Symposium Title: Novel Memory and Learning Interventions in Intellectual Disability

Chair: Jamie Edgin

Discussant: Natalia Arias-Trejo

Overview: In the four session presentations, we overview four novel memory and learning interventions in intellectual disability syndromes, including interventions in fragile X syndrome and Down syndrome. First, these findings emphasize that task engagement under specific conditions can be beneficial to memory retention at long-intervals and increases in adaptive learning behaviors. Second, the session will describe individual differences in the response to cognitive interventions, including how sleep disturbances may interact with intervention outcomes. The first paper highlights the findings from a randomized control trial of Cogmed working memory training in 100 children with fragile X syndrome, including the factors leading to variation in treatment response (Paper 1). In Paper 2, a novel intervention is conducted to increase task engagement in infants with Down syndrome, and Paper 3 highlights how social skills training may influence engagement and enhance long-term memory in this group. Finally, Paper 4 shows substantial differences in memory retention after a 1-month delay after children with DS were tested on materials, rather than passively viewed repetitions of information. In total, this session will overview promising new non-pharmacological methods of cognitive intervention that could stand alone or be coupled in future intervention treatment trials to maximize memory and learning in intellectual disability syndromes.

1: University of Arizona, Tucson, AZ
2: Universidad Nacional Autónoma de México, Mexico City, Distrito Federal, Mexico

Paper 1 of 4

Paper Title: Cogmed “Deep Dive”: Child, Cognitive Training, and Environmental Factors Contributing to Clinical Improvement in Children with Fragile X Syndrome

Authors: David Hessl, Haleigh Scott, Yueju Li, and Danielle Harvey

Introduction: We previously completed a randomized, triple-blinded, parallel two-arm controlled trial of Cogmed Working Memory Training in 100 children and adolescents with fragile X syndrome (FXS; 63 male, 37 female; 15.28 +/- 3.36 yrs.) (Hessl et al. 2018). This study was undertaken to determine whether 5-6 weeks of daily computer-based and caregiver-supported cognitive training has beneficial effects of executive function and behavior in children with the disorder. The study design compared the publicly-available adaptive Cogmed training, which adapts difficulty level (memory span) depending on performance, to non-adaptive training (the control condition), for which span level remains fixed at 2 items but is otherwise identical. Primary results of the trial showed that overall the children undergoing adaptive training were able to make modest gains in memory span during the course of training. The working memory evaluated on a standardized test and selective domains of EF (distractibility, cognitive flexibility), as well as parent- and teacher-reported attention and EF significantly improved across the full study sample, with many changes maintained at follow-up. However, comparisons of improvement between adaptive and non-adaptive conditions did not differ, making it unclear whether the training itself, some other aspect of the intervention, or other factors contributed to these improvements. The purpose of the present study is to conduct a “deep
dive” into the trial-by-trial Cogmed training data to identify parameters of high and low quality training and to examine child, parent training aide, and environmental factors that may be associated with response to this intervention and clinical changes in cognition and behavior.

**Methods:** We measured parent stress and psychological health such as anxiety and depression using the Symptom Checklist 90 Revised and the Parenting Stress Index, and the quality of the home environment was captured by direct observation and parent interview using the disabilities version of the HOME inventory. Child characteristics included baseline cognitive level, behavior problems and age. SES and parent education level were also considered. Trial-by-trial Cogmed data for each game were the primary focus for identification of training patterns, although daily-level summaries were also assessed. We used semiparametric mixture models fit to the trial-level and daily level data to identify clusters of participants with differing training parameters for each game; separate models were fit to early training (first 3 weeks) and later training periods. Consistency of participant-level cluster assignments for each training parameter across games was assessed and subgroups were then identified based on the most common cluster across games. Child and parent/training aide characteristics were compared between the identified subgroups using two-sample t-tests or chi-square tests to assess factors associated with particular training patterns. Post-training outcomes were also compared between subgroups using ANCOVA, similar to the original trial analyses. Finally, ANCOVAs were fit including factors related to the child, parent/training aide, and the home as predictors of post-assessment outcomes to determine factors associated with the response to the intervention.

