המרכז הלאומי ע"ש עזריאלי
לחקר אוטיזם ונוירו-התפתחות

I-MAR 2022

Winners of Poster Contest

First Place

An ADNP mouse carrying the most prevalent/severe mutation: Repair by the ADNP fragment NAP.

Gidon Karmon, Shlomo Sragovich, Gal Hacohen-Kleiman, Inbar Ben-Horin-Hazak, Petr Kasparek, Björn Schuster, Radislav Sedlacek, Metsada Pasmanik-Chor, Paschalis Theotokis, Olga Touloumi, Sofia Zoidou, Linxuan Huang, Pei You Wu, Roy Shi, Oxana Kapitansky, Alexandra Lobyntseva, Eliezer Giladi, Guy Shapira, Noam Shomron, Stefan Bereswill, Markus M. Heimesaat, Nikolaus Grigoriadis, R. Anne McKinney, Moran Rubinstein and Illana Gozes. TAU.

Second Place

Feasibility of OT-ParentShip: An intervention program for parents of adolescents with autism- A pilot study.

Batel Wachspressa, Einav Kahlon, Adina Maeir; Itai Berger, Tal Mazor-Karsenty. HUJI

Third Place

The importance of language delays as an early indicator of subsequent ASD diagnosis in public healthcare settings.

Tanya Nitzan, Judah Koller, Michal Ilan, Michal Faroy, Analya Michaelovski, Idan Menashe, Gal Meiri, Ilan Dinstein. BGU.

An ADNP mouse carrying the most prevalent/severe mutation: Repair by the ADNP fragment NAP

Sagol School of Neuroscience
Sackler Faculty of Medicine
Tel Aviv University

Gidon Karmon[1], Shlomo Sragovich[1], Gal Hacohen-Kleiman[1], Inbar Ben-Horin-Hazak[1], Petr Kasparek[2], Björn Schuster[2], Radislav Sedlacek[2], Metsada Pasmanik-Chor[3], Paschalis Theotokis[4], Olga Touloumi[4], Sofia Zoidou[4], Linxuan Huang[5], Pei You Wu[5], Roy Shi[5], Oxana Kapitansky[1], Alexandra Lobyntseva[1], Eliezer Giladi[1], Guy Shapira[7], Noam Shomron[7], Stefan Bereswill[6], Markus M. Heimesaat[6], Nikolaus Grigoriadis[4], R. Anne McKinney[5], Moran Rubinstein[1, 8] and Illana Gozes[1]*

Background: Autism Spectrum disorder (ASD) is a complex neurodevelopmental disease, affecting ~1.5% of children worldwide with no known cure or clear etiology to date. ASD is highly heritable which implies shared genes and pathways. Activity-dependent neuroprotective protein (ADNP) was discovered by our laboratory (1997) as a protein essential for brain formation (2003). In 2014, *de novo* truncating mutations in ADNP were identified as present in at least 0.17% of ASD cases, making ADNP one of the most frequent ASD associated genes. Patients exhibit intellectual disabilities, ASD and motor deficits, among their myriad of symptoms. With over 200 diagnosed patients and a projection of thousands of patients, it is of interest to further understand the *in vivo* function of ADNP, and its mechanism in relation to the ADNP syndrome and ASD.

RESULTS: We have recently published a new ADNP syndrome model, the Tyr mouse (Biol Psychiatry. 2021 Sep 28:S0006-3223(21)01630-9). In short, mimicking humans, CRISPR (clustered regularly interspaced short palindromic repeats)–Cas9 editing produced mice carrying heterozygous Adnp p.Tyr718* (Tyr), a paralog of the most common ADNP syndrome mutation. Phenotypic rescue was validated by treatment with the microtubule/autophagy-protective ADNP fragment NAPVSIPQ (NAP). Phenotypically, Tyr mice, similar to patients with ADNP syndrome, exhibited delayed development coupled with sex-dependent gait defects. Speech acquisition delays paralleled sex-specific mouse syntax abnormalities. Anatomically, dendritic spine densities/morphologies were decreased with NAP amelioration. These findings were replicated in our Adnp+/− mouse (J Clin Invest. 2018 Nov 1;128(11):4956-4969) including Foxo3 deregulation, required for dendritic spine formation. Early-onset tauopathy was accentuated in males (hippocampus and visual cortex), mimicking humans, and was paralleled by impaired visual evoked potentials and correction by acute NAP treatment. RNA sequencing of spleens, representing a peripheral biomarker source, revealed Tyr-specific sex differences (e.g., cell cycle), accentuated in females and corrected by NAP. Differentially expressed, NAP-correctable transcripts, including the autophagy and microbiome resilience–linked FOXO3, were also deregulated in human patient-derived ADNP-mutated lymphoblastoid cells.

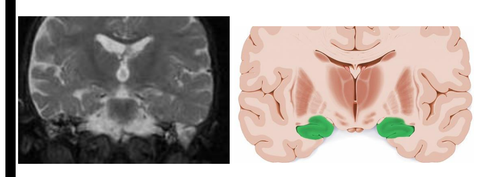
CONCLUSIONS:

This newly discovered ADNP/NAP target FOXO3 controls the autophagy initiator LC3 (microtubule-associated protein 1 light chain 3), with known ADNP binding to LC3 augmented by NAP, protecting against tauopathy. NAP amelioration attests to specificity, with potential for drug development targeting accessible biomarkers.

