

534   needed to explore this possibility.

537   **Conflict of Interest:** The authors have no conflicts of interests to declare.

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Figure Captions

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935   *Figure 1.* Diagram of the experimental protocol

936   *Figure 2.* Model for the mediation analysis, which assessed the direct effect of rTMS on PAF
937   or CME (a path), the direct effect of rTMS on pain outcome (c path), and the indirect effect
938   of rTMS on pain (a + b path).

939   *Figure 3.* Mean ratings (±SEM) for the primary outcomes (pain upon chewing and yawning)
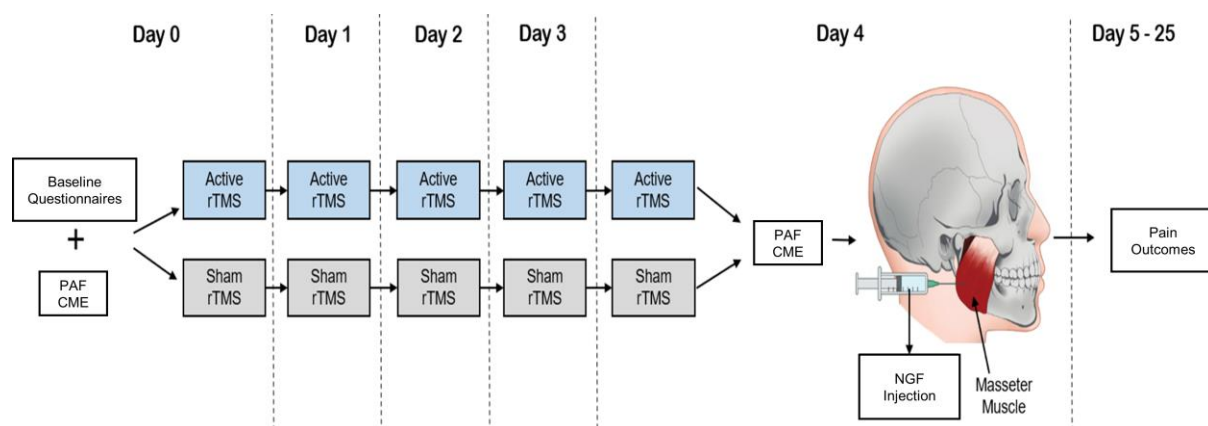940   in each group as a function of timepoint.

941   *Figure 4.* Mean ratings (±SEM) for the secondary outcomes, including pain during activities
942   not directly relevant to the pain model (A), functional limitation (B), muscle soreness and (C)
943   in each group as a function of timepoint.

944   *Figure 5.* A: Mean spectral plots for each group at Day 0 (pre-rTMS) and Day 4 (post rTMS).
945   B: Mean topographical plots of the identified sensorimotor alpha component for group at Day
946   0 (pre-rTMS) and Day 4 (post rTMS). C: Violin plots showing individual data points for peak
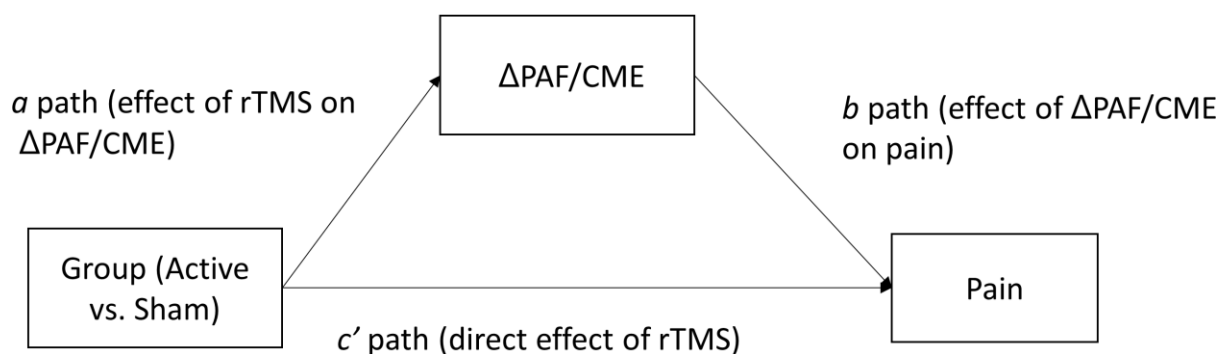947   alpha frequency for each group at Day 0 (pre-rTMS) and Day 4 (post rTMS)