Results: Subgrouping analyses identified two clear clusters with relatively homogeneous patterns across games: one subgroup has performance that remains relatively flat during both earlier and later weeks of training, and a second group has clearly increasing trends in performance. Analyses of trial reaction times and standard deviation of reaction time (potentially an index of attention) identified a subgroup with smaller standard deviations and improving consistency in response over time, and a subgroup with much faster reaction times. Analyses of differences between clusters and predictors of clinical outcomes are underway and will be reported.

Discussion: Ours is the only known clinical trial of any type of cognitive intervention for people with FXS, and therefore the dataset represents an important opportunity to learn about predictors of performance in learning paradigms and factors determining potential responders and non-responders to this type of treatment that can guide the design of future interventions. The results of these analyses may also establish links between training performance and outcomes that can tell us whether the Cogmed itself or other factors contributed to the observed gains in the children.

**References/Citations:**


**Paper 2 of 4**

**Paper Title:** Developing a Phenotype-Informed Micro-Intervention to Advance Goal-directed Behavior in Infants with Down syndrome

**Authors:** Deborah Fidler, Ph.D., Emily Schworer, M.S., Amy Needham, PhD, Mark Prince, Ph.D., & Lisa Daunhauer, Sc.D.

**Introduction:** The etiology-focused approach to intellectual disability research has long held the promise of translational impact. Recent applications of phenotype-related findings into education and intervention have generated encouraging results (Dimitropoulos, Zyga, & Russ, 2017; Lemons et al., 2015; LeJeune et al., 2018). However, translational work of this nature poses implementation challenges related to logistics, cost-benefit concerns, and confounds related to within-syndrome variability in presentation. In this study, we report findings from a proof-of-concept project designed to deliver a phenotype-informed micro-
intervention to infants with Down syndrome (DS). The micro-intervention aimed to address the predisposition in this population to pronounced delays in the development of motor skills and goal-directed behavior by targeting the critical milestone of reaching (see Fidler et al., 2019 for a review). As reaching facilitates the development of infant representations of objects via manual exploration, we sought to prompt changes in this motor skill that would likely produce changes in early learning. We adopted a low-cost, parent-mediated approach (Needham et al., 2002) that has been empirically shown to facilitate the development of reaching behavior and object exploration in typically developing pre-reaching infants. In addition to reporting intervention effects, we aimed to identify which infants with DS were in need of the intervention, and the window of time in development when infants were most likely to respond to the treatment.

**Methods:** Participants were 73 infants with DS and their caregivers (CA = 10.04 months, SD = 4.03; Bayley Scales of Infant Development-III [BSID-III] Cognitive age equivalent = 7.17 mos, SD = 2.91). Infants and their caregivers participated in one assessment visit to screen for the infant’s eligibility to participate in the intervention study. Visit 1 involved administering the BSID-III and a battery of laboratory tasks, including a measure of reaching behavior. Two block-related manipulation items on the BSID-III were used as a screener for eligibility in the intervention. **Intervention conditions.** Infants who qualified for the intervention were randomly assigned to either a treatment (n = 21) or a control group (n= 19) individually or by site. Both groups were given instructions for 5-10 minute daily parent-child social interactions with a standardized toy set for 2-3 weeks. The treatment condition also involved the use of a pair of infant-sized mittens, affixed with the soft side of strips of Velcro, and the toy sets were covered with the complementary side of Velcro. Caregivers in the treatment group were given instructions to facilitate reaching behavior in their infant via use of the mittens. Infants in both groups participated in post-test laboratory assessments after 2-3 weeks. Comparisons of pre- and posttest performances emphasized magnitude of effect and confidence intervals, as per Cumming (2012).