Implications beyond ADNP syndrome:

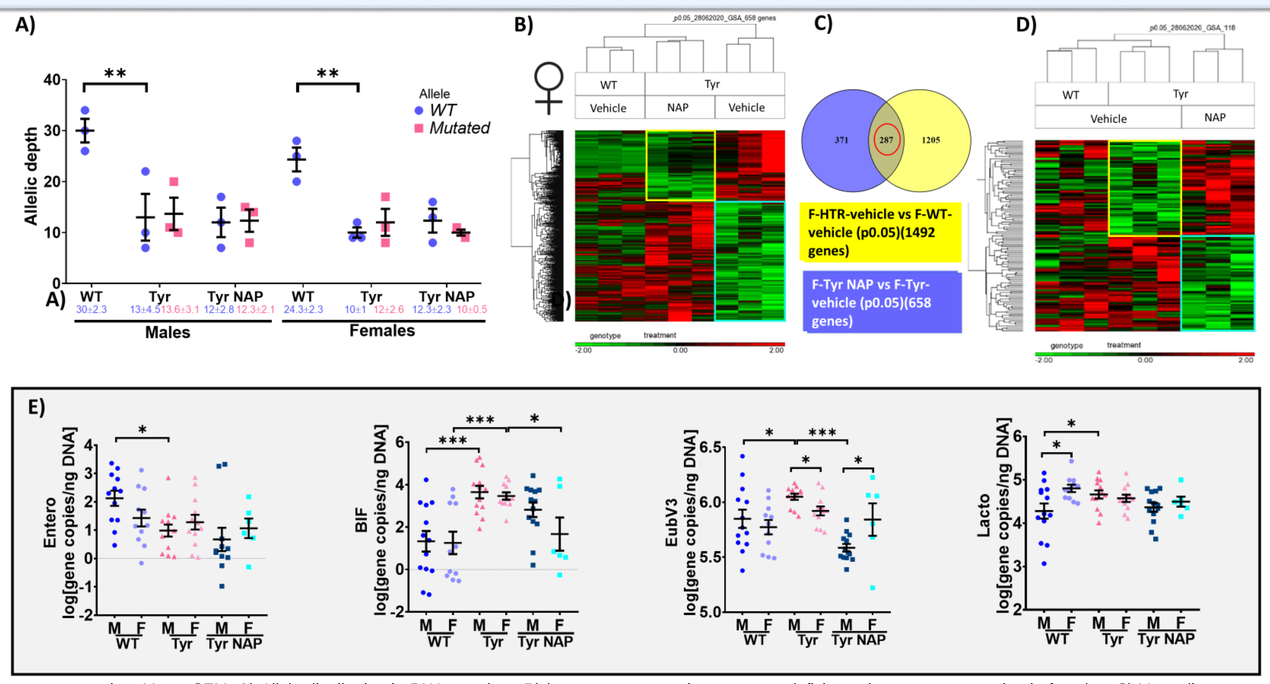
Interestingly, a recent independent paper ties another autism leading gene POGZ, as an ADNP-binding partner with POGZ deficits linked with ADNP deficits, suggesting common pathways (Cell Rep. 7/12 2021; 37 (10), 110089), and further potential for ADNP-related therapeutics, like NAP.

ADNP syndrome MRI scans



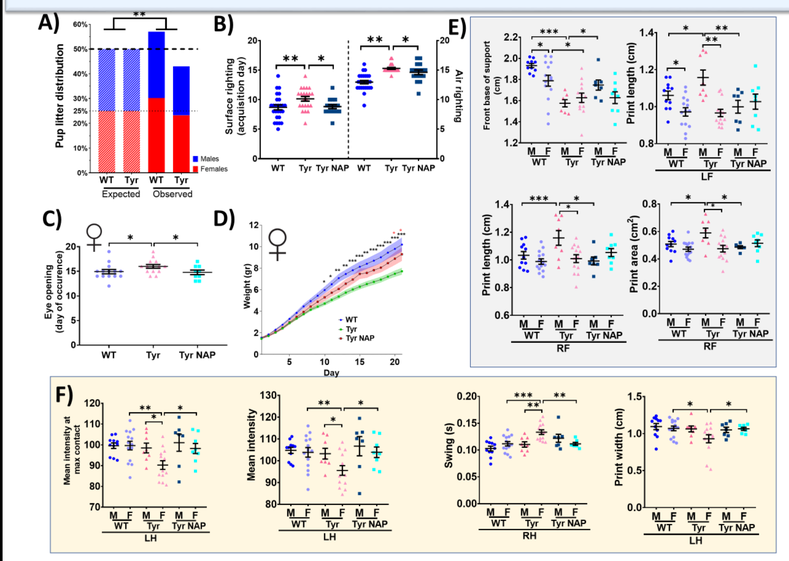
The human condition (*de novo* heterozygous p.Tyr* ADNP mutation) shows Incomplete hippocampal inversion - an anatomic pattern whereby the hippocampus is more rounded, vertical and medially positioned than normal (volumetric T2-MRI).
Gozes et al., Front Endocrinol (Lausanne). 2017 May 19;8:107.

Tyr-mice express the Tyr mutated allele coupled to 50% reduction in WT Adnp transcript levels and microbiota revealing sex and genotype effects, corrected by NAP treatment



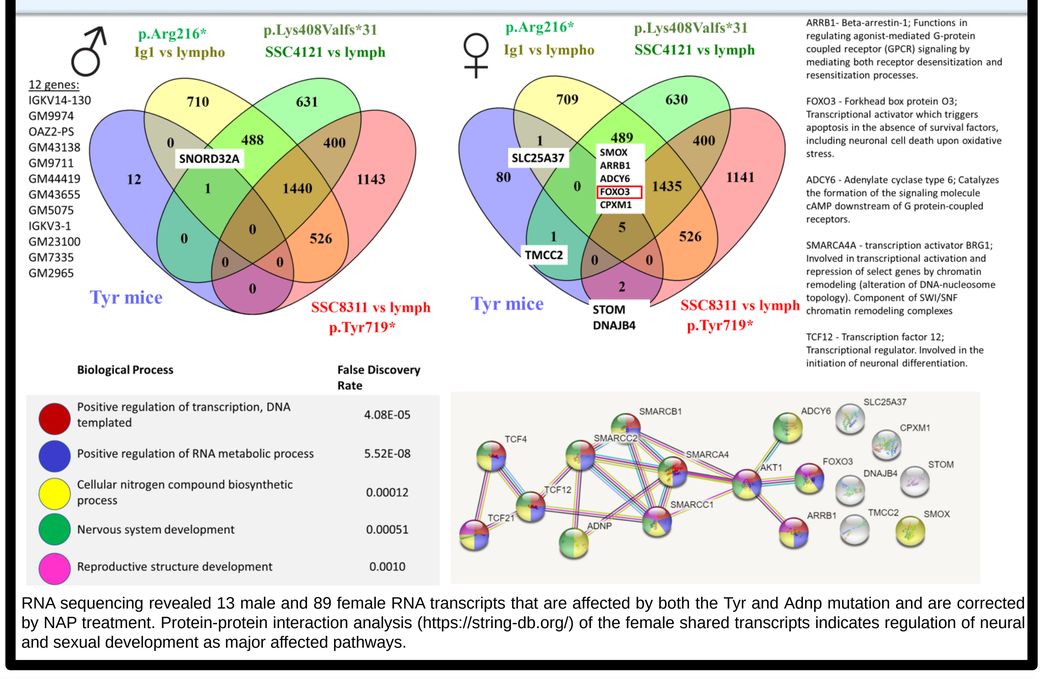
Data are expressed as Mean±SEM. **A**) Allele distribution in RNA-seq data. **B**) heatmap accentuating genotype deficits and treatment correction in females. **C**) Venn diagram comparing 658 differentially expressed genes (DEGs) due to NAP treatment of Tyr-mice with 1492 DEGs due to the Tyr mutation (comparison vs. WT). **D**) A heatmap showing a lower number of genotype deficits and treatment correction in males. **E**) Two-way ANOVA with Tukey post hoc test was performed to assess real-time PCR microbiota loads. M-male, F-female.

