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Publication Date	2017-06-13
Publication Information	Moriarty, Orla, Ruane, Nancy, O'Gorman, David, Maharaj, Chris H., Mitchell, Caroline, Sarma, Kiran M., Finn, David P., McGuire, Brian E. (2017). Cognitive Impairment in Patients with Chronic Neuropathic or Radicular Pain: An Interaction of Pain and Age. Frontiers in Behavioral Neuroscience, 11(100). doi: 10.3389/fnbeh.2017.00100
Publisher	Frontiers Media
Link to publisher's version	https://doi.org/10.3389/fnbeh.2017.00100
Item record	http://hdl.handle.net/10379/15077
DOI	http://dx.doi.org/10.3389/fnbeh.2017.00100

Cognitive impairment in patients with chronic neuropathic or radicular pain: An interaction of pain and age

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1   Abstract:

2   A growing body of empirical research has confirmed an association between chronic pain and

3   cognitive dysfunction. The aim of the present study was to determine whether cognitive

4   function is affected in patients with a diagnosis of chronic neuropathic or radicular pain

5   relative to healthy control participants matched by age, gender and years of education. We

6   also examined the interaction of pain with age in terms of cognitive performance. Some

7   limitations of previous clinical research investigating the effects of chronic pain on cognitive

8   function include differences in the pain and cognitive scale materials used, and the

9   heterogeneity of patient participants, both in terms of their demographics and pathological

10   conditions. To address these potential confounds, we have used a relatively homogenous

11   patient group and included both experimental and statistical controls. We have also

12   specifically investigated the interaction effect of pain and age on cognitive performance.

13   Patients (n=38) and controls (n=38) were administered a battery of cognitive tests measuring

14   IQ, spatial and verbal memory, attention and executive function. Educational level,

15   depressive symptoms and state anxiety were assessed as were medication usage, caffeine and

16   nicotine consumption to control for possible confounding effects. Both the level of depressive

17   symptoms and the state anxiety score were higher in chronic pain patients than in matched

18   control participants. Chronic pain patients had a lower estimated IQ than controls, and

19   showed impairments on measures of spatial and verbal memory. Attentional responding was

20   altered in the patient group, possibly indicative of impaired inhibitory control. There were

21   significant interactions between chronic pain condition and age on a number of cognitive

22   outcome variables, such that older patients with chronic pain were more impaired than both

23   age-matched controls and younger patients with chronic pain. Chronic pain did not appear to

24   predict performance on the Wisconsin Card Sorting Task, which was used a measure of

25 executive function. This study supports and extends previous research indicating that chronic

26 pain is associated with impaired memory and attention.

27 Perspective: Compared to healthy control participants, patients with chronic neuropathic or

28 radicular pain showed cognitive deficits which were most pronounced in older pain patients.

29

30 **Introduction**

31 Chronic pain is a debilitating condition associated with biopsychosocial consequences.

32 Subjective reports by chronic pain patients and objective empirical research have

33 demonstrated that chronic pain is associated with cognitive deficits in various domains of

34 functioning including, attention, working memory and executive function (Moriarty et al.,

35 2011; Berryman et al., 2013; Moriarty and Finn, 2014). However, the problem of pain-related

36 cognitive impairment remains under-researched due to various methodological barriers

37 (McGuire, 2013).

38 Research suggests that cognitive deficits occur across a range of pain conditions (e.g.

39 migraine (Meyer et al., 2000; Calandre et al., 2002; Mongini et al., 2005), fibromyalgia

40 (Grace et al., 1999; Park et al., 2001; Luerding et al., 2008) or diabetic neuropathy (Ryan et

41 al., 1992; Ryan et al., 1993), but less emphasis has been placed on examining specific pain

42 types (e.g. neuropathic, inflammatory), irrespective of their etiology. One study comparing

43 different types of pain found that attention was impaired to a similar extent in rheumatoid

44 arthritis, musculoskeletal pain and fibromyalgia patients compared with healthy controls

45 (Dick et al., 2002). Conversely, there is evidence that emotional decision making was

46 impaired in lumbar spinal or radicular pain of the lower back, but not in Complex Regional

47 Pain Syndrome (CRPS) (Apkarian et al., 2004), and general cognitive functioning was worse

48 in neuropathic pain patients than in patients with a diagnosis of mixed neuropathic and

49 nociceptive pain (Povedano et al., 2007). Although previous investigations of cognition in

50 chronic pain have included neuropathic pain patients as part of a wider sample, few studies

51 have examined performance specifically in neuropathic/radicular pain. In one of these

52 studies, Povedano et al. (2007) reported cognitive impairment in a neuropathic pain cohort

53 compared with the normative sample for the Mini Mental State Exam (MMSE). Two

54 limitations of the study were the absence of a matched comparison group, and the reliance on

55 the MMSE, which may not detect subtle deficits in particular cognitive domains.

56 Increasing age is consistently associated with cognitive decline (Salthouse, 1996; Salthouse et

57 al., 1998), and there is evidence to suggest that age may moderate the impact of pain on

58 cognitive performance in human and animal models (Leite-Almeida et al., 2009; Oosterman

59 et al., 2013). Based on the hypothesis that pain competes for available attentional resources

60 (Eccleston, 1994; Eccleston and Crombez, 1999), it could be predicted that the negative

61 effect of pain on cognitive function would exacerbated as cognitive function declines with

62 age. However, a positive relationship between reported pain ratings and executive function

63 has also been demonstrated in elderly populations (Scherder et al., 2008; Oosterman et al.,

64 2009). This may simply suggest that pain report is less reliable in the case of more severe

65 cognitive decline, but demonstrates that age is an important determinant of the relationship

66 between pain and cognitive function, and thus requires further investigation.

67 The aim of the present study was to investigate the effects of pain on cognitive functioning,

68 which would address, where possible, the limitations associated with previous research.

69 Specific barriers to, and limitations of, previous research in this area have been described

70 (McGuire, 2013). We have attempted to account, where possible, for potential confounding

71 factors by including an age-, gender- and education level-matched comparator group, by

72 using a comprehensive cognitive test battery, by directly investigating the interaction effect

73 of pain and age on cognitive outcomes, by focusing on a relatively homologous group of pain

74 patients, and by statistically controlling for factors such as nicotine, caffeine and alcohol

75 consumption which may affect cognitive performance. These include differences in the pain

76 and cognitive scale materials used, and the heterogeneity of patient participants both in terms

77 of their demographics and pathological conditions. Therefore, the study was designed to

78 investigate cognitive functioning specifically in patients with chronic neuropathic or radicular

79 pain, to probe performance in a variety of cognitive domains by exposing participants to a

80 comprehensive battery of well-validated cognitive tests, and to minimize potential confounds

81 such as level of education, affective state, and consumption of nicotine, alcohol and caffeine.

82 Our specific hypotheses were that: (1) chronic neuropathic/radicular pain patients would

83 demonstrate impairments in cognitive performance compared with healthy participants even

84 after controlling for potentially confounding factors (2) in models predicting the effect of

85 pain on cognitive performance, a pain x age interaction would emerge whereby older

86 individuals with chronic pain would display the greatest levels of impairment (3) in pain

87 patients, cognitive performance would be predicted by the severity of their pain.

88 **Materials and Methods**

89 *Participants*

90 A total of 38 chronic pain patients and 38 control participants took part in the study. Patients

91 with chronic neuropathic pain or radiculopathy (minimum of 3 months, diagnosed by a

92 specialist pain physician) were identified from the database of patients attending a tertiary pain

93 management clinic at Galway University Hospital, Galway, Ireland. Recruitment of control

94 participants was achieved through placement of advertisements in public places and in the local

95 and national print media. Exclusion criteria were: age less than 18 years; self-reported

96 diagnosis of pre-existing cognitive impairment or major psychiatric illness (including major

97   depressive disorder or generalised anxiety disorder); self-reported history of substance abuse,

98   diabetes, epilepsy, seizures or traumatic brain injury; and in the case of control participants,

99   self-reported history of chronic pain. Patient and control groups were matched by gender, age,

100   and education (Table 1). All participants gave informed written consent, in person, prior to the

101   test session, and all testing procedures were carried out at University Hospital Galway or

102   National University of Ireland, Galway. The study received full institutional approval from the

103   Research Ethics Committee of the National University of Ireland, Galway and from the Galway

104   University Hospitals Research Ethics Committee.

105   *Procedure*

106   Patient participants were sent (by post) an information sheet and an invitation to participate in

107   the research study, at least one week in advance of the assessment. To reduce patient burden,

108   chronic pain patients were invited to complete the assessment on the day of a routinely

109   scheduled appointment at the pain clinic. The testing was completed in advance of the clinic

110   appointment to avoid the potentially confounding effects of interventional analgesic

111   treatments. Where patients could not attend on the day of their appointment, but consented to

112   participate, the assessment was scheduled for an alternative date. Medication status at the time

113   of the assessment was not evaluated. For control participants, an outline of the study was

114   provided in the public advertisements, and each participant was provided with a more detailed

115   information sheet by the examiner prior to consenting to take part in the study.

