Study Protocol and Statistical Analysis Plan

Study Title: Mental Imagery Therapy for Autism (MITA) - an Early Intervention Computerized Brain Training Program for Children With ASD

Abstract

Imagination exercises administered by caregivers were investigated in a three-year-long observational trial of 3,540 children with autism ages 2-12 years. Tablet-based verbal and nonverbal tasks modeled on language therapy and emphasizing mental juxtaposition of objects were organized into an app called *Mental Imagery Therapy for Autism* (MITA). MITA children were matched to the 'treatment-as-usual' participants (TaU, N=5,226) using propensity-score analysis. Both younger (2-5 years of age) and older children (5-12 YOA) in MITA and TaU groups improved their symptoms over time, but on an annualized basis, younger MITA children improved their language and communication skills 3-fold faster than TaU group. We conclude that imagination exercises delivered by caregivers may be an effective supplement to language therapy administered by specialists.

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MITA group

The MITA app was made available gratis at all major app stores in February 2016. Once the app was downloaded, the caregiver was asked to register and to provide demographic details, including the child's diagnosis and age. Caregivers consented to anonymized data analysis and completed Autism Treatment Evaluation Checklist (ATEC) (Rimland & Edelson, 1999). The first evaluation was administered approximately one month after the first use of MITA and once 100 puzzles had been completed. The subsequent evaluations were administered at three-month intervals. Parents were asked to complete evaluations independently of a child's actual use of MITA.

From this pool of potential study participants, we selected participants based on the following criteria:

1) Consistency: Participants must have filled out at least three ATEC evaluations and the interval between the first and the last evaluation was six months or longer.

2) Diagnosis: The subject must have self-reported their diagnosis as ASD.

3) Maximum age: Participants older than twelve years of age were excluded from this study.

4) Minimum age: Participants who completed their first evaluation before the age of two years were excluded from this study.

5) Minimal ATEC severity: Participants with initial ATEC scores of less than 20 were excluded.

6) Language: Participants who indicated their primary language was not English were excluded from the study.

After excluding participants that did not meet these criteria, there were 3,540 total participants.

Control group

Independently from MITA, ATEC responses were collected by the Autism Institute from participants voluntarily completing online ATEC evaluations from 2013 to 2019. Little is known about their treatment, but it is unlikely that many of them used MITA. Accordingly, these participants served as a 'treatment as usual' control. Participant selection was described in detail in Ref. (Mahapatra et al., 2018). In short, participants were selected based on the following criteria:

1) Completeness: Participants who did not provide a date of birth (DOB) were excluded. As participants' DOB were utilized to determine age, the availability of DOB was necessary.

2) Consistency: Participants had to have completed at least three questionnaires and the interval between the first and the last evaluation was one year or longer.

3) Maximum age: Participants older than twelve years of age were excluded from this study.

As diagnosis was not part of the ATEC questionnaire, some neurotypical participants could be present in the database. To limit the contribution from neurotypical children, we excluded participants that may have represented the neurotypical population by using the *Minimum age* and *the Minimal ATEC severity* criteria.

4) Minimum age: Participants who completed their first evaluation before the age of 2 were

excluded from this study, as the diagnosing of ASD in this age group is uncertain and the parents of some of these young cases may have completed the ATEC because they wanted to check whether their normal child had signs of autism.

5) Minimal ATEC severity: Participants with initial ATEC scores of less than 20 were excluded.

6) **Language**: Participants who indicated their primary language was not English were excluded from the study.

After excluding participants that did not meet these criteria, there were 5,226 total participants.

Outcome measures

A caregiver-completed Autism Treatment Evaluation Checklist (ATEC) (Rimland & Edelson, 1999) was used to track the efficacy of a treatment. ATEC is comprised of four subscales: 1) Speech/Language/Communication, 2) Sociability, 3) Sensory/Cognitive Awareness, and 4) Physical/Health/Behavior. The first subscale, Speech/Language/Communication, contains 14 items and its score ranges from 0 to 28 points. The Sociability subscale contains 20 items within a score range from 0 to 40 points. The third subscale, Sensory/Cognitive awareness, has 18 items and scores range from 0 to 36 points. Finally, the Health/Physical/Behavior subscale contains 25 items and scores range from 0 to 75 points. The scores from each subscale are combined in order to calculate a Total Score, which ranges from 0 to 179 points. A lower score indicates lower severity of ASD symptoms and a higher score correlates with more severe symptoms of ASD.

Statistical analysis

The framework for evaluation of ATEC score changes over time was explained in detail in Ref. (Mahapatra et al., 2018). In short, the concept of a "Visit" was developed by dividing the three-year-long observation interval into 3-month periods. All evaluations were mapped into 3-month-long bins with the first evaluation placed in the first bin. When more than one evaluation was completed within a bin, their results were averaged to calculate a single number representing this 3-month interval. It was then hypothesized that there was a three-way interaction between an age group, Visit, and treatment. Statistically, this hypothesis was modeled by applying the Linear Model with repeated measures, where a three-way interaction term was introduced to test the hypothesis. Least squares means (LS Means) and LS Means differences were calculated for all ATEC subscales (Language, Sociability, Cognitive awareness, and Health) at all visits. Participants in the MITA group were matched to those in TaU group using propensity score analysis (Schneider, Carnoy, Kilpatrick, Schmidt, & Shavelson, 2007) based on age and all four ATEC subscales at baseline.

References

Mahapatra, S., Khokhlovich, E., Martinez, S., Kannel, B., Edelson, S. M., & Vyshedskiy, A. (2018). Longitudinal Epidemiological Study of Autism Subgroups Using Autism Treatment Evaluation Checklist (ATEC) Score. *Autism and Developmental Disorders*, *1*(12). https://doi.org/10.1007/s10803-018-3699-2

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