Tyr-mice are developmentally impaired in a sex-dependent manner: NAP repairs



Data are expressed as Mean±SEM. **A**) A two tailed binomial test revealed that a significantly lower number of Tyr mouse pups survive at postnatal day 1. **B**) Surface-righting (pup righting itself on all 4 paws on a flat surface) and air-righting (righting to the correct orientation mid-air). **C**) Eye opening. D) Female weight (genotype and NAP effects marked with black and red asterisks respectively). **E,F**) Gait of 9.23± 0.15-week-old mice was analyzed. M-male, F-female.

RNA sequencing of mouse spleens reveals Adnp Tyr genotype-affected/NAP corrected mRNA species that are shared with ADNP mutated human lymphoblastoid cells



ARRB1- Beta-arrestin-1; Functions in regulating agonist-mediated G-protein coupled receptor (GPCR) signaling by mediating both receptor desensitization and resensitization processes.

FOXO3 - Forkhead box protein O3; Transcriptional activator which triggers apoptosis in the absence of survival factors, including neuronal cell death upon oxidative stress.

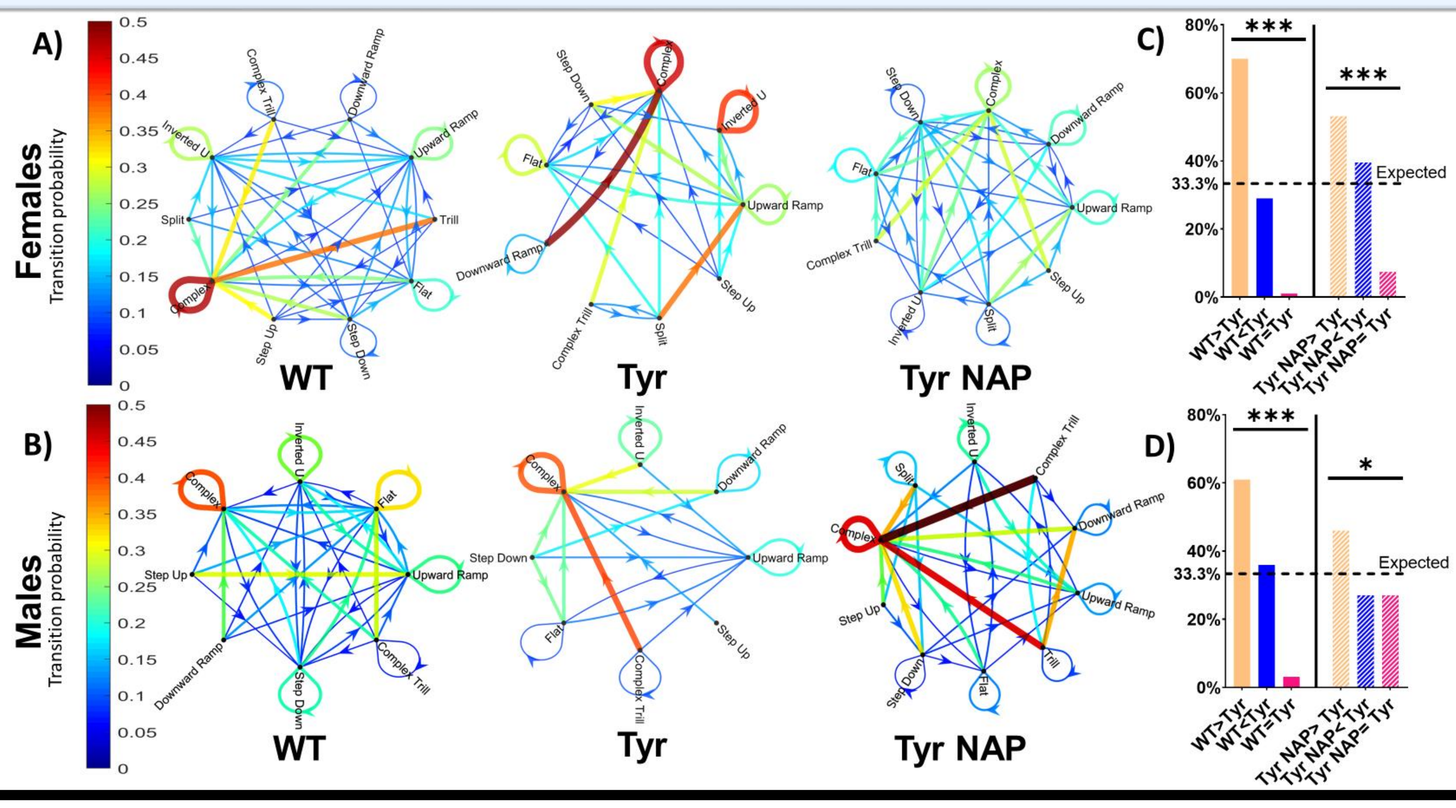
ADCY6 - Adenylate cyclase type 6; Catalyzes the formation of the signaling molecule cAMP downstream of G protein-coupled receptors.

SMARCA4A - transcription activator BRG1; Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes

TCF12 - Transcription factor 12; Transcriptional regulator. Involved in the initiation of neuronal differentiation.

