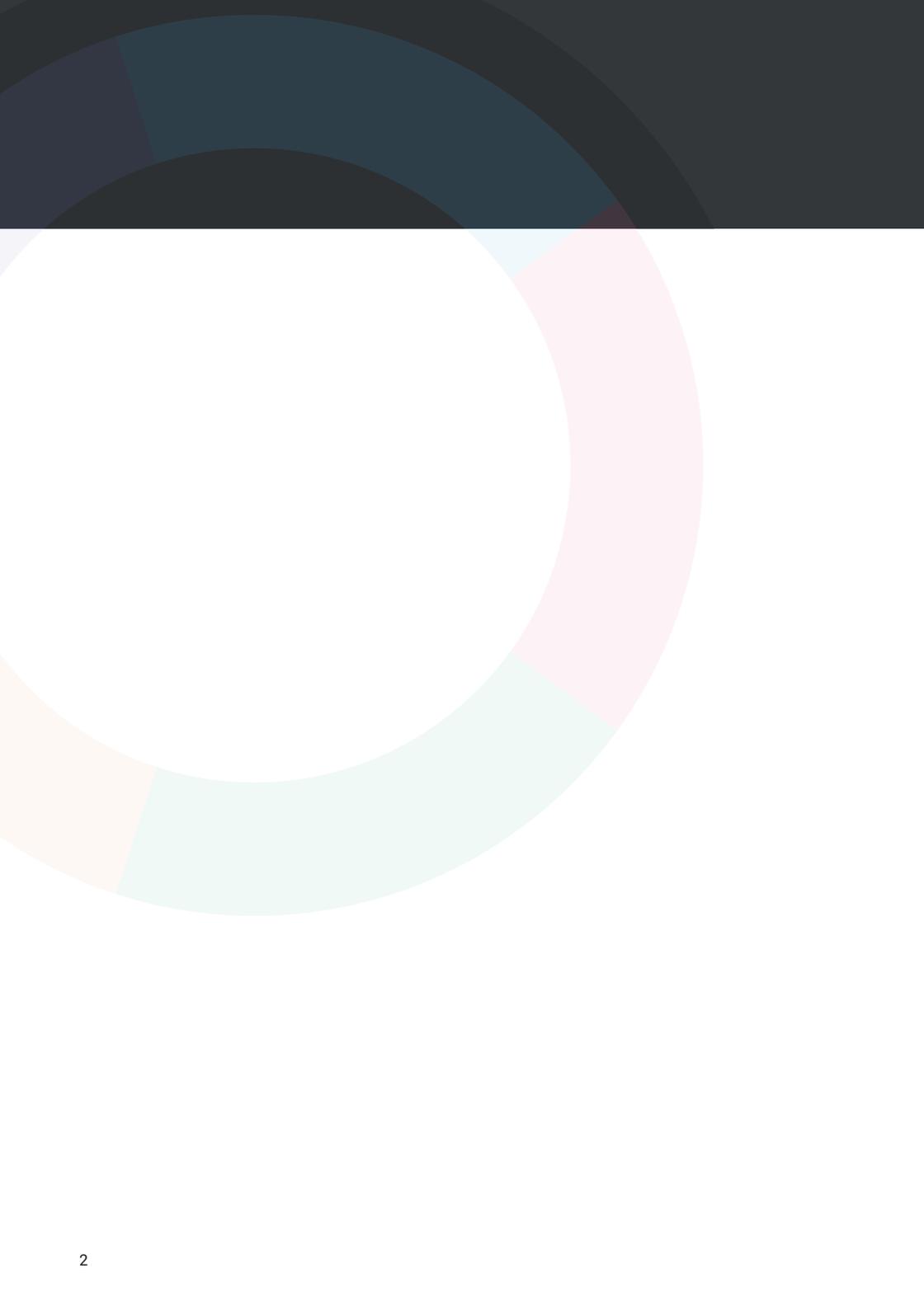


THINC-it[®] **physician guide**





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1. Introduction

Research into major depressive disorder (MDD) has shown that many patients experience difficulties with their cognition. Cognitive functioning is divided into various abilities, frequently impaired in patients with depression, and include remembering (memory), concentration (attention), and the ability to organise thoughts and make decisions (executive function). Of note, objective testing of changes in cognitive function often yields different results from patients' subjective self-reports.

Research has also shown that between episodes of depression, up to 40% of patients experience difficulties with their cognitive functioning. These difficulties often lead to problems at work/school, such as absence and impaired productivity. Recently, psychiatrists, psychologists and GPs have developed a brief, easy-to-use digital tool to help assess cognitive functioning. This tool, named THINC-it®, is based on a combination of specific (traditional) neuropsychological tests assessing cognitive functioning, in conjunction with a patient-reported questionnaire.