948   *Figure 6.* Mean masseter motor maps for each group at Day 0 (pre-rTMS) and Day 4 (post
949   rTMS). The maps show the normalized MEP amplitude at each stimulation site relative to the
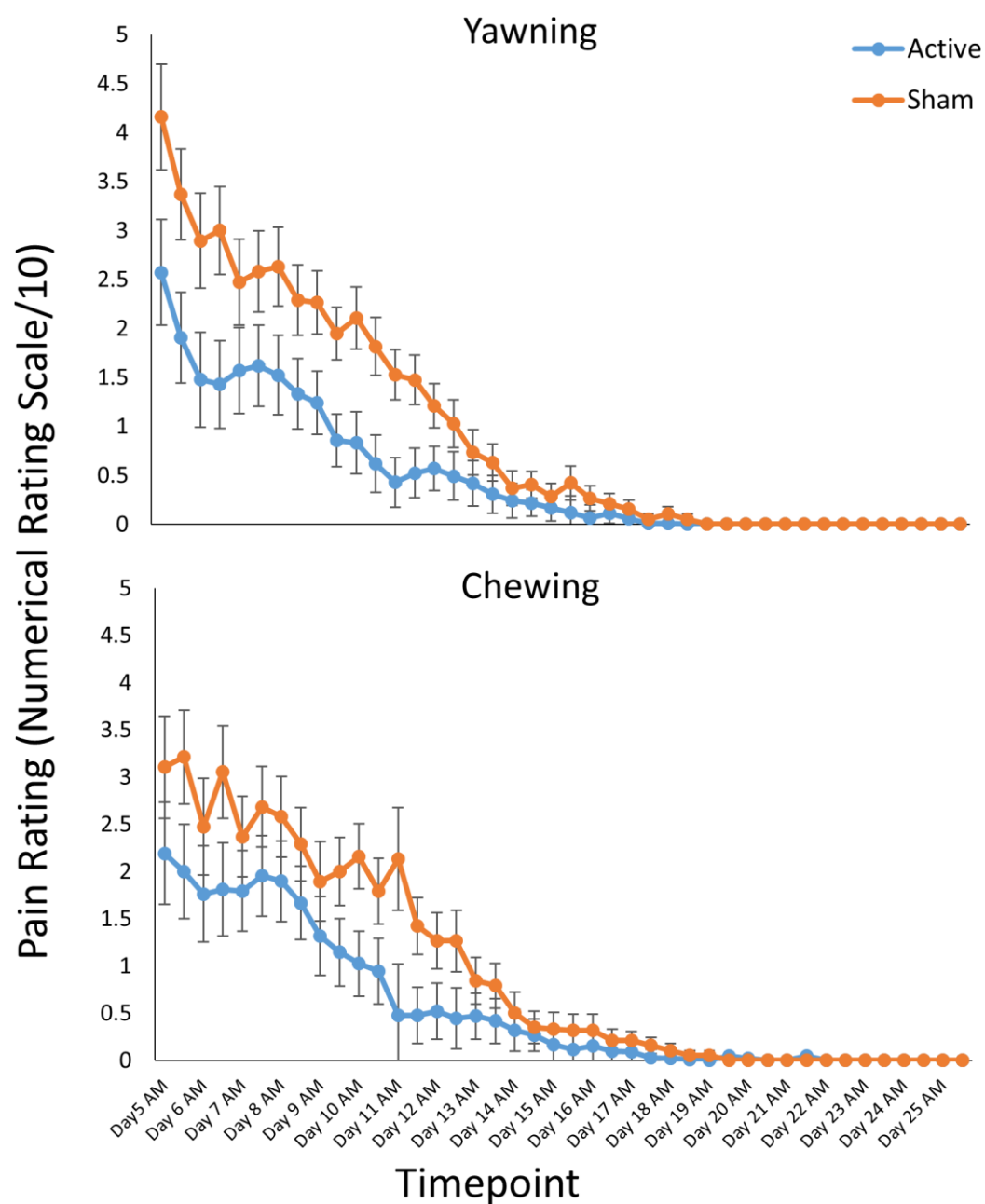950   vertex in both lateral-medial and posterior-anterior dimensions.

951   *Figure 7.* Scatter plots showing the association between peak alpha frequency and
952   corticomotor excitability on Day 4 against the mean pain rating (chewing and yawning)
953   across the first week (Day 5-11).

