



## Observational study

## Pain and major depressive disorder: Associations with cognitive impairment as measured by the THINC-integrated tool (THINC-it)



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## H I G H L I G H T S

- Pain and major depressive disorder have independent and overlapping effects on cognitive function.
- Few studies have primarily aimed to evaluate the combinatorial effect of comorbid pain and major depressive disorder on cognitive function.
- The THINC-integrated tool (THINC-it) is a recently validated cognitive assessment battery that evaluates both objective and subjective aspects of cognitive function in individuals with major depressive disorders.
- Results from the study herein demonstrated that on the THINC-it, subjective ratings of cognitive function were more highly correlated with objective cognitive measures in adults with major depressive disorder and concurrent pain.

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## A B S T R A C T

**Objectives:** To examine the role of pain on cognitive function in adults with major depressive disorder (MDD).

**Methods:** Adults (18–65) with a Diagnostic and Statistical Manual – Fifth Edition (DSM-5)-defined diagnosis of MDD experiencing a current major depressive episode (MDE) were enrolled ( $n_{MDD} = 100$ ). All subjects with MDD were matched in age, sex, and years of education to healthy controls (HC) ( $n_{HC} = 100$ ) for comparison. Cognitive function was assessed using the recently validated THINC-integrated tool (THINC-it), which comprises variants of the choice reaction time (i.e., THINC-it: *Spotter*), One-Back (i.e., THINC-it: *Symbol Check*), Digit Symbol Substitution Test (i.e., THINC-it: *Codebreaker*), Trail Making Test – Part B (i.e., THINC-it: *Trails*), as well as the Perceived Deficits Questionnaire for Depression – 5-item (i.e., THINC-it: *PDQ-5-D*). A global index of objective cognitive function was computed using objective measures from the THINC-it, while self-rated cognitive deficits were measured using the PDQ-5-D. Pain was measured using a Visual Analogue Scale (VAS). Regression analyses evaluated the role of pain in predicting objective and subjective cognitive function.

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**Results:** A significant between-group differences on the VAS was observed ( $p < 0.001$ ), with individuals with MDD reporting higher pain severity as evidenced by higher scores on the VAS than HC. Significant interaction effects were observed between self-rated cognitive deficits and pain ratings ( $p < 0.001$ ) on objective cognitive performance (after adjusting for MADRS total score), suggesting that pain moderates the association between self-rated and objective cognitive function.

**Conclusions:** Results indicated that pain is associated with increased self-rated and objective cognitive deficits in adults with MDD.

**Implications:** The study herein provides preliminary evidence demonstrating that adults with MDD reporting pain symptomatology and poorer subjective cognitive function is predictive of poorer objective cognitive performance. THINC-it is capable of detecting cognitive dysfunction amongst adults with MDD and pain.

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## 1. Introduction

It has been reported that approximately 40% of the general population experiencing chronic pain, and up to 69% of patients observed in primary care settings experiencing chronic pain, meet diagnostic criteria for major depressive disorder (MDD) [1]. Available evidence indicates that chronic pain and MDD are highly comorbid conditions; moreover, it is well established that chronic pain and MDD share similar determinants including, but not limited to, female sex, advanced age, and lower socioeconomic status [2–5]. Consequently, the overlapping phenotypic presentation of pain and MDD has contributed to insufficiencies in timely and accurate diagnoses of both conditions, as well as the initiation of guideline-concordant care [3].

Traditionally, chronic pain has been characterized by the length of time (i.e., greater than 6 months) with medically unexplained pain often assumed to be associated with psychological factors. In the last decade, the operational definition of pain, notably chronic pain, has transmuted to reflect more recent conceptualizations of the mechanisms responsible for its manifestation [2,6,7]. For example, recent evidence suggests that neuroplastic changes resulting from injury and/or disease processes alters the processing of afferent input via peripheral and central signalling systems. Taken together, the International Association for the Study of Pain has described chronic pain as persistent and intractable with no adaptive purpose over a prolonged period of time (e.g., longer than 6 months) with no identifiable medical explanation [2,6,7].

The foregoing similarities are further complicated by having shared “non-mood” symptoms including, but not limited to, cognitive impairment [8–10]. Pain has been posited to be a contributing factor in the manifestation of depressive symptoms and is commonly associated with cognitive impairment in disparate patient populations [9–11]. Moreover, both pain and MDD have discrete yet overlapping pathogenetic substrates. For example, decreased dopamine levels in the prefrontal cortex have been implicated in pain sensation, which contribute to alterations in synaptic plasticity and memory [11]. Similarly, the serotonergic, norepinephrine, and glutamatergic systems have been implicated in anti-nociceptive activity, global cognitive function, and mood [12–14]. Additionally, antidepressants have consistently been demonstrated to decrease chronic pain in both depressed and non-depressed subjects via disparate overlapping mechanistic pathways [15]. Taken together, it is likely that alterations in the underlying mechanisms involved in the processing of pain negatively impact global cognitive function.

The primary objectives of the analyses herein were to examine between-group differences in the experience of pain in subjects with and without MDD, and to evaluate the role of pain in predicting objective and subjective cognitive function. We hypothesized that adults with MDD would be differentially affected by pain and that pain would be independently associated with both objective and self-rated cognitive function.

## 2. Methods

### 2.1. Subjects

A total of 207 subjects ( $n_{MDD} = 100$ ;  $n_{HC} = 107$ ) were enrolled in the study. Subjects were recruited via the Brain and Cognition Discovery Foundation (BCDF), located in Toronto, Ontario, Canada. Study approval was granted by a community Institutional Review Board (IRB). All eligible subjects provided informed written consent.

### 2.2. Subjects with major depressive disorder

All subjects with MDD met diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). A healthcare provider confirmed the presence of both a current and prior major depressive episode (MDE) validated by previous treatment and the MINI International Neuropsychiatric Interview (M.I.N.I.) Plus 5.0 for DSM-IV-TR. Patients were provided with ongoing provision of care, regardless of their decision to enrol in and/or complete the study. Subjects were prospectively verified to be currently depressed (i.e., total Montgomery-Åsberg Depression Rating Scale [MADRS] score  $\geq 22$ ) with a current MDE duration of  $\geq 3$  months [17].

### 2.3. Healthy controls

Healthy controls were specified a priori to be age-, sex-, and education-matched to individuals recruited to the MDD group. Rolling enrolment resulted in seven additional HC subjects being recruited that did not match individuals within the MDD group based on the aforementioned criteria, and were therefore excluded from endpoint analyses (i.e., final  $n_{HC} = 100$ ). Exclusion criteria for HC included having a current diagnosis or history of a mental disorder (confirmed by self-report measures and the M.I.N.I. for DSM-IV-TR); a first-degree relative with a diagnosis made by a healthcare provider of a mood or psychiatric disorder; unstable medical disorder(s); taking any medication that, in the opinion of the investigator, might affect cognitive function; and alcohol consumption within 8 h prior to the THINC-it administration.

## 3. Measures

### 3.1. Primary assessment instruments

The primary assessment instruments of the original clinical trial were: the THINC-it, the MADRS to establish a dimensional severity measure for depression, the Identification Task IDN and OBK task from the CogState (<https://cogstate.com/clinical-trials/computerized-assessment/>) battery, as well as the pen-and-paper

versions of the DSST, TMT-B and PDQ-5-D. The purpose of the foregoing additional cognitive tests was to evaluate the procedural validity of the THINC-it, which has been reported elsewhere [16].

### 3.2. THINC-it

The THINC-it is a computerized cognitive assessment tool accessible via computer/tablet. The tool uses a variety of commonly used and validated cognitive assessments, including the choice reaction time (i.e., *Spotter*), the One Back Memory (OBK) task (i.e., *Symbol Check*), Digit Symbol Substitution Test (DSST) (i.e., *Codebreaker*), and the Trail Making Test – Part B (TMT-B) (i.e., *Trails*). The THINC-it also includes the Perceived Deficits Questionnaire for Depression – 5-item (i.e., *PDQ-5-D*) to measure self-reported cognition [18–21]. All tests were carefully selected to allow for use in routine clinical care as a valid and time-efficient screening tool for patients (ClinicalTrials.gov Identifier: NCT02508493). The rationale for the foregoing tests have been described in detail elsewhere [16].

### 3.3. Secondary assessment instruments

Secondary assessment instruments included the following: Endicott Workplace Productivity Scale (EWPS), Sheehan Disability Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), Clinical Global Impression (CGI), Generalized Anxiety Disorder 7-item (GAD-7), WHO-5 Well-being Index (WHO-5), the Visual Analogue Scale (VAS) for pain, and the 5-item as well as 20-item Perceived Deficits Questionnaire (PDQ-5-D and PDQ-20-D, respectively). Additionally, the National Adult Reading Test – Revised (NART-R) was included as an estimate of IQ and a satisfaction questionnaire regarding the THINC-it [22].

Herein, the VAS for pain was included in analyses as a measure of self-reported pain. The VAS for pain is a subjective measure consisting of a 10 centimetre horizontal line, which seeks to measure pain experienced in the previous 24 h on a continuum. At either end of the horizontal line are descriptor items, i.e. “No pain” and “Worst possible pain.” Subjects indicate their pain experience by placing a vertical mark on the line between these two items. The VAS is scored by measuring, in centimetres, from the left end of the line to the subject’s mark on the line. The reliability and sensitivity of the VAS for ratings of pain are well established [23].

## 4. Procedure

All subjects received primary and secondary assessments sequentially. The THINC-it component measures were administered in the following order: *Spotter*, *Symbol Check*, *Codebreaker*, *Trails* and *PDQ-5-D*. After administration of the IDN and OBK using CogState software, pen-and-paper versions of the DSST, TMT-B, and PDQ-5-D were administered. Subjects with MDD completed all assessments during a single visit. Healthy controls completed the full set of cognitive assessments (i.e., THINC-it tool, CogState, and pen-and-paper tasks) three separate times during the first visit to account for practice effects, and once a week later during the second visit to evaluate temporal reliability of the THINC-it.

Upon completion of all cognitive assessments, subjects completed all secondary assessments. All subjects completed a VAS for pain based on their pain level during the past 24 h [24]. A more detailed description of the procedures has been described elsewhere [16]. Herein, analyses of cognitive performance were delimited to THINC-it measures (i.e., *Spotter*, *Symbol Check*, *Codebreaker*, *Trails*, and *PDQ-5-D*).

## 5. Statistical analysis

All analyses were performed on subjects that completed the THINC-it in its entirety; data were excluded if subjects failed to complete the THINC-it tasks (i.e.,  $n_{MDD} = 10$ ;  $n_{HC} = 8$ ). The primary reasons for not completing the THINC-it in its entirety were inability to perform specific tasks that comprise THINC-it for subjects with MDD, or lack of motivation/unwillingness to complete THINC-it tasks for HC subjects.

Z-scores were calculated to compare performance on both objective and subjective cognitive assessments on the THINC-it, pain (as measured by the VAS), and depressive symptom severity (as assessed by the MADRS total score). Calculation methods of the Z-scores have been published elsewhere [16]. Briefly, Z-scores were calculated using the mean and standard deviation (SD) values from the HC group as reference. The THINC-it composite score, a Z-score in and of itself, was calculated for each subject using the equally weighted sum of Z-scores of objective measures of cognition (i.e., *Spotter*, *Symbol Check*, *Codebreaker*, and *Trails*).

Independent samples *t*-tests were used to assess and compare demographic and clinical characteristics among subjects between-groups. Means and SDs are reported. Since Z-scores for the MDD group were calculated relative to performance of the HC group, only means and SDs of the MDD group are reported.

Simple linear regressions were conducted to assess the association between the MADRS total Z-score and VAS Z-scores, as well as between Z-scores for the PDQ-5-D and THINC-it composite score. Hierarchical linear regressions were performed to evaluate VAS Z-scores as a predictor of PDQ-5-D Z-score and THINC-it composite score, while controlling for MADRS total Z-score.

An exploratory moderational analysis was performed using a generalized linear model to investigate interaction effects in predicting THINC-it composite scores. Statistical significance was set at a level of  $p < 0.05$ .

## 6. Results

### 6.1. Participant characteristics

A total of 100 individuals with MDD and 100 age-, sex-, and education-matched healthy controls were included in the study. Demographic and clinical characteristics are provided in Table 1. Significant differences were noted in race between the HC and MDD groups. Subjects with MDD were primarily comprised of Caucasians whereas HC subjects were primarily comprised of East Asians.

### 6.2. Primary analyses

#### 6.2.1. Between-group differences in pain reporting on the Visual Analogue Scale

An independent samples *t*-test was used to assess and compare whether subjects with MDD demonstrated a statistically significant difference in mean self-reported experience of pain over a 24-h time period, as measured by the VAS, compared to age-, sex-, and education-matched HC. Results demonstrated a statistically significant difference in subjects’ self-reported pain rating between the two groups, with the MDD group reporting more pain than the HC group ( $M = 2.90$ ,  $SD = 2.80$ ),  $t(120) = 6.62$ ,  $p < 0.001$ .

#### 6.2.2. Association between pain and depression severity

A simple linear regression analysis was conducted to evaluate the effect of pain on depression severity. The regression equation was significant,  $t(170) = 7.34$ ,  $b = 5.56$ ,  $p < 0.001$ , with depression severity accounting for a significant proportion of the variability in pain scores,  $R^2 = 0.24$ ,  $F(1, 170) = 53.9$ ,  $p < 0.001$ .

**Table 1**

Demographic and clinical characteristics of subjects with major depressive disorder and healthy controls.

| Characteristic                                              | MDD (n = 100) | Healthy control (n = 100) | p-value     |
|-------------------------------------------------------------|---------------|---------------------------|-------------|
| Age, years [mean (SD)]                                      | 42.60 (13.63) | 39.98 (14.38)             | –           |
| Gender, n (%)                                               |               |                           |             |
| Female                                                      | 58 (58.00)    | 58 (58.00)                | –           |
| Male                                                        | 42 (42.00)    | 42 (42.00)                | –           |
| Race/Ethnicity, n (%)                                       |               |                           |             |
| Caucasian                                                   | 85 (85.00)    | 56 (56.00)                | $p < 0.001$ |
| Black                                                       | 3 (3.00)      | 9 (9.00)                  | $p = 0.074$ |
| Hawaiian                                                    | 0 (0.00)      | 1 (1.00)                  | $p = 0.32$  |
| Asian                                                       | 8 (8.00)      | 31 (31.00)                | $p < 0.001$ |
| Native American                                             | 2 (2.00)      | 0 (0.00)                  | $p = 0.16$  |
| South Asian                                                 | 2 (2.00)      | 3 (3.00)                  | $p = 0.65$  |
| Education, years (from Grade 1) [mean (SD)]                 | 16.33 (3.24)  | 16.26 (2.73)              | $p = 0.087$ |
| MADRS score [mean (SD)]                                     | 33.16 (6.23)  | 0.77 (1.42)               | $p < 0.001$ |
| NART-R full-scale IQ                                        | 113.69 (7.21) | 111.87 (6.63)             | $p = 0.032$ |
| NART-R verbal IQ                                            | 112.60 (8.22) | 110.52 (7.56)             | $p = 0.030$ |
| NART-R performance IQ                                       | 111.80 (3.88) | 110.82 (3.57)             | $p = 0.038$ |
| Age at onset of first depressive episode [mean (SD)]        | 20.72 (12.80) | –                         | –           |
| Age at first treatment for depression [mean (SD)]           | 26.30 (13.38) | –                         | –           |
| No. of lifetime hospitalizations for depression [mean (SD)] | 0.52 (1.32)   | –                         | –           |
| No. of lifetime depressive episodes <sup>a</sup>            |               |                           |             |
| 2 lifetime major depressive episodes (%)                    | 24.00         | –                         | –           |
| ≥3 lifetime major depressive episodes (%)                   | 58.00         | –                         | –           |

<sup>a</sup> n = 19 provided a response of “uncertain”.

### 6.2.3. Association between pain and subjective/objective cognitive function

Hierarchical linear regression analyses were completed to determine the associations between VAS scores and the THINC-it composite score, as well as between VAS scores and the PDQ-5-D, both while controlling for MADRS total score.

In predicting PDQ-5-D scores, Model 1 included only VAS scores as the independent variable. VAS scores significantly predicted PDQ-5-D ( $t[170] = -6.74$ ,  $b = -1.14$ ,  $p < 0.001$ ), accounting for a significant proportion of the variance in PDQ-5-D scores ( $R^2 = 0.21$ ,  $F[2,170] = 45.4$ ,  $p < 0.001$ ). However, when MADRS total score was included in Model 2 as a covariate, VAS scores no longer significantly predicted PDQ-5-D ( $t[169] = -1.46$ ,  $b = -0.18$ ,  $p = 0.15$ ), but MADRS total score was a significant predictor of PDQ-5-D ( $t[169] = -15.8$ ,  $b = -0.173$ ,  $p < 0.001$ ). The overall model was significant in predicting PDQ-5-D ( $R^2 = 0.682$ ,  $F[2,169] = 181.2$ ,  $p < 0.001$ ).

In predicting THINC-it composite scores, Model 1 included VAS scores as the sole independent variable. Scores on the VAS significantly predicted THINC-it composite scores in Model 1,  $t(170) = -2.69$ ,  $b = -0.125$ ,  $p = 0.008$ . However, when MADRS total score was included as a covariate in Model 2, neither VAS scores nor MADRS total scores were significant predictors of THINC-it composite scores ( $ps > 0.05$ ). Although neither of the predictor variables were independently significant in predicting THINC-it composite scores, the overall model remained significant,  $R^2 = 0.053$ ,  $F(2,169) = 4.77$ ,  $p = 0.010$ .

## 7. Secondary analyses

### 7.1. Association between subjective and objective cognitive function

In an effort to replicate previous findings on the relationship between subjective and objective cognitive function, a simple linear regression analysis was conducted to assess if perceived cognitive deficits predicted objective cognitive function in our sample of patients with MDD. Scores on the PDQ-5-D significantly predicted THINC-it composite scores,  $t(180) = 2.28$ ,  $b = 0.041$ ,  $p = 0.024$ , and accounted for a significant proportion of the variance,  $R^2 = 0.028$ ,  $F(1,180) = 5.20$ ,  $p = 0.024$ .

### 7.2. Exploratory moderational analysis

As a result of the significant association between subjective and objective cognitive function, we carried out an exploratory generalized linear model to investigate potential interactive effects between pain, depression severity, and perceived cognitive deficits in predicting objective cognitive function. A significant interaction effect was observed between PDQ-5-D and VAS scores in predicting THINC-it composite scores,  $b = 0.078$ , 95% CI: 1.02, 1.15,  $p = 0.010$ .

## 8. Discussion

The results of our study replicate results from existing studies insofar as individuals with MDD are differentially affected by pain [25]. Our study results extend knowledge further by identifying an interaction effect between subjective cognitive function and pain ratings in predicting objective cognitive performance. More specifically, among individuals reporting increased pain severity, subjective ratings of cognitive function were highly correlated with objective cognitive measures. The foregoing observation provides a further refinement of the relationship between subjective and objective cognitive performance mediated by pain, whereas minimal correlation has been previously reported [9,10,26].

Pain is a complex, subjective, multidimensional phenomenon that is heterogeneous in both experience and presentation, ranging from acute (e.g., traumatic injury) to recurrent (e.g., migraine) and chronic (e.g., rheumatoid arthritis) pain. In addition to being an emotional and somatic experience, pain variably influences cognitive function [11,25,27]. In a prospective diffusion-tensor imaging study evaluating the impact of chronic pain on cognition, psychosocial outcomes, and mood in brain regions implicated in pain modulation, emotion, and cognition (i.e., anterior insula, anterior cingulate gyrus, and uncinate fasciculus), results demonstrated that reductions of white matter volume in the right fronto-insular cortex of the orbitofrontal cortex were observed in pain patients who demonstrated significantly poorer cognitive function than HC [28].

There are several non-mutually exclusive interpretations to our primary finding that subjective ratings of cognitive function are more highly correlated with objective cognitive measures in adults with MDD and concurrent pain. Namely, it could be

posited that individuals with MDD and high pain levels represent a severe subpopulation with more pronounced alterations in brain neural structure and circuits that results in increased consistency of subjective ratings and objective performance on cognitive measures. Moreover, mechanisms implicated in the mediation of pain (e.g., inflammation and opioidergic systems) may result in adverse changes to neural structures subserving objective cognitive measures. A separate hypothesis could be that pharmacological treatment for pain in individuals with MDD exerts a direct, independent, and clinically significant effect on objective and subjective measures of cognitive function (i.e., “iatrogenic effects”). The foregoing hypothesis is unlikely in this database given the few patients who received anti-nociceptive therapies. Finally, a common distal event (e.g., childhood adversity) may in fact be a determinant linking our finding insofar as exposure to environmental pathogens and other social determinants of health may have had a deleterious effect on neural structures subserving both subjective and objective cognitive function and pain.

Notwithstanding the implicit association between pain and cognition, relatively few studies have primarily aimed to elucidate the role of pain on cognitive function in a highly comorbid clinical population, namely MDD. Taken together, these results indicate that not only is pain more common in MDD, but that individuals with concurrent pain are more likely to evince cognitive impairment. Moreover, clinicians attempting to assess cognitive function in adults with MDD perhaps could rely on self-reported cognitive measures as a proxy of objective cognitive function in patients experiencing pain symptomatology [8–10].

Strengths of the analyses herein are provided by our study's exploration and comparison of associations between “non-mood” symptoms (i.e., pain and cognitive impairment) among adults with MDD. Data from subjects with MDD were compared to age-, sex-, and education-matched healthy controls, providing the opportunity to examine associations between cognitive function, presence/absence of a clinical diagnosis of MDD, depression severity, and pain. In addition, both objective cognitive performance and subjects' perceived cognitive deficits were captured using the THINC-it, providing the opportunity to evaluate these disparate cognitive constructs in association with pain amongst adults with MDD.

Limitations of the foregoing analyses include, but are not limited to, delimiting analyses to individuals who were capable of fully completing the THINC-it cognitive testing ( $n_{\text{MDD}} = 90$ ;  $n_{\text{HC}} = 92$ ); use of a single item self-report measure of pain (i.e., the VAS); and post hoc exploratory analyses of baseline assessments. The extrapolation of the results herein are based on extant literature describing chronic pain; however, pain ratings were only collected from the previous 24 h and a measure of chronic pain was not included. Notwithstanding these limitations, the preliminary results presented herein suggest that depression severity is a significant determinant of pain, and pain demonstrates a modulatory role between perceived cognitive deficits and objective cognitive performance.

Taken together, these observations provide the impetus to screen for pain in adults with MDD notably in situations where persisting functional problems are observed. In addition, a hypothesis that is derived from our findings is the effective treatment of pain in MDD may also increase cognitive, and functional, outcomes in persons with MDD. Research that aims to measure cognitive function in MDD should seek to adjust for the effect of pain measures on cognitive-dependent measures [3,29].

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## Ethical Issues

No ethical issues were reported in the present study.

## Conflict of interest

Dr. Roger S. McIntyre has received Research Grants from: Stanley Medical Research Institute, Lundbeck, Janssen Ortho, Purdue, AstraZeneca, Shire, Pfizer, Otsuka, and Allergan. He is on the Advisory Board for: Lundbeck, Pfizer, AstraZeneca, Eli Lilly, Janssen Ortho, Purdue, Johnson & Johnson, Moksha8, Sunovion, Mitsubishi, Takeda, Forest, Otsuka, Bristol-Myers Squibb, and Shire. He has also been a Speaker for: Lundbeck, Pfizer, AstraZeneca, Eli Lilly, Janssen Ortho, Purdue, Johnson & Johnson, Moksha8, Sunovion, Mitsubishi, Takeda, Forest, Otsuka, Bristol-Myers Squibb, and Shire. All other authors have nothing to disclose. All authors declare no conflict of interest.

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