Title: Pharmacologically Restoring White Matter Deficits in a Mouse Model of Down Syndrome

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Introduction: The white matter of the brain, formed by oligodendrocytes, provides the insulation for axons that is critical for proper neuronal communication. Changes in myelination can reduce the speed of neuronal communication and result in widespread alterations throughout the central nervous system, such as loss of motor skills and cognitive impairment. Prior work detailing changes in gene expression due to the triplication of human chromosome 21 identified disruptions in genes related to oligodendrocyte precursor cells (OPCs) and the maturation of the oligodendrocyte lineage1. The Ts65Dn mouse model of Down syndrome recapitulates these white matter alterations; when analyzing the development of OPCs to mature oligodendrocytes, trisomic cells display delayed maturation both *in vitro* and *in vivo*. This cellular change is correlated with functional deficits as well, such as slower action potential conduction velocities compared to disomic littermates2. Taken together, this data suggests that impairments in oligodendrocyte lineage maturation impairs neuronal communication and function. Thus, promoting the development of OPCs may be a potential target for the treatment of the cognitive deficits in individuals with Down syndrome.

A number of drug compounds have been identified to promote remyelination in demyelinating disorders like multiple sclerosis. Two of these drugs, clemastine and benztropine, act on OPCs to promote their differentiation and maturation3,4. The goal of this project is to test whether these compounds are capable of increasing the percent of mature oligodendrocytes, thus increasing myelination and improving the functional and behavioral deficits in Ts65Dn animals.

Method: Ts65Dn animals and their euploid littermates were injected subcutaneously with either clemastine or benztropine (10mg/kg/day) or a saline control from P7-P21 (n=6 per genotype, per treatment group). Following treatment, tissue was collected and processed for immunohistochemistry and stained for Olig2, Ng2, and CC1, to label the entire oligodendrocyte population, OPCs, and mature oligodendrocytes, respectively. Labeled cells within the corpus callosum were counted and analyzed as percent of total population of oligodendrocytes. Statistical analysis was done using a Student’s T-test to compare changes in oligodendrocyte populations between genotypes as well as between treatment conditions within genotypes.

Result: Results indicate that subcutaneous injections of 10mg/kg/day of clemastine from P7-P21 significantly increase the number of mature oligodendrocytes in both control and trisomic animals, compared to saline treated controls. Treatment with benztropine did not significantly increase the percentage of mature oligodendrocytes in trisomic animals but shows a trend in this direction (p=0.067).

Discussion: This *in vivo* trial treatment demonstrates that pharmacological agents identified to promote remyelination in demyelinating disorders are effective at increasing OPC maturation in a model of Down syndrome. Our future work is focused on understanding the behavioral and functional changes due to treatment with these compounds using behavioral tasks Ts65Dn mice are known to have deficits in, such as Morris water maze task, and compound action potential recordings to measure speed of neuronal communication. With this completion of this work, we will provide novel preclinical evidence that targeting the maturation of oligodendrocytes to improve cognitive function is a treatment option for individuals with Down syndrome.

References/Citations:

Title: Two To Eleven Years: Exploring Early Predictors of Development in Children with ASD

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Introduction: Individuals with autism spectrum disorder (ASD) exhibit a wide range of cognitive ability, with some falling far below the mean and others far above (Keen & Ward, 2004). Early intervention aims to improve developmental outcomes for these individuals, and both comprehensive interventions and targeted interventions have been shown to improve child outcomes (e.g. Kasari, et al., 2015; Virues-Ortega, 2010). Due to heterogeneity in response to intervention, the next step is to individualize early interventions (Stahmer, et al., 2011). Longitudinal investigations are essential for identifying early targets that impact later developmental outcomes. The current study follows a group of children over a 7-year period to explore the early characteristics in toddlerhood (age 22-36 months) that predict cognitive and adaptive functioning at 9.4-11.4 years.

Method: 86 toddlers with ASD and their primary caregiver participated in the original investigation (Kasari, et al., 2015), and 23 (26.7%) returned for the seven-year follow-up. Of the children who returned to follow-up, the initial average chronological age was 2.62 years (SD= 0.33 years), with a Mullen Developmental Quotient of 67.78 (SD=17.04). This is roughly equivalent to the demographics of the original study sample which yielded an average age of 2.62 years and average DQ of 68 (Kasari, et al., 2015). At follow-up, their average age was 10 years (SD= 0.47 years), with an average global cognitive standard score of 101.89 (SD=28.61), as measured by the DAS.