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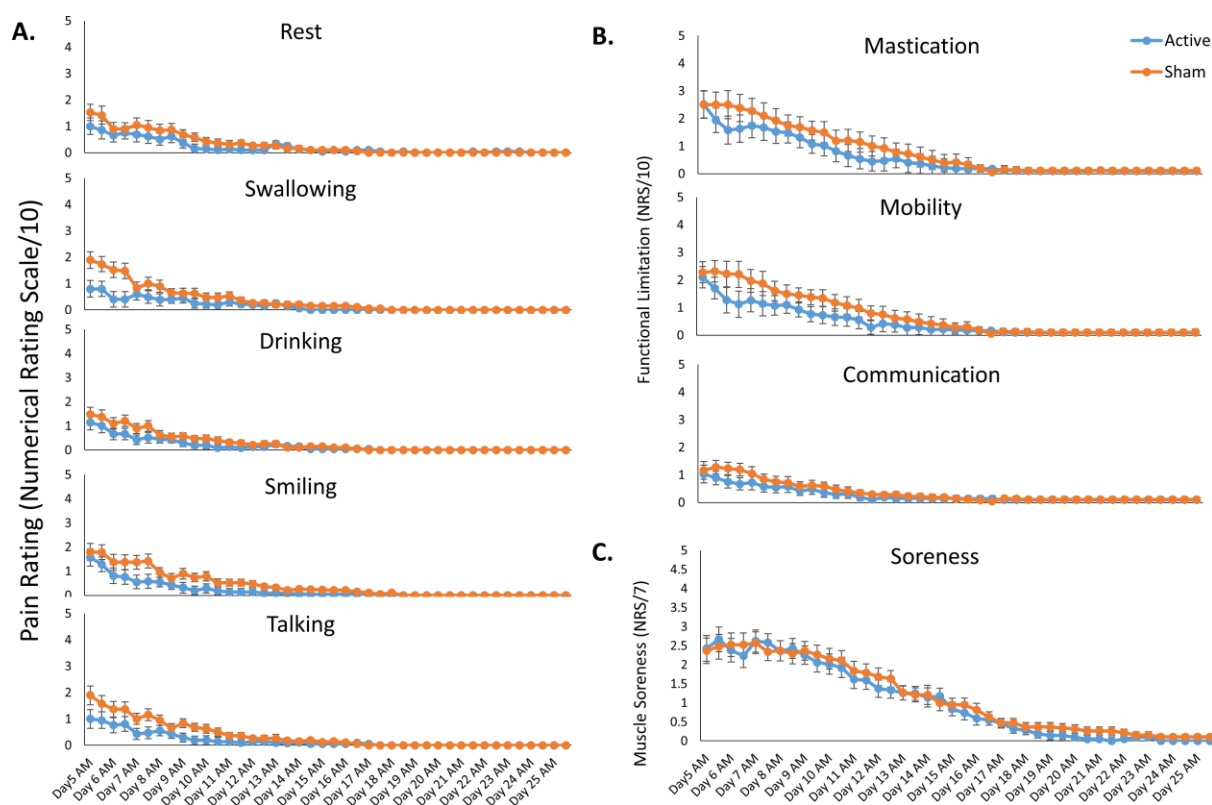1036

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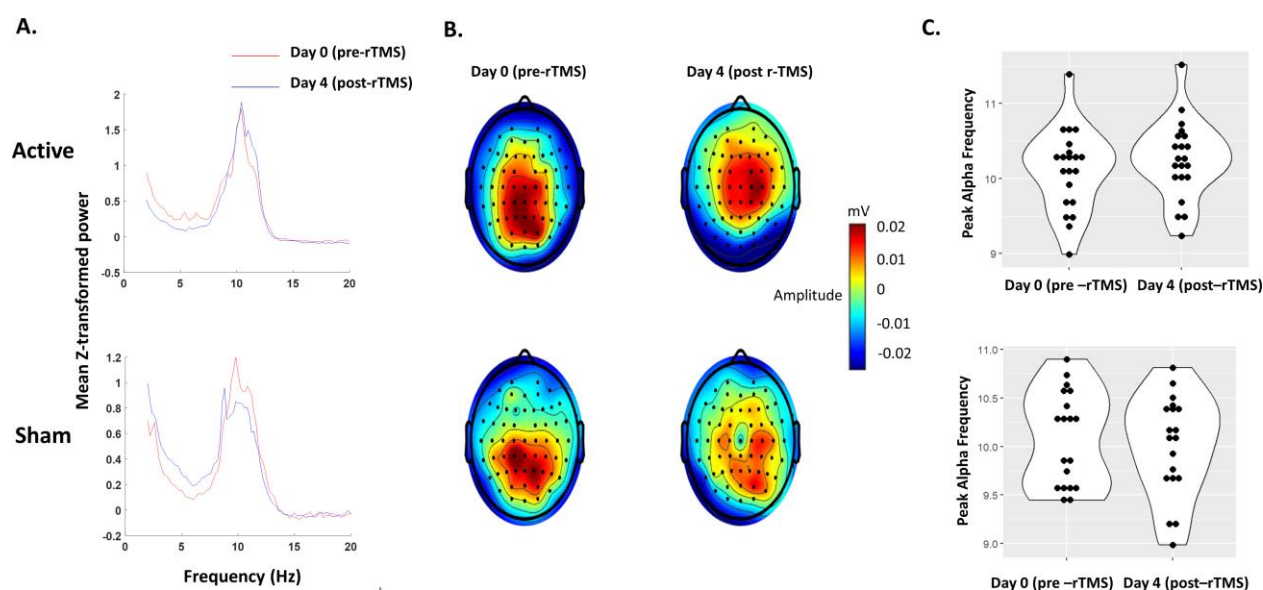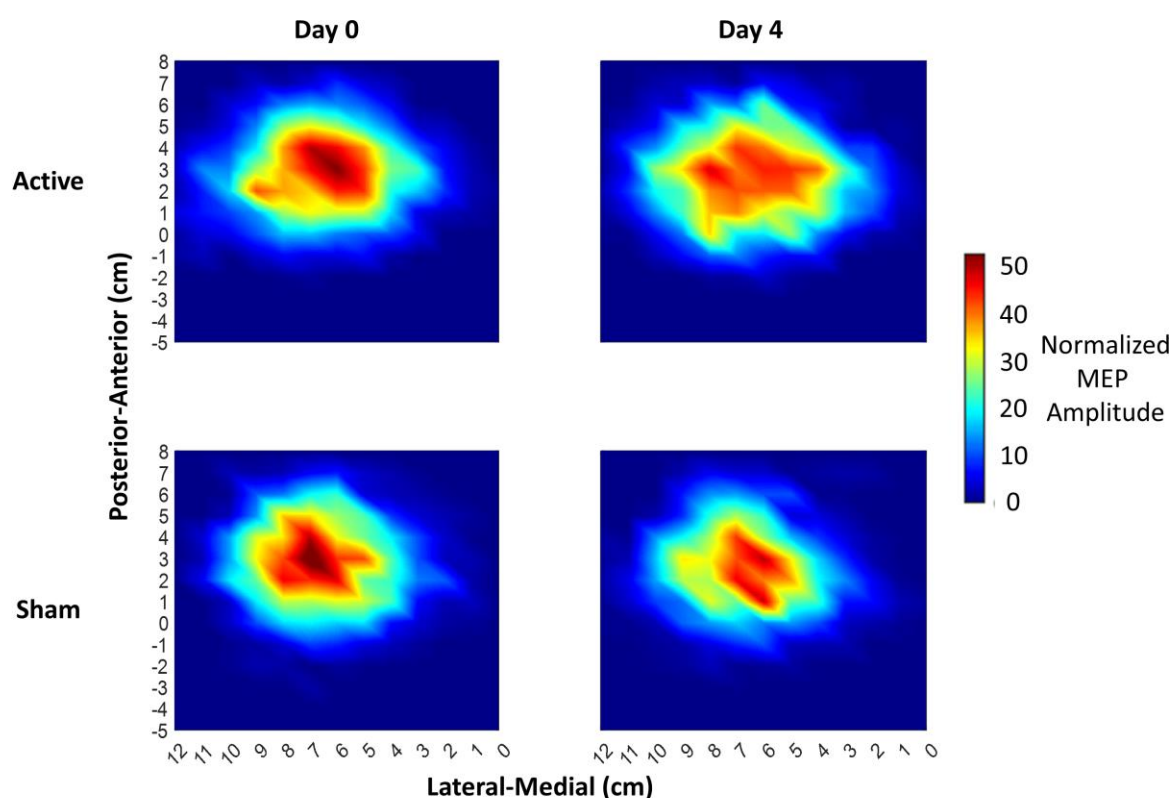
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1074 **Tables**
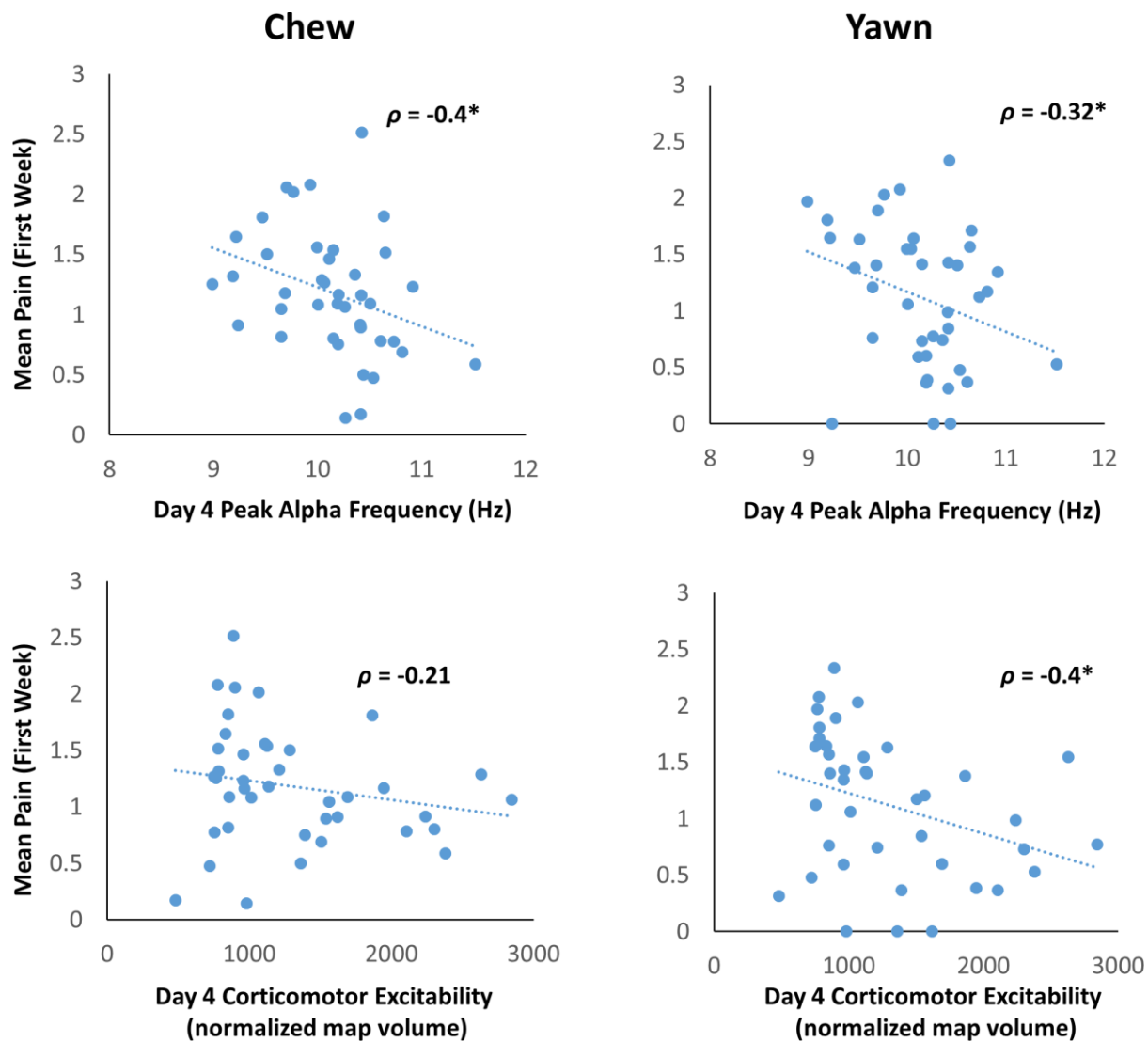
1075 **Table 1**. Participant Characteristics. Data are means (SD) or numbers (%). PCS, Pain
1076 Catastrophizing Scale; PSS, Perceived Stress Scale; PHQ, Patient health questionnaire; PILL,
1077 Pennebaker Inventory of Limbic Languidness Questionnaire; SF-8 (PCS, MCS), Short-Form-
1078 8 health questionnaire (physical component summary, mental component summary); BPI,
1079 Brief Pain Inventory Pain Severity and 7-item Interference subscales.

		Active rTMS	**Sham rTMS**
Sample size		21	19
Sex (F,M)		11, 10	11, 8
Age (years)		22.2 ± 3.0	24.4 ± 5.4
PCS		8.6 ± 8.4	10.6 ± 8.4
PSS		17.5 ± 6.6	18.7 ± 3.1
Sleep Scale	**Total sleep (hours)**	7.3 ± 1.2	6.9 ± 0.9
	Total sleep score	40.5 ± 8.3	43.9 ± 5.0
PHQ		0.9 ± 1.4	0.5 ± 0.8
PILL		94.7 ± 31.4	85.8 ± 20.8
SF-8 PCS		1.9 ± 0.5	1.8 ± 0.5
SF-8 MCS		1.9 ± 0.9	1.8 ± 0.7
BPI Inventory		0.5 ± 1.0	0.1 ± 0.2
BPI Interference		1.0 ± 1.3	0.5 ± 0.6
Correctly identified group allocation		13/21 (62%)	9/17 (53%)

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