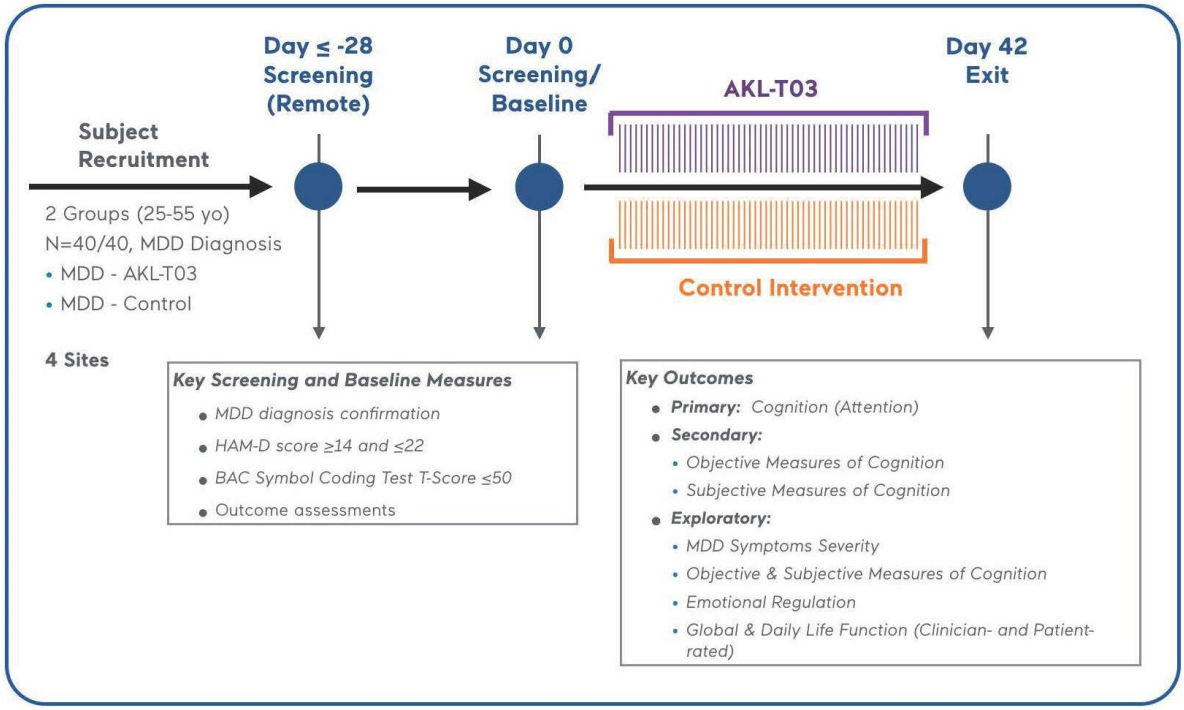
Data supplement for Keefe et al., Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry (doi: 10.1176/appi.ajp.21020125)

CONTENTS

FIGURE S1. Study design and protocol



DATA AVAILABILITY

The STARS-MDD investigators agree to share de-identified individual participant data, the study protocol, and the statistical analysis plan with academic researchers 6 months after publication and following completion of a Data Use Agreement. Proposals should be directed to medinfo@akiliinteractive.com.

COMPLETE LIST OF INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- ≥ 25 and ≤55 years of age at time of informed consent
- Male or female
- Primary diagnosis of recurrent Major Depressive Disorder (MDD) according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as confirmed by MINI Version 7.0.2.
- Pre-Screening (Day≤-28) Remote or In-Clinic
- Screening/Day 0 (in-clinic)
- HAM-D-17 score ≥14 and ≤22
- BAC Symbol Coding Test, T-test score <50
- On stable antidepressant medication for ≥8 weeks prior to screening/baseline, with stable dose for ≥4 weeks prior to baseline/baseline, with or without stable adjunct psychotherapy (excluding DBT or CBT) for ≥12 weeks.
- Access to and self-report of ability to connect wireless devices to a functional wireless network
- Ability to follow written and verbal instructions (English) as assessed by the PI and/or study coordinator
- Normal color vision as tested by Ishihara Color Blindness Test
- Able to comply with all testing and requirements