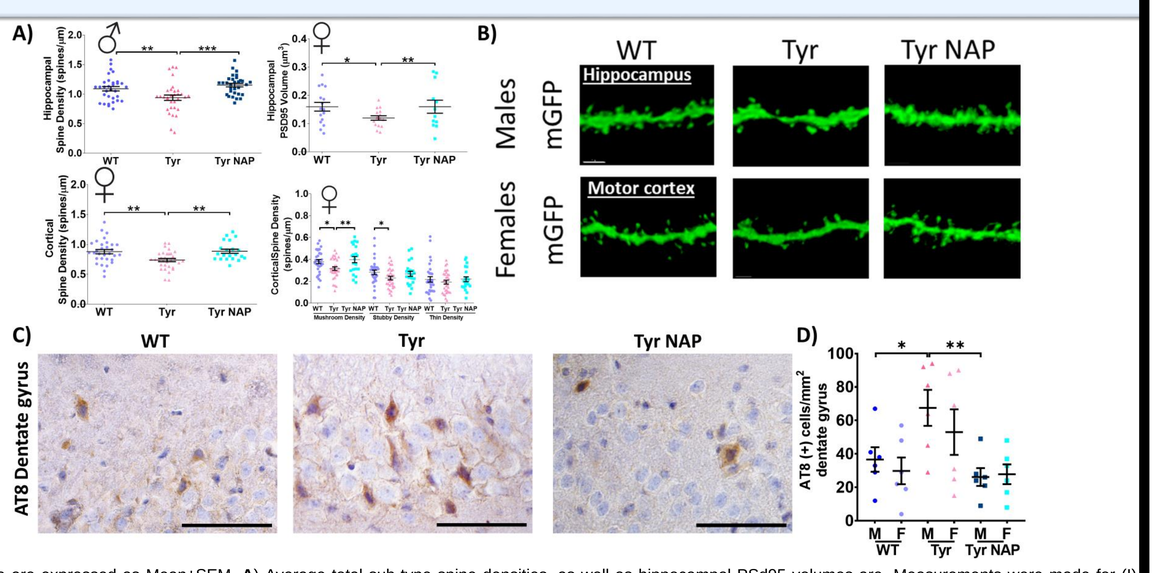
RNA sequencing revealed 13 male and 89 female RNA transcripts that are affected by both the Tyr and Adnp mutation and are corrected by NAP treatment. Protein-protein interaction analysis (https://string-db.org/) of the female shared transcripts indicates regulation of neural and sexual development as major affected pathways.

Tyr-mice exhibit impaired syntax in a sex-dependent manner: NAP repairs



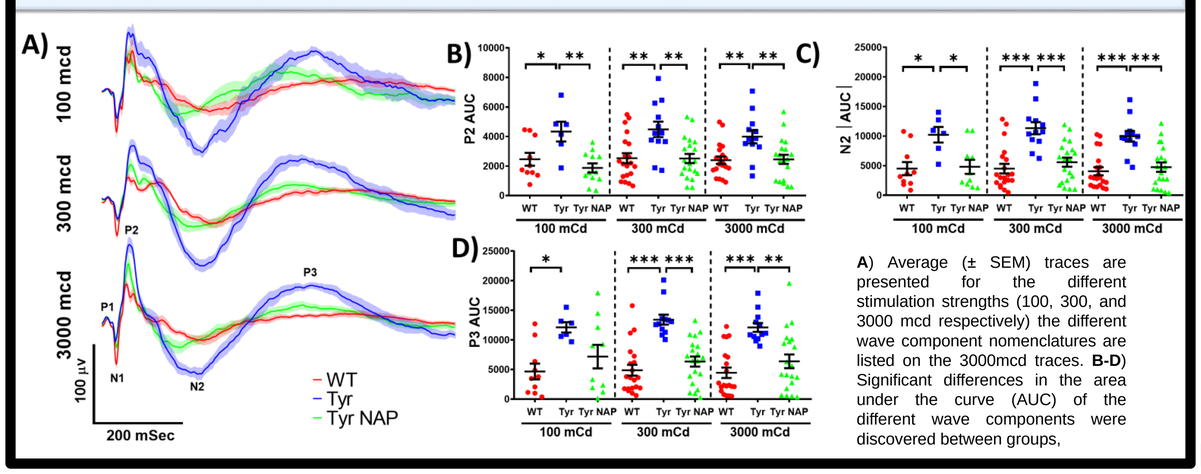
Syntax transition probability chart is presented for females (**A**) and males (**B**) and was generated using the DeepSqueak algorithm (males: WT n=12, Tyr n=14, Tyr NAP n=10; females: WT n=20, Tyr n=9, Tyr NAP n=9). Syllables measured included: upward ramp, flat, inverted U, complex, step up, downward ramp, step down, complex trill, split, and trill. An evident decrease in syntax complexity was observed between WT and Tyr females with a marked improvement with NAP treatment. The same effect can be observed between WT and Tyr males with NAP improvement between Tyr and Tyr NAP male pups. **C** and **D**) In females and males (respectively) to quantify this difference, Xi-square analysis was performed

Tyr-mice exhibit a sex-linked reduction in dendritic spines, paralleled by tauopathy: NAP repairs



Data are expressed as Mean±SEM. **A**) Average total sub-type spine densities, as well as hippocampal PSd95 volumes are. Measurements were made for (I) density of dendritic spines (GFP puncta label), with and without classification into subgroups on the basis of the following morphology types: stubby spines (<0.5 µm in length, lacking a clear head); mushroom spines (mushroom-shaped head, approximately 1 µm in length); and thin spines (with an elongated narrow neck with a distinctive head) (7); (II) density of shaft synapses (postsynaptic density PSD95 puncta immunogold labeling, representing immature synapses); and (III) shaft synapse volume (PSD95, puncta volume, representing the degree of synapse maturity). **B**) Representative images are shown for the male hippocampus and female motor cortex dendritic spine staining. Scale bar: 2 µm. **C and D**) AT8 (hyperphosphorylated Tau) stains were evaluated in the dentate gyrus. C: Representative stained samples of the male dentate gyrus. Scale bar: 100 µm. D) Quantitation of positive cells/mm2. M-male, F-female.