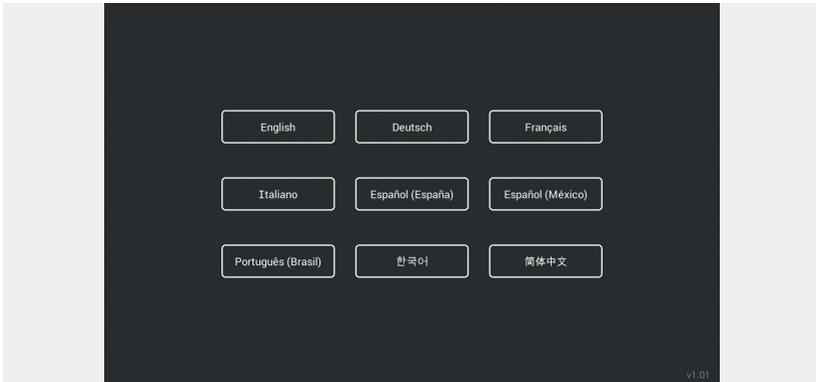
THINC-it® is a screening tool designed to measure cognition and provides important data for an overall evaluation of whether cognitive functioning is impaired.

This manual includes sections describing the operation of the THINC-it® software (Section 2) including instructions for use in the clinical setting (Section 3), interpretation of the results (Section 4) and an appendix summarising data from the validation of the tool (Section 5).

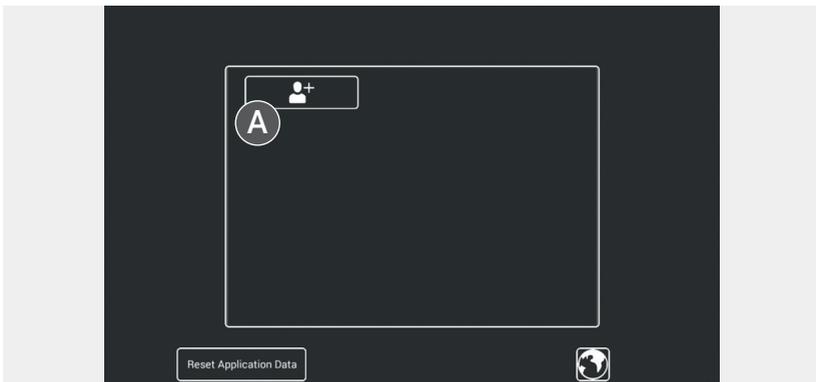
2. THINC-it® operation guide

This guide covers operation of the THINC-it® application for iPad, Android tablet, Windows PC and Mac OS X.

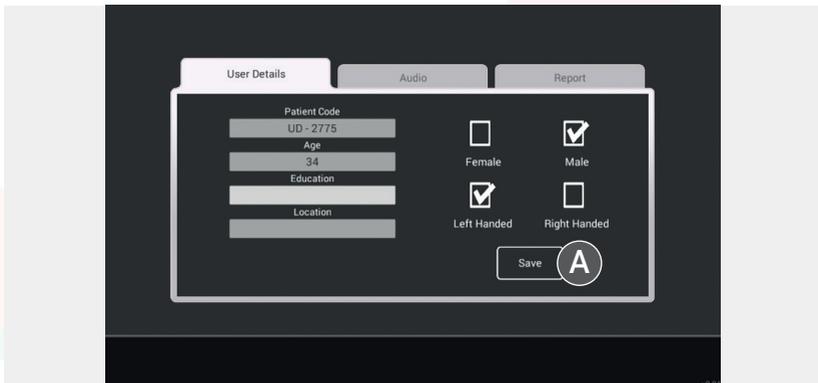
- 2.1 Select your desired language (PC and Mac only). You may return to this screen at any time from the main menu and change the application language.



- 2.2 The THINC-it® application allows for multiple user profiles on a single device (up to many thousands if required). Data for each user will be stored within their profile. Click/touch button (A) to create a new user.



2.3 Enter user details, as free text (eg 'Education' may be numeric and/or text data). As well as the core fields, you have the option of turning off audio and the ability to add notes about the user. You may navigate between the 'User Details', 'Audio' and 'Report' tabs without losing any data already entered but you must subsequently return to the 'User Details' tab and click/touch the 'Save' button (A) to proceed. A 'Patient Code' must be entered before the user can be saved. **NOTE – On some devices (iOS, Android), the 'Report' tab may provide the additional option of designating a report email address to which test data can be exported. If so, ensure you return to the 'User Details' tab and click/touch 'Save' to proceed.**



2.4 This is the THINC-it® main menu screen. The patient code of the currently selected user is displayed at the bottom of the screen for reference.



The THINC-it® application comprises five game or tests, represented by the five coloured icons.



Perceived Deficits Questionnaire for Depression five-item version (PDQ-D5) – self-report (subjective) questionnaire about cognition.



“Spotter” – a reaction time test of attention.



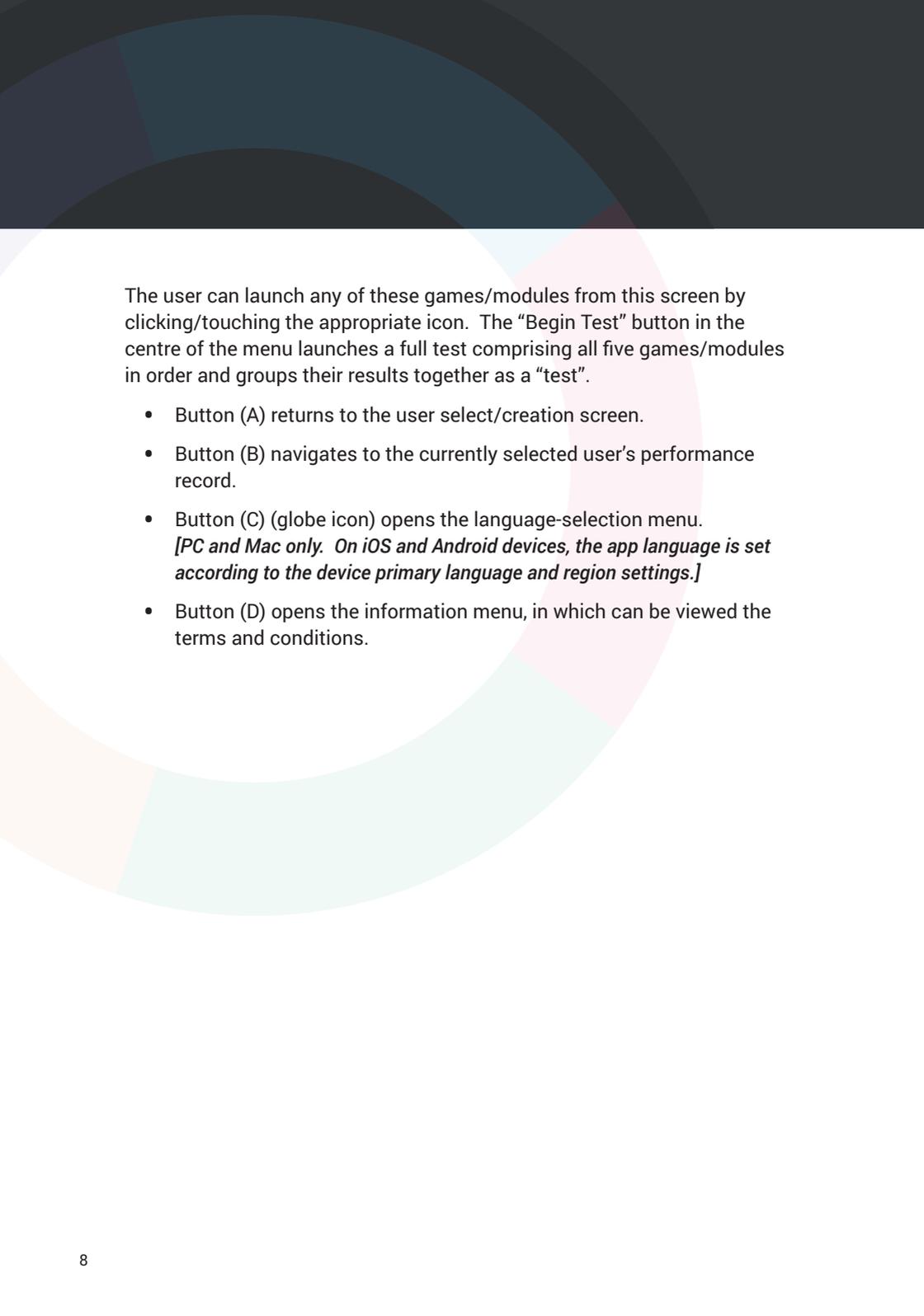
“Symbol Check” – a test of working memory.



“CodeBreaker” – a coding test that measures a variety of cognitive skills.