Predictors: Cognitive scores from the original study were measured with the Mullen Scales of Early Learning (MSEL), while initiations of joint attention (IJA), frequency diversity of play acts, and engagement were coded from parent-child interactions taped at entry. Outcomes: At the 7-year follow-up visit, cognitive skills were assessed with the Differential Ability Scales (DAS-II), vocabulary was measured with the Peabody Picture Vocabulary Test (PPVT-4), and adaptive skills were measured with the Vineland Adaptive Behavior Scales (VABS-II). Linear regression was used to explore potential early predictors of adaptive and cognitive functioning at the follow-up, approximately 7 years later.

Result: DAS verbal ability was predicted by IJA scores (β=3.45, p=0.006), and increased diversity of functional play at entry (β=2.52, p=0.019). Similarly, PPVT standard scores from the follow-up were best predicted by increased diversity of functional play at entry (β=1.84, p=0.037). VABS adaptive behavior composite standard scores were best predicted by increased diversity of functional play at entry (β=1.15, p=0.020), and IJA at entry (β=1.49, p=0.04). Within the VABS subdomains, both socialization skills and daily living skills were predicted by entry IJA (β=1.335, p=0.016; β=1.82, p=0.02) and entry diversity of functional play (β=1.157, p=0.02, B=1.413, p=0.005). All relationships are positive, with higher scores at entry predicting higher scores at follow-up.

Discussion: This exploratory look at factors that contribute to cognitive and adaptive outcomes points to play skills and initiations of joint attention as important predictors of outcome in children with ASD. Increased play diversity seems directly related to not only expressive language, but social and daily living skills as well. Although limited by a small sample size and attrition, the returning sample matched the DQ and age of the original study, and therefore we believe these findings are representative of the cohort. This study highlights the important role of early IJA and play skills in the developmental trajectory of children with ASD, particularly the importance of play diversity in expressive language, and bolsters previous findings by Kasari and colleagues (2012), which found that baseline play diversity at 42 months predicted cognitive scores at 8 years of age.

References:


Title: Use of Parent-Child Language Samples to Assess Child Language Abilities in a Clinic and from a Distance

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Introduction: Success of pharmaceutical and behavioral interventions hinge on the quality of the outcome measures used to assess change over the course of the intervention. Recent studies have focused on the use of naturalistic approaches to outcome measurement in areas such as language development. In the case of fragile X syndrome (FXS), there are data to suggest that expressive language samples collected under structured but naturalistic conditions involving interactions with an examiner, yield psychometrically sound outcome measures. Children with FXS, however, have severe cognitive impairments and heightened levels of challenging behaviors, making it difficult to capture a representative sample of expressive language ability using only structured, examiner-based interactions alone. Thus, there is a need to explore other natural language sampling procedures. The current study was designed to determine how expressive language samples collected in structured but naturalistic interactions with a parent compare to those collected in examiner-controlled interactions, as well as to standardized measures of language. Further, this study was designed to compare the collection of these parent interaction-derived expressive language samples collected in a clinic with those collected in the home though distance video technology as way to examine the feasibility of assessing child abilities using such technology.

Method: Twenty dyads of children with FXS, ages 10 to 17 years, and their mothers participated. During a visit to the clinic, mother-child dyads completed the telling of a wordless picture book (‘Frog, Where are You?’ or ‘One Frog Too Many’) with minimal instructions regarding how to complete the task. While in the clinic, children completed the telling of a wordless picture book (‘Frog Goes to Dinner’ or ‘Frog on His Own’) with an examiner as well as standardized measures of language, including expressive vocabulary derived from the EVT-2 and expressive syntax derived from the syntax construction subtest of the CASL. After completing the examiner-administered assessments at the clinic, parent-child dyads completed the telling of three additional wordless picture books at home while project staff observed and recorded via distance teleconferencing. Parent-Child Language Samples (PCLS) and Examiner-Child Language Samples (ECLS) were transcribed using SALT software and analyzed to derive the child language variables of interest: (1) Number of Different Words (NDW) and (2) Mean Length of Utterance in Morphemes (MLUm).