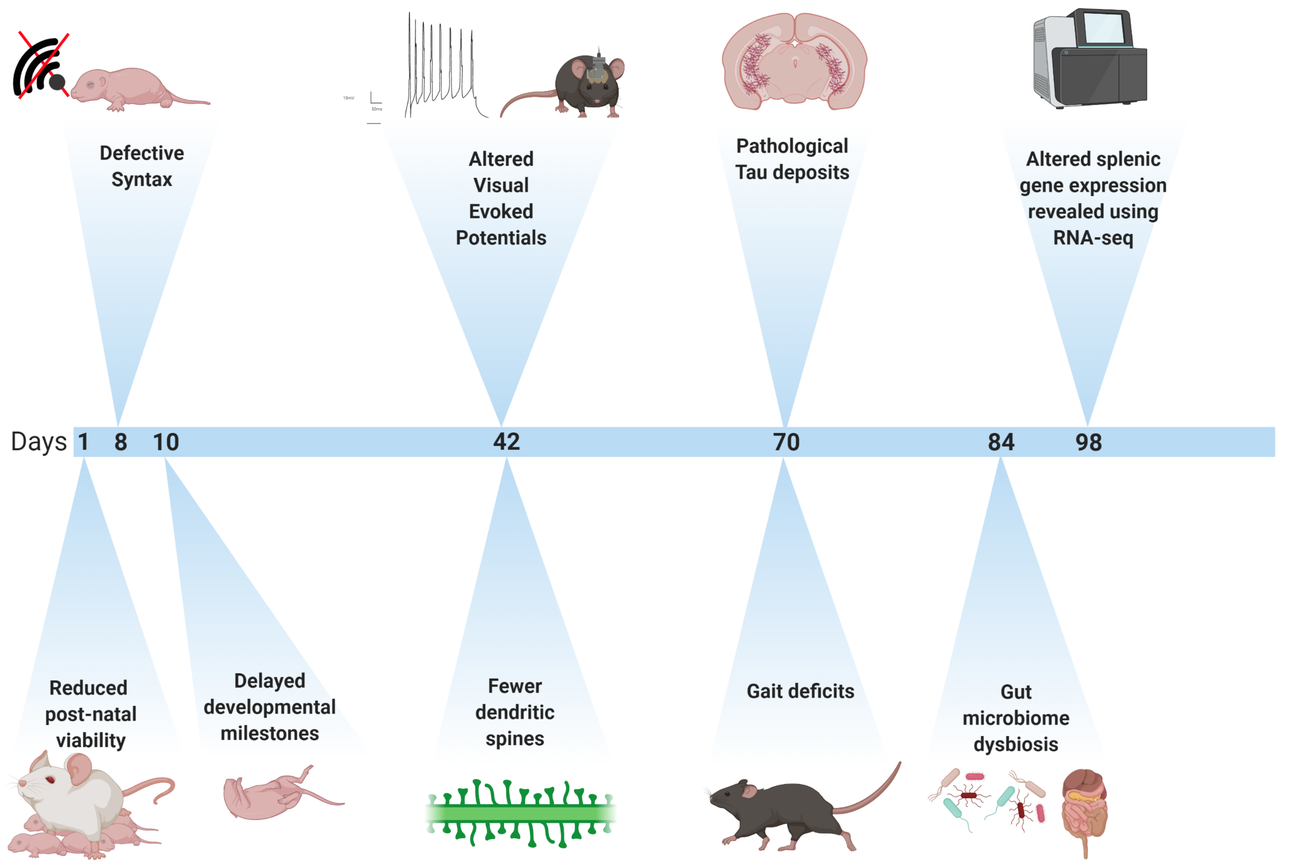
Visual evoked potentials (VEP) are impaired in male Tyr-mice paralleling tauopathy: NAP corrects



A) Average (± SEM) traces are presented for the different stimulation strengths (100, 300, and 3000 mcd respectively) the different wave component nomenclatures are listed on the 3000mcd traces. **B-D**) Significant differences in the area under the curve (AUC) of the different wave components were discovered between groups,

Summary

Mutated Tyr mouse mimicking life-long ADNP syndrome reveals noval biomarkers



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Feasibility of OT-ParentShip: An intervention program for parents of adolescents with autism- A pilot study

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The Israeli Meeting for Autism Research (I-MAR) 2022

Azrieli National Centre for Autism and Neurodevelopment Research

INTRODUCTION

Parents of children with autism face a variety of difficulties, among which are decreased resilience and heightened stress. Recent studies have shown that parental well-being affects the child's well-being, and that parents are primary mediators of their child's development[1]. The ***OT-Parentship*** is a validated[2] short-term occupational therapy intervention for parents of adolescents with High Functioning Autism Spectrum Disorder (HFASD), that aims to promote parental resilience and enhance adolescents' participation in daily life.

Objectives

To examine the ***OT-Parentship*** feasibility and explore the modifiability of parental resilience following intervention.

METHODS

Design: A mixed-method, one-group, pretest (Time 1)– posttest (Time 2) and follow up (Time 3).

Participants: Parents (n = 4 - both parents, n = 6 - mothers) of 10 adolescents with autism: five boys (M=14.32 years, SD=1.98), five girls (M=13.95 years, SD=1.06).

Inclusion criteria: Parents - difficulties or unmet functional needs in relation to raising their adolescent; Adolescent- a score indicating non-typical functioning in at least one of the following areas: sensory processing, executive function, or social-communication skills.

Procedure:

Pre-research stage

Assessment of:

1. **The adolescent's multi- dimensional profile** in four dimensions:
   - **Sensory-motor:** Sensory Profile 2 (SP2)[3]
   - **Cognitive-behavioral:** The Behavior Rating Inventory of Executive Function (BRIEF)[4]
   - **Social communicative:** Social Skills Improvement System (**SSIS**)[5]
   - **Motivational** (questionnaire developed for this study).
2. **Parental resilience:** Autism: Parenting Questionnaire (**APQ**)[6] (**Time 1**).

Sessions 1-11

11 individual weekly sessions of 90 minutes each according to the *OT-ParentShip* protocol (analyzing the adolescent's profile, examining daily situations and identifying barriers and bridges in the parent, the adolescent and the environment), during which **parents set functional goals** (the Canadian Occupational Performance Measure- **COPM**[7]) and practice structured problem solving.

Session 12

Semi-structured interview to assess intervention outcome (**Time 2**):

1. **Satisfaction with the intervention** (questionnaire developed for this study).
2. **Parental resilience** (APQ).