116   *Demographics*

117   Demographic information, including age, gender and number of years of education, was

118   collected for all participants using a standard form. In addition, participants were asked to

119   estimate, if applicable, the length of time since they had last consumed nicotine and/or caffeine.

120

121 *Pain assessment*

122 Participants in the patient group were asked to complete the Chronic Pain Grade (CPG)

123 Questionnaire (Von Korff et al., 1992). This 7-item scale provides measures of current pain

124 and pain over the previous three months, as well as a measure of pain-related disability and an

125 overall chronic pain grade classification. The CPG has been validated as a self-completion

126 measure and is widely used in chronic pain research (Elliott et al., 1999; Dunn et al., 2008;

127 Raftery et al., 2011). In addition, pain patient participants were asked to indicate painful areas

128 on a manikin diagram and to estimate the number of months since the diagnosis of their pain.

129 The total number and drug classification of patients' analgesic medications were also recorded.

130 *Perceived impact of pain*

131 Patients' subjective ratings of the perceived impact of pain on cognitive function

132 (concentration, memory, problem solving and decision making) were recorded on a 10-point

133 Likert scale where 0 was "no interference" and 10 was "extreme interference". This single-

134 item scale was developed by the research team and was phrased in a manner similar to other

135 CPG "interference" items - 'In the past three months, how much has pain interfered with your

136 concentration, memory, problem solving or decision making?' The response was recorded on

137 a 10-point Likert scale where 0 was "no interference" and 10 was "extreme interference".

138

139 *Depressive symptoms and state anxiety*

140 Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9)

141 depression scale (Kroenke et al., 2001). This questionnaire is based on the Diagnostic and

142 Statistical Manual of Mental Disorders-IV criteria, and has been widely used in research

143 (Kroenke et al., 2001; Kroenke and Spitzer, 2002; Lowe et al., 2004). Scores were computed

144 to give a tentative diagnosis of depression and a measure of symptom severity. The

145 questionnaire responses also gave an indication of symptom-related functional impairment

146 (ability to "work, take care of things at home or get along with other people"). The level of

147 anxiety at the time of cognitive testing was measured using the 'state' portion of the State-Trait

148 Anxiety Inventory (STAI), Form Y (Spielberger et al., 1983). The STAI-S (20 items) provides

149 a measure of 'state' or current anxiety at the time of completing the questionnaire.

150 *Neuropsychological Tests*

151 *General Intellect*

152 An estimate of participants' intelligence quotient (IQ) was obtained using a two-test short-form

153 of the Wechsler Adult Intelligence Scale-III (WAIS-III, (Wechsler, 1997a)), the Digit-Symbol

154 Coding and Information subtests. Estimated full-scale IQ obtained using this dyadic short form

155 of the WAIS-III has been shown previously to correlate (r^2=0.82) with IQ values obtained

156 using the full 12-subtest scale (Sattler and Ryan, 2001), and this combination of subtests was

157 chosen based on its relatively short administration time. In the Digit-Symbol Coding subtest,

158 participants were presented with nine digit-symbol pairs followed by a list of digits only.

159 Participants were required to fill in the symbol corresponding to each digit as quickly as

160 possible on a standard form. For the Information subtest, the participant was required to answer

161 a series of factual general knowledge questions about common events, objects, places and

162 people. Raw scores for both subtests were converted to age-adjusted scaled score equivalents

163 using the WAIS-III Administration and Scoring Manual (Wechsler, 1997a). Full-scale IQ was

164 then estimated from the sum of the scaled scores using the extrapolation tables taken from

165 Sattler and Ryan (2001).

166

167 *Verbal Memory*

The Logical Memory subtests I and II of the Wechsler Memory Scale-III (WMS-III, (Wechsler, 1997b)) were used to assess short- and long-term verbal memory and recognition memory. Two different stories (A and B) were read to the subject, and immediately afterwards the subject was asked to retell the story from memory.

After an interval of approximately 25 minutes, the participant was again asked to recall as many details as possible from both stories A and B. For recognition memory, the participant was required to give "Yes" or "No" answers to a set of 30 questions relating to stories A and B, which includes a mixture of correct and incorrect statements about the story content. Participants were scored on the accuracy of the story recall ("story" and "theme" units) and number of correct responses to recognition questions. Raw scores were converted to age-adjusted scaled score equivalents using the WMS-III Administration and Scoring Manual (Wechsler, 1997b).

Spatial Memory

The spatial span subtest of the WMS-III was used to measure short-term spatial memory capacity. The test was administered using the spatial span board, which consists of 10 cubes with the numbers 1 to 10 printed on the sides of the cubes facing the examiner. For spatial span forward, the examiner tapped the cubes in a specified sequence pattern and then asked the participant to tap the same sequence. For spatial span backward (reverse), the participant was asked to tap the sequence in reverse order. The sequence length increased until the participant could no longer replicate the sequence correctly. Raw scores were converted to age-adjusted scaled score equivalents using the WMS-III Administration and Scoring Manual (Wechsler, 1997b).

Attention/Vigilance and psychomotor speed

193 The Continuous Performance Test – Identical Pairs (CPT-IP), adapted from the MATRICS

194 (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus

195 Cognitive Battery (Nuechterlein and Green, 2004), was used to measure attention and

196 vigilance. This computerized test required the participant to monitor a series of 4-digit numbers

197 as they appeared briefly on the computer screen. The participant responded to the sequential

198 appearance of identical pairs of numbers by clicking a mouse as quickly as possible. The

199 number of correct responses, the number of incorrect responses and the reaction time were

200 recorded automatically. Incorrect responses were categorised as "false alarms" (i.e., responses

201 to similar, but not identical, numbers presented in sequence) or random responses. The D-prime

202 (range 0–4.2), an indication of the rate of hits to false alarms, was also calculated as an index

203 of attention. The average reaction times to both hits and false alarms during the CPT-IP trial

204 were used as tentative measures of psychomotor speed.

205

206 *Executive Function*

207 Executive function was assessed using the Wisconsin Card Sorting Test – Computerized

208 Version 4 (WCST-CV4). This test measured the respondent's ability to adapt to changing

209 schedules of reinforcement (i.e., the "rules" about the task) and thus assesses cognitive

210 flexibility, a key component of executive functioning (Berg, 1948) . The computerised version

211 used in this study presented the participant with four key cards and a stimulus card. The cards

212 were matched according to one of three categories: colour, shape or quantity of items on the

213 card. Matching is achieved by placing the cursor on the key card selected and left clicking the

214 mouse. The participants were not told how to match the cards, but they were given verbal and

215 visual feedback on whether each match was "right" or "wrong". The category by which the

216 cards were to be matched changed without warning after presentation of every ten stimulus

217 cards; the subject was required to recognise the changed "rules" and identify the new

218 presentation pattern. Raw scores and demographically (age and education) corrected standard

219 scores were computed for five outcome measures: percentage errors, percentage perseverative

220 (repetitive) responses, percentage perseverative errors, percentage non-perseverative errors

221 and, percentage conceptual level responses. Raw scores were also computed for the number of

222 categories completed, the number of trials to complete the first category, number of failures to

223 maintain set and a learning-to-learn score (indicative of conceptual efficiency across

224 consecutive categories).