Result: Pearson correlations were computed among measures. Child language measures derived from the PCLS were significantly correlated with child performance on both the EVT-2 and CASL. Further, Child NDW during the PCLS was significantly correlated with child NDW and MLUm during the ECLS, whereas child MLUm during the PCLS was significantly correlated with child MLUm during the ECLS but not child NDW. The patterns of associations was the same for both clinic-based and home-based PCLS.

Discussion: Results from this study yield promising, yet preliminary, support for the use of a familiar caregiver to capture child language abilities through language samples collected both in a clinic and from a distance. This has several important implications for FXS and, perhaps, other disorders. Given the challenging behaviors experienced by children with FXS, in particular increased rates of anxiety, the use of a familiar caregiver could decrease the burden and stress placed on the child that interacting with a novel person might incur while still yielding a representative measure of child ability. Further, given the low incidence of FXS, being able to capture child abilities remotely benefits the family by decreasing the burden and challenges related to travel and could improve generalizability of findings to environments most representative of the child’s daily life. Use of distance technology can further expand the scope of our research by recruiting more diverse sample, including those from more rural communities and families who are unable to participate due to the burden of travel.

References/Citations:

Title: Predictors of Word Combinations by Toddlers Who Participated in Parent-Coached Language Interventions

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Introduction: Much of what we know about language development is based on longitudinal studies of typically developing children (Bates et al., 1988; Bloom, 1970; Brown, 1973) For typically developing children, the transition from single to early-word combinations occurs at around two years of age when children demonstrate a vocabulary of about 50 words. However, little is known about early word combinations of children with expressive communication delays who use Augmentative and Alternative Communication (AAC). Wilkinson, Romski, and Sevcik (1994) reported that youth with intellectual and developmental disabilities used their available symbol vocabularies to build complex structures for their own communication purposes. Romski et al. (2010) found that children with developmental delays and less than 10 spoken words made more expressive vocabulary gains in parent-coached AAC interventions than children who were in parent-coached language interventions with no access to AAC. This study used extant data from two parent-coached language interventions (Romski et al., 2010; Romski et al., 2018) to examine predictors of target vocabulary combinations made by children who have significant expressive language and developmental delays. These predictors included receptive language at baseline, access to AAC, and multiple language outcomes (e.g., target vocabulary size, MLU, and total number of turns) during the final language intervention session.

Method: Extant data were used from 113 parent-toddler dyads who participated in two parent-coached language interventions (Romski et al., 2010; Romski et al., 2018). Toddlers ranged in age between 24-36 months and demonstrated significant developmental and expressive language delays (less than ten spoken intelligible words) at the onset of both studies. Receptive and expressive language skills were assessed using the Mullen Scales of Early Learning (MSEL), the Vineland Adaptive Behavior Scales (VABS), The MacArthur–Bates Communicative Development Inventory (MCDI), and Sequenced Inventory of Communication Development (SICD). Before intervention, toddlers were assigned an individualized list of target vocabulary words that they did not produce or understand. Parent-toddler dyads were assigned to one of four intervention groups; three out of the four had access to AAC and one group was assigned to a spoken language condition with no access to AAC. Target vocabulary size (number of target vocabulary words used), MLU, and total number of turns were language outcomes used in this analysis. A structural equation model (SEM) was implemented to examine whether a latent variable of receptive language skills at baseline, access to AAC (access versus no access to a speech generating device), and language outcomes (target vocabulary size, MLU, and total number of turns) predicted frequency of target vocabulary combinations made by the children during session 24, the final language intervention session.

Results: Twenty-two of the 113 toddlers (19%) combined target vocabulary words. Thus, frequency of vocabulary combinations was considered a count data outcome. Two nested count data models were compared: Poisson and Negative Binomial SEM. The dispersion parameter ($\alpha$) for the negative binomial model was 4.87, which was significantly greater than zero ($P=.001$), indicating that the data were overdispersed. Overdispersion suggested that the negative binomial model was a better fit than the Poisson model. The parameter estimate for vocabulary size was .167 for the negative binomial model, which was statistically significant ($P=.002$). Hence, for each one unit increase in vocabulary size, target word combinations increased by about 16%. The parameter estimate for access to AAC was .881, which was also statistically significant ($P<.001$). Children who had access to AAC had 88% more target vocabulary combinations than children who did not have access to AAC. Receptive language and total number of turns did not significantly predict children’s frequency of vocabulary combinations.

