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Method: Participants with chronic pain (n=41) completed standardised neuropsychological tests, and self-report measures of cognitive functioning, pain, mood, and sleep, as part of a broader study investigating cognitive performance in pain.

Results: Average neuropsychological test performance was subtly below normative means (within one standard deviation). Twenty-five percent of the sample scored substantially below age-adjusted norms on one or more objective tests. There were moderate-to-large associations between objective performance (e.g., Trail-Making B) and subjective cognitive complaints (e.g., Everyday Memory Questionnaire-Revised), controlling for age and education level. This was moderated by anxiety, such that subjective-objective relationships were particularly strong in those with higher anxiety. Poorer test performance was associated with higher pain intensity, and catastrophising. Subjective-objective cognition relationships remained after controlling for catastrophising.

Conclusion: Patients' self-reported cognitive concerns concurred with objectively measured performance, independent of age, education and catastrophising. Moreover, those with severe anxiety were more accurate in predicting their cognitive performance. The findings highlight some interesting cognition-mood relationships, and suggest that easy-to-administer questionnaires, such as the Everyday Memory Questionnaire-Revised and the Behavior Rating Inventory of Executive Function - Adult Version, may be useful to capture cognitive concerns in clinical settings.

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Title: Relationship between self-reported cognitive difficulties, objective neuropsychological test performance and psychological distress in chronic pain

Running head: Subjective and objective cognition in chronic pain

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Significance: Cognitive concerns in chronic pain reflected objective neurocognitive performance. This was moderated by anxiety, such that self-reported cognition was more consistent with objective performance in those with high anxiety. Our findings suggest that reported cognitive concerns should be heeded, and self-report measures may be used clinically to facilitate dialogue about cognitive functioning.

Abstract

Background: Persons with chronic pain often report problems with cognitive abilities, such as memory or attention. There is limited understanding of whether objective performance is consistent with subjective reports, and how psychological factors contribute. We aimed to investigate these relationships in a group of patients expressing cognitive concerns, and evaluate the utility of self-report tools for pain management settings.

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Conclusion: Patients' self-reported cognitive concerns concurred with objectively measured performance, independent of age, education and catastrophising. Moreover, those with severe anxiety were more accurate in predicting their cognitive performance. The findings highlight some interesting cognition-mood relationships, and suggest that easy-to-administer questionnaires, such as the Everyday Memory Questionnaire-Revised and the Behavior Rating Inventory of Executive Function - Adult Version, may be useful to capture cognitive concerns in clinical settings.

Keywords: chronic pain, neuropsychology, attention, working memory, cognitive function

1. Introduction

Chronic pain often brings with it a host of associated symptoms including reduced efficiency of cognitive skills (Moriarty, McGuire, & Finn, 2011; Rathbone et al., 2016). Around 50% of people living with pain report cognitive difficulties (McCracken & Iverson, 2001; Westoby, Mallen, & Thomas, 2009), occurring in the domains of attention, processing speed, working memory and executive functions (Moriarty et al., 2011). Chronic pain is already known to be a leading global cause of disability (Rice, Smith, & Blyth, 2016; Vos et al., 2015), and compromised cognitive functioning may further limit activity participation, especially with withdrawal from occupational activities. Further, the integrity of cognitive processes such as executive control has been directly linked to the ability to regulate responses to pain, in both chronic and experimental pain models (Bjekić, Živanović, Purić, Oosterman, & Filipović, 2017; Karsdorp, Geenen, & Vlaeyen, 2014; Solberg Nes, Roach, & Segerstrom, 2009; Verhoeven et al., 2011; Wiech, Ploner, & Tracey, 2008). However, there remains relatively limited understanding of how the everyday cognitive difficulties reported by patients map onto cognitive impairment as measured by standardised neuropsychological tests. Additionally, there is a lack of consensus on how symptoms of psychological distress moderate this relationship.

Recent studies have provided preliminary evidence that cognitive concerns do indeed reflect poorer performance on neuropsychological tests. Landro et al. (2013) and Tesio et al. (2015) showed associations between subjective appraisals of cognition and poorer attention and executive function performances in patients with chronic pain, which persisted when adjusting for the role of depressive symptoms. In contrast, others have found no association between self-reported and objective cognitive performance, and concluded that cognitive concerns are a subjective experience related to severity of pain, fatigue, or mood symptoms, but not reflected in performance measures (Walitt et al., 2016). Such discrepancies may be due to considerable variation in sample characteristics such as size and heterogeneity, with some studies reporting on specific populations (e.g. fibromyalgia) and others including a broad range of chronic pain conditions. Further, prior studies have not specifically investigated the relationship between self-reported and objective measures of cognition in patients who present with cognitive concerns.

Importantly, there is also wide variation in measurement of cognition, including different self-report tools and performance tests (Ojeda, Failde, Duenas, Salazar, & Eccleston, 2016), with some studies using computerised experimental tasks and others using standardised neuropsychological tests. Moreover, many studies included only one measure of mood, such

as depression, but failed to capture other fundamental psychological symptoms known to be highly relevant to chronic pain, such as anxiety, catastrophising, and self-efficacy, and clinical issues such as sleep disturbance (Menefee et al., 2000).

Given the limitations of previous research, the objectives of the present study were threefold: 1) to assess the convergence of self-reported cognitive concerns with objectively measured neuropsychological performance in a sample of patients for whom cognitive functioning was a concern; 2) to investigate the contribution of pain severity, psychological distress, and sleep to this relationship; and, 3) to evaluate measures of self-reported cognition that may be of practical use in a pain clinic setting to screen for cognitive impairment, considering cost, accessibility and ease of administration.

2. Methods

2.1. Participants and procedures

Forty-one participants were recruited as part of a study investigating the effect of computerised cognitive training on cognitive performance in chronic pain (Clinical Trials registry number NCT02440490). Criteria for inclusion were chronic back (including widespread pain), age 18-65, proficiency in English language (sufficient to comprehend informed consent and task instructions, evaluated during phone screening and confirmed during assessment session), and no supertherapeutic dosages of opioid or benzodiazepine medication ($<120\text{mg/day}$ morphine equivalent; $<20\text{mg/day}$ benzodiazepine) according to guidelines set out in the Medication Quantification Scale (Harden et al., 2005). Participants were included if they verbally reported experiencing cognitive changes since the onset of their pain, but had no prior history of acquired brain injury, epilepsy or other neurological disorder that may affect cognitive abilities, and consumed no more than 10 alcoholic drinks per week (where one standard drink = 10 grams of alcohol, as per Australian Government Department of Health guidelines).

All procedures were conducted in accordance with protocols approved by The Alfred Hospital and Monash University ethics committees, and participants gave written informed consent. In this cross-sectional study, participants completed a battery of neuropsychological tests and questionnaires as described below, in a single session of 2 hours duration. Two participants were excluded due to a demonstrated lack of understanding of the requirements of participation and suspected compromised ability to accurately report cognitive and psychological status on the questionnaires. The first excluded participant completed all questionnaires rapidly with a response style that indicated a lack of thorough or accurate completion, and the other was suspected to have a pre-existing cognitive impairment

(estimated IQ on the Test of Premorbid Functioning was >2 standard deviations below the normative mean, falling within the Borderline Impaired range).

2.2. Cognitive tests

2.2.1. The Trail-Making Test (Reitan, 1955) is a paper-and-pencil task comprising two parts. In Part A, participants sequentially connect scattered numbers on a page in chronological order. In Part B, participants alternate between numbers and letters (i.e., 1–A–2–B–3–C etc.), forcing continual switching of attention between the two sequences. Scores for each part reflect the time taken to correctly complete the sequence, such that higher scores represent poorer performance (i.e., longer time required). Trail-making is considered a measure of processing speed and cognitive flexibility, and is highly sensitive to neurological dysfunction (Bowie & Harvey, 2006).

2.2.2. The Symbol-Digit Modalities Test (SDMT) (Smith, 1991) is a paper-and-pencil test of attention and information processing speed. It consists of a series of abstract symbols that participants must match to a set of corresponding digits using a key. Participants are required to write the appropriate digit in a box below the symbol as quickly as possible. The score generated is the number of digits correctly filled in 90 seconds, with higher scores representing better performance.

2.2.3. The Stroop Color and Word Test (Stroop) (Golden, 1978) was included as a measure of inhibitory control. It comprises a Word page (the words “red”, “blue”, and “green”) where words are read aloud as quickly as possible; followed by a Colour page (a series of crosses printed in red, blue, and green ink) for which participants must state the colours aloud; and, finally a Colour-Word page (words printed in colours that do not match, e.g., the word “red” printed in blue ink). The participant is required to ignore the word and state the colour of the ink it is printed in. Due to the incongruence of colour and word and the automatic nature of word-reading, this requires inhibitory control to override the most automatic response, which is to read the word. The test is timed and the number of correct items stated aloud in 45 seconds forms a raw score. The Colour-Word score was used in the present analysis as a measure of inhibitory control, where higher numbers indicate better performance.

2.2.4. The Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) is a test of executive control, specifically the ability to “shift set”, think flexibly and adapt to changing parameters. It requires participants to match a set of cards to one of four stimulus cards, on the basis of either its colour, shape, or number. They are not told the criterion on which to match the cards, but are given feedback on each match

(“correct” or “incorrect”), allowing them to learn the correct matching criterion. Once 10 consecutive correct matches are made, this is considered a complete “category” and the criterion for matching changes unbeknownst to the examinee. The test continues until 6 complete categories have been achieved, or until all 128 cards have been used. The number of Perseverative Errors, that is the number of times the examinee continued responding to the previous matching criterion even when this was no longer rewarding (i.e. they were told “incorrect”) can be used as a measure of inflexible thinking, and is considered the most sensitive single metric of executive control generated by this task (Strauss, Sherman, & Spreen, 2006). Higher numbers of perseverative errors indicate longer persistence in an ineffective response pattern.

2.2.5. The Test of Premorbid Functioning (TOPF) (Wechsler, 2009) is used in neuropsychological practice as a method of estimating premorbid intelligence quotient (IQ). It consists of 70 English words with phonetically irregular pronunciations, which the examinee is asked to read aloud. The number of correctly pronounced words is summed to create a total score, which is converted to a standardised score based on age-matched normative data. Consistent with all Wechsler intelligence tests, the mean standardised score is 100 with a standard deviation of 10. Word-reading ability correlates strongly with overall intelligence and is relatively resistant to neurological impairment (Franzen, Burgess, & Smith-Seemiller, 1997) and therefore was used to characterise participants’ premorbid (before pain onset) functioning. Note that the TOPF may provide a slight underestimate of IQ in some cases, e.g. in people who have more aptitude for visual than verbal tasks, or for whom English is a second language.

2.3. Self-report questionnaires

2.3.1. Cognitive functioning

2.3.1.1. The Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, Fitzgerald, & Parkes, 1982) is a 25-item inventory listing various examples of attention or concentration lapses, for which respondents rate the frequency of occurrence from 0 “never” to 4 “very often”. Item scores were summed to create a total score for the measure.

2.3.1.2. The Everyday Memory Questionnaire – Revised (EMQ-R) (Royle & Lincoln, 2008) comprises 13 items, revised from the original 35- and 28-item versions. Each item is an instance of memory or attention failure, for which respondents report the frequency of occurrence on a 5-point scale from “Once or less in the last month” to “Once or more in a day”, and items are summed to create a total. Although it is ostensibly a questionnaire about

memory, it also includes items relating to attention and working memory (Royle & Lincoln, 2008).

2.3.1.3. The Behaviour Rating Inventory of Executive Function – Adult (BRIEF-A) (Roth, Isquith, & Gioia, 2005) is a 75-item list of behaviours that respondents must rate in terms of how often each was a problem for them over the past month (“never”, “sometimes”, or “often”). Responses sum to form 9 separate subscales, each designed to capture a different aspect of executive functioning in order to form a ‘profile’: Inhibit, Shift, Emotional Control, Initiate, Self Monitor, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials. To ascertain clinically elevated problems, raw scores for each subscale are converted to T-scores, adjusted for age based on published normative data, and clinical elevation is defined as any T-score >65 (Roth et al., 2005).

2.3.2 Pain

2.3.2.1. The Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994) is used to measure pain intensity, rated on four numeric scales from 0 “no pain” to 10 “pain as bad as you can imagine” over the last week, and an average score is calculated. Scores ≥ 4 may be classified as moderate-severe pain (Gerbershagen, Rothaug, Kalkman, & Meissner, 2011; Kapstad, Hanestad, Langeland, Rustoen, & Stavem, 2008). Pain interference, i.e. the extent to which the pain disrupted seven aspects of daily living such as work and relationships, is rated from 0 “did not interfere” to 10 “completely interfered” over the last week, and an average score is calculated.

2.3.2.2. Other aspects of pain were recorded during the assessment, including pain duration, origin (e.g. injury/surgery or gradual onset), and location on the body.

2.3.3 Psychological factors

2.3.3.1. The Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988) is used to capture emotional and somatic symptoms of anxiety. It consists of 21 items, each of which is rated for severity from 0 “not at all” to 3 “severely”. Total scores are classified as minimal (0-7), mild (8-15), moderate (16-25) and severe (26-63) (Beck & Steer, 1990).

2.3.3.2 The Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a psychometrically validated, widely used questionnaire designed to capture symptoms of depression. Four severity options are provided for each symptom and respondents circle the one most applicable to them. Ratings for each item are summed to create a total score, classified as minimal (0-13), mild (14-19), moderate (20-28) and severe (29-63) (Beck, Steer, & Brown, 1996).

2.3.3.3 Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995) comprises 13 items measuring exaggeratedly negative responses to or thoughts about pain. Respondents rate how frequently they have each thought on a 5-point scale, from 0 “not at all” to 4 “all the time”. Total scores >30 suggest clinically relevant levels of catastrophising (Sullivan, 2009).

2.3.3.4 The Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007) is a 10-item scale on which respondents rate their confidence in their own ability to perform certain activities or participate in various aspects of life despite their pain, on a scale from 0 “not at all confident” to 6 “completely confident”. Total scores <30 indicate moderately low self-efficacy and scores < 20 indicate severely low self-efficacy.

2.3.4 Sleep

2.3.4.1. The Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989) is a widely used 19-item questionnaire assessing multiple aspects of sleep over the past month, including sleep duration, latency (i.e. how long it takes to fall asleep), disturbances, habitual efficiency (hours slept as a proportion of time spent in bed), use of sleep medication, daytime dysfunction and overall subjective quality. These subscales are combined to form a global score, where higher numbers indicate greater sleep disturbance. In chronic pain patients, a cut-point of >6 on the PSQI has been shown to provide optimal sensitivity and specificity for detecting disordered sleep (Alsaadi et al., 2013).

2.4 Statistical analysis

Data were analysed with SPSS Version 23. Missing data were minimal, except for the WCST and PSQI variables, which respectively had 4 and 7 participants providing incomplete responses preventing a total score from being calculated. For these instances, missing values were replaced using a multiple imputation procedure implemented in SPSS. Scores on the BRIEF-A were converted to standardised T-scores according to the BRIEF-A manual (Roth et al., 2005), and compared to the clinical cut-off of 65 using a one-sample t-test. For the CFQ and EMQ-R, there are no published standardised scores or normative means appropriate for comparison with this sample, so mean scores are provided for descriptive purposes only and not compared with a clinical cut-off.

For examination of neurocognitive test scores against expected performance, raw scores on the SDMT, Trail-making A and B, Stroop and WCST were converted to z-scores based on existing normative data for each test. Z-scores were calculated as: (participant score - normative mean)/normative standard deviation, where a z-score of 0 represents the normative mean (i.e. how we would expect participants to perform based on their age) and scores

between -1 and +1 represent performance falling within one standard deviation below or above the normative mean.

Relationships among reported and tested cognitive difficulties, pain, and psychological variables were explored using partial correlation, controlling for age and highest level of education achieved (classified as high school or tertiary; no participants had primary school only). The initial correlation matrix comprised 15 variables, which met the requirement for a minimum of 2 subjects per variable (Austin & Steyerberg, 2015). Several variables displayed non-normal distribution of scores (EMQ-R, BAI, Trail-making test A and B, WCST), therefore a non-parametric statistic was used for all analyses (Spearman's rho). To control for multiple comparisons, a false discovery rate (FDR) of 0.05 was implemented, which is a recommended alternative to Bonferroni correction (Glickman, Rao, & Schultz, 2014). The FDR uses the distribution of p values in a set of analyses to take into account the frequency of true null hypotheses, and is suitable for exploratory analyses while retaining greater power than Bonferroni correction.

Significant associations between objective cognitive performance and subjective measures were subsequently entered into a follow-up correlation analysis controlling for age, education, and catastrophising. Post-hoc moderation analyses were conducted to probe significant subjective-objective relationships, to determine whether these relationships were moderated by depression, anxiety, or catastrophising. A series of nine additional hierarchical regressions were conducted to examine moderated effects (i.e., three significant subjective-objective relationships, by three possible moderators). Using centred variables, age and education were controlled for in the first step, main effects of subjective reported cognition and psychological variable were entered in the second and third steps respectively, and the interaction between the subjective measure and psychological variable was entered in the final step. Interaction terms which contributed significant additional predictive value to the model over and above the main effects were taken to indicate significant moderation (Baron & Kenny, 1986), and were followed up with post-hoc examination of simple slopes.

3. Results

3.1 Patient characteristics

Characteristics of the sample are presented in Table 1. Participants ranged in age from 22-65 years (mean 42.97) with estimated IQ scores comparable to the general population (mean 102.08, sd 11.21, where the population average is 100). All participants had back pain, and the majority also reported other localised or widespread body sites affected by pain. Nearly half of the sample were not currently working or studying on account of their pain.

For those taking opioid medications (38.5%), median intake was 20mg daily morphine equivalent (interquartile range = 7.8-55.0).

-- Insert Table 1 here --

3.2 Overall performance

Overall group-level data are shown below for the BRIEF-A (Fig. 1). Of the nine subscales, Working Memory was the most elevated; that is, participants rated working memory items to be most problematic. On the Working Memory subscale, 24 (61.5%) participants scored in the clinically elevated range (> 65), and the group mean was significantly above the cut-off (mean = 69.8, sd = 12.8, $t(38) = 2.34$, $p=.02$). Group means for the other self-reported cognition measures in our sample were 51.18 (sd 21.65) out of a possible maximum of 100 on the CFQ, and on the EMQ-R a mean of 21.56 (sd 14.34) out of a possible maximum of 52. Although no clinical cut-offs are available for these measures, higher scores on both measures indicate a higher level of reported problems.

-- Insert Fig. 1 here --

Neuropsychological test performance relative to normative means is displayed in Fig. 2. Clinically relevant scores ($z\text{-score} < -1.5$) were found in 12.8% of participants on the SDMT, 7.7% for Trail-making A, 20.5% on Trail-making B, 20.5% on the Stroop and 25.6% on the WCST. Participants who scored substantially below expected levels on the WCST and Stroop did not differ from those scoring in the “normal range” on any demographic or clinical characteristic (gender, pain intensity or interference, pain duration, depression, anxiety, self-efficacy, catastrophising, sleep quality, or medication intake). Participants scoring substantially below expected levels on Trail-making B, however, had significantly higher pain intensity (mean 6.51 for lower scorers; 5.18 for normal range scorers, $p<.05$) and pain interference (mean 7.75 for lower scorers; 5.92 for normal range scorers, $p<.05$).

-- Insert Fig. 2 here --

3.3 Relationship between self-report and test scores

Correlations between self-report measures and neuropsychological test performance are shown in Table 2. Given that the Working Memory subscale of the BRIEF-A was clinically elevated for two thirds of the sample, and all 9 BRIEF-A subscale scores were highly correlated with one another (r values ranging from 0.44 to 0.85, $p<.005$ in all cases), we only analysed the Working Memory scale to avoid inclusion of multiple highly correlated and redundant scales. As seen in Table 2, the EMQ-R and Working Memory subscale are significantly correlated with aspects of cognitive test performance. Test performance also showed associations with pain intensity and catastrophising (Table 2). As expected, measures

of psychological distress were strongly correlated with one another, as were the three measures of self-reported cognition (these are not displayed in the manuscript; for full correlation matrix of comparisons amongst all variables, refer to Supporting Information, Table S1). The CFQ did not significantly correlate with any cognitive test. Further investigation into the subscales of the CFQ can also be found in Supporting Information (Results S1).

-- Insert Table 2 here --

3.4 Controlling for psychological distress

Given that higher catastrophising was moderately correlated with poorer test performance (on the Trail-making test in particular), correlations between self-report measures and objective cognitive tests were re-analysed controlling for catastrophising. Although this reduced the magnitude of the relationships, correlations remained significant between Trail-making B and the Working Memory scale, $r = 0.37$, $p = .027$; Trail-making B and the EMQ-R, $r = 0.33$, $p = .047$; and SDMT and the Working Memory scale, $r = -0.41$, $p = .013$. The relationship between WCST and pain intensity was no longer significant after controlling for catastrophising, $r = 0.28$, $p = .093$.

--Insert Table 3 here --

-- Insert Fig. 3 here --

3.5 Moderation analysis

Moderation analyses of the significant relationships between subjective (EMQ-R and Working Memory scale) and objective measures (SDMT, Trail-making B) by symptoms of depression, anxiety, and pain catastrophising showed the following: In the first step, age and education significantly contributed to the prediction of objective cognitive performance in all cases. In the second step, in all cases, subjective measures significantly contributed to the prediction of the objective measure, as per the correlations reported above. In the third step, none of the psychological variables as unique predictors contributed additional predictive value over and above the main effect of subjective cognition. In the final step, interactions between each subjective measure and depression or catastrophising were not significant. That is, depression and catastrophising did not moderate the association between subjective cognition and objective performance (see Table 3 for R^2 change and β values in each model). However, the interactions between each subjective measure (EMQ-R and BRIEF-A Working Memory) and anxiety were significant in all instances. Post-hoc probing at 1.00 SD above and below the group mean on anxiety (BAI mean 16.72, SD 12.52) revealed that, in all three tests, subjective cognition significantly predicted objective performance specifically in those

with the most severe anxiety symptoms i.e., BAI scores > 29.24 , “Severe” range), compared with those reporting no anxiety symptoms (i.e., BAI scores < 4.19 , “Normal” range) (see Fig. 3).

4. Discussion and conclusions

4.1 Cognitive performance and relationship to self-report

In a sample of persons with chronic pain and cognitive concerns, we found that average cognitive performance fell below age-matched normative means, yet still within the clinically normal range, on standardised neuropsychological tests of speed, complex attention and executive functions. This finding is consistent with previous research in chronic pain patients showing that although cognitive deficits clearly exist, they may be subtle (Rathbone et al., 2016). Up to 25% of our sample performed clinically worse than age expectations (defined as more than 1.5 standard deviations below the normative mean), reflecting a level of difficulty that would impact negatively on usual daily functioning. This is consistent with the findings of Landro et al. (2013), where approximately 20% of patients attending a pain clinic performed below clinical cut-offs on neuropsychological tests of inhibitory control (a component of executive functioning).

We found moderate-to-large associations between self-reported cognitive difficulties and objective neuropsychological test performance. These associations were stronger than those reported in prior similar studies (e.g. Gelonch, Garolera, Valls, Rosselló, & Pifarré, 2016; Landro et al., 2013), which found small-to-medium correlation coefficients. This may be primarily due to differences in study inclusion criteria, whereby the present study specifically recruited persons who felt that they had cognitive problems, as opposed to a heterogeneous group of pain clinic attendees who may or may not have had cognitive concerns. Our study comprised a more homogeneous sample that allowed us to identify clearer relationships between objective and subjective cognitive difficulties.

4.2 Contribution of secondary clinical factors

Of the pain-related clinical factors measured (i.e., anxiety, depression, catastrophising, self-efficacy, sleep disturbance symptoms), we found that catastrophising was most strongly related to objective cognitive performance. In contrast to prior studies (e.g. Landro et al., 2013), we found only modest, non-significant associations between cognitive performance and depression or anxiety. Reported sleep quality was not significantly related to any self-reported or objectively measured cognitive functions in the present study. Indeed, sleep quality does not always contribute significantly to cognitive performance in chronic pain

samples (Dick & Rashiq, 2007; Karp et al., 2006; Lee, Kang, & Cho, 2017), and the role of sleep in cognition may vary from sample to sample.

Controlling for catastrophising slightly reduced the strength of the relationship between subjective and objective cognitive functioning, however the associations remained moderate and significant. Thus subjective concerns were reflected in measured cognitive performance, even in those with higher catastrophising tendencies. This provides further evidence that reported cognitive complaints are not purely a reflection of distress or unfounded concern. Moreover, according to moderation analyses, subjective-objective relationships were particularly strong in those with more severe anxiety symptoms. We found that among participants with more severe anxiety, those who reported fewer cognitive problems performed better on the neurocognitive tests than those who reported more cognitive problems. Reports of impaired cognition were, therefore, most accurate in those with clinically elevated anxiety. Although this analysis was based on relatively small numbers, the clinical relevance of this finding highlights that those with cognitive concerns may previously have been dismissed due to high anxiety (e.g. clinicians may perceive anxious persons as more likely to report unfounded concerns); however, these patients might, in fact, be accurately reporting an objectively measurable impairment. Causal relationships should, however, be further examined in future studies.

There is no question that psychological disturbances such as anxiety, depression, and catastrophising are highly prevalent in patients with chronic pain (Crofford, 2015; Erickson, 2005; McWilliams, Cox, & Enns, 2003), regardless of whether these characteristics were present before or after pain became chronic. There is also no doubt that psychological dysfunction gives rise to impaired attention, working memory, and other cognitive skills (Airaksinen, Larsson, & Forsell, 2005; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008). In pain research and practice, there appears to be almost an unstated requirement to prove that cognitive deficits are independent of mood disorders in order for them to be considered valid complaints in their own right. There is a commonly held view that cognitive concerns raised by patients are a product of psychological distress. Such complaints are then likely to be dismissed or not considered reflective of objective impairment. In our sample, tangible performance reflected self-reported problems most reliably in those with greater psychological distress (i.e. higher anxiety). We would argue, therefore, that even in cases where psychological states play a large role in cognitive difficulties, these are still legitimate complaints that may translate to poorer functioning in daily life and may independently impact upon participation in occupational and social

activities. In cases where mood contributes to cognitive impairment, interventions targeting alleviation of psychological distress could be particularly beneficial as they may have the added benefit of improving cognitive functioning (de Lange et al., 2008; Kearney et al., 2016; Stange et al., 2011). Ultimately, we acknowledge that various facets of pain (the emotional, the physical and the cognitive) do not occur in isolation, and that a multidimensional approach to clinical assessment and treatment should be taken.

4.3 Utility of different measures in detecting cognitive concerns

While this study did not seek to validate any particular measure of cognitive functioning, we now consider the potential sensitivity and utility of various measures to identify probable cognitive difficulties in this population.

Three self-report measures of cognitive concerns were administered: the BRIEF-A, the EMQ-R, and the CFQ. On the BRIEF-A, the working memory subscale was particularly elevated in this sample, with nearly two thirds of participants scoring in the clinically elevated range. This degree of perceived working memory deficit is consistent with previous research, including our previous study using the BRIEF-A in which we sampled from a sample of pain clinic attendees (Baker, Gibson, Georgiou-Karistianis, Roth, & Giummarra, 2016), and another study in patients with fibromyalgia (Gelonch et al., 2016). Scores on the working memory subscale and the EMQ-R were robustly associated with objective tests of speed and complex attention, suggesting that they may be useful indicators of cognitive difficulty in persons with pain. The EMQ-R in particular may hold advantages over the BRIEF-A in that it is free, easily -accessible and quicker to administer, and we would recommend trialling this measure in the pain clinic setting. The CFQ, in contrast, did not show strong relationships with any neuropsychological test. It may be that the CFQ captures some of the subjective concerns expressed by patients, but it was not as sensitive as the other measures (i.e., EMQ and BRIEF-A Working Memory subscale) to formally tested cognitive deficits experienced in this group. We also note that new self-report measures of cognition specifically for pain populations have been developed since the present study commenced, such as the Multidimensional Inventory of Subjective Cognitive Impairment by Kratz, Schilling, Goesling, and Williams (2015). This inventory was designed to measure “fibro-fog” in fibromyalgia, but it may be sensitive to cognitive difficulties across other chronic pain conditions.

Regarding objective neuropsychological tests, the Trail-Making Test, especially part B which involves flexibly switching attention back and forth, showed sensitivity to impairment in chronic pain (i.e. captured poorer performances), and had the strongest concurrence with

self-reported difficulties in our study. Several other studies have found the Trail-making test B to be sensitive to the cognitive differences between persons with and without chronic pain (Tesio et al., 2015; Weiner, Rudy, Morrow, Slaboda, & Lieber, 2006), and to be predictive of chronic pain outcomes (Attal et al., 2014; Boggero, Eisenlohr-Moul, & Segerstrom, 2016).

The WCST was related to intensity of pain in our sample, in keeping with previous research (Verdejo-Garcia, Lopez-Torrecillas, Calandre, Delgado-Rodriguez, & Bechara, 2009). This suggests that participants with more severe pain may adopt inflexible problem-solving strategies given that they tended to continue responding in an ineffective way even after receiving feedback about their errors. This begs the question of how such thinking styles might relate to real-life behaviours, or whether this plays a role in the persistence of pain in the first place (e.g., how effectively can these patients apply flexible problem-solving to manage their chronic pain condition). The Stroop test, in this study, was not associated with any self-reported cognitive difficulties. This was somewhat surprising given previous work showing a relationship between Stroop performance and the EMQ (28-item version) (Landro et al., 2013), and pain (Bjekić et al., 2017).

4.4 Caveats

Limitations to the generalisability of the present findings should be considered. First, given that our study comprised a self-selected sample of people who enrolled in the study due to interest in participating in a program designed to improve cognitive skills, they likely had a degree of insight into their cognitive challenges, which may not be the case for all others with chronic pain. As the ability of self-report cognitive measures to detect impairment relies on self-awareness of the respondent, any self-report screening tool should be supplemented with clinical examination.

Second, this study did not allow for an in-depth examination of the effects of medications on cognition. The effects of medication in this sample were, however, expected to be minimal given that those with high doses of opioids and benzodiazepines were excluded, and the potential medication detriment of all medications taken for pain was not associated with either subjective complaints or neuropsychological test performance. Nonetheless, the findings are may not generalise to those taking higher dosages of opioid or benzodiazepine medications, which may independently impact on neuropsychological functioning (Block & Cianfrini, 2013).

4.5 Conclusions

Here we show that self-reported cognitive difficulties, specifically on the EMQ-R and Working Memory subscale of the BRIEF-A, are associated with performance on standard

neuropsychological measures in people with chronic pain and cognitive concerns, especially in those with higher anxiety. We recommend using a self-report tool such as the EMQ-R to document cognitive concerns in chronic pain patients as a gateway to both validating their concerns and opening up a conversation about cognition in the presence of chronic pain. This conversation may pave the way towards providing education about cognition, and exploring potential strategies for managing everyday attention or memory problems (Baker, Georgiou-Karistianis, Gibson, & Giummarra, 2017), and a neuropsychologist may be consulted if concerns extend beyond the skills of the clinician in the pain clinic.

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Author Contributions

KSB was responsible for data collection, analysis, and drafting of the manuscript. All authors contributed to the design of the study, discussed the results, provided comments and approved the final manuscript.

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Figure legends

Fig. 1. Average T-scores for each subscale of the BRIEF-A. Scores above the dotted line (>65) are considered clinically elevated.

Fig. 2. All individual patient standardised scores on each cognitive test, adjusted for age, with a mean of 0 and standard deviation of 1. Scores lower than -1.5 (demarcated by dotted line) are considered below age-related expectations. Stroop = colour-word score; WCST = number of perseverative errors on the WCST. Circles represent scores that greater than 1.5 times the interquartile range.

Fig 3. Simple slopes for the relationship between a) SDMT and reported Working Memory (wm) problems on the BRIEF-A, b) Trail-making B and reported Working Memory problems on the BRIEF-A, and c) Trail-making B and reported Everyday Memory problems on the EMQ-R, each displayed at high (1.00 SD above the mean: 29.24, Severe range, n=6) and low (1 SD below the mean: 4.19, Normal range, n=6) levels of anxiety symptoms on the BAI. ** indicates slopes significant at $p < .01$.

Table 1. Sample demographics and pain characteristics.

Characteristic		
Age	m (sd)	42.97 (12.77)
Gender (females)	n (%)	24 (61.5%)
Education years	m (sd)	14.74 (3.73)
Tertiary education	n (%)	25 (64.1%)
Estimated IQ	m (sd)	102.08 (11.21)
Currently working or studying	n (%)	22 (56.4%)
Pain duration in years	m (sd)	12.15 (10.47)
Pain location		
Back only	n (%)	10 (25.6%)
Other localised	n (%)	21 (53.8%)
Widespread	n (%)	6 (15.4%)
Joint	n (%)	5 (12.8%)
Medications		
Opioid (range 1-94mg)	n (%)	15 (38.5%)
Benzodiazepine (range 1-5mg)	n (%)	9 (23.1%)
Antidepressant	n (%)	14 (35.9%)
Pregabalin/Gabapentin	n (%)	9 (23.1%)

Notes: Means and standard deviations are displayed for continuous variables, and number and percentage for categorical variables. Estimated IQ is based on standardised Test of Premorbid Functioning (TOPF) scores, although note that this may be an underestimate of IQ for several participants with English as a second language (n=3) or hearing impairment (n=1). Under Pain location, participants may fall under more than one category. Opioid dosage range is given in terms of daily morphine equivalence ("Opioid dose equivalence: Calculation of oral Morphine Equivalent Daily Dose (oMEDD)," 2014). Benzodiazepine range given as diazepam equivalent ("Benzodiazepine Equivalency", Farinde, A., 2017 available at <http://emedicine.medscape.com/article/2172250-overview>).

Table 2. Partial correlations between self-report measures and neuropsychological tests, controlling for age and education level.

Self-report measures	Clinically relevant	Cognitive tests				
		SDMT	Trail-making A	Trail-making B	Stroop	WCST
Working memory (BRIEF-A)	24 (61.5%)	-0.45**	0.11	0.44**	-0.19	-0.08
Everyday memory (EMQ-R)	--	-0.32	0.07	0.44**	-0.22	0.07
Cognitive failures (CFQ)	--	-0.30	-0.02	0.25	-0.30	-0.21
Pain intensity (BPI)	34 (87.2%)	-0.16	0.21	0.26	-0.10	0.43**
Pain interference (BPI)	34 (87.2%)	-0.20	0.20	0.30	-0.29	0.22
Depression (BDI)	18 (46.2%)	-0.05	-0.08	0.22	-0.09	0.10
Anxiety (BAI)	18 (46.1%)	-0.20	-0.03	0.17	-0.29	-0.11
Catastrophising (PCS)	13 (33.3%)	-0.20	0.22	0.34*	-0.31	0.28
Self-efficacy (PSEQ)	19 (48.7%)	0.17	-0.10	-0.23	0.02	-0.26
Sleep (PSQI)	26 (66.7%)	0.19	-0.28	-0.22	0.07	0.01

Notes: * indicates correlations significant at $p < .05$, ** indicates correlations significant at a False Discovery Rate adjusted p value of < 0.05 . For variables with existing cut-points for clinical relevance, proportions of the sample who scored in the elevated range (BRIEF-A > 65 ; PSQI > 6) or moderate-severe range (BPI ≥ 4 ; BDI ≥ 20 ; BAI ≥ 16 ; PSEQ < 30) are displayed.

Table 3. Moderation analyses of the three significant objective-subjective cognition relationships by symptoms of

Reported cognition measure:	Outcome: SDMT		TMT-B		TMT-B	
	BRIEF-A (wm)		BRIEF-A (wm)		EMQ-R	
	ΔR^2	β	ΔR^2	β	ΔR^2	β
DEPRESSION						
Step 1. Age & education	0.25**		0.23*		0.23*	
Step 2. Reported cognition	0.09*	-0.39*	0.16**	0.39*	0.22**	0.60**
Step 3. Depression	0.03	0.19	0.00	-0.02	0.22	-0.24
Step 4. Reported cognition x depression	0.001	-0.03	0.01	0.08	0.38	0.20
ANXIETY						
Step 1. Age & education	0.26**		0.24**		0.24**	
Step 2. Reported cognition	0.01*	-0.25	0.15**	0.25	0.22**	0.34*
Step 3. Anxiety	0.001	0.01	0.01	0.04	0.001	-0.05
Step 4. Reported cognition x anxiety	0.07*	-0.29*	0.18**	0.45**	0.15**	0.44**
CATASTROPHISING						
Step 1. Age & education	0.26**		0.24**		0.24**	
Step 2. Reported cognition	0.01*	-0.28	0.15**	0.24	0.22**	0.32*
Step 3. Catastrophising	0.003	-0.07	0.04	0.22	0.01	0.10
Step 4. Reported cognition x catastrophising	0.001	-0.03	0.01	0.12	0.05	0.26

psychological distress: depression, anxiety, and catastrophising

Notes: BRIEF-A (wm) = the Working Memory subscale from the Behavior Rating Inventory of Executive Function-Adult version. SDMT=Symbol Digit Modalities Test. TMT-B = Trail-making Test B. EMQ-R = Everyday Memory Questionnaire-Revised. Values displayed are R^2 change for each sequential step in the hierarchical regression model, and beta coefficients for individual predictors in the final step. * $p < 0.05$, ** $p < 0.01$. Significant interaction terms indicate moderation by the psychological distress variable.

Behavior Rating Inventory of Executive Function-Adult (BRIEF-A)

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