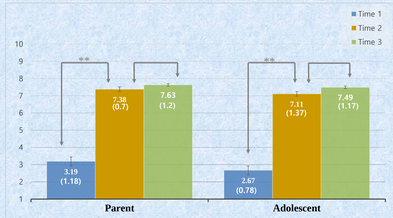
Session 13

Follow up session 3 months post intervention (**Time 3**):

1. **Parental resilience** (APQ).
2. **Functional goal attainment for parent and adolescent** (COPM).
3. **Transfer goal attainment** (COPM).

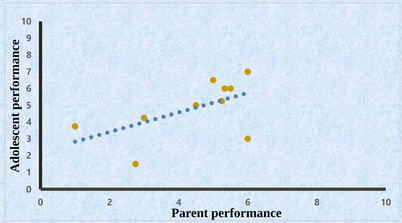
QUANTITATIVE RESULTS

Occupational Goals: Time 1, 2 and 3 (COPM)



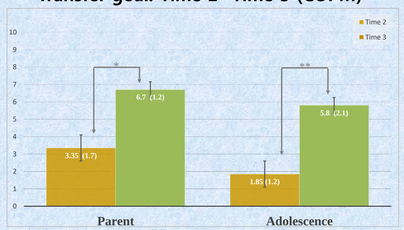
Mother: (Z= 2.81, p= .005**), (Z= .88, p=NS);
Adolescent: (Z= 2.8, p= .005**), (Z=.72, p=NS).

Correlation between mother and adolescent performance Δ scores (COPM: Time 3 - Time 1)



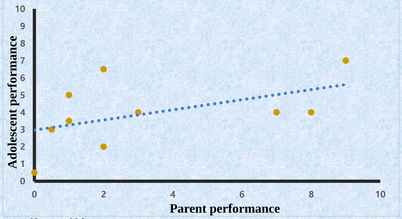
r_s = .512, p = .065.

Transfer goal: Time 2- Time 3 (COPM)



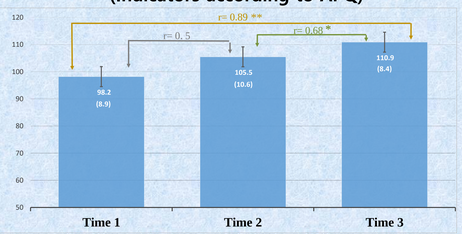
Mother (Z= 2.67, p= .008*); Adolescent (Z= 2.81, p= .005**).

Correlation - mother and adolescent performance Δ transfer goal scores (COPM: Time 3 - Time 2)



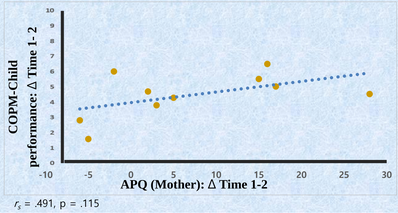
r_s = .63, p = .026.

Parental resilience -Time 1, 2 and 3 (Indicators according to APQ)



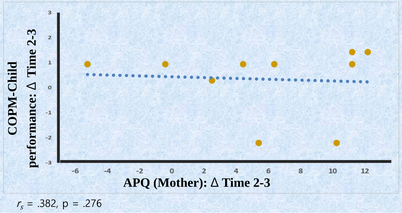
Time 1- Time 2: (Z=1.582, p= .114), Time 2- Time 3: (Z=2.143, p= .032*),
Time 1- time 3: (Z=2.807, p= .005**)

Correlation - COPM child performance and APQ total Δ scores from Time 1 to Time 2



r_s = .491, p = .115

Correlation - COPM child performance and APQ total Δ scores from Time 2 to Time 3



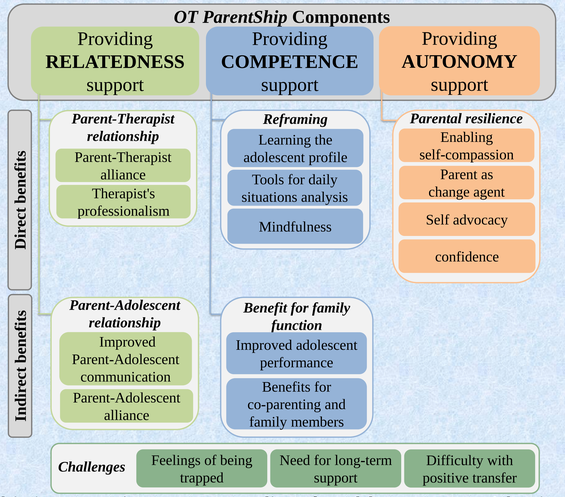
r_s = .382, p = .276

Contact: Batel.wachspress@mail.huji.ac.il

QUALITATIVE RESULTS

In a qualitative analysis of the experience and insight of four families, six over-arching themes were identified, shedding light on the therapeutic components and change mechanisms of *OT-ParentShip*.

Self-Determination Theory[8] was found to be a suitable theoretical framework that demonstrates, among others, the therapeutic components enabling the success of the intervention:



OT-ParentShip intervention seems to directly address parents' basic psychological needs for autonomy, competence, and relatedness, and indirectly addresses these same needs on part of the adolescent through a change in parental comportment.

DISCUSSION

OT-ParentShip intervention led to a significant improvement in adolescents' participation and heightened parental resilience. Results support the feasibility of the *OT-ParentShip* as a strength-based family centered intervention program that provides parents of adolescents with HFASD with a deep understanding of their child's unique profile, an opportunity to analyze everyday situations, and promotes them in acquiring practical tools and strategies for coping with everyday functional challenges. Due to the small sample size and the absence of a control group, it is necessary to further evaluate the effectiveness of the *OT-ParentShip* protocol through a broad randomized controlled trial.

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The importance of language delays as an early indicator of subsequent ASD diagnosis in public healthcare settings

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Background

Early diagnosis of ASD is essential for enabling earlier access to services and ASD-specific interventions that improve clinical outcomes[1,2,3]. The current mean diagnosis age in clinical settings is >3.5 years of age [4] and standardized ASD screening tools are used by <50% of physicians [5,6]. Hence there is a clear need to emphasize easily identifiable signs of ASD risk that can help reduce the age of diagnosis in public healthcare settings.

Previous studies have demonstrated that age of ASD diagnosis is associated with a variety of child, parent, and societal characteristics including language delays, which are prevalent in most children with ASD[7]. However previous studies have not examined whether some characteristics predict age of diagnosis more strongly than others.

Objectives:

1. Determine the relative utility of standardized language, cognitive, and ADOS scores in predicting age of ASD diagnosis in a public healthcare setting.
2. Identify specific expressive language milestones that are early signs of ASD risk.

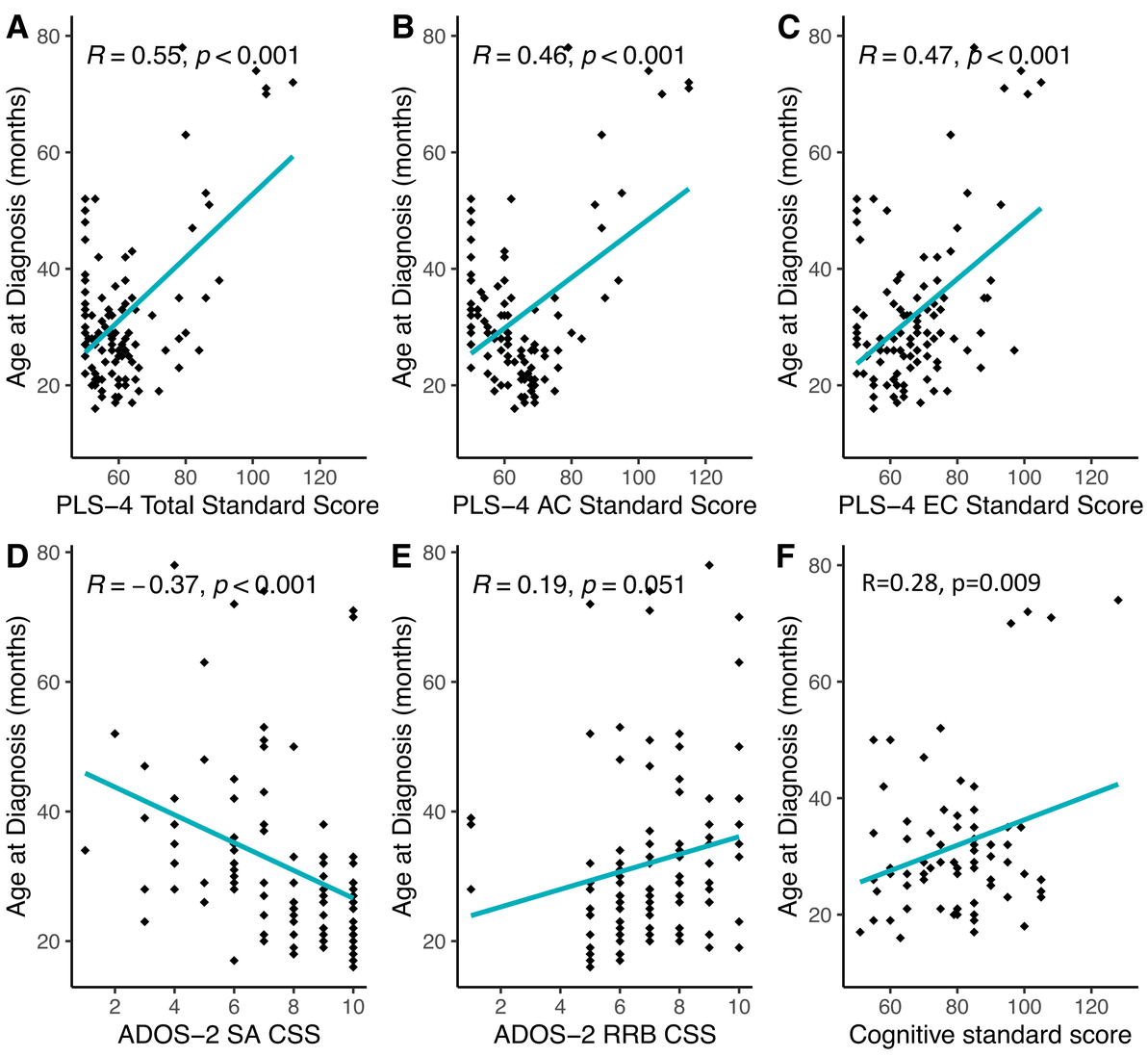
Methods

We analyzed data from 104 Hebrew-speaking children (mean age 31.6 months) with ASD. All children completed the Preschool Language Scale, 4th edition (PLS-4) and the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2). 84 children (~81%) completed either the Bayley Scales of Infant and Toddler Development, 3rd Edition (~69%), the Mullen Scales of Early Learning (~15 %), or the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (~15%).

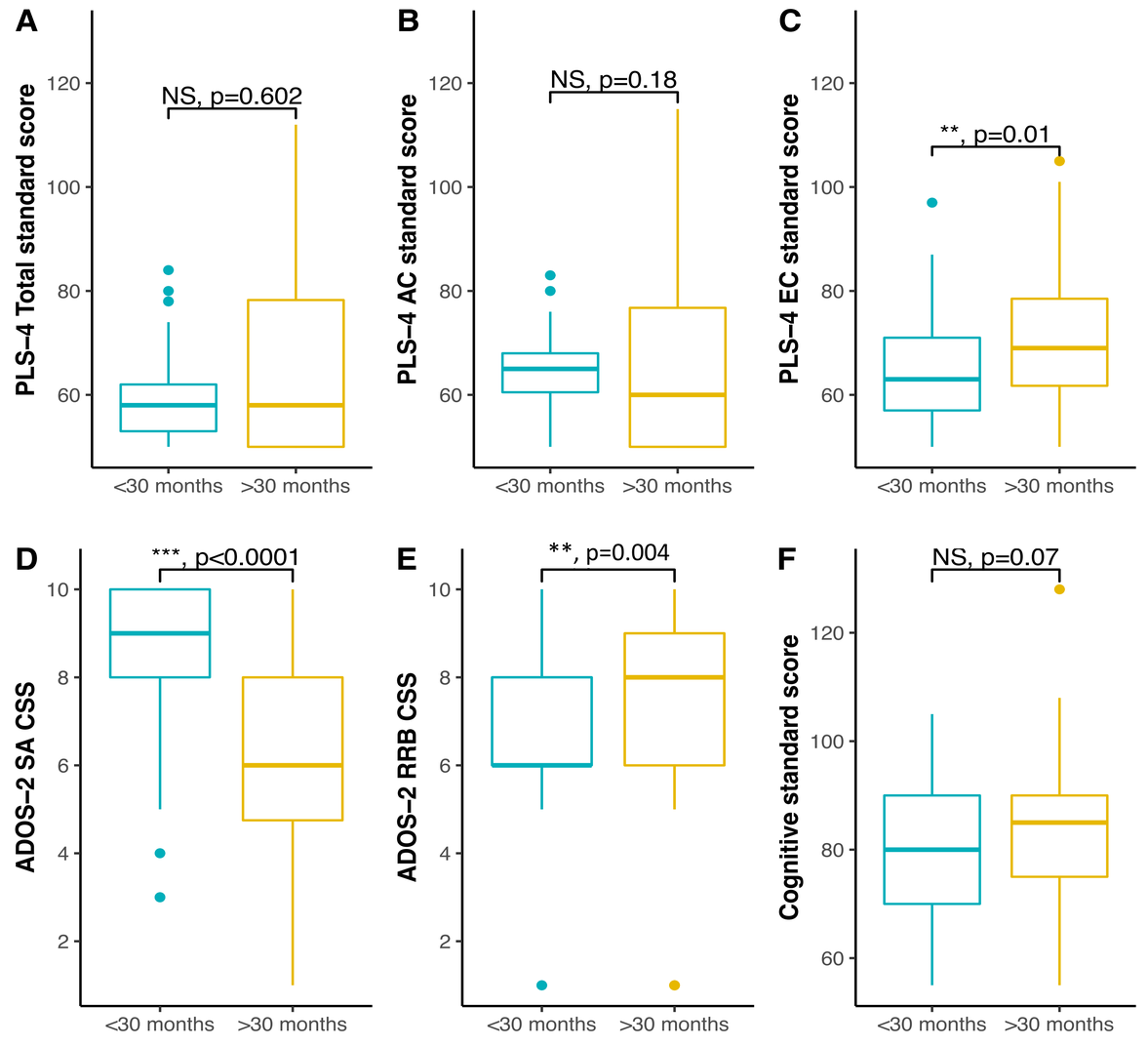
We calculated Pearson's correlation coefficients to assess the relationships between continuous variables (e.g., age and PLS-4 scores) and performed a stepwise regression analysis to determine the relative contribution of the PLS-4 scores, cognitive scores, ADOS SA CSS, and ADOS RRB CSS (i.e., independent variables) in predicting age of ASD diagnosis (i.e., dependent variable). We compared children diagnosed with ASD before 30 months of age with children diagnosed at older ages using t-tests and Mann-Whitney U tests.

Results

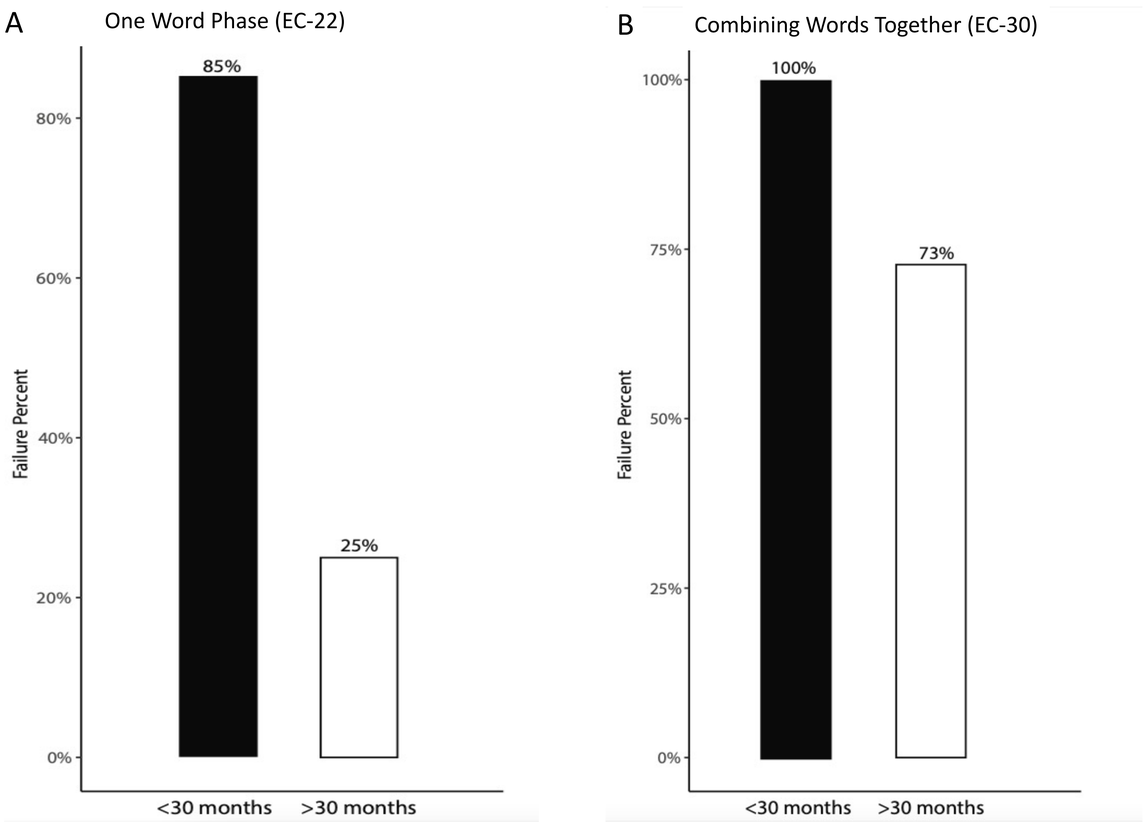
Relationship between Age of Diagnosis and Behavioral Assessments



Comparison of Children Diagnosed Early and Late



Expressive Language Delays at Diagnosis



One-word phase (EC-22): the ability of to spontaneously produce 5-10 words (typically achieved by 12-18 months of age)

Combining words together (EC-30): the ability to produce word combinations involving a noun, verb, place, adjective, preposition, or possession (typically achieved by 24 months of age).

Predictors of Early ASD Diagnosis

Variable	*B*	*SE. B*	*β*	R^2	ΔR^2
Step 1				0.299	**0.299*****
PLS-4 Total Standard Scores	0.54	0.08	**0.56*****		
Step 2				0.393	**0.093*****
PLS-4 Total Standