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# **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*

168 The Logical Memory subtests I and II of the Wechsler Memory Scale-III (WMS-III, (Wechsler,  
169 1997b)) were used to assess short- and long-term verbal memory and recognition memory.  
170 Two different stories (A and B) were read to the subject, and immediately afterwards the  
171 subject was asked to retell the story from memory.

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

180

### 181 *Spatial Memory*

182 The spatial span subtest of the WMS-III was used to measure short-term spatial memory  
183 capacity. The test was administered using the spatial span board, which consists of 10 cubes  
184 with the numbers 1 to 10 printed on the sides of the cubes facing the examiner. For spatial span  
185 forward, the examiner tapped the cubes in a specified sequence pattern and then asked the  
186 participant to tap the same sequence. For spatial span backward (reverse), the participant was  
187 asked to tap the sequence in reverse order. The sequence length increased until the participant  
188 could no longer replicate the sequence correctly. Raw scores were converted to age-adjusted  
189 scaled score equivalents using the WMS-III Administration and Scoring Manual (Wechsler,  
190 1997b).

191

### 192 *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  $\beta$  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

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

426 Pain chronicity was found to contribute significantly to the models of FSIQ ( $\beta = 0.31$ ,  
427  $p = 0.05$ ), immediate verbal memory ( $\beta = 0.47$ ,  $p = 0.003$ ) and delayed verbal memory ( $\beta =$   
428  $0.40$ ,  $p = 0.02$ ). The association was positive in each of these cases, suggesting that  
429 performance improved with an increasing duration of pain. The contribution of chronicity was  
430 also close to significance in the hit response reaction time model ( $\beta = 0.36$ ,  $p = 0.07$ ), which  
431 would suggest an increase in reaction time with increased pain chronicity.

432 The number of painful areas was found to be an effective predictor of immediate verbal  
433 memory (story-unit recall:  $\beta = -0.34$ ,  $p = 0.05$ ; theme-unit recall:  $\beta = -0.37$ ,  $p = 0.04$ ) and  
434 delayed verbal memory ( $\beta = -0.35$ ,  $p = 0.04$ ), whereby “more painful sites” was associated  
435 with poorer performance. The interaction of the number of painful areas and age was a  
436 significant contributor to the model of the spatial span reverse trial ( $\beta = -0.36$ ,  $p = 0.03$ ,  
437 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

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

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

531         The absence of any effects of pain or pain-age interaction on the WCST was  
532 unexpected given the strong body of literature to suggest that executive functions (and  
533 analogous cognitive flexibility in rodents) are impaired in chronic pain (Grisart and Van der  
534 Linden, 2001; Apkarian et al., 2004; Mongini et al., 2005; Karp et al., 2006; Leite-Almeida et  
535 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.

560 *Limitations*

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

583 *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.

589

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596

597

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821 Table 1: Demographic information

	<b>Chronic pain</b>	<b>Control</b>
	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 $\geq$ 45 years / < 45 years	Total aged $\geq$ 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

	<b>Chronic Pain</b>	<b>Control</b>
	Mean (standard deviation)	Mean (standard deviation)
<b>State Anxiety:</b>		
SAI total score	42.84 (12.48)	28.58 (7.40)***
<b>Depression:</b>		
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 <sup>†</sup>	50.0	0***
% of participants with a “major” depressive disorder classification <sup>††</sup>	36.8	0***
% of participants with depression-related functional impairment	86.8	18.9***

826

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.

836

837

838 Table 3: Group Comparisons of Cognitive outcomes

	<b>Chronic Pain</b>	<b>Control</b>
	Mean (Standard deviation)	Mean (Standard deviation)
<b>Estimated full scale IQ</b>	87.61 (14.83)	103.16 (13.10)***
<b>Verbal Memory:</b>		
<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)
<b>Spatial Memory:</b>		
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)*
<b>Attention:</b>		
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)*
<b>Psychomotor speed:</b>		
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)
<b>Executive Function</b>		
<b>(Raw scores):</b>		
% 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)
<b>(Standard Scores):</b>		
% 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)

839 \*p&lt;.05, \*\*p&lt;.01, \*\*\*p&lt;.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
<b>Block 1</b>								
Years of Education ( $\beta$ )	0.37***	0.07	-	0.23	0.07	- 0.22*	- 0.17	-
Last Caffeine ( $\beta$ )	-	-	-	-	-	- 0.11	-	-
Gender ( $\beta$ )	-	-	-	-	-	-	-	0.21
PHQ Severity Score ( $\beta$ )	- 0.003	-	-	-	- 0.59**	-	-	-
SAI Total Score ( $\beta$ )	- 0.124	- 0.27	- 0.23	-	-	-	-	-
<b>Block 2</b>								
Pain condition ( $\beta$ )	0.33*	0.021	0.08	0.21 <sup>#</sup>	- 0.36 <sup>†</sup>	- 0.14	- 0.12	0.12
Age ( $\beta$ )	- 0.16	- 0.29*	- 0.27**	0.14	- 0.36**	0.28*	0.36***	0.15
<b>Block 3</b>								
Pain condition x age ( $\beta$ )	0.03	0.20 <sup>+</sup>	0.30**	0.01	- 0.04	- 0.25*	- 0.20 <sup>†</sup>	0.24*
<b>Total R<sup>2</sup></b>	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

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , <sup>†</sup> $p = 0.06$ , <sup>#</sup> $p = 0.07$ , <sup>+</sup> $p = 0.08$

Table 5: Pain variables – descriptive data

<b>Pain Variable</b>	<b>Mean (Standard deviation)</b>
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

<b>Medication variable</b>	
	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
<b>Participant characteristics</b>										
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
<b>Cognitive variables</b>										
Estimated FSIQ	0.49**	-0.27*	0.01	0.52**	0.21	0.10	0.06	-0.17	-0.47**	-0.42**
<b>Immediate Verbal Memory:</b>										
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*
<b>Delayed Verbal Memory:</b>										
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
<b>Spatial Memory:</b>										

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
<b>Attention:</b>										
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*
<b>Psychomotor Speed:</b>										
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
<b>Executive Function:</b>										
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 1 <sup>st</sup> 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
<b>Immediate Verbal Memory:</b>									
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
<b>Delayed Verbal Memory:</b>									
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
<b>Spatial Memory:</b>									
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
<b>Attention:</b>									
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
<b>Psychomotor Speed:</b>									
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
<b>Executive Function:</b>									
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 1 <sup>st</sup> 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
<b>Immediate Verbal Memory:</b>									
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
<b>Delayed Verbal Memory:</b>									
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
<b>Spatial Memory:</b>									
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
<b>Attention:</b>									
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
<b>Psychomotor Speed:</b>									
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
<b>Executive Function:</b>									
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 1 <sup>st</sup> 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
<b>Immediate Verbal Memory:</b>									
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
<b>Delayed Verbal Memory:</b>									
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
<b>Spatial Memory:</b>									
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
<b>Attention:</b>									
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
<b>Psychomotor Speed:</b>									
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
<b>Executive Function:</b>									
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 1 <sup>st</sup> 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

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