**Results:** **Within-group variability.** Of the 73 infants recruited into the study, 40 (54.8%) demonstrated a need for the intervention. Infants who qualified for the intervention had a mean CA of 6.93 months (SD = 2.39; range = 4.0- 13.0 mos) and a mean BSID-III cognitive age equivalent of 4.90 months (SD = 1.26). Infants who did not qualify were chronologically older (M = 13.59 mos; SD = 2.33), and developmentally more advanced (BSID Cognitive Scales AE M = 9.91; SD = 1.74). **Treatment effects.** The treatment and control groups were equivalent on BSID-III Cognitive age equivalent scores at pretest. Pretest mean latency to contact objects in the treatment group was 9.37 s (SD = 7.20) and 8.60 s (SD = 10.11) in the control group, $d = .08$, 95% CI [-.06, .77]. At posttest, the mean latency to make contact with objects in the treatment group was reduced to 3.97 s on average (SD = 3.57), while the control group had a mean latency of 7.69 s (SD = 7.06; $d = .66$; 95% CI [-1.37, 0.02]). This group comparison is large in magnitude (a 3.72 s difference) and reflects a .9 SD improvement (95% CI [-1.64, -.25]) in the treatment group from pre- to posttest. Though similar at pretest, the mean frequency of reach attempts differed among the groups at posttest, with the treatment group producing approximately 1 SD more reach attempts than the control group (Treatment M= .36, SD = .36; Control M=.10, SD = .16; $d = .93$; 95% CI [.24, 1.60]). Subsequent analysis of change scores demonstrated that infants who were ages 5-10 months had the strongest response to the mittens intervention (i.e. the largest magnitude of change as measured by effect size).

**Discussion:** As both a proof-of-concept and an intervention study, our team implemented a phenotype-informed micro-intervention tailored to address an area of potential developmental vulnerability in infants with DS. For this study, we targeted a key developmental milestone, reaching behavior, which emerges later in infancy in DS than in TD infants. Reaching behavior is foundational for an infant’s ability to explore objects and to learn about object properties, and exploratory behavior is known to be a critical context where an infant formulates early representations of objects and their affordances (Fidler et al., 2019). Follow up data collection is needed to determine whether downstream cognitive effects are observed as a result of facilitated reaching in the treatment group. Results of this study suggest that phenotype-informed, targeted intervention is feasible, and a potentially effective model for translational work in neurogenetic syndromes.
References:


---

Paper 3 of 4

**Paper Title:** Participation in Social Skills Therapy and Recall Memory by Children with Down Syndrome: Associations with Encoding and One-Month Delayed Recall

**Authors:** Angela Lukowski

**Introduction:** Children with DS commonly experience cognitive challenges, including impaired long-term recall memory for temporal order information (Milojevich & Lukowski, 2016). Given this information, researchers should identify and study potential moderators of cognitive performance with the goal of identifying modifiable contextual factors that may positively impact functional outcomes. Previous research conducted with individuals on the autism spectrum has indicated that participation in social skills therapy (SST) is positively associated with various cognitive abilities (Cappadocia & Weiss, 2011; Hwang & Hughes, 2000). For this reason, the present study was conducted to examine whether parent-reported participation in SST was associated with encoding and one-month delayed recall performance by young children with DS.

**Method:** Nineteen children with DS (11 girls, mean chronological age = 33 months) were recruited from local early intervention centers and other organizations that provide services to children with developmental disabilities and their families. Children were recruited to participate in a larger study on recall memory in children with DS and their typically developing peers (Milojevich & Lukowski, 2016). Each child participated in an elicited imitation assessment at two study sessions. At the first session, children were presented with four novel three-step event sequences. After a brief child-controlled baseline period, a researcher demonstrated each event sequence twice in succession with narrative. Immediate imitation was permitted as an index of encoding. Children returned to the university approximately one month later. Children were presented with two of the same sequences that were modeled at the first session, two sequences that were perceptually distinct but functionally identical.

---

4 University of California, Irvine
to those used at the first session, and two novel control sequences. Parents also completed questionnaires in which they reported on demographic information and on the intervention experienced by their child, including SST.