225

226 *Statistical design and analysis*

227 Data were analysed using the Statistical Package for the Social Sciences (SPSS, version 18,

228 IBM Corp., USA) for Windows. The statistical analyses were performed in two distinct phases;

229 the first included both patient and control participant data, while the second included patient

230 data only. Assumptions of the relevant tests were checked using a range of graphical (e.g., box

231 plots, normality plots) and inferential tests of normality.

232 *Analysis by pain condition (Phase I)*

233 In this phase of analysis, hypotheses (1) and (2), as stated in the Introduction, were tested: (1)

234 chronic neuropathic/radicular pain patients would demonstrate impairments in cognitive

235 performance compared with healthy participants even after controlling for potentially

236 confounding factors (2) in models predicting the effect of pain on cognitive performance, a

237 pain x age interaction would emerge whereby older individuals with chronic pain would

238 display the greatest levels of impairment. The first level of analysis was the computation of

239 descriptive and inferential statistics. This was followed by correlation analyses of cognitive

240 outcome measures and participant characteristics aimed at identifying potential covariates.

241 The variables included in the correlation analyses were: age, gender, number of years of

242 education, smoking status and time since last nicotine consumption, time since last caffeine

243 consumption, as these variables can predict cognitive performance (Rohrbaugh et al., 1988;

244 Foulds et al., 1996; Mancuso et al., 1999; Brice and Smith, 2001; Kelemen and Creeley,

245 2001; Moore et al., 2009), as well as examining depression and anxiety scores as correlates.

246 We intended controlling for correlates of the outcomes when testing our hypotheses. This

247 would allow us to examine the extent to which the hypothesized effects emerged, having held

248 constant important correlates of the outcome being investigated.

249   Hierarchical multiple regression analyses were used to test the hypotheses; groups were

250 coded as -1 (patient group) and +1 (control group), age was mean-centred, and an interaction

251 term (group $(-1/+1)$ x age (mean-centred)) was calculated. The purpose of centring was to

252 minimise multicollinearity (arising, in this case, from entering both the variables and their

253 interaction into the regression equation). Participant-characteristic variables that were

254 correlated with the cognitive outcomes were entered into the first block of the regression model.

255 Values for significance levels and β coefficients quoted in the text are for the overall model.

256 Interaction plots for estimated marginal means (2x2 ANCOVA with patient vs control and age

257 median-split at 45 years) were used for visualisation of the directionality of effects and for

258 determining the nature of the interaction between variables.

259

260 *Analysis by pain variable (Phase II)*

261 The second phase of the study tested hypothesis (3), as stated in the Introduction: in pain

262 patients, cognitive performance would be predicted by the severity of their pain. As in Phase

263 I, an interaction effect between pain variables and age was also hypothesized, and this was

264 tested in the analyses. The pain variables investigated were present pain intensity, pain-

265 related disability score, number of painful areas and pain chronicity (number of months since

266   diagnosis of pain). Additional patient characteristics investigated as potential covariates were

267   the presence or absence of medication (and different medication sub-groups), total number of

268   medications, percentage pain relief from medications, and self-assessed impairment of

269   cognitive function. Descriptive and inferential statistics relating to pain information (for

270   patient participants only, $n = 38$) were calculated. Correlation matrices, using the patient

271   group data only, were constructed to identify potential covariates. Each of the pain variables

272   was centred, and interaction terms with mean-centred age were calculated. Hierarchical

273   regression analyses were again used to test the hypothesis.

274

275   **Results**

276   *Participant characteristics*

277   Demographic and psychological descriptors of pain patient and control groups are presented in

278   Tables 1 and 2. Basic between-group comparisons were used to test the extent to which the

279   matching procedure was successful. There were no significant differences between patient and

280   control groups in age, gender, years of education or duration since last consumption of caffeine

281   or nicotine. There were, however, significantly more smokers in the patient group than in the

282   control group, and patients exhibited higher depressive-symptom scores, increased depression-

283   related functional impairment and greater levels of state anxiety than controls (see Tables 1

284   and 2).

285

286   [TABLE 1 HERE]

287   [TABLE 2 HERE]

288

289   *Cognitive variables*

290   *Analysis by pain condition (Phase I)*

291   Prior to testing the hypothesised effects, group differences (patient versus control) were

292   explored. Results indicated consistently lower outcome scores in the patient group, or higher

293   scores on reverse scales (number of false alarms and number of random responses in the CPT-

294   IP, and raw scores for % errors, % perseverative responses, % perseverative errors, % non-

295   perseverative errors, number of trials to complete the first category and failure to maintain set

296   in the WCST, see Table 3).

297

298   [TABLE 3 HERE]

299

300   A correlation matrix of participant characteristic and cognitive outcome variables was used to

301   identify potential covariates (see Supplementary Table S1). Gender and smoker/non-smoker

302   classifications were correlated with a number of cognitive measures (gender correlated with

303   immediate verbal memory and reaction time; cigarette smoking correlated with immediate

304   verbal memory, while a large number of the outcomes were positively correlated with years of

305   education and negatively correlated with measures of depression and state anxiety.

306   Interestingly, the duration since last consumption of caffeine was positively correlated with

307   scores measuring attentional performance.

308   The hypotheses predicted an effect of participant group (patient or control) and an

309   interaction effect of group and age, and were tested through a series of individual hierarchical

310   regressions for each of the cognitive outcomes. Significant covariates of the dependent variable

311   (identified by correlation analysis) were entered in the first block, group (patient vs. control,

312   coded $-1/+1$) and age (mean-centred) were entered in block 2, and the interaction term (pain x

313   age) was entered in block 3. Statistics for cognitive variables predicted by group or by the

314   interaction term (at levels close to or below the *p*=0.05 level of statistical significance) are

315   presented in Table 4.

316   In the regression model predicting estimated full scale IQ (FSIQ), years of education,

317   PHQ-9 severity score and STAI-S total score were entered as controls in block 1. PHQ severity

318   score and STAI-S total score were found to be correlated; however, the observed variance

319   inflation factors (VIFs) were less than 10, suggesting that the assumption of minimal

320   multicollinearity was not violated and that scores can be assumed to reflect independent

321   constructs. Years of education significantly contributed to the FSIQ model ($\beta = 0.37$, $p <$

322   0.001), as did the presence of pain ($\beta = 0.33$, $p = 0.04$). Interaction plots showed that FSIQ

323   scores were decreased in the presence of pain. Neither age nor the interaction term made any

324   significant contribution to the model (see Table 4).

325

326   [TABLE 4 HERE]

327

328   Immediate verbal memory was measured as story-unit and theme-unit recall scores and

329   a learning-slope score. Presence of a chronic pain diagnosis, age, and their interaction term

330   made no contribution to the story-unit or theme-unit regression models. There were no

331   significant predictor variables of the theme-unit model, and only gender significantly

332   contributed to the story recall unit model ($\beta = 0.24$, $p = 0.04$). In the case of learning slope, the

333   contribution of STAI-S total score (entered in the first block) approached significance ($\beta =$

334   -0.27, $p = 0.06$). There was a significant contribution of age ($\beta = -0.29$, $p = 0.02$); the

335   interaction term of pain and age was also associated with an effect close to statistical

336   significance ($\beta = 0.20$, $p = 0.08$, Table 4), with interaction plots suggesting that older pain

337   patients performed worse than controls of a similar age and worse than younger pain patients.

338　Delayed verbal memory was also measured with story-unit and theme-unit recall scores, as

339　well as with a recognition-memory index and with percentage retention. In a manner similar to

340　the case of immediate verbal memory, neither pain condition, age, nor their interaction

341　significantly contributed to either story-unit or theme-unit models, and none of the additional

342　predictor variables significantly affected these models. Furthermore, no significant predictors

343　of percentage retention were identified (though the effect of age was close to significance: $\beta =$

344　-0.21, $p = 0.08$). Recognition memory, however, was significantly predicted by both age ($\beta =$

345　-0.27, $p = 0.01$) and the pain-age interaction term ($\beta = 0.30$, $p = 0.006$, Table 4), with poor

346　performance particularly evident in older pain patients.

347　　　Spatial memory was assessed in forward and reverse trials of the spatial span task. Total

348　spatial span and forward trial scores were not predicted by any of the three main independent

349　variables of interest (pain, age, pain x age interaction), or by any of the control measures

350　entered into the model. Effects close to the level of statistical significance were associated with

351　the presence of pain ($\beta = 0.21$, $p = 0.07$) and years of education ($\beta = 0.23$, $p = 0.06$) in the

352　reverse scores model (Table 4).

353　　　Attention was measured using the CPT, the outcome variables of which were the

354　numbers of hits, false alarms and random responses. The number of hits in the CPT was

355　significantly predicted by age ($\beta = -0.36$, $p = 0.002$) and there was also a trend for a

356　contribution of chronic pain ($\beta = -0.36$, $p = 0.06$, Table 4). The control variable of depressive-

357　symptom score (PHQ severity) was also a significant contributor to the model ($\beta = -0.59$, $p =$

358　0.002, Table 4). The slopes of the interaction plot indicated a reduced number of hits in the

359　control group compared with the patient group; however, the group means in fact indicate an

360　increased number of hits in the control participants compared with the patient group. Further

361　analysis revealed a strong negative association between PHQ severity score and pain condition

362　($r^2 = -0.83$, $p<0.001$). Therefore, despite tolerance and VIF values being within accepted limits,

363   the relationship between PHQ severity score and pain condition may have affected the overall

364   predictive capability of the model. Age ($\beta = 0.28$, $p = 0.02$) and the age x pain interaction term

365   ($\beta = -0.25$, $p = 0.02$) made significant contributions to the regression model for number of false

366   alarms (Table 4). The number of random responses was influenced by age ($\beta = 0.36$, $p = 0.001$)

367   and there was a near-significant effect for the age x pain interaction term ($\beta = 0.20$, $p = 0.06$,

368   Table 4). In the case of the model fitted for D-prime scores, age ($\beta = -0.34$, $p = 0.003$) and

369   PHQ severity scores ($\beta = -0.33$, $p = 0.07$) emerged as predictors. There were no significant

370   effects of pain or pain-age interaction.

371   The reaction times to both hits and false alarms in the CPT task were considered

372   measures of psychomotor speed. There were no main effects of age or pain. Though the

373   individual contributions of age and presence of pain were non-significant, the pain-age

374   interaction term significantly contributed to the model for "hit" reaction time ($\beta = 0.24$, $p =$

375   0.03, Table 4). This interaction effect was approaching significance in the case of "false alarm"

376   reaction time ($\beta = 0.21$, $p = 0.08$), though the overall model was not significant. The interaction

377   plots suggest that reaction time increased with the presence of pain in the younger participants

378   but was reduced in the presence of pain in the older group.

379   The independent variables of pain, age, and age x pain interaction did not predict any

380   of the WCST standard scores or the secondary outcomes (number of categories completed,

381   number of trials to first category, failure to maintain set and learning-to-learn score). The only

382   significant predictor was age (number of categories completed: $\beta = -0.28$, $p = 0.02$), whereby

383   older people achieved lower scores than younger participants.

384

385   *Analysis by pain variable (Phase II)*

386   Table 5 shows descriptive statistics for variables unique to the pain patient group and Table 6

387   provides an overview of patients' medication status. Seventy-nine percent of patients were

388   receiving long-term medication for the treatment of pain. Opioids were the most commonly

389   prescribed class of medication, followed by anticonvulsants. The "other" category included

390   classes of analgesics taken by a small number of participants within the sample. These

391   treatments included: antispasmodics, benzodiazepines and other sedative hypnotics, local

392   anaesthetics, and transient receptor potential vanilloid 1 (TRPV1) ligands (capsaicin), as well

393   as adjunctive therapies such as acupuncture and spinal-cord stimulation. In cases where a drug

394   had more than one indication (for example, benzodiazepines used as a muscle relaxant, as an

395   anxiolytic or as treatment for insomnia), the precise reason for which it was prescribed was not

396   queried. More than half (55%) of the patient participants were taking three or more different

397   drugs to manage their pain. The average subjectively-reported relief provided by

398   pharmacological treatments was 37%.

399

400   [TABLE 5 HERE]

401   [TABLE 6 HERE]

402

403   A correlation matrix of cognitive outcome variables and general participant

404   characteristics was again constructed to identify significant correlations to be entered as control

405   variables in the regression models (see Supplementary Table S2). Similarly to Phase I, years

406   of education correlated with a large proportion of the outcome measures. The only other

407   significant correlations were between: duration since last consumption of nicotine and the

408   spatial span forward trial; depression score and number of hits, false-alarm reaction time and

409   WCST failures to maintain set; and STAI-S total score and false alarm reaction time.

410   Correlations between cognitive outcomes and patient-specific variables, including medications

411   and patients' subjective assessment of the effect of their pain on cognitive function were also

412   investigated (see Supplementary Table S3). Anticonvulsant treatment was found to correlate

significantly with learning-slope performance suggesting lower scores in those receiving anticonvulsant medications. On the other hand, antidepressant treatment was associated with higher scores on the attention task and improved WCST performance as indicated by a decrease in the number of trials required to complete the first category. Self-assessment of the effect of pain on cognitive function was positively correlated with the failure to maintain set in the WCST. All significant correlations were entered as control variables in the hierarchical regression analyses. The hypothesis stated that pain variables, and the interaction of these variables with age, would predict differences in cognitive outcomes, and this was again tested through a series of hierarchical regressions. Significant covariates of the dependent variable were entered in the first block. Each pain variable (present pain intensity, average pain intensity, pain-related disability score, pain chronicity and the number of painful areas) was tested individually. Both the pain variable and age were centred and entered in block 2, and the interaction term was entered in block 3.

Pain chronicity was found to contribute significantly to the models of FSIQ ($\beta = 0.31$, $p = 0.05$), immediate verbal memory ($\beta = 0.47$, $p = 0.003$) and delayed verbal memory ($\beta = 0.40$, $p = 0.02$). The association was positive in each of these cases, suggesting that performance improved with an increasing duration of pain. The contribution of chronicity was also close to significance in the hit response reaction time model ($\beta = 0.36$, $p = 0.07$), which would suggest an increase in reaction time with increased pain chronicity.

The number of painful areas was found to be an effective predictor of immediate verbal memory (story-unit recall: $\beta = -0.34$, $p = 0.05$; theme-unit recall: $\beta = -0.37$, $p = 0.04$) and delayed verbal memory ($\beta = -0.35$, $p = 0.04$), whereby "more painful sites" was associated with poorer performance. The interaction of the number of painful areas and age was a significant contributor to the model of the spatial span reverse trial ($\beta = -0.36$, $p = 0.03$, ANOVA $p = 0.06$) and the number of random responses on the CPT ($\beta = 0.30$, $p = 0.03$).

438   Chronic pain grade significantly predicted D-prime scores of attention ($\beta = -0.43$, $p =$

439   0.002), as did disability score ($\beta = -0.28$, $p = 0.03$). The interaction term of disability score by

440   age also made a significant contribution to the memory retention model ($\beta = -0.47$, $p = 0.006$),

441   while the interaction of present pain intensity and age had an effect close to significant on the

442   number of hits in the CPT ($\beta = -0.31$, $p = 0.07$). The negative association indicates that worse

443   pain was associated with a lower performance level on this task. In general, therefore, aspects

444   of verbal memory and attention appear to be related to a variety of pain symptom and disability

445   variables. When the total number of medications, and individual medication classifications,

446   were entered as variables of interest, no main effects were observed on any of the cognitive

447   outcome measures.

448

449   **Discussion**

450   This study adds to the evidence base that chronic pain patients are impaired on memory and

451   attention tasks; in this case, in patients with neuropathic or radicular pain. Although matched

452   for age and education, IQ was significantly lower in neuropathic/radicular pain patients than in

453   controls and IQ score was significantly predicted by pain in the regression model. There was a

454   trend for pain-related deficits in reversal of spatial memory in the spatial-span task, and the

455   pain-age interaction negatively predicted verbal memory performance. A pattern of abnormal

456   responding on the attention task was observed in pain patients, particularly in the older group.

457   Performance on the Wisconsin Card Sorting Task was not affected by the presence of pain or

458   by pain-age interaction. Individual pain variables (number of painful areas, pain intensity, pain-

459   related disability) were inversely correlated with cognitive performance, in particular those

460   related to memory. Conversely, there was a positive relationship between pain duration and

461   measures of IQ and verbal memory. The findings of the study are considered below.