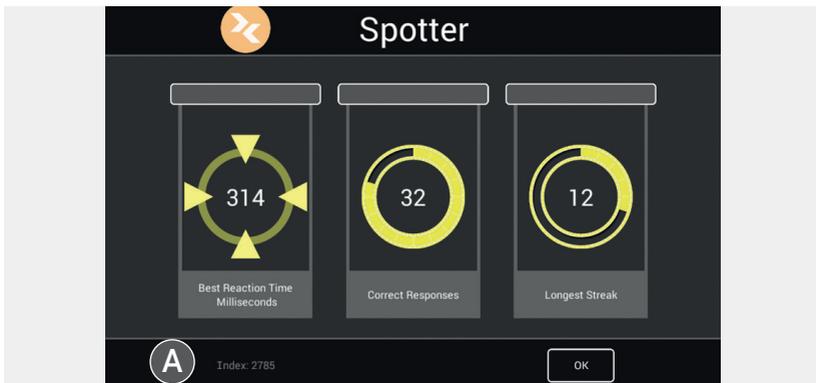
“Trails” – a test of executive function.



The user can launch any of these games/modules from this screen by clicking/touching the appropriate icon. The “Begin Test” button in the centre of the menu launches a full test comprising all five games/modules in order and groups their results together as a “test”.

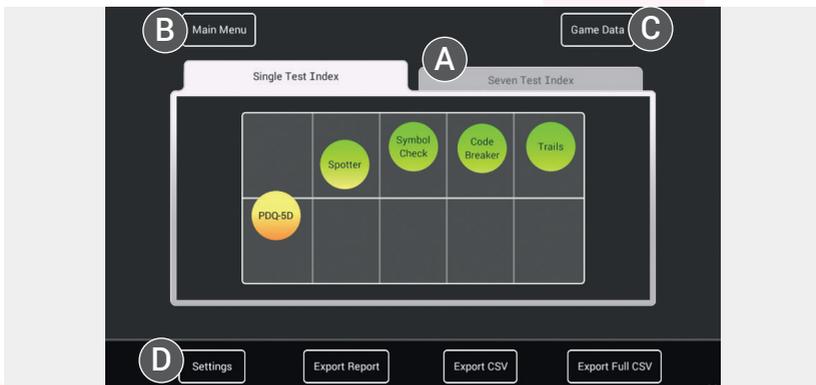
- Button (A) returns to the user select/creation screen.
- Button (B) navigates to the currently selected user’s performance record.
- Button (C) (globe icon) opens the language-selection menu.
[PC and Mac only. On iOS and Android devices, the app language is set according to the device primary language and region settings.]
- Button (D) opens the information menu, in which can be viewed the terms and conditions.

- 2.5 On completion of a game (excluding the PDQ-D5), a results screen will be displayed.



This screen will be displayed after each game regardless of whether it is played individually **OR** as part of a full test. The three scores displayed in the boxes are feedback designed to encourage the user to play to the best of their ability on repeated use. These should not be taken as a performance metric in a clinical sense. The “Index” score in the bottom left (A) is an overview performance metric: the minimum is 0 and the maximum is 4000, with higher scores indicating better performance. This value is entered into the user’s performance-data record and displayed in the graphs referenced below. The program automatically saves and date-time stamps a user’s test score – a user does not need to take any action to save their score.

2.6 A user performance-data record is available for each full test (comprising all five games/modules). The central graph displays the relative scores in the five modules of the most recently completed assessment. You can cycle back through test scores using the arrow buttons at either side of the graph (where data are available).



- Button (A) switches to an overlaid view of the last seven completed tests.
- Button (B) returns to the main menu.
- Button (C) switches to a view of the individual game/module performance records.
- Button (D) navigates to the user details interface, allowing you to modify or update the user's information, notes and settings.

2.7 A user performance-data record for the last seven completed tests can also be displayed. The tick boxes under the graph can be used to turn on/off the graph data for individual games/modules.



Buttons (A), (B) and (C) allow you to export a user's performance data from the app.

NOTE – These data exports are VERY detailed and feature not only the index scores displayed in these graphs but also ALL of the contributing data input, stimulus, latency and error.

- Button (A) exports an RTF¹ file report of the data within the currently displayed tests. It includes a graph image.
- Button (B) exports a CSV² file containing the data within the currently displayed tests.
- Button (C) exports a CSV file containing ALL the performance data within the profile of the current user, **regardless of which data are currently displayed on screen**. WARNING – likely to be a very large amount of data.

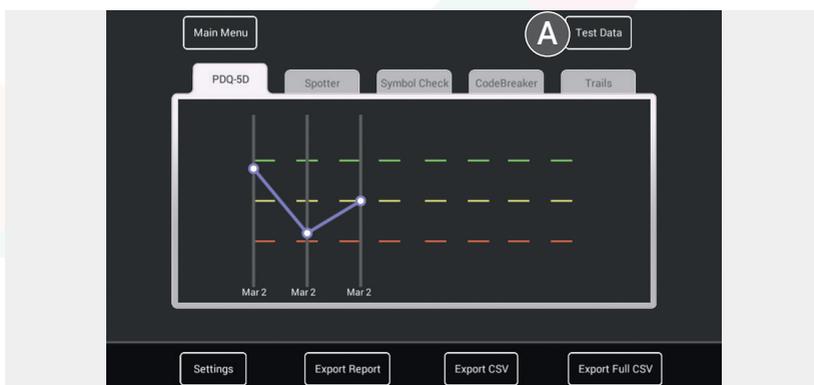
¹RTF, rich text format file.

²CSV, comma-separated values file (stores tabular data [numbers and text] in plain text).

- **NOTE:**

- » On a PC/Mac, clicking any of these buttons generates a data report that can be saved to the desktop/file-management system.
- » On an iOS device, clicking any of these buttons generates an email to the address entered on the 'Report' tab of the 'User Details' screen to which the data will be exported. If this information was not provided, a message will appear: "Missing user information: Report Email Address", and clicking 'OK' will allow the user to enter an email address.

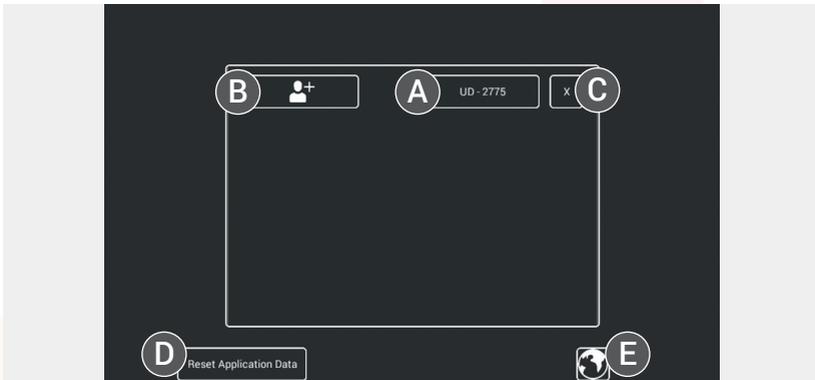
2.8 Data can also be accessed that show the user performance-data record for individual games/modules. Button (A) returns to full test index data display. Export buttons function the same way on this screen.



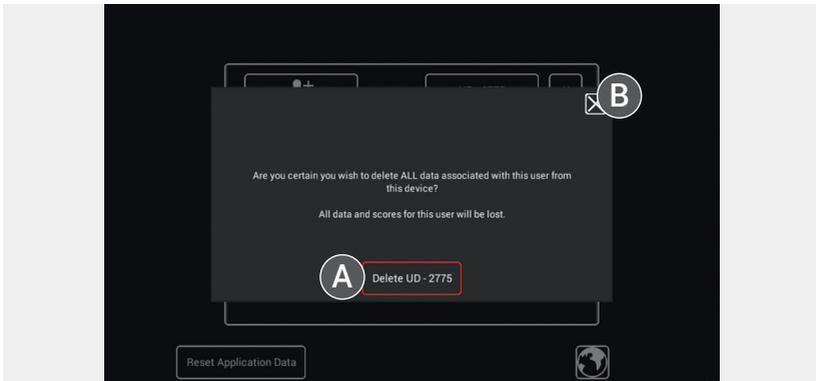
- 2.9 To change users, return to the main menu screen, then click/touch the user-select button (A). This will take you to the user-selection screen.



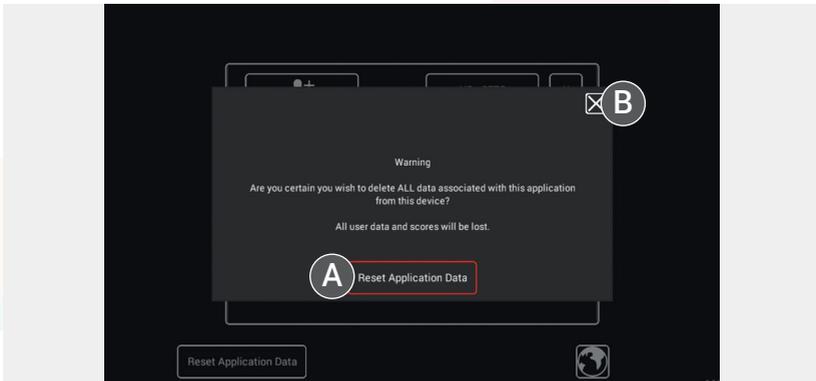
2.10 From this user-selection screen, you can change the user, manage existing user profiles or create new ones. Here we can see one existing user (A). To create a new user, click/touch button (B). To delete an existing user, click the button marked “x” next to their patient code (C). Button (D) is used to reset the entire application and delete ALL data including ALL user profiles *[PC and Mac only]*. Note – the language menu is also accessible from this screen (E).



2.11 When deleting a user, you will be presented with a confirmation screen as shown below. **WARNING – deleting a user profile will delete ALL the performance data held under that profile.** If you are absolutely certain you wish to delete a user and ALL their associated data, click/touch button (A). **This is a non-reversible action.** If you change your mind or have reached this screen by accident, click/touch the close “x” button (B) and the user data/profile will remain.



2.12 *[PC and Mac only]* If you click/touch the “Reset application data” button, you will be presented with a confirmation screen as shown below. Resetting application data (A) will delete ALL user profiles, data and preferences from the app, and essentially reset it to default specification. **ALL data will be LOST if you confirm this action! This feature is primarily to clear a machine of all data before uninstalling the program. As a last resort, it can also be used to clear corrupt or rejected data. In either case, it is not recommended that you take this action unless ALL current data have been exported and stored externally.** If you change your mind or have reached this screen by accident, click/touch the close “X” button (B) and the app will remain as it is.





3. Individual test instructions

THINC-it® is comprised of four game-like cognitive tests inspired by well-known psychological assessments: Choice Reaction Time task (Spotter), the *n*-back memory task (Symbol Check), Digit Symbol Substitution Test (CodeBreaker) and the Trail Making Test – Part B (Trails), supplemented by the subjective, self-reported PDQ-D5. Each of the assessment tools has been used in studies involving adults with depression and has been used to evaluate domains of cognitive functioning known to be affected in depression (ie executive function, learning/memory and attention). Each of the original individual objective and subjective measures of cognition contained within the THINC-it® tool has previously been validated to be sensitive to cognitive deficits in depression and independent of cultural background (McIntyre et al. 2013; Joy et al. 2004; Kane et al. 2007; Edman et al. 1983; Reitan 1958).

Each test is accessed from the central hub and includes a tutorial. You may wish to work through these tutorials to ensure each task is fully understood. Once begun, each game cannot be interrupted.

The tests in THINC-it® all require the patient to concentrate. Unsurprisingly, interruptions that disturb the patient's concentration are very likely to impact on their test performance. To give the patient the chance to perform to the best of their ability, it is helpful to have them take the THINC-it® tests in as quiet and comfortable environment as you have available. In a psychiatric clinic, the patient should ideally perform THINC-it® in a separate room on their own. In a busy family practice, there is the option to consider a nurse's room if no spare testing rooms are available. We appreciate that this may not be possible in every setting; we would, however, strongly recommend the use of headphones if a separate room is not available.

We would also recommend that patients are advised before beginning the THINC-it® tests that it is normal for concentration, memory and other domains of cognition to be reduced during an episode of depression, thus avoiding major negative reactions to a poor performance result.

3.1 Spotter



The Spotter game is inspired by the *Choice Reaction Time* task, capable of assessing **attention** and **executive function**, and takes 2 minutes to complete. A series of arrows will appear, facing either left or right. Users are required to select the left or right direction as quickly as possible depending on the direction of the arrow. Their response causes the next arrow to appear. The user is scored on speed and accuracy – care must be taken not to press the key before the arrow appears.

3.2 Symbol Check



The Symbol Check game is inspired by the *n-back* task, capable of evaluating **working memory**, **executive function** and **attention/concentration**, and takes 2 minutes to complete. Users are presented with a laterally moving sequence of symbols, the first of which is then hidden. The patient must correctly recall the hidden symbol as quickly as possible. Users are scored on speed and accuracy.

3.3 CodeBreaker



The CodeBreaker game is inspired by the *Digit Symbol Substitution Test*, capable of identifying deficits in the domains of **executive function**, **processing speed** and **attention/concentration**, and takes 2 minutes to complete. Six symbols are numbered consecutively. Users are presented with a series of numbers that they must then match with the correct corresponding symbol as quickly as possible. Users are scored on speed and accuracy.

3.4 Trails



The Trails game is inspired by the *Trail Making Test*, capable of evaluating **executive function**, and includes one test of 18 connecting points. Beginning with the letter 'A', the user must trace a line to the number 1, then continue to the letter 'B' followed by the number '2' and so forth. Alternate from letter to number as quickly as possible, continuing until all have been connected. If the line touches a letter or number that is not the next in the sequence, the user must restart from the last correct digit. The user should complete the task as quickly as possible.

3.5 PDQ-D5



The questionnaire is accessed from the main menu and includes the five questions from the *Perceived Deficits Questionnaire* that broadly evaluate attention/concentration and planning/organisation, as well as retrospective and prospective memory. The patient should select the appropriate response for each question considering their experiences during the previous 7 days.

4. Interpretation

THINC-it® has demonstrated acceptable concurrent validity and temporal reliability in healthy individuals (18–65 years of age) matched on age (± 2 years), sex and years of education (± 2 years) to patients with MDD (McIntyre et al. In submission).

Once completed, THINC-it® produces results that are easy to understand. THINC-it® performance results are immediately available and simply presented using a colour scheme (**green, amber, red**) indicating cognitive performance compared to healthy age-, sex- and education-matched comparison individuals. Data from the patient assessment can be confidentially stored and compared to later assessments, including a measure of sensitivity to change with treatment; moreover, a quantitative output can be obtained (eg to incorporate in an electronic medical record).

Green Cognitive performance within 0.5 standard deviation (SD) of healthy age-, sex- and education-matched comparison individuals; consistent with expectation, no concerns.

Amber Cognitive performance within 0.5 to 1.0 SD below healthy control individuals; therefore, clinical interpretation is required.

Red Cognitive performance of 1.0 SD or more below healthy control individuals; therefore, clinical interpretation is required. Consider taking action as appropriate (eg in-depth examination, optimise treatment, follow-up visit).



It is important to keep in mind that cognitive function is compromised in different conditions affecting the brain, including dementia, traumatic brain injury and infection. Additionally, people naturally vary across the day in their levels of performance. Cognitive performance can also be affected by a wide variety of factors, such as lack of sleep, alcohol use or emotional stress. It is recommended that an initial 'red' performance result be repeated (the participant may not have fully understood the instructions or may have felt highly anxious), with consistent results confirming that clinical interpretation is required.

While the THINC-it® tests are likely to be subject to a modest learning effect, this is expected to be minimal once a patient is familiar with the tool.

Please note that these results are only one aspect to consider when assessing a patient with depression. For example, the Patient Health Questionnaire (PHQ-9) and measures of patient functioning should also be considered to determine any areas that require specific focus.

The data collected by THINC-it® contribute to the overall clinical information amassed for each patient, assisting the physician in making an informed clinical judgement.

5. Additional information

5.1 Validation study data

The recent THINC-it® validation study (McIntyre et al. In submission) has yielded the statistics required for the calculation of reliable change indices. This methodology will permit the evaluation of individual patient scores to determine whether there has been a real change from Test 1 to Test 2, or whether changes are more likely due to measurement error.

Significant differences in cognitive performance between patients with MDD and healthy control individuals using the total composite z-score of the THINC-it® tool and an independent evaluation of the PDQ-D5 z-score was observed at the $p < 0.05$ and $p < 0.001$ levels, respectively. Overall, 78.9% of patients with MDD performed 0.5 SD or more below the mean for healthy control individuals and 43.3% of patients with MDD performed 1 SD or more below. Conversely, 81.5% of healthy control individuals performed better on the THINC-it® tool when compared to the mean for patients with MDD.

Concurrent validity and internal consistency were examined for participants with MDD (Table 1). Concurrent validity was examined by comparing the THINC-it® subtests to equivalent cognitive tests and pen-and-paper assessment. The PDQ-D5 was compared to both the pen-and-paper version of the PDQ-D5 and to the PDQ-20 pen-and-paper scale. Internal consistency of the PDQ-D5 and THINC-it® composite scores was assessed using Cronbach's alpha.

Table 1. Psychometric properties in patients with MDD (n=90).

THINC-it® measure	Concurrent validity	Cronbach's alpha	Temporal reliability (V1_A1 to V2) [95% CI]	Temporal reliability (V1_A3 to V2) [95% CI]	Stability as WSD (for PDQ 'internal consistency') [95% CI]
Spotter (total number of correctly identified symbols)	0.316	-	-	-	-
Spotter (mean reaction time for all correct responses)	0.341	-	0.79 [0.7, 0.85]	0.86 [0.8, 0.9]	73.5 [66.3, 80.7]
Symbol Check (total number of correctly identified symbols)	0.135	-	0.74 [0.64, 0.82]	0.88 [0.83, 0.92]	5.9 [5.3, 6.5]
Symbol Check (mean reaction time for all correct responses)	-0.026	-	-	-	-
CodeBreaker (number correct)	0.701	-	0.81 [0.73, 0.87]	0.80 [0.72, 0.86]	11.23 [10.1, 12.3]
Trails (time taken to complete)	0.029	-	0.62 [0.48, 0.73]	0.82 [0.74, 0.88]	17.3 [15.6, 19.0]
PDQ-D5 (score)	0.926 (pen & paper) 0.866 (PDQ-20)	0.790	0.71 [0.6, 0.8]	0.76 [0.66, 0.83]	0.76 [0.68, 0.83]
THINC-it® total	-	0.528	-	-	-

Temporal reliability is a measure of how consistent test performance is across time, usually 1 week or more. Test stability determines how stable performance is across a very short period of time. The stability measurement is based on 3 'back-to-back' assessments of the measures in typical control individuals. These are the assessments listed as V1, A1–A3. The first temporal reliability measure is based on V1 A1 compared to V2. The second temporal reliability measure is based on a comparison of V1 A3 with V2.
V, visit; A, attempt; CI, confidence interval; WSD, within-subject standard deviation.

6. References

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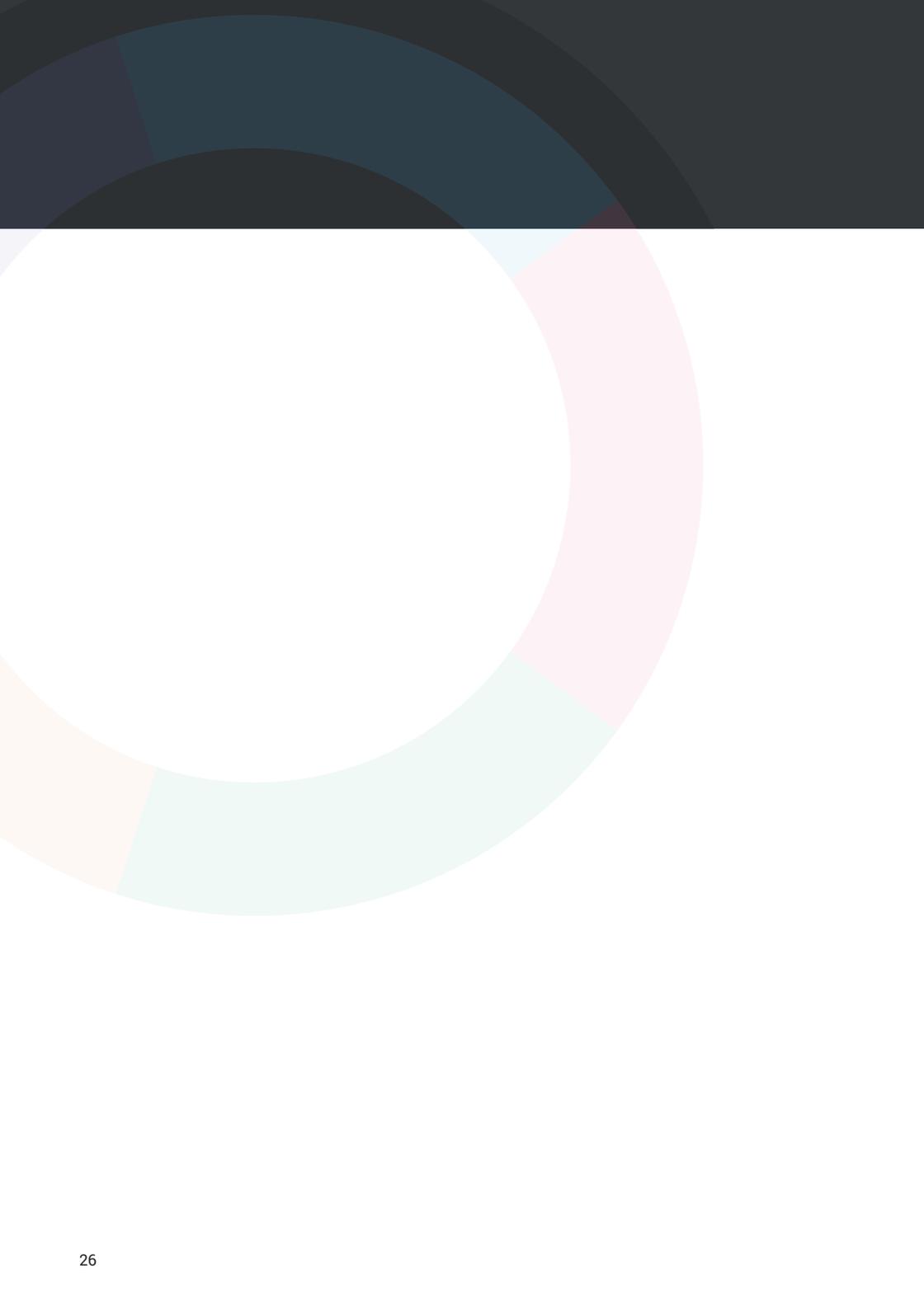
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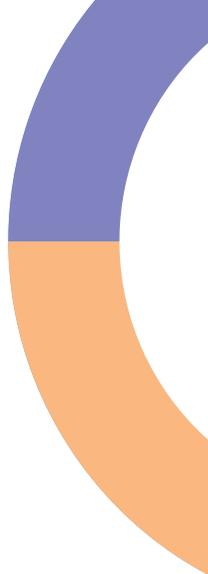
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Date of preparation: April 2017

THINC-it 