Exclusion criteria

- Current controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms including but not limited to post-traumatic stress disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive-compulsive disorder, severe depressive or anxiety disorder, conduct disorder, ADHD or other symptomatic manifestations that in the opinion of the Investigator may confound study data/assessments.
- Initiation or completion of psychotherapy within the last 12 weeks prior to screening/baseline. The participant should inform the Investigator if they intend to change their psychotherapy during the 6 weeks of the study. Participants who have been in psychotherapy consistently for more than 12 weeks may participate if their routine is stable throughout the study.
- Participant is currently considered at risk for attempting suicide by the Investigator, has made a suicide attempt within the past year, or is currently demonstrating active suicidal ideation or self-injurious behavior, as measured by CSSRS.
- Motor condition (e.g. physical deformity of the hands/arms) that prevents game playing as reported by the participant or observed by the Investigator.
- Recent history (6 months prior to screening/baseline) of substance use disorder
- History of seizures (excluding febrile seizures), a tic disorder, significant tics, a current diagnosis of Tourette's Disorder.
- Self-report of recent episodes (within the past week) of nausea, vomiting and/or dizziness.

- Participation in a clinical trial within 3 months prior to screening.
- Color blindness as detected by Ishihara Color Blindness Test
- Regular use of psychoactive drugs other than antidepressants, including stimulants that in the opinion of the Investigator may confound study data/assessments.
- Use of benzodiazepines >3 times per week and/or within 24 hours of baseline and exit visit assessments prohibited.
- Use of marijuana or alcohol on the day of clinical visits before baseline or exit assessments, no tobacco within 30 minutes of TOVA
- Any other medical condition that in the opinion of the Investigator may confound study data/assessments.
- Previous exposure to Akili products.
- Another household member who is/has participated in this trial
- Concomitant Medication and Treatment
- No new concomitant medications are permitted during the study with the exception of common over-the-counter (OTC) (e.g. ibuprofen, acetaminophen) and prescription medications (e.g. antibiotics) for minor transient ailments. Use of some non-sedating antihistamines is allowed. Study Investigators can approve short-term use of other medications that are not anticipated to confound study assessments.
- No initiation or change in psychotherapy or any other non-pharmacological treatment for MDD or other mental health issues.
- No current participation in or recent completion of any cognitive remediation program.

COMPLETE LIST OF ASSESSMENTS

Test of Variables of Attention (TOVA)

TOVA is an FDA cleared (K173915-K170082) continuous performance test (CPT). CPT are the most frequently used objective neuropsychological assessments in both clinical and research contexts to evaluate different attentional (e.g. sustained) and attentional control related (e.g., conflict resolution) measures via continuous stimulus presentation of targets and non-targets (1). TOVA has been validated and normed by gender and for ages 4-80, and has good internal consistency, temporal stability and reproducibility (2-4). Response time in Half 1 (highly infrequent targets) is a proxy for sustained attention, as require to be focused on a task without being distracted.

Brief Assessment of Cognition (BAC)

BAC is quick and easy to administer while preserving the human interaction of traditional neurocognitive testing that is necessary for impaired populations. The BAC measures performance across multiple cognitive domains: processing speed, working memory, executive functions, etc. It is scientifically validated, with a large database of available normative data, with alternate forms for reaped testing and high reliable and sensitive to impairments (5).

From the battery we included the following:

Symbol coding test (SCT). The SCT is a neuropsychological test of attention and information processing speed. In this test, the taker writes numerals 1-9 as matches to non-meaningful symbols on a response sheet for 90s, as based on a key provided to them. (5)

Trail-Making Test A-B (TMT-A/TMT-B). The Trail-Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts in which the patients are instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. In Part A, the circles are numbered 1-25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1-13) and letters (A-L), as in Part A, the patient draws line to connect the circles in an ascending pattern, but with the added task of alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc) (6).

Letter and number sequencing (LNS). LNS task is a working memory capacity measure included as part of the Wechsler Adult Intelligence Scale-III and IV batteries. The task involves hearing a series of letters and digits, and then reporting back the stimuli with the letters in alphabetical order and digits in ascending numerical order (7).

CLINICAL OUTCOME MEASURES

Hamilton Depression Rating scale (HAM-D, 17-item)

The HAM-D is the most widely used clinician-administered depression assessment scale. The original version contains 17 items, pertaining to symptoms of depression experienced over the past week. For each item the clinician has to indicate on a scale 0 [absent] to 4 [patient verbal/non-verbal complaint] which best characterizes the patient (8).

Cognitive and Physical Functioning Questionnaire (CPFQ)

The CPFQ is a brief patient reported scale (7 items) developed to measure cognitive and executive dysfunction in mood and anxiety disorder (9).

Perceived Deficits Questionnaire - Depression (PDQ)

The PDQ is a brief patient rated scale (20 items) developed to assess subjective cognitive dysfunction in people with depression. The PDQ generates a total score and 4 subscale scores (attention/concentration, retrospective memory, prospective memory, and planning/organization) (10).

Work and Social Adjustment Scale (WSAS)

The WSAS is a brief (5 items) self reported global measure of functional impairment used in adult and youth health (11).

Quality of Life Enjoyment and Satisfaction (Q-LES-Q)

The Q-LES-Q is a self administered questionnaire (16 items short form) that captures life satisfaction in various areas of daily functioning (12).

Patient Health Questionnaire–9 (PHQ-9)

The PHQ-9 is the major depressive disorder module of the full PHQ which scores each of the nine DSM-V criteria. It is used to monitor the severity of depression and response to treatment (13).

REFERENCES

1. Riccio CA, Reynolds CR, Lowe P, Moore JJ: The continuous performance test: A window on the neural substrates for attention? Arch Clini Neuropsychol 2002; 17(3): 235-272. https://academic.oup.com/acn/article-abstract/17/3/235/2090
2. Leark RA, Dupuy TR, Greenberg LM, Kindschi CL, Hughes SJ: Professional Manual Test Of Variables of Attention Continuous Performance Test. In *Edition Number* (Vol. 8), 2016. http://www.tovatest.com/
3. Llorente AM, Amado AJ, Voigt RG, Berretta MC, Fraley JK, Jensen CL, et al: Internal consistency, temporal stability, and reproducibility of individual index scores of the Test of Variables of Attention in children with attention-deficit/hyperactivity disorder. Arch Clin Neuropsychol 2001; 16(6):535-546. https://doi.org/10.1016/S0887-6177(00)00065-2
4. Llorente AM, Voigt R, Jensen CL, Fraley JK, Heird WC, Rennie KM: The Test of Variables of Attention (TOVA): Internal Consistency (Q1 vs. Q2 and Q3 vs. Q4) in Children with Attention Deficit/Hyperactivity Disorder (ADHD). Child Neuropsychol 2008; 14(4):314-322. https://doi.org/10.1080/09297040701563578
5. Atkins AS, Tseng T, Vaughan A, Twamley EW, Harvey P, Patterson T, et al: Validation of the tablet-administered Brief Assessment of Cognition (BAC App). Schizophr Res 2017; 181:100-106. https://doi.org/10.1016/j.schres.2016.10.010
6. Reitan RM, Wolfson D: . (1985). The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press, 1985
7. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR: Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry 1997; 54(2):159-165. https://doi.org/10.1001/archpsyc.1997.01830140071013
8. Hamilton M: A rating scale for depression. J Neurol, Neurosurgery, and Psychiatry 1960; 23(1):5662. https://doi.org/10.1136/jnnp.23.1.56
9. Fava, M., Iosifescu, D. V., Pedrelli, P., & Baer, L. (2009). Reliability and validity of the Massachusetts general hospital cognitive and physical functioning questionnaire. Psychotherapy and psychosomatics, 78(2), 91-97.
10. Lam, R. W., Lamy, F. X., Danchenko, N., Yarlas, A., White, M. K., Rive, B., & Saragoussi, D. (2018). Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. Neuropsychiatric disease and treatment, 14, 2861.

11. Mundt, J., Marks, I., Shear, M., & Greist, J. (2002). The Work and Social Adjustment Scale: A simple measure of impairment in functioning. British Journal of Psychiatry, 180(5), 461-464. doi:10.1192/bjp.180.5.461
12. Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. (1993). Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacology bulletin.
13. Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine, 16(9), 606-613.