462   *Participant characteristics*

463 Comparison of patient and control groups revealed that the proportion of smokers was greater

464 in pain patients than in matched healthy controls, consistent with previous findings (Ekholm et

465 al., 2009; Zvolensky et al., 2009). However, smoking status and the time since last nicotine

466 consumption were correlated with very few cognitive outcomes.

467 There were no between-group differences in the time since last caffeine consumption;

468 however, the duration since last consumption was positively correlated with measures of

469 attention, suggesting improved performance with increased duration since last caffeine intake,

470 an effect inconsistent with the recognised acute effect of caffeine as a CNS stimulant (Brunye

471 et al., 2010). It is possible that negative effects of caffeine withdrawal on attention may have

472 diminished with time since last consumption, or tolerance to the effects of caffeine may develop

473 in heavy users (Fredholm et al., 1999). Regularity and average quantity of caffeine

474 consumption was not measured in this study but should be considered for future studies.

475 Depressive-symptom and anxiety scores were significantly elevated in pain patients,

476 consistent with the well-documented relationship between chronic pain and affective disorders

477 (McCracken et al., 1996; Von Korff and Simon, 1996; Gureje et al., 1998; Oosterman et al.,

478 2009; Lee et al., 2010; Raftery et al., 2011). Notably, 50% of patient participants met the PHQ

479 diagnostic criteria for depression (compared with 0% control participants) and over 70% of

480 patients scored higher than the standard normative scores, compared with 18% of the controls.

481 While state anxiety score is not necessarily indicative of an anxiety disorder, these results

482 suggest that pain patients were more susceptible to situational anxiety associated with the

483 assessment or with their clinic visit, than were controls.

484 Recording medication use is important in studies examining the influence of pain on

485 cognitive performance (McGuire, 2013). Within our patient group, five medication

486 classifications were identified. Although anticonvulsant and antidepressant treatments were

487   found to correlate with several cognitive measures, neither treatment significantly contributed

488   to the overall regression models for cognitive variables. This is perhaps surprising given that

489   analgesic agents, in particular opioids, tricyclic antidepressants and anticonvulsants, have been

490   linked with cognitive dysfunction and somnolence (Kerr et al., 1991; Spring et al., 1992; Raja

491   et al., 2002; Salinsky et al., 2010). However, in the presence of chronic pain, negative effects

492   of these treatments may be diminished, or cognitive performance may improve (Jamison et al.,

493   2003; Kendall et al., 2010) as pain and its associated cognitive deficits are alleviated.

494   *Cognitive measures*

495   In regression analysis, a significant effect of pain condition was found on general intelligence

496   as measured by the WAIS dyad, with patients having lower IQs than controls, despite matching,

497   and statistically accounting, for years of education. This may be further evidence of cognitive

498   impairment in pain patients, as the WAIS subtests draw on cognitive resources such as attention

499   and memory (Groth-Marnat, 2009).

500   The fact that no association was found between pain and performance on the spatial

501   span forward task is surprising, given evidence from previous clinical (Dick and Rashiq, 2007;

502   Luerding et al., 2008) and preclinical (Leite-Almeida et al., 2009; Hu et al., 2010; Ren et al.,

503   2011) studies showing a negative association between neuropathic pain and spatial memory. A

504   trend for an effect of group was observed in the reversal of spatial memory assessed in the

505   spatial span task, with patients scoring lower than controls. The reverse spatial span task shows

506   some conceptual similarities to the rodent Morris water maze reversal task, and deficits in this

507   task have previously been demonstrated in a rat model of neuropathic pain (Leite-Almeida et

508   al., 2009; Moriarty et al., 2016). A significant group-age interaction effect was observed in the

509   assessment of verbal recognition memory, with the data indicating a pain-related effect

510   specifically in older participants. Deficits in recognition memory have been observed

previously in chronic pain (fibromyalgia) patients, independent of an interaction with age (Park et al., 2001). Recognition memory deficits have also been shown in rodent models of chronic pain (Cain et al., 1997; Lindner et al., 1999; Millecamps et al., 2004; Kodama et al., 2011). Thus, pain, or the interaction of pain with age, contributed to decreased IQ and deficits on specific subtests of memory.

There was no effect of pain condition or pain-age interaction on the D-prime measure of attention in the CPT, contrary to previous findings of impaired attention in chronic pain (Eccleston, 1994; Grisart and Plaghki, 1999; Dick et al., 2002; Veldhuijzen et al., 2006; Dick and Rashiq, 2007; Oosterman et al., 2011) and pain-related attentional deficits in rodent models of chronic pain (Cain et al., 1997; Lindner et al., 1999; Millecamps et al., 2004; Boyette-Davis et al., 2008; Pais-Vieira et al., 2009; Kodama et al., 2011). A pain-age interaction effect was observed in the model for the number of false alarms (and for number of random responses, though this was just below the level of statistical significance). There was also a significant effect of the interaction term in the model for reaction time. Younger controls had shorter reaction times than younger pain patients, but older patients were quicker to respond than older controls. Thus, older patients had increased incorrect responses and also tended to respond faster, possibly indicative of impaired inhibitory control. Impaired inhibitory control could be associated with underlying dysfunction of the prefrontal cortex (PFC), and it is known that there are morphological, neuroplastic and neurochemical changes in the PFC related to chronic pain (Moriarty et al., 2011).

The absence of any effects of pain or pain-age interaction on the WCST was unexpected given the strong body of literature to suggest that executive functions (and analogous cognitive flexibility in rodents) are impaired in chronic pain (Grisart and Van der Linden, 2001; Apkarian et al., 2004; Mongini et al., 2005; Karp et al., 2006; Leite-Almeida et al., 2009; Verdejo-Garcia et al., 2009; Walteros et al., 2011). However, a number of previous

536 studies failed to show an effect of pain on executive function (Suhr, 2003; Scherder et al.,

537 2008). The lack of an effect may be due limitations of the WCST measure itself (though this

538 test specifically has been used previously in fibromyalgia patients where deficits have been

539 observed). It is possible that there may have been decreased motivation towards the end of

540 the test session, though participants appeared to engage with the task and reduced motivation

541 was not noted by the experimenter. There is therefore a need for further research on the effect

542 of pain and the pain-age interaction on executive functioning, preferably utilizing a wide

543 range of executive-function measures.

544   The number of painful areas reported was a predictor of verbal memory, with scores

545 decreasing as pain diffuseness increased. Pain chronicity was found to be a positive predictor

546 of IQ and verbal memory. Some studies have shown that pain chronicity was not associated

547 with differences in cognitive function (Eccleston, 1994; Alanoglu et al., 2005), whereas others

548 have shown that duration of a painful illness was inversely related to cognitive performance

549 (Calandre et al., 2002; Apkarian et al., 2004; Ryan, 2005; Verdejo-Garcia et al., 2009). A

550 positive correlation, as observed herein, has not been demonstrated previously, but may

551 represent a habituation or compensation mechanism induced in prolonged pain states. Further

552 investigation of this theory is warranted.

553   Pain intensity was not generally associated with alterations in cognitive function, which

554 suggests that other aspects of the pain experience may contribute to changes in cognition.

555 Chronic pain grade and pain-related disability negatively affected aspects of attention,

556 suggesting that this cognitive domain may be more susceptible to the affective or disabling

557 dimensions of pain. Interactions between pain variables and age also made contributions to

558 memory and attention outcomes, again indicating an important interplay between these

559 variables.

Limitations

A sample size of 76 could be considered relatively small, however, sample sizes of this order have been used previously in pain-cognition studies (Eccleston, 1994; Grace et al., 1999; Grisart and Plaghki, 1999; Park et al., 2001; Dick et al., 2002; Apkarian et al., 2004; Harman and Ruyak, 2005; Mongini et al., 2005; Karp et al., 2006; Dick and Rashiq, 2007; Rodriguez-Andreu et al., 2009; Verdejo-Garcia et al., 2009; Walteros et al., 2011). While we attempted to address some of the shortcomings of previous studies, we may not have been able to do so adequately. The pain variable measures and the records of current medication use relate only to the patient subset of participants and so sample size is further reduced for these measures (*n* = 38). Therefore, effects of medication on cognitive outcomes cannot be ruled out completely, notwithstanding the application of appropriate statistical controls. The apparent clinical under-recognition of depression within the present sample of pain patients means that the effects of depression could not be controlled for experimentally. Depression was strongly correlated with presence of pain and was also significantly correlated with a number of cognitive outcomes. In spite of this, significant contributions of pain and pain-age interaction to some cognitive scores were found, over and above the contribution of depression. It is unlikely that the study is compromised by the presence of undiagnosed depression, since an increased prevalence of depression is known to be associated with chronic pain (Von Korff and Simon, 1996; Raftery et al., 2011). Since it is not known whether this series of tasks has been used in combination previously, it is possible that the order in which the tests were administered may have affected task performance. Motivation may affect performance of attentional tasks in chronic pain (Keogh et al., 2013) and was not measured here, but no obvious decrease in participant effort or motivation was observed during the assessment.

Conclusions

584 This study provides further support for the theory that pain affects cognition and that the

585 relationship is influenced by age. The cognitive outcomes affected were mainly within the

586 domains of memory and attention, with IQ and psychomotor speed also affected. Further

587 research is required to determine whether the present set of outcomes represents a specific

588 signature of cognitive performance in neuropathic and radicular pain.

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821   Table 1: Demographic information

	Chronic pain	Control
	Total (Male, Female)	Total (Male, Female)
Total number of participants	38 (16, 22)	38 (16, 22)
	Mean (standard deviation)	Mean (standard deviation)
Age (years)	45.6 (9.9)	44.2 (10.4)
Duration since last consumption of:		
Nicotine (hrs)	1.6 (3.5)	3.1 (6.6)
Caffeine (hrs)	5.3 (10.7)	5.8 (8.3)
Years of Education	13.8 (3.8)	15.2 (3.0)
	Total aged ≥ 45 years / < 45 years	Total aged ≥ 45 years / < 45 years
Number of participants in each age classification	22 / 16	17 / 21
	Percentage of participants in group	Percentage of participants in group
% of participants who smoke	50.0	18.4**

822

823   *p<.05, **p<.01, ***p<.001

824

825   Table 2: Psychological Variables

	Chronic Pain	**Control**
	Mean (standard deviation)	Mean (standard deviation)
State Anxiety:		
SAI total score	42.84 (12.48)	28.58 (7.40)***
Depression:		
Depression severity score	13.30 (5.13)	1.79 (2.20)***
	Percentage of participants in group	Percentage of participants in group
% of participants with clinically relevant depression scores[†]	50.0	0***
% of participants with a "major" depressive disorder classification[††]	36.8	0***
% of participants with depression-related functional impairment	86. 8	18.9***

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827

828   *p<.05, **p<.01, ***p<.001

829   [†]Clinically relevant depressive symptoms were considered if the participant's answers fell within the highlighted
830   section of the 9-item Patient Health Questionnaire (PHQ-9) on four or more items, one of which corresponded
831   to items 1 or 2

832   [††]The putative type of depressive disorder was classified as "major depressive disorder" depending on the
833   number of items answered in the highlighted section of the PHQ-9

834   [†††]Depression-related functional impairment was assessed by item 10 of the PHQ-9, and deemed present if the
835   item was endorsed as "somewhat difficult" or greater.

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Table 3: Group Comparisons of Cognitive outcomes

	Chronic Pain	Control
	Mean (Standard deviation)	Mean (Standard deviation)
Estimated full scale IQ	87.61 (14.83)	103.16 (13.10)***
Verbal Memory:		
<u>Immediate:</u>		
Unit Recall	8.61 (3.10)	11.58 (2.77)***
Theme Recall	8.45 (3.11)	10.76 (2.42)**
Learning Slope	3.97 (2.73)	4.89 (2.70)
<u>Delayed:</u>		
Unit Recall	9.24 (2.60)	11.24 (2.66)**
Theme Recall	9.24 (2.74)	10.58 (2.89)
Recognition	25.11 (3.14)	26.37 (2.30)
% Retention	77.78 (13.31)	77.34 (15.10)
Spatial Memory:		
Forward	8.42 (2.94)	9.87 (3.35)*
Reverse	9.42 (3.59)	11.03 (2.81)*
Total	8.66 (3.40)	10.45 (3.06)*
Attention:		
Hits	22.16 (3.99)	23.50 (3.90)
False Alarms	8.42 (5.20)	6.47(3.70)
Randoms	3.34 (4.10)	2.11 (2.893)
CPT D Prime	1.11 (0.38)	1.29 (0.30)*
Psychomotor speed:		
Hits reaction time (s)	544.38 (75.34)	559.59 (665.40)
False alarm reaction time (s)	562. 72 (112.69)	566.51 (126.00)
Executive Function		
(Raw scores):		
% Errors	35.42 (19.01)	28.95 (18.42)
% Perseverative Responses	21.50 (18.25)	16.03 (14.31)
% Perseverative Errors	18.87 (13.74)	14.11 (11.07)
% Non-perseverative Errors	16.61 (10.50)	14.82 (10.81)
% Conceptual Level Responses	52.76 (27.69)	63.16 (25.36)
Categories Completed	3.63 (2.59)	4.63 (2.12)
Trials to First Category	38.37 (44.64)	31.03 (37.34)
Failure to Maintain Set	0.95 (1.16)	0.63 (1.15)
Learning to Learn	0.15 (6.18)	0.86 (4.10)
(Standard Scores):		
% Errors	86.05 (15.86)	91.00 (17.81)
% Perseverative Responses	89.92 (20.34)	95.03 (19.50)
% Perseverative Errors	88.74 (19.68)	94.79 (19.22)
% Non-perseverative Errors	88.18 (16.58)	90.34 (15.76)
% Conceptual Level Responses	84.84 (16.71)	90.84 (18.14)

*p<.05, **p<.01, ***p<.001

Table 4: The contribution of pain, pain-age interaction and other factors to cognitive outcome measures

	Estimated FSIQ	Verbal Learning Slope	Verbal Recognition Memory	Spatial Span Reversal	CPT Hit Responses	CPT False Alarm Responses	CPT Random Responses	CPT Hit Reaction Time
Block 1								
Years of Education (β)	0.37***	0.07	-	0.23	0.07	- 0.22*	- 0.17	-
Last Caffeine (β)	-	-	-	-	-	- 0.11	-	-
Gender (β)	-	-	-	-	-	-	-	0.21
PHQ Severity Score (β)	- 0.003	-	-	-	- 0.59**	-	-	-
SAI Total Score (β)	- 0.124	- 0.27	- 0.23	-	-	-	-	-
Block 2								
Pain condition (β)	0.33*	0.021	0.08	0.21$^{\#}$	- 0.36†	- 0.14	- 0.12	0.12
Age (β)	- 0.16	- 0.29*	- 0.27**	0.14	- 0.36**	0.28*	0.36***	0.15
Block 3								
Pain condition x age (β)	0.03	0.20^{+}	0.30**	0.01	- 0.04	- 0.25*	- 0.20†	0.24*
Total R^2	0.45	0.19	0.21	0.11	0.26	0.29	0.25	0.16

FSIQ: Full Scale Intelligence Quotient, CPT: Continuous Performance Task, PHQ: Patient Health Questionnaire, SAI: State Anxiety Inventory

*p<.05, **p<.01, ***p<.001, †$p = 0.06$, $^{\#}p = 0.07$, $^{+}p = 0.08$

Table 5: Pain variables – descriptive data

Pain Variable	Mean (Standard deviation)
Present pain intensity	5.63 (3.63)
Average pain intensity	73.16 (13.67)
Pain-related disability score	79.39 (15.12)
Chronic pain grade	3.53 (0.65)
Number of painful areas	5.87 (3.63)
Pain chronicity (months)	101.45 (86.43)
Self-assessed effect of pain on cognition	6.45 (2.74)

Table 6: Breakdown of Patient Medications

Medication variable	
	Percentage
% receiving medication	78.9
% receiving opioids	63.2
% receiving anticonvulsants	42.1
% receiving antidepressants	31.6
% receiving NSAIDs	39.5
% receiving other medication	39.5
	Mean (Standard deviation)
% reported pain relief from medications	36.59 (27.04)
Total number of medications	2.7895 (2.04223)