**Results:** Parents reported that 6 children were either participating in SST at the time of the study or had previously participated in this intervention (SST+ group); the remaining 13 children had never participated in this therapy (SST- group). When considering encoding performance, analyses of variance revealed that children in both groups showed evidence of recalling the individual target actions that made up the events and their order relative to baseline, and that children in the SST+ group performed more target actions and actions in the correct order relative to children in the SST- group. When considering one-month delayed recall, children in both groups recalled the target actions that made up the events relative to novel control sequences tested at the same session. Similar to what was observed at the first session, children in the SST+ group performed more target actions on familiar events after the one-month delay relative to children in the SST- group. Significant effects were not found at the one-month delay when considering memory for temporal order. Finally, mediation analyses were conducted to determine whether encoding performance mediated the association between group and delayed recall performance. Evidence of mediation was obtained when considering memory for the individual target actions that made up the events as well as their order.

**Discussion:** Taken together, the results of this exploratory study suggest that participation in SST is associated with enhanced encoding and one-month delayed recall memory. In particular, children in the SST+ group demonstrated better encoding of individual target actions and their order, as well as better recall of individual target actions after a one-month delay, relative to children in the SST- group. Moreover, the results of mediation analyses suggested that participation in SST impacted long-term recall memory through enhanced encoding. Future research remains to be conducted, however, given the small sample size and the correlational nature of this work. Subsequent studies should focus on randomly assigning children to various intervention opportunities to determine causality as well as on identifying the particular characteristics of SST that contribute to enhanced encoding and long-term recall. The findings of such research would likely have significant implications for promoting encoding and long-term recall memory by children with DS.

**References:**


Introduction: The creation of memories and their storage over time is a key developmental process. This ability to encode and recall experiences allows children to do things like find their way home and adapt to changing environments, and it is crucial in acquiring knowledge and applying it on a day to day basis. Various memory encoding strategies have been studied in typical adults, with two of the most commonly used being retrieval practice and restudying. Restudying provides multiple opportunities to encode information and reinforce what has been encoded, for example, flashcard learning. Testing, also referred to as retrieval practice, requires the participant to actively recall information, either immediately after encoding or following a delay. Recent work has suggested that retrieval practice may serve to strengthen and integrate cortical based neural representations. While retrieval practice has been shown to benefit long-term retention, the impact of these methods has been examined less in children and very rarely in atypically developing groups. Given the robust nature of these effects across a number of studies, and availability even to infants, retrieval practice has the potential to influence memory retention in developing populations with significant memory impairment, such as individuals with Down syndrome (DS).

Methods: Therefore, the current study examined long-term episodic memory across a one-month delay, manipulating the presentation of episodic information to compare retrieval versus restudy of arbitrary event sequences within subjects (deferred imitation of 3-step arbitrary actions). Retrieval rates were compared at 5 minute and one month delays in 30 children with DS (ages 6-18 years) compared to 33 typical matched control individuals (3-6 years). The paradigm used for this study was adapted from Milojevich & Lukowski (2016) and was adjusted for school-age TD children and individuals with intellectual disability, including DS. Each sequence included three target actions. There were three conditions that manipulated different ways the sequences were encoded. Each participant saw a total of six sequences, two in each of the three sequence conditions: 1) Model, Model, Model (MMM) in which the sequence was modeled 3 times; 2) Model, Model, 20 second pause (MMP); and 3) Model, Model, Test (MMT), the condition that determined if a “testing effect” was present.

Results: Our results suggest that typical developing children and children with DS significantly benefit from retrieval opportunities and show the “testing effect” compared to repetition. While both groups show a benefit of retrieval opportunities while learning (massed practice, Figure 1), typically developed children showed greater retention after a single spaced retrieval opportunity. Figure 1 shows retention after 1 month in each condition. Strikingly, memory deficits in DS were reduced to the level of controls with a retrieval opportunity. Also of interest was that sleep deficits only related to weakly encoded memories, or the conditions without testing.
Figure 4. Mean N of actions and pairs recalled at 1 month in the DS (blue) and TD (orange) groups, across the three conditions. +/- 1 SEM

Discussion: Memory is not uniformly impaired in intellectual disability, and differing learning and encoding methods can reveal divergent patterns of long-term retention. Specifically, testing of memories can be of benefit over long delays, even in groups with substantial memory impairment. Finally, some of these methods can counteract loss associated with sleep deficits. Finally, these results have implications for future educational strategies in intellectual disability.

References/Citations: