The THINC-Integrated Tool (THINC-it) Screening Assessment for Cognitive Dysfunction:

Validation in Patients With Major Depressive Disorder

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ABSTRACT

Objective: To validate the THINC-integrated tool (THINC-it)—a freely available, patient-administered, computerized screening tool integrating subjective and objective measures of cognitive function in adults with major depressive disorder (MDD).

Methods: Subjects aged 18 to 65 years (n = 100) with recurrent MDD experiencing a major depressive episode of at least moderate severity were evaluated and compared to age-, sex-, and education-matched healthy controls (n = 100). Between January and June 2016, subjects completed the THINC-it, which includes variants of the Choice Reaction Time Identification Task (IDN), One-Back Test, Digit Symbol Substitution Test, Trail Making Test–Part B, and the Perceived Deficits Questionnaire for Depression–5-item (PDQ-5-D).

Results: The THINC-it required approximately 10 to 15 minutes for administration and was capable of detecting cognitive deficits in adults with MDD. A total of 44.4% of adults with MDD exhibited cognitive performance at ≥ 1.0 SD below that of healthy controls on standardized mean scores of the THINC-it. Concurrent validity of the overall tool, based on a calculated composite score, was acceptable ($r = 0.539$, $P < .001$). Concurrent validity of the component tests ranged from −0.083 (IDN) to 0.929 (PDQ-5-D). Qualitative survey results indicated that there was a high level of satisfaction and perceived value in administering the THINC-it regarding its impact on the appropriateness and quality of care being received.

Conclusions: The THINC-it is a valid and sensitive tool for detecting cognitive dysfunction in adults with MDD that is free, easy to use, and rapidly administered. The THINC-it should be incorporated into the assessment and measurement of all patients with MDD, particularly among those with enduring functional impairment.

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During the past decade, it has been increasingly recognized that deficits across multiple domains of cognitive function are commonly experienced by those with major depressive disorder (MDD) and mediate poor psychosocial and workplace outcomes.[1–16] Moreover, insufficient outcomes in MDD are observed in persons who are "euthymic," underscoring the mediational role of other non-mood MDD domains in determining health outcomes.[4,7–10]

The mediational role of cognitive function in affecting health outcomes in MDD invites the need for direct assessment of cognitive functions with tools that are freely available, computerized, user-friendly, and patient-administered that provide actionable information.[17–19] Screening instruments for dementing disorders and rating scales for depression (eg, Mini-Mental State Examination [MMSE]) are suboptimal for screening cognitive dysfunction in adults with MDD due to ceiling effects and insufficient sensitivity and ecological validity.[20,21] The gold standard for assessing cognitive performance in MDD and other disorders (ie, by employing a comprehensive cognitive evaluation via established neuropsychological tests) is too unwieldy, time-consuming, and, in many cases, expensive for real-world implementation. Moreover, in many communities, timely access to comprehensive cognitive evaluation is not possible.[22]

In keeping with the view that measurement-based care improves health outcomes in MDD, we developed the THINC-integrated tool (THINC-it), a computerized cognitive screening tool that assesses both objective and subjective measures of cognition and that can be easily administered to, and used by, patients with MDD. The psychometric properties of the THINC-it in healthy subjects have been established elsewhere (J.H., unpublished data, 2017). In the present study, conducted between

January and June 2016, we provide the validation results, specifically on sensitivity and concurrent validity, of the THINC-it in adults 18 to 65 years of age with MDD.

Clinical Points

- Cognitive dysfunction is a critical determinant of functional outcomes in major depressive disorder (MDD).
- Hitherto, assessment of cognitive dysfunction has not been standard practice in the assessment and treatment of MDD in large part due to the unavailability of appropriate, scalable, free, point-of-care instruments.
- The THINC-integrated tool (THINC-it) is sensitive and valid at detecting cognitive dysfunction in MDD, providing actionable information to patients and health care providers, and should be a component of measurement-based care.

METHODS

Subjects

Subjects with MDD. A total of 100 subjects with MDD were enrolled in the study (ClinicalTrials.gov identifier: NCT02508493). Patients were recruited via the Brain and Cognition Discovery Foundation (BCDF) located in Toronto, Ontario, Canada. The BCDF is affiliated with the Mood Disorders Psychopharmacology Unit (MDPU) at the University Health Network, an outpatient tertiary care center for individuals with mood disorders in Toronto. Patients with MDD were referred by psychiatrists in the MDPU to participate in the study based on the presence of a current major depressive episode (MDE). Referrals from the clinic resulted in the generation of a convenience sample.

The study was approved by a community Institutional Review Board—an independent ethics committee acting in accordance with good clinical practices (eg, ICH GCP Guidelines), Health Canada regulations and in compliance with US Food and Drug Administration 21 Code of Federal Regulations (CFR) parts 50 and 56, US Department of Health and Human Services 45 CFR part 46, and the Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans (http://irbservices.com/about-us/). Enrollment in the study was voluntary and all eligible subjects provided informed written consent. The ongoing provision of care for subjects with MDD was not contingent on enrollment and/or completion of the study protocol. Individuals with MDD who completed the single study visit received a financial compensation of $50 CAD.

The presence of both a current and a prior episode validated by previous treatment (eg, guideline-informed pharmacotherapy and/or manual-based psychotherapy) was established using the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), and confirmed using the Mini-International Neuropsychiatric Interview (MINI) Plus 5.0.0 for *DSM-IV-TR*. Subjects with MDD were moderately to severely depressed, operationalized as a score ≥ 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS), with a current MDE duration of ≥ 3 months. If currently being treated, subjects had to have been receiving a stable antidepressant dose or regimen for a minimum of 2 weeks prior to the study visit. Enrollment and active participation in psychotherapy was not an exclusion factor.

Subjects with MDD were excluded from participating in the present study on the basis of the following: current alcohol and/or substance use disorder confirmed by the MINI; comorbid psychiatric disorder(s), as confirmed by the MINI, of primary clinical concern; use of medications approved for and/or employed off-label to treat cognitive dysfunction (eg, psychostimulants), as adjudicated by BCDF clinicians; use of medication that, in the opinion of the investigator, might affect cognitive function (eg, corticosteroids, β-blockers); use of benzodiazepines within 12 hours, or consumption of alcohol within 8 hours, prior to THINC-it administration, verified by self-report; physical, cognitive, or language impairment evaluated by the clinician as severe enough to adversely affect the validity of the data derived from the cognitive tests; history of diagnosis of a reading disability, dyslexia, or clinically significant learning disorder; electroconvulsive therapy in the last 6 months; history of moderate or severe head trauma (eg, loss of consciousness for > 1 hour); and other neurologic disorders or unstable systemic medical diseases that, in the opinion of the investigator, are likely to affect the central nervous system.

Healthy control subjects. The a priori study design specified an equal number of healthy control subjects (HC) between the ages of 18 and 44 years and 45 and 65 years, matched by age (± 2 years), sex, and education (± 2 years) to the MDD group. Healthy controls were recruited to participate in the study primarily using paper and online advertisements disseminated in the downtown Toronto area. In keeping with a pragmatic approach to subject recruitment, HC were enrolled on a rolling basis *pari passu* with MDD subjects, resulting in 7 additional subjects who did not match the MDD group on age, sex, and education and were therefore excluded from endpoint analyses (ie, final $n_{HC} = 100$).

Healthy control subjects enrolled in the study had no current or past history of mental illness, confirmed by the MINI, and had no first-degree relatives with a mental illness diagnosis made by a health care provider. Additionally, HC were excluded based on presence of an unstable medical disorder or use of any medication that, in the opinion of the investigator, might affect cognitive function (eg, corticosteroids, β-blockers); and consumption of alcohol within 8 hours prior to THINC-it administration, verified by self-report. All eligible subjects provided informed written consent. Healthy control subjects who successfully completed the 2 study visits received a financial compensation of $100 CAD (ie, $50 CAD per visit) for their participation.

Measures

THINC-it. The THINC-it is a computerized cognitive assessment tool developed by the THINC Task Force,

comprising experts in psychology, psychiatry, primary care, psychometrics, neuroscience, and scale development (website: http://thinc.progress.im/en). The THINC-it is administered via computer or tablet and comprises variations of carefully selected, well-known cognitive assessments: the Identification Task (IDN) using the Choice Reaction Time paradigm (ie, THINC-it: Spotter), the One-Back Test (OBK; ie, THINC-it: Symbol Check), the Digit Symbol Substitution Test (DSST; ie, THINC-it: Codebreaker), and the Trail Making Test–Part B (TMT-B; ie, THINC-it: Trails), supplemented by the subjective, self-reported Perceived Deficits Questionnaire for Depression–5-item (ie, THINC-it: PDQ-5-D).[23–26] These tests were selected with the principal goal of being valid, acceptable, and time-efficient for screening of patients in routine clinical care.[23,24,27–29] The THINC-it is meant to be used as a holistic cognitive assessment tool without being parsed into its component tasks.

Each of the foregoing cognitive assessment tools has been employed in studies involving adults with MDD and evaluates domains of cognitive function affected in MDD (ie, executive functions, learning/memory, attention, and processing speed).[30] Validation reports of the original individual objective and subjective measures of cognition contained within the THINC-it are published elsewhere; the measures have been shown to be sensitive to cognitive deficits in MDD and independent of cultural background.[21,23,24,27,31]

The THINC-it can be completed by patients in approximately 10 to 15 minutes with minimal instruction prior to administration; the instructions were specifically constructed to accommodate patients with limited education (ie, grade 6). In addition, via integrated computerized and automatic algorithms, the THINC-it provides an easy and immediate summary of specific test results. The THINC-it was designed for routine use in specialty and primary care practice and can be self-administered by patients. There is no requirement for the tool to be administered or scored by a health care professional. Patient performance results are immediately available and simply presented using a color scheme (ie, green indicating cognitive performance within 0.5 standard deviations [SDs] of healthy age-, sex-, and education-matched comparison subjects; yellow suggesting cognitive performance within 0.5 to 1.0 SD below HC; and red highlighting performance of ≥ 1.0 SD below HC).