Table S1: Bivariate correlation matrix of participant characteristics and cognitive outcomes – r correlation coefficients

	Group	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Participant characteristics										
Group	1									
Age	−0.08	1								
Gender	0.00	−0.01	1							
Years of Education	0.21	−0.27*	0.04	1						
Smoker classification	0.33**	0.07	0.06	0.20	1					
Time since last nicotine	0.03	−0.35	−0.05	−0.10	0.28	1				
Time since last caffeine	0.10	−0.40**	0.17	−0.07	0.10	0.42*	1			
Time since last alcohol	−0.28*	0.084	0.03	−0.13	−0.33**	0.08	−0.02	1		
Depression score	−0.84**	−0.01	−0.07	−0.26*	−0.27*	0.19	−0.07	0.23	1	
State anxiety score	−0.59**	−0.03	−0.06	−0.36**	−0.09	0.37	0.08	0.21	0.69**	1
Cognitive variables										
Estimated FSIQ	0.49**	−0.27*	0.01	0.52**	0.21	0.10	0.06	−0.17	−0.47**	−0.42**
Immediate Verbal Memory:										
Story Unit Recall	0.46**	−0.13	0.26*	0.28*	0.28*	0.25	0.10	−0.25*	−0.45**	−0.32**
Theme Unit Recall	0.39**	−0.07	0.17	0.19	0.26*	0.00	−0.04	−0.22	−0.36**	−0.21
Learning slope	0.17	−0.28*	−0.07	0.24*	−0.01	0.04	0.09	−0.11	−0.11	−0.24*
Delayed Verbal Memory:										
Unit Recall	0.36**	−0.13	0.10	0.32**	0.13	0.20	−0.05	−0.22	−0.37**	−0.29*
Theme Recall	0.22	−0.15	0.14	0.16	0.13	−0.07	0.03	−0.30*	−0.19	−0.13
Recognition	0.17	−0.19	0.15	0.21	0.21	0.19	−0.01	−0.13	−0.22	−0.23*
% Retention	−0.02	−0.20	−0.12	0.21	−0.16	0.05	−0.20	−0.03	0.02	−0.10
Spatial Memory:										

	Group	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Forward	0.23*	−0.12	0.03	0.11	0.17	−0.15	0.17	−0.15	−0.25*	−0.24*
Reverse	0.24*	0.07	−0.14	0.23*	0.01	−0.04	−0.05	−0.23	−0.22	−0.22
Total	0.27*	−0.02	−0.07	0.18	0.12	−0.05	0.05	−0.21	−0.24*	−0.22

Table S1: continued from previous page

	Group	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Attention:										
Hits	0.17	−0.34**	−0.05	0.24*	−0.02	0.08	0.11	0.01	−0.31**	−0.21
False alarms	−0.17	0.35**	−0.04	−0.34**	0.07	−0.33	−0.30*	0.12	0.16	0.06
Randoms	−0.16	0.35**	0.03	−0.36**	0.01	−0.17	−0.16	0.06	0.14	0.18
D-Prime	0.23*	−0.45**	0.00	0.41**	−0.06	0.31	0.24*	−0.10	−0.28*	−0.16
T-score	0.22	−0.44**	−0.01	0.39**	−0.08	0.36	0.25*	−0.09	−0.29*	−0.23*
T-score corrected	0.18	−0.29*	0.13	0.35**	−0.08	0.27	0.19	0.00	−0.30*	−0.27*
Psychomotor Speed:										
Hit reaction time	0.11	0.15	0.25*	−0.09	0.13	0.12	−0.02	−0.07	−0.07	0.04
False Alarm reaction time	0.01	0.02	0.23*	0.08	0.11	0.25	0.05	−0.07	0.09	0.14
Executive Function:										
Errors	0.15	−0.17	0.11	−0.04	−0.02	0.11	0.24*	−0.16	−0.13	−0.11
Perseverative responses	0.13	−0.07	0.17	−0.20	−0.03	0.13	0.24*	−0.13	−0.15	−0.01
Perseverative errors	0.16	−0.08	0.17	−0.18	−0.03	0.12	0.23	−0.15	−0.16	−0.03
Non-perseverative errors	0.07	−0.24*	0.07	0.03	−0.01	0.06	0.20	−0.10	−0.04	−0.17
Conceptual level responses	0.18	−0.19	0.09	−0.01	0.02	0.06	0.24*	−0.16	−0.14	−0.12
Categories completed	0.20	−0.29*	−0.01	0.26*	0.00	0.07	0.19	−0.18	−0.24*	−0.21
Trials to 1st category	−0.14	0.17	−0.09	−0.15	0.06	0.15	−0.27*	0.00	0.19	0.27*
Failure to maintain set	−0.20	0.19	0.11	−0.06	−0.10	0.26	−0.15	0.35**	0.27*	0.13
Learning to learn	0.06	−0.19	0.09	−0.03	−0.09	0.21	−0.16	−0.11	0.05	0.13

*$p < 0.05$, **$p < 0.01$

Table S2: Correlation matrix of general *patient* characteristics and cognitive outcomes – r correlation coefficients

	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Estimated FSIQ	−0.27	0.08	0.53**	0.08	0.17	0.02	−0.24	−0.08	−0.05
Immediate Verbal Memory:									
Unit Recall	−0.32	0.31	0.43**	0.03	0.06	0.15	−0.08	−0.06	−0.02
Theme Recall	−0.13	0.26	0.33*	0.17	−0.07	−0.00	−0.03	0.03	0.14
Learning slope	−0.43**	0.15	0.23	0.03	0.11	0.30	−0.13	−0.04	−0.22
Delayed Verbal Memory:									
Unit Recall	−0.26	0.12	0.45**	−0.03	0.01	0.05	0.08	−0.02	−0.01
Theme Recall	−0.30	0.19	0.33*	0.11	0.04	0.06	−0.17	0.01	0.14
Recognition	−0.40*	0.10	0.38*	−0.05	0.25	0.03	−0.03	0.03	−0.08
% Retention	−0.08	−0.19	0.19	−0.16	−0.25	−0.22	0.16	0.18	0.08
Spatial Memory:									
Forward	−0.10	0.14	0.09	0.04	0.46*	0.18	−0.13	−0.04	0.00
Reverse	0.06	−0.14	0.29	−0.18	0.25	−0.12	−0.12	0.03	−0.10
Total	−0.05	−0.04	0.22	−0.06	0.41	0.02	−0.20	0.04	0.00
Attention:									
Hits	−0.27	−0.13	0.13	−0.16	0.12	0.19	0.03	−0.36*	−0.10
False alarms	0.54**	−0.20	−0.38*	0.22	−0.34	−0.31	0.29	−0.03	−0.06
Randoms	0.45**	−0.02	−0.43**	0.06	−0.41	−0.19	0.13	0.00	−0.04
D-Prime	−0.49**	0.12	0.41*	−0.19	0.34	0.29	−0.18	−0.19	0.00
T-score	−0.54**	−0.02	0.36*	−0.27	0.31	0.31	−0.17	−0.16	0.04
T-score corrected	−0.31	0.11	0.35*	−0.33	0.16	0.28	−0.01	−0.30	−0.07
Psychomotor Speed:									
Hit reaction time	−0.12	0.23	−0.10	−0.07	0.11	−0.09	0.42*	0.32	0.11
False Alarm reaction time	−0.24	0.01	0.02	0.00	0.17	−0.06	0.23	0.49**	0.34*

Table S2: continued from previous page

	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Executive Function:									
Errors	−0.26	0.08	0.05	−0.16	0.19	0.18	−0.18	0.10	0.08
Perseverative responses	−0.07	0.16	−0.16	−0.18	0.20	0.15	−0.13	0.01	0.08
Perseverative errors	−0.09	0.16	−0.14	−0.19	0.20	0.13	−0.16	0.02	0.10
Non-perseverative errors	−0.32	0.12	0.07	−0.07	0.16	0.18	−0.01	0.09	−0.10
Conceptual level responses	−0.29	0.11	0.11	−0.10	0.17	0.18	−0.17	0.12	0.07
Categories completed	−0.35*	0.08	0.41*	−0.01	0.10	0.15	−0.19	−0.06	−0.05
Trials to 1st category	0.15	−0.11	−0.19	0.25	0.14	−0.15	−0.12	0.02	0.18
Failure to maintain set	0.23	−0.04	−0.16	−0.11	0.24	0.02	0.54**	0.40*	0.18
Learning to learn	−0.19	0.12	0.01	0.00	0.40	−0.11	−0.28	0.20	0.07

*$p < 0.05$, **$p < 0.01$

Table S3: Correlation matrix of patient-specific characteristics and cognitive outcomes – r correlation coefficients

	Medication	Opioid	Anti-convulsant	Anti-depressant	NSAID	Other	Number of medications	% Pain relief	Self-assessed cognition
Estimated FSIQ	−0.08	0.12	−0.01	−0.24	−0.02	−0.12	0.06	−0.04	−0.16
Immediate Verbal Memory:									
Unit Recall	−0.15	0.12	0.15	−0.09	−0.07	−0.12	0.08	−0.13	−0.26
Theme Recall	−0.02	0.10	0.06	0.03	−0.19	0.13	−0.11	−0.21	−0.07
Learning slope	−0.22	0.15	0.37*	0.01	0.03	−0.11	−0.14	−0.06	−0.06
Delayed Verbal Memory:									
Unit Recall	−0.18	0.12	0.25	−0.03	0.03	−0.05	−0.04	−0.17	−0.07
Theme Recall	−0.19	0.12	0.17	−0.02	−0.13	0.13	−0.11	−0.22	−0.08
Recognition	0.06	−0.08	−0.08	−0.29	−0.28	−0.21	0.19	0.05	−0.10
% Retention	0.07	−0.14	0.11	0.06	0.14	0.09	−0.06	0.05	0.25
Spatial Memory:									
Forward	−0.19	0.13	0.01	0.22	0.08	−0.03	−0.27	−0.14	−0.10
Reverse	−0.25	0.22	0.00	−0.10	0.02	−0.13	0.02	−0.21	−0.18
Total	−0.25	0.21	0.01	0.02	0.01	−0.08	−0.13	−0.25	−0.06
Attention:									
Hits	−0.06	0.00	0.18	−0.20	0.09	0.18	−0.04	0.01	−0.29
False alarms	−0.27	0.26	−0.05	0.30	−0.02	0.30	−0.26	0.10	0.05
Randoms	−0.24	0.11	0.10	0.29	0.28	0.13	−0.25	0.00	0.12
D-Prime	0.17	−0.17	0.11	−0.38*	0.06	−0.17	0.14	−0.14	−0.18
T-score	0.06	−0.13	0.11	−0.30	0.11	−0.05	0.08	−0.17	−0.18
T-score corrected	0.08	−0.15	0.04	−0.35*	0.11	−0.01	0.11	−0.11	−0.14
Psychomotor Speed:									
Hit reaction time	0.21	−0.02	0.05	−0.15	−0.02	−0.13	0.22	−0.06	−0.02
False Alarm reaction time	0.26	0.00	0.05	−0.09	−0.04	−0.15	0.22	−0.13	0.21

Table S3: continued from previous page.

	Medication	Opioid	Anti-convulsant	Anti-depressant	NSAID	Other	Number of medications	% Pain relief	Self-assessed cognition
Executive Function:									
Errors	−0.19	0.27	0.12	−0.27	0.08	−0.03	−0.01	−0.25	−0.03
Perseverative responses	−0.32[*]	0.31	0.10	−0.14	0.01	0.12	−0.13	−0.22	−0.01
Perseverative errors	−0.31	0.30	0.10	−0.14	0.01	0.14	−0.14	−0.24	0.01
Non-perseverative errors	0.01	0.04	0.22	−0.22	0.20	−0.25	0.10	−0.11	−0.06
Conceptual level responses	−0.18	0.27	0.12	−0.29	0.06	−0.06	0.02	−0.25	−0.04
Categories completed	−0.07	−0.01	0.00	−0.29	−0.06	−0.05	0.09	−0.12	−0.24
Trials to 1st category	0.07	−0.06	−0.03	0.34[*]	−0.15	0.14	−0.15	0.07	−0.04
Failure to maintain set	0.09	0.01	−0.09	−0.23	−0.10	−0.05	0.18	−0.09	0.45[**]
Learning to learn	0.04	−0.22	0.00	0.14	−0.24	0.28	−0.10	−0.01	−0.04

*$p < 0.05$, **$p < 0.01$

Table S2: Correlation matrix of general *patient* characteristics and cognitive outcomes – r correlation coefficients

	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Estimated FSIQ	−0.27	0.08	0.53**	0.08	0.17	0.02	−0.24	−0.08	−0.05
Immediate Verbal Memory:									
Unit Recall	−0.32	0.31	0.43**	0.03	0.06	0.15	−0.08	−0.06	−0.02
Theme Recall	−0.13	0.26	0.33*	0.17	−0.07	−0.00	−0.03	0.03	0.14
Learning slope	−0.43**	0.15	0.23	0.03	0.11	0.30	−0.13	−0.04	−0.22
Delayed Verbal Memory:									
Unit Recall	−0.26	0.12	0.45**	−0.03	0.01	0.05	0.08	−0.02	−0.01
Theme Recall	−0.30	0.19	0.33*	0.11	0.04	0.06	−0.17	0.01	0.14
Recognition	−0.40*	0.10	0.38*	−0.05	0.25	0.03	−0.03	0.03	−0.08
% Retention	−0.08	−0.19	0.19	−0.16	−0.25	−0.22	0.16	0.18	0.08
Spatial Memory:									
Forward	−0.10	0.14	0.09	0.04	0.46*	0.18	−0.13	−0.04	0.00
Reverse	0.06	−0.14	0.29	−0.18	0.25	−0.12	−0.12	0.03	−0.10
Total	−0.05	−0.04	0.22	−0.06	0.41	0.02	−0.20	0.04	0.00
Attention:									
Hits	−0.27	−0.13	0.13	−0.16	0.12	0.19	0.03	−0.36*	−0.10
False alarms	0.54**	−0.20	−0.38*	0.22	−0.34	−0.31	0.29	−0.03	−0.06
Randoms	0.45**	−0.02	−0.43**	0.06	−0.41	−0.19	0.13	0.00	−0.04
D-Prime	−0.49**	0.12	0.41*	−0.19	0.34	0.29	−0.18	−0.19	0.00
T-score	−0.54**	−0.02	0.36*	−0.27	0.31	0.31	−0.17	−0.16	0.04
T-score corrected	−0.31	0.11	0.35*	−0.33	0.16	0.28	−0.01	−0.30	−0.07
Psychomotor Speed:									
Hit reaction time	−0.12	0.23	−0.10	−0.07	0.11	−0.09	0.42*	0.32	0.11
False Alarm reaction time	−0.24	0.01	0.02	0.00	0.17	−0.06	0.23	0.49**	0.34*

Table S2: continued from previous page

	Age	Gender	Years of Education	Smoker	Time since last nicotine	Time since last caffeine	Time since last alcohol	Depression score	State anxiety score
Executive Function:									
Errors	−0.26	0.08	0.05	−0.16	0.19	0.18	−0.18	0.10	0.08
Perseverative responses	−0.07	0.16	−0.16	−0.18	0.20	0.15	−0.13	0.01	0.08
Perseverative errors	−0.09	0.16	−0.14	−0.19	0.20	0.13	−0.16	0.02	0.10
Non-perseverative errors	−0.32	0.12	0.07	−0.07	0.16	0.18	−0.01	0.09	−0.10
Conceptual level responses	−0.29	0.11	0.11	−0.10	0.17	0.18	−0.17	0.12	0.07
Categories completed	−0.35*	0.08	0.41*	−0.01	0.10	0.15	−0.19	−0.06	−0.05
Trials to 1st category	0.15	−0.11	−0.19	0.25	0.14	−0.15	−0.12	0.02	0.18
Failure to maintain set	0.23	−0.04	−0.16	−0.11	0.24	0.02	0.54**	0.40*	0.18
Learning to learn	−0.19	0.12	0.01	0.00	0.40	−0.11	−0.28	0.20	0.07

*$p < 0.05$, **$p < 0.01$