Unique Protocol NCT ID: NCT02361762

Brief Title: Gaming for Autism to Mold Executive Skills Project (GAMES)

Title: Electrophysiological Response to Executive Control Training

IDs: R00HD071966 [U.S. NIH Grant/Contract Award Number]

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Participants.

Participants will be 60 7- to 11-year-olds with ASD: 30 will be randomly assigned to training and 30 to waitlist. It is anticipated that 80 children with ASD will be recruited to obtain a final sample with artifact free data.

Recruitment & Diagnostic Procedures.

Children will be recruited from the institution's research participant registry, clinical referrals, and advertising. Recruitment will also target the local ASD community (service providers, clinicians, and parent advocacy groups). Participants will also be recruited via fliers, bulletins and local media.

Intelligence will be assessed using the Wechsler Abbreviated Scale of Intelligence-II (WASI-II) and the WASI-II verbal comprehension index will be used to control for individual and group differences in language ability. *Diagnosis* of autism spectrum disorder will be made using DSM-V criteria following administration of gold-standard measures for assessment of ASD symptoms: the Autism Diagnostic Interview (ADI-R) and the Autism Diagnostic Observation Schedule-2 (ADOS-2). The presence and potential impact of ADHD symptoms will be assessed via the Child Behavior Checklist (CBCL).

Exclusionary criteria for all participants will be assessed by administration of a screening interview during enrollment and will include presence of seizures; medical disorders or injuries with implications for the central nervous system or that require regular psychoactive medication that alter EEG processes; and non-English speaking children. An additional exclusion criterion for children with ASD is IQ < 80.

Assessment Procedures. Electrophysiological and behavioral responses will be recorded. Behavioral and electrophysiological measures will be collected via computer to control social demands between tasks used to assess ERP response and behavior, which is important for studying executive control in ASD.

Electrophysiological measures of executive control. Two ERP assessments will be used to measure neural function. Practice will be given before both tasks to ensure understanding. The *Child ANT* consists of a cue followed by congruent or incongruent trial in equal proportion for 108 trials. Stimuli are cartoon fish with arrow shaped gills, mice with arrow shaped noses, and birds with arrow shaped beaks. Trials begin with a cue presented for 150 ms, followed by a fixation of 450 ms. The target and flankers follow and remain until a response is made (left/right button press) corresponding to the direction of the central target (e.g., a fish) or 2000 ms elapse. This method has been used with children without ASD as young as 4 years of age. The *Go/Nogo* task consists of a cue followed by a go or nogo stimulus. The cue is presented for 500 ms, followed by a go or nogo stimulus presented for 500 ms at 1500 ms after the cue. The next trial follows 500 ms after a button press or 1000 ms after no response (Nogo trials). 150 total trials will be presented with 3 breaks. The visual cued go/nogo method has been used with 6-year-olds.

Electrophysiological acquisition. Electrical brain activity will be examined using high-density EEG (128 channel Hydrocel Geodesic Sensor Net, GSN; EGI, Eugene OR) in an electrically shielded, sound-attenuated laboratory. The HCGSN is reliable and application is fast, making it an ideal device for EEG collection with children. Net preparation will follow manufacturer specifications. Stimuli will be presented via E-Prime-2 software (PST, Inc, Pittsburgh PA) while children sit 75 cm from the screen. A large screen will obscure the back of the monitor and the computer equipment from the child's view. Impedances will be kept below 50 kΩ. Amplification will be set at 1000; data will be filtered at 0.1 Hz and 200 Hz. Continuous EEG recording will occur at 500 Hz and signals will be referenced to the vertex electrode.

Aim 2 behavioral assessment. Data will be collected during three lab visits, beginning with diagnostic and cognitive assessment followed by ERP assessment (Child ANT, Go/Nogo). In addition, Theory of Mind will be assessed with five tasks: Social Attribution Task, Perception Knowledge, Location Change False Belief, Unexpected-contents False Belief, and the Theory of

Mind Test. These tasks allow for sufficient variability to detect individual differences at the planned age range. Parent and teacher report of social function and social symptoms will be collected via the Social Skills Improvement System and Social Responsiveness Scale-2, respectively.

Aim 3 behavioral assessment. Data will be collected before and after training with the same battery of tasks. In addition to ERP (Child ANT, Go/Nogo), the behavioral assessment battery will include executive control measures (Stroop, Change Task, and Hungry Donkey Task) and a brief (non-conflict) task (Backward Digit Span). Parent and teacher report of executive function will also be collected at baseline using the BRIEF questionnaire. At post-testing, ERP, behavioral measures of executive control and parent/teacher report of executive control will be collected again. TOM tasks (SAT, Perception Knowledge, False Belief tasks, and the TOM Test) as well as parent and teacher report measures (SSIS, SRS) will also be collected. Results from Aims 1-2 will be used to further inform decisions about which measures to prioritize in post-training testing, which will be important for obtaining artifact free ERP data from the majority of children with ASD across time points.

Summary of measures in Electrophysiological and Behavioral Battery with children with ASD

Construct and Type	**Measure Name and Citation**
Autism Symptoms-Diagnosis	Autism Diagnostic Observation Schedule-2 (ADOS-2)
Autism Symptoms-Diagnosis	*Autism Diagnostic Interview-Revised (ADI-R)*
Intelligence/Verbal Intelligence	Wechsler Abbreviated Scale of Intelligence-2 (WASI-2)
Conflict Processing-ERP	Cued Go/Nogo
Conflict Processing-ERP	Child Attention Network Task (Child ANT)
Conflict Processing	Hungry Donkey Task
Conflict Processing	Change Task
Conflict Processing	Stroop Task
Exec. Control at home/school	*BRIEF Parent and Teacher Surveys*
Theory of Mind	Social Attribution Task (SAT)
Theory of Mind	Perception Knowledge
Theory of Mind	Location Change False Belief
Theory of Mind	Unexpected-contents False Belief
Theory of Mind	TOM Test
Social function at home/school	*Social Skills Improvement System-Parent & Teacher Surveys (SSIS)*
Social symptoms home/school	*Social Responsiveness Scale-Parent & Teacher Surveys (SRS*)
*Working Memory	Backward Digit Span

Note: Measures with * will serve as contrasts to Executive Control Measures for Brain-Behavior comparisons. *Italicized measures are parent report.*

Intervention: Brief computerized executive control training. Children with ASD will be randomly assigned to either computer training or a waitlist control condition following a list generated by a staff member independent of the research team using a computer algorithm to generate a random order. Training designed to directly target executive control and attention will follow the basic protocol used with TD children. Ten training visits will occur over a 2-3-month period. A research assistant or graduate student will conduct visits, so the assessment team may remain naïve to treatment status. *Four training exercises* appropriate for typically developing children 6 years and older will be used, including anticipation, stimulus discrimination, conflict resolution, and inhibition tasks. *Criteria for progress* throughout each level are based on the number of consecutive correct responses. Our current pilot study is evaluating the optimal duration. In more recent work, Rueda and her colleagues have used a 10-hour training protocol instead of a 5-hour protocol. Based on our current piloting, we plan to deliver the same duration of training to each participant, such that if children with ASD pass all training activities a shorter duration, additional training will be provided in conflict resolution and inhibition tasks until the training hours are completed. Both groups will return to the lab for follow-up testing 2-3 months after baseline assessment, after which the waitlist group will be offered training if it is efficacious. *Training modifications* will be made following piloting if needed and may include: allowing

children to pick characters that are highly motivating, reducing language demands, and extending tasks for older children.

Attrition will be addressed by recruiting additional participants. Attrition is expected to be very low, given 0% attrition with similar, brief computer training for individuals with ASD.

Analyses.

Electrophysiological Analyses. Trials will be processed using Netstation (EGI; Eugene, OR). Data will be filtered with a 0.1-30 Hz bandpass filter. Then data will be segmented into target-locked epochs around the stimulus. Segment files will be inspected for artifacts using both artifact detection tools and visual inspection of files with recoded IDs (to reduce potential for bias) by a staff member naïve to group assignment. To ensure that number of trials discarded due to artifact does not bias the results, the number of trials will be included in analyses as a covariate. Data will be averaged for stimulus type, and re-referenced to an average reference based on previous reports.

Statistical Analyses.

To assess potential training effects on ERP components**,** repeated-measures ANCOVA will be calculated by comparing groups (trained/waitlist) and within subjects effects of condition (congruent/ incongruent or Go/Nogo) and time point (baseline/post treatment) and number of trials covaried. ANCOVA controlling for baseline performance will be used to test executive control behavior (Hungry Donkey, Stroop, Change Task) and parent/teacher BRIEF scores pre/post training. Second, to test generalization of training to social measures, ANCOVA controlling for baseline will be used to assess differences in social cognition (TOM composite), social function (SSIS), and social symptoms (SRS). As a control condition, ANCOVA will also be used to measure potential changes with a non-conflict task (Backward Digit Span). *Power:* Given the proposed sample size of 30 children per group and a correlation of 0.3 or greater, with power of 0.8 and alpha = 0.05, a moderate effect size ($f^2 = 0.21$) would be detected via repeated measures ANCOVA. ANCOVA with 1 covariate will have 0.8 power to detect a large effect size ($f^2 = 0.37$) for behavioral and parent report tasks after training.