Spotter. Following the Choice Reaction Time paradigm, Spotter presents subjects with an arrow facing either left or right, and subjects are required to press the corresponding button (left or right) to match the direction of the arrow. The latency before presentation of the cue varies between trials, and the cue may appear on the left or right side of the screen. Subjects are required to press the appropriate key as quickly as possible. Shorter reaction times denote better cognitive performance. The test consists of 40 trials in 2 minutes.

Symbol Check. Symbol Check presents subjects with a continuously moving sequence of symbols across the screen. A legend of 5 possible symbols is presented at the bottom of the screen. Subjects are required to proactively view the symbol before it is hidden in order to correctly identify it before time runs out by pressing on the appropriate symbol in the legend. As the sequence moves to the left (ie, by subject response or time-out), symbols are hidden in consecutive order. The test consists of 40 trials in 2 minutes. Both latency and accuracy of trials are assessed in this test.

Codebreaker. A legend of numbers, ranging from 1 to 6, and their corresponding symbols is provided at the top of the screen. Codebreaker requires subjects to match a list of symbols to their corresponding numbers based on the legend. Subjects are presented with a series of numbers and are required to match as many symbols to numbers as possible in 2 minutes by tapping on the correct symbol at the bottom of the screen. A greater number of correct symbols matched is representative of better cognitive performance.

Trails. Similar to the TMT-B, Trails requires subjects to trace a line connecting consecutive letters and numbers (ie, beginning at "A" and proceeding to "1"), alternating as quickly as possible and continuing until all letters and numbers have been touched. Subjects must trace a continuous line without lifting their finger. If the line touches a letter or number out of sequence, the subject must restart from the last correct circle. All letters and numbers are hidden, with the exception of "A," until the subject touches "A" to start the test. Shorter completion time denotes greater cognitive performance.

PDQ-5-D. The PDQ-5-D includes 5 questions assessing issues with attention, memory, and concentration in the past 7 days. Subjects rate their difficulty experienced with each question on a Likert scale that ranges from 1 ("Never") to 5 ("Very Often [More Than Once a Day]"). Higher scores on the PDQ-5-D denote greater subjective cognitive impairment. The primary outcome variables for each of the THINC-it component tests are described in Table 1.

Primary assessment instruments. In addition to the THINC-it, other primary assessment instruments included the IDN and the OBK from the CogState battery (https://cogstate.com/clinical-trials/computerized-assessment/) as well as the pen-and-paper versions of the DSST, TMT-B, and PDQ-5-D. In addition, the 20-item PDQ (PDQ-20) was included. These tests served as measures to evaluate the procedural validity of the neuropsychological THINC-it domains.

The MADRS[32] was administered to measure severity of depressive symptoms. The MADRS consists of 10 items assessing severity of 10 commonly experienced depressive symptoms and has demonstrated sensitivity, reliability, and validity.[33]

Secondary assessment instruments. The National Adult Reading Test–Revised (NART-R) was included as an estimate of IQ.[34] A 7-question self-rated assessment of subject acceptance and satisfaction with the THINC-it was administered. Additional secondary assessment instruments included the Endicott Workplace Productivity Scale, Sheehan Disability Scale, Pittsburgh Sleep Quality Index, Clinical Global Impressions scale, Generalized Anxiety Disorder 7-item, WHO-5 Well-being Index, and the visual analog scale (VAS) for pain. With the exception

Table 1. Description of Cognitive Tasks in Conventional and THINC-it Tests

Test Type	Test	Abbreviation	Outcome Measure
Conventional	CogState Identification Task	IDN	Log-transformed reaction time (seconds)
	CogState One-Back Test	OBK	Log-transformed reaction time (seconds), accuracy of trials
	Digit Symbol Substitution Test	DSST	Total number correct
	Trail Making Test–Part B	TMT-B	Time to complete (seconds)
	Perceived Deficits Questionnaire–20-item	PDQ-20	Sum of items
	Perceived Deficits Questionnaire for Depression–5-item	PDQ-5-D	Sum of items
THINC-it	Spotter	…	Log-transformed reaction time (seconds)
	Symbol Check	…	Log-transformed reaction time (seconds), accuracy of trials
	Codebreaker	…	Total number correct
	Trails	…	Time to complete (seconds)
	Perceived Deficits Questionnaire for Depression–5-item	PDQ-5-D	Sum of items

Abbreviation: THINC-it = THINC-integrated tool.
Symbol: … = not applicable.

Table 2. Demographic and Clinical Characteristics of Subjects With Major Depressive Disorder and Healthy Controls

	Major Depressive Disorder (n = 90)		Healthy Controls (n = 92)		
Variable	Mean	SD	Mean	SD	*P* Value
Age, y	40.68	13.68	39.46	14.75	.563
Education, y	16.54	3.31	16.26	2.76	.530
Estimated IQ	113.72	7.25	111.98	6.69	.093
	n	%	n	%	
Sex					.984
Female	51	56.7	52	56.5	
Male	39	43.3	40	43.5	
Race/ethnicity					<.001**
White	69	76.7	41	44.6	
Asian	8	8.9	34	37.0	
Other	13	14.4	17	18.5	
	Mean	SD	Mean	SD	
MADRS total score	32.66	6.05	0.82	1.46	<.001**
Age at onset of MDD, y	19.54	12.62	…	…	…
Age at first treatment for MDD, y	26.50	12.73	…	…	…
	n	%			
No. of MDEs[a]					
2	10	11.6	…	…	…
≥3	50	58.1	…	…	…
No. of hospitalizations					
1	14	15.6	…	…	…
≥2	10	11.1	…	…	…

[a]Missing data for n = 19 subjects.
**P value is significant at the .01 level.

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode.
Symbol: … = not applicable.

of the NART-R and the patient satisfaction questionnaire, secondary assessments are not reported herein and will be reported elsewhere.

Procedure

Upon confirmation of study eligibility, all primary assessment instruments were sequentially administered, followed by the secondary assessment instruments. The sequence of the THINC-it component scales remained identical for all subjects throughout the study, and they were administered in the following order: PDQ-5-D, Spotter, Symbol Check, Codebreaker, and Trails. The IDN and OBK tests were administered using CogState software followed by the pen-and-paper versions of the DSST, TMT-B, and PDQ-5-D in the same order of administration as in the THINC-it. The order of administration of the THINC-it and the CogState tasks/pen-and-paper versions were alternated between subjects to account for potential order effects.

Subjects with MDD received all cognitive assessments 1 time during a single visit. Healthy control subjects completed the full set of cognitive assessments (ie, THINC-it, CogState, and pen-and-paper tasks) 3 times on visit 1 and once during visit 2 one week later. The second visit was incorporated to evaluate estimates of temporal reliability (reported elsewhere).

Statistical Analysis

The overarching aim of the validation herein was to evaluate and compare the extent of cognitive dysfunction in adults with MDD compared to HC matched on age, sex, and years of education. Extant literature indicates that the effect size for cognitive deficits in first- and multiple-episode MDD patients is approximately 0.3–0.7 (Cohen *d*).[35] Notwithstanding the range of reported effect sizes, a modal estimate of 0.4 is instantiated by meta-analysis across disparate domains.[36] Based on an effect size of 0.4, it was estimated that a sample size of 100 per group of evaluable subjects would be sufficient (with a power level of 0.8 and a probability level of .05).

z Scores were calculated for all THINC-it and CogState/pen-and-paper tests referencing HC performance on the THINC-it tasks using the equation [$participant_x$ score on $test_y$ – mean of HC on $test_y$]/standard deviation of HC on $test_y$. All *z* scores were sign-adjusted, such that higher *z* scores denote better performance. The primary analysis evaluated whether cognitive dysfunction in adults with MDD could be detected using a composite *z* score, defined as the equally weighted mean of *z* scores of all THINC-it tasks performed (ie, Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D) compared to the HC group. Additionally, another composite *z* score was calculated delimited to the objective component THINC-it tasks performed (ie, Spotter, Symbol Check, Codebreaker, and Trails) for comparison with the HC group. Likewise, an analysis evaluating whether subjective cognitive complaints in adults with MDD could be detected when compared to the HC group was performed using the *z*

Table 3. Mean Difference in Performance on Individual THINC-it Tests and Composite Scores Between Subjects With MDD and Healthy Controls

Measure	Mean Difference (SE)	*P* Value	95% CI	Cohen *d*
Spotter	−0.59 (0.15)	<.001**	−0.88 to −0.30	0.56
Symbol Check	−0.12 (0.10)	.240	−0.32 to 0.08	0.17
Codebreaker	−0.15 (0.14)	.290	−0.43 to 0.13	0.16
Trails	−0.04 (0.14)	.777	−0.32 to 0.24	0.04
PDQ-5-D	−3.95 (0.23)	<.001**	−4.40 to −3.50	2.58
Objective composite score	−0.23 (0.09)	.013*	−0.40 to −0.05	0.37
Total composite score	−0.97 (0.08)	<.001**	−1.14 to −0.80	1.70

*P value is significant at the .05 level.
**P value is significant at the .01 level.
Abbreviations: MDD = major depressive disorder, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, THINC-it = THINC-integrated tool.

score for the PDQ-5-D independent of the composite *z* score derived for the objective cognitive tasks in THINC-it.

For calculation of the total THINC-it composite score, each of the THINC-it tasks was assigned a weight of 0.20; the 2 subtest scores of Symbol Check (ie, log-transformed reaction time [in seconds], and arcsine square root transformation of proportion correct trials) were each assigned a weight of 0.10. Likewise, each of the aforementioned 4 objective component tasks contained in the THINC-it was assigned a weight of 0.25 for calculation of the THINC-it objective composite score; the 2 subtest scores of Symbol Check were each assigned a weight of 0.125. Individuals who did not complete the full set of objective and subjective THINC-it tasks, and any identifiable outliers, were excluded from the analysis.

Between-group comparisons were evaluated using independent-samples *t* tests for continuous variables. Mean differences (MDs), standard errors (SEs), and 95% confidence intervals (CIs) are presented. Chi-square tests of independence were conducted to assess differences between groups on categorical variables. Concurrent validity was examined by comparing the THINC-it subtests to equivalent cognitive tests as previously described (ie, CogState and pen-and-paper cognitive tasks) using Pearson product moment correlations. The PDQ-5-D was compared to both the pen-and-paper version of the PDQ-5-D and the PDQ-20 pen-and-paper scale. Internal consistency of the PDQ-5-D and THINC-it composite scores was assessed using the Cronbach α. Analyses of concurrent validity and internal consistency were delimited to subjects with MDD.

RESULTS

Subject Characteristics

The demographics and clinical characteristics of subjects with MDD and HC are presented in Table 2. Of the 264 individuals who were assessed for eligibility, 46 were lost to follow-up, 3 declined to participate, and 15 were excluded. The primary reason for exclusion of subjects with MDD (n = 3) was not fulfilling the inclusion criteria (eg, asymptomatic at the time of assessment). The primary reason for exclusion of HC (n = 12) was not fulfilling the inclusion criteria (eg, having a first-degree relative with a clinically diagnosed mood and/or psychiatric disorder). The remaining subjects (ie, MDD: n = 100; HC: n = 100) were available for completing their assessments for 1 visit (MDD) or 2 visits separated by a 1-week period (HC).

The primary analysis of the results from subjects with MDD compared to performance of HC (visit 1, attempt 1) was performed on subjects who completed the THINC-it in its entirety (ie, MDD: n = 90; HC: n = 92). Data were excluded for 10 MDD and 8 HC subjects who did not complete the THINC-it tasks. The primary reasons for not completing the THINC-it in its entirety were due to subject inability/unwillingness to complete the tasks. No between-group differences in age or sex were observed; however, there was a significant between-group difference in race (Table 2).

Differences in the Composite THINC-it Score

Significant differences in objective cognitive performance between subjects with MDD and HC using the total composite *z* score of the THINC-it (MD [SE] = −0.23 [0.09], *P* = .013; 95% CI, −0.40 to −0.05) were detected. Likewise, a significant difference in the PDQ-5-D *z* score was also observed (MD [SE] = −3.95 [0.23], *P* < .001; 95% CI, −4.40 to −3.50). Overall, 32.2% of subjects with MDD performed between 0.5 and 1 SD below the mean for HC, and 44.4% performed 1 SD or more below the mean for HC. Conversely, 97.8% of HC subjects performed better on the THINC-it when compared to the mean for subjects with MDD. The mean differences in performance between the 2 groups for each of the 5 tests of the THINC-it (ie, Spotter, Symbol Check, Codebreaker, Trails, and PDQ-5-D), as well as objective and total THINC-it composite scores, are presented in Table 3. Effect sizes, measured by Cohen *d*, ranged from 0.04 (Trails) to 2.58 (PDQ-5-D). Subgroup analyses by age (18–45 vs 46–65 years) and sex (male vs female) revealed no differences in the THINC-it total composite score.

Reliability and Validity of the THINC-it

Concurrent validity and internal consistency were examined among subjects with MDD. Concurrent validity was highest between Codebreaker and the DSST ($r_{90} = 0.692$, *P* < .001), with the lowest concurrent validity noted for Spotter and CogState IDN ($r_{83} = -0.083$, *P* = .454). Estimates of internal consistency were calculated for the PDQ-5-D, all 5 tests of the THINC-it, and the 4 objective tests of the THINC-it; additionally, internal consistency was calculated for both the PDQ-5-D and the PDQ-20, all 5 pen-and-paper tests, and the 4 objective pen-and-paper tests for comparison. The results from these analyses are presented in Table 4.

Feasibility and Patient Satisfaction

Among MDD and HC subjects, about 9 of 10 successfully completed administration of the THINC-it. On average, individuals with MDD required approximately 10 to 15 minutes for scale completion.

Table 4. Psychometric Properties of THINC-it Among Subjects With MDD

Concurrent Validity				
THINC-It Test	Pen-And-Paper Test	n	Pearson *r*	*P* Value
Spotter	IDN	83	−0.083	.454
Symbol Check	OBK	87	−0.146	.176
Codebreaker	DSST	90	0.692	<.001**
Trails	TMT-B	90	−0.132	.215
PDQ-5-D	PDQ-5-D	90	0.929	<.001**
PDQ-5-D	PDQ-20	90	0.862	<.001**
THINC-it objective composite score	Objective composite score	81	0.134	.231
THINC-it total composite score	Total composite score	81	0.539	<.001**

Internal Consistency			
Test	n	No. of Items	Cronbach α
Pen-and-paper PDQ-5-D	90	5	0.785
Pen-and-paper PDQ-20	87	20	0.937
Pen-and-paper objective composite score	81	4	0.350
Pen-and-paper total composite score	81	5	0.130
THINC-it PDQ-5-D	90	5	0.769
THINC-it objective composite score	90	4	0.551
THINC-it total composite score	90	5	0.370

**P value is significant at the .01 level.
Abbreviations: DSST = Digit Symbol Substitution Test, IDN = Identification Task, OBK = One-Back Test, PDQ-5-D = Perceived Deficits Questionnaire for Depression–5-item, PDQ-20 = Perceived Deficits Questionnaire for Depression–20-item, THINC-it = THINC-integrated tool, TMT-B = Trail Making Test–Part B.

Table 5. Qualitative Survey Responses on the THINC-it Questionnaire (N = 200)[a]

	Strongly Agree		Agree		Neutral		Disagree		Strongly Disagree	
Questionnaire Item	MDD	HC	MDD	HC	MDD	HC	MDD	HC	MDD	HC
I like when my symptoms of depression are evaluated with measurement tools[b]	17	…	42	…	29	…	7	…	5	…
I can predict my cognitive function without the use of the THINC-it	3	8	11	38	46	37	29	14	11	3
I would use the THINC-it on a regular basis to evaluate my cognitive function	14	13	44	34	33	32	4	18	4	3
The time required to complete the THINC-it is reasonable	26	22	59	66	13	10	2	1	0	1
I found the THINC-it user-friendly and easy to navigate	28	35	45	57	18	3	7	4	1	1
I prefer to use the electronic measure of cognition (ie, the THINC-it)	18	21	37	40	37	32	5	3	1	3
Evaluating my cognitive function is relevant to my quality of life and functioning	24	22	51	40	21	35	2	2	1	1
The instructions for the THINC-it are understandable	22	28	50	58	19	9	8	4	1	1
I prefer the pen-and-paper–based measures of cognition	4	3	13	17	51	39	24	34	8	6
Measuring my ability to think is the most relevant aspect of my depression[b]	12	…	36	…	35	…	12	…	4	…

[a]All values shown as percentages. Qualitative feedback was quantified as follows: strongly disagree (1), disagree (2), neutral (3), agree (4), strongly agree (5).
[b]Questionnaire items not comparable to healthy controls as they apply only to subjects with MDD.
Abbreviations: HC = healthy controls, MDD = major depressive disorder, THINC-it = THINC-integrated tool.
Symbol: … = not applicable.

The results from the patient satisfaction questionnaire are presented in Table 5. Results indicate that subjects with MDD reported difficulties in predicting their cognitive function without the use of a measurement tool. Moreover, they endorsed appreciation for having their cognitive function evaluated by the THINC-it, indicating that the THINC-it was user-friendly, was easy to navigate, and provided understandable instructions.

DISCUSSION

The results herein indicate that the THINC-it is a sensitive tool to detect cognitive dysfunction in adults 18 to 65 years old with MDD. In addition to detecting cognitive deficits, the THINC-it was able to quantify the magnitude of cognitive deficit in MDD. The percentage of individuals exhibiting a clinically significant deficit in cognitive function

identified in our MDD sample is similar to what has been reported elsewhere with other, more comprehensive and time-consuming testing.[35,37] Nine of 10 subjects were able to complete the THINC-it assessment, most within 10 to 15 minutes, and viewed favorably its potential impact on their clinical care.

As has been established (J.H., unpublished data, 2017), the THINC-it has high temporal reliability as well as concurrent validity with other computerized and pen-and-paper–based cognitive measures (ie, DSST). Among subjects with MDD, concurrent validity ranged from low to high across the various tests included in the THINC-it, with Codebreaker and the PDQ-5-D demonstrating strong concurrent validity with their pen-and-paper counterparts. Overall, on the basis of the THINC-it total composite score, we have established that the THINC-it has an acceptable level of concurrent validity with other computer-based and pen-and-paper tests that have been previously established as capable of detecting and measuring cognitive dysfunction in MDD.[18,38–40]

The advantages of the THINC-it include, but are not limited to, the fact that it includes both subjective and objective measures of cognitive function. It is critical to have both sets of tests since subjective and objective measures are not highly correlated[17] and both independently contribute to patient functioning.[41] Moreover, subjective measures of cognitive function are influenced to a greater extent by the presence and severity of depressive symptoms than are objective measures.[42–44] Moreover, the THINC-it can provide a repository of information related to the patient administering the tool that can be made available in print form or digitally for uploading to electronic health records. Patient confidentiality is preserved within the THINC-it apparatus.

It is not known to what extent the THINC-it would be capable of detecting cognitive deficits across other mental and medical disorders. It is also yet unknown if the THINC-it identifies cognitive deficits unique to MDD or for all depressions. The THINC-it, however, provides an integrated and composite assessment of multiple cognitive domains. It would be a reasonable expectation, albeit a hypothesis, that the THINC-it would be capable of detecting cognitive dysfunction in many common and severe mental disorders that manifest cognitive impairment (eg, schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder).

Several limitations to the present study warrant consideration. Analyses herein were delimited to a sample of 182 subjects; future studies employing the THINC-it should strive for larger sample sizes to better estimate widespread acceptability of the THINC-it. Our results do not control for circadian fluctuations in cognitive ability, as subjects participated in the study at all time points throughout the day based on their availability. The present validation study was completed by outpatients with MDD; we believe, however, that the relatively brief administration of the THINC-it (ie, 10–15 minutes) and the instructions built into the THINC-it obviate the need for professional support staff. Additionally, our subjects with MDD were required to be experiencing chronic, moderate-to-severe depression to enroll in the study, with the majority of subjects with MDD experiencing more than 3 previous MDEs. Therefore, our results may not be reflect the cognitive abilities of subjects with less severe MDD.

The pertinence of cognitive dysfunction in MDD warrants its screening and assessment, and preliminary evidence exists suggesting that some modalities of treatment are capable of directly and independently improving cognitive function.[45–47] The THINC-it is the first freely available (http://thinc.progress.im/en/form/download-thinc-it-tool), self-administered, computerized screening tool for cognitive dysfunction in MDD. Due to its clinical utility and sensitivity to detecting cognitive dysfunction in MDD, the THINC-it should be incorporated into the assessment and measurement of all patients with MDD, particularly among those with enduring functional impairment. Future studies will need to establish impact on health outcomes and cost-effectiveness as well as sensitivity to change.

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PriceSpective, Probiodrug, Prophase, Prostrakan, Regeneron, Reviva, Roche, Sanofi, Servier, Takeda, TransTech Pharma, and Velacor. In addition, Dr Harrison has a patent Cognition training system pending to MyCognition. **Dr Barry, Mr Best, Dr Klag**, **Ms Carmona,** and **Ms Lee** have no conflicts to disclose.

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Role of the sponsor: The THINC-it Task Force members were entirely responsible for the aims, objectives, hypotheses, design, analysis, and manuscript preparation. The funding agency (H. Lundbeck A/S Copenhagen, Denmark) was encouraged to provide input regarding the trial design. All final decisions pertaining to the sponsor's input were adjudicated by Drs McIntyre and Harrison.

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REFERENCES

1. Wisniewski SR, Rush AJ, Nierenberg AA, et al. Can phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. *Am J Psychiatry*. 2009;166(5):599–607.
2. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743–800.
3. Shilyansky C, Williams LM, Gyurak A, et al. Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry*. 2016;3(5):425–435.
4. McIntyre RS, Soczynska JZ, Woldeyohannes HO, et al. The impact of cognitive impairment on perceived workforce performance: results from the International Mood Disorders Collaborative Project. *Compr Psychiatry*. 2015;56:279–282.
5. Brewster GS, Peterson L, Roker R, et al. Depressive symptoms, cognition, and everyday function among community-residing older adults. *J Aging Health*. 2017;29(3):367–388.
6. Graziane JA, Beer JC, Snitz BE, et al. Dual trajectories of depression and cognition: a longitudinal population-based study. *Am J Geriatr Psychiatry*. 2016;24(5):364–373.
7. Jaeger J, Berns S, Uzelac S, et al. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res*. 2006;145(1):39–48.
8. Baune BT, Miller R, McAfoose J, et al. The role of cognitive impairment in general functioning in major depression. *Psychiatry Res*. 2010;176(2–3):183–189.
9. Evans VC, Iverson GL, Yatham LN, et al. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. *J Clin Psychiatry*. 2014;75(12):1359–1370.
10. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs*. 2010;24(4):267–284.
11. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2010;363(27):2611–2620.
12. Wykes T, Haro JM, Belli SR, et al; ROAMER Consortium. Mental health research priorities for Europe. *Lancet Psychiatry*. 2015;2(11):1036–1042.
13. Rush AJ. Isn't it about time to employ measurement-based care in practice? *Am J Psychiatry*. 2015;172(10):934–936.
14. Yeung AS, Jing Y, Brenneman SK, et al. Clinical Outcomes in Measurement-based Treatment (Comet): a trial of depression monitoring and feedback to primary care physicians. *Depress Anxiety*. 2012;29(10):865–873.
15. Guo T, Xiang Y-T, Xiao L, et al. Measurement-based care versus standard care for major depression: a randomized controlled trial with blind raters. *Am J Psychiatry*. 2015;172(10):1004–1013.
16. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. *CNS Spectr*. 2015;20(suppl 1):20–30, quiz 31.
17. Harrison JE, Lam RW, Baune BT, et al. Selection of cognitive tests for trials of therapeutic agents. *Lancet Psychiatry*. 2016;3(6):499.
18. Woo YS, Rosenblat JD, Kakar R, et al. Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clin Psychopharmacol Neurosci*. 2016;14(1):1–16.
19. McIntyre RS, Lee Y. Cognition in major depressive disorder: a Systemically Important Functional Index (SIFI). *Curr Opin Psychiatry*. 2016;29(1):48–55.
20. Robbins TW, James M, Owen AM, et al. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia*. 1994;5(5):266–281.
21. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;30(6):515–527.
22. Culpepper L. Impact of untreated major depressive disorder on cognition and daily function. *J Clin Psychiatry*. 2015;76(7):e901.
23. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(7):271.
24. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol—coding subtest across the adult lifespan. *Arch Clin Neuropsychol*. 2004;19(6):759–767.
25. Marquand AF, Mourão-Miranda J, Brammer MJ, et al. Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *Neuroreport*. 2008;19(15):1507–1511.
26. Bruder GE, Alvarenga JE, Alschuler D, et al. Neurocognitive predictors of antidepressant clinical response. *J Affect Disord*. 2014;166:108–114.
27. Kane MJ, Conway ARA, Miura TK, et al. Working memory, attention control, and the N-back task: a question of construct validity. *J Exp Psychol Learn Mem Cogn*. 2007;33(3):615–622.
28. Trueman RC, Brooks SP, Dunnett SB. Choice reaction time and learning. In: Seel NM, ed. *Encyclopedia of the Sciences of Learning*. New York NY: Springer US; 2012:534–537.
29. Lam RW, Saragoussi D, Danchenko N, et al. QL4: psychometric validation of Perceived Deficits Questionnaire—Depression (PDQ-D) in patients with major depressive disorder (MDD). *Value Health*. 2013;16(7):A330.
30. McIntyre RS. *Cognitive Impairment in Major Depressive Disorder: Clinical Relevance, Biological Substrates, and Treatment Opportunities*. Cambridge, UK: Cambridge University Press; 2016.
31. Edman G, Schalling D, Levander SE. Impulsivity and speed and errors in a reaction time task: a contribution to the construct validity of the concept of impulsivity. *Acta Psychol (Amst)*. 1983;53(1):1–8.
32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
33. Müller MJ, Szegedi A, Wetzel H, et al. Moderate and severe depression: gradations for the Montgomery-Asberg Depression Rating Scale. *J Affect Disord*. 2000;60(2):137–140.
34. Bright P, Jaldow E, Kopelman MD. The National Adult Reading Test as a measure of premorbid intelligence: a comparison with estimates derived from demographic variables. *J Int Neuropsychol Soc*. 2002;8(6):847–854.
35. Rock PL, Roiser JP, Riedel WJ, et al. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*. 2014;44(10):2029–2040.
36. Phillips WJ, Hine DW, Thorsteinsson EB. Implicit cognition and depression: a meta-analysis. *Clin Psychol Rev*. 2010;30(6):691–709.
37. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol*. 2006;21(7):623–643.
38. Damschroder L, Hall C, Gillon L, et al. The Consolidated Framework for Implementation Research (CFIR): progress to date, tools and resources, and plans for the future. *Implement Sci*. 2015;10(1):A12.
39. McKnight PE, Kashdan TB. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. *Clin Psychol Rev*. 2009;29(3):243–259.
40. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139(1):81–132.
41. Thomas Gualtieri C. Computerized neurocognitive testing and its potential for modern psychiatry. *Psychiatry (Edgmont)*. 2004;1(2):29–36.
42. Farrin L, Hull L, Unwin C, et al. Effects of depressed mood on objective and subjective

measures of attention. *J Neuropsychiatry Clin Neurosci*. 2003;15(1):98–104.
43. Lahr D, Beblo T, Hartje W. Cognitive performance and subjective complaints before and after remission of major depression. *Cogn Neuropsychiatry*. 2007;12(1):25–45.
44. Lehrner J, Moser D, Klug S, et al. Subjective memory complaints, depressive symptoms and cognition in patients attending a memory outpatient clinic. *Int Psychogeriatr*. 2014;26(3):463–473.
45. Theunissen EL, Street D, Højer AM, et al. A randomized trial on the acute and steady-state effects of a new antidepressant, vortioxetine (Lu AA21004), on actual driving and cognition. *Clin Pharmacol Ther*. 2013;93(6):493–501.
46. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557–1567.
47. Papakostas GI. Antidepressants and their effect on cognition in major depressive disorder. *J Clin Psychiatry*. 2015;76(8):e1046.