Discussion: While receptive vocabulary did not predict the frequency of target word combinations of children with severe developmental delays, target vocabulary size was a significant predictor of target word combinations. This finding suggests that similar to typically developing children, lexical acquisition facilitates emergence of early grammar in children with severe
language and developmental delays. In addition, access to AAC within daily routines can assist with not only increasing expressive vocabulary size, but can also facilitate emerging word combinations.

References/Citations:

Title: Language Switching and AAC: An Investigation of Spanish-English Bilingual Children with and without Language Impairments

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Introduction: Children with intellectual and developmental disabilities have traditionally been excluded from bilingual language research. Researchers, however, are increasingly aware of the need for more systematic research to understand language and cognitive development in bilingual children with intellectual and developmental disabilities (Rhodes & Washington, 2016). Codeswitching, or alternating between more than one language, is an important and frequent aspect of language use among bilingual children and adults (Grosjean, 2010). Little is known about language switching when a modality other than spoken communication is used. Children with complex communication needs are unable to rely on natural speech to communicate and may instead use alternative or augmentative communication (AAC) modalities to express themselves and interact with others. Many children, including those with language impairments, grow up in bilingual communities where bilingualism is a necessity rather than a choice, and lack of access to a heritage language may negatively influence a child’s connection to their community and culture (Yu, 2013). Like bilingual children with typical development, bilingual children with disabilities who use AAC are often shifting between different language environments at home, school, in therapy, and in the community. Emerging evidence suggests that in children with communication impairments, code-switching is not significantly different in terms of type or frequency of switches when compared to children with typical development (Gutiérrez-Clellen, Simon-Cereijido, & Erickson Leone, 2012). Despite the availability of bilingual AAC devices that allow the user to communicate in more than one language and alternate between languages, little research has been conducted to address assessment and intervention concerns for bilingual children who use AAC. The current study compared the ability of bilingual children with typical development and language impairment to conceptually discriminate (i.e., language switch) using AAC.

Method: Data were collected from 44 parent-child dyads. Child participants (28 males, 16 females) were exposed to English and Spanish on a regular basis and ranged in age from 4;0 – 6;11 (M age = 5;5). Participants with language impairment scored at least 1 standard deviation below the mean on the Bilingual English-Spanish Assessment (Peña, Gutiérrez-Clellen, Iglesias, Goldstein, & Bedore, 2014; BESA) (n = 13). Each child’s primary caregiver completed a family demographic form to provide information about their child’s medical history, ethnicity, their own language background, and their own educational achievement and employment. In addition, primary caregivers completed the Bilingual Input-Output Survey; BIOS; (Peña et al., 2014) which provided an estimate of relative language use and exposure during a typical week and was used to determine language dominance (i.e., Spanish Dominant, Balanced Bilingual, English Dominant). Each child completed the following standardized assessments: the BESA (Peña et al., 2014) to measure expressive and receptive vocabulary and grammar, and the Leiter International Performance Scales, Third Edition (Roid, Miller, Pomplun, & Koch, 2013) to assess nonverbal cognitive ability and processing speed. All participants completed an experimental language-switching task in which they were asked to locate images of vocabulary words in Spanish and English using a Spanish and English speech-generating device (SGD). The vocabulary displays were identical across both AAC devices except for the language of the speech output (i.e., English and Spanish) and the background color. Three practice trials and 13 experimental trials were presented in a mixed block of stay and switch trials. On switch trials, the participant was required to label a target word using the SGD in the language that was different from the previous trial. On stay trials, the same language as the previous trial was presented. The outcome measure for the Experimental Task was the number of correct responses.

Results: Nonparametric statistics were used to compare participants with language impairment to those with typical development on performance on the experimental task. Results from a Mann-Whitney U test showed that children with language impairments demonstrated significantly lower performance on the experimental language switching task (p < .05) compared to their peers without language impairment. Further analysis indicated no significant differences between groups on additional measures including nonverbal IQ, language dominance, and frequency of parent code-switching.

Discussion: Results from this study indicate that children with language impairments have more difficulty understanding language categories and conceptually discriminating between languages when shown picture symbols on an SGD. Despite overall poorer performance on the experimental task, children with language impairments demonstrated an array of abilities on the task. Some children with language impairments did not have difficult with the language-switching task, indicating that factors other than language ability may contribute to conceptual language discrimination. This study paves the way for further
assessment and intervention studies to investigate how best to support bilingual children with language impairments and developmental disabilities who may benefit from AAC.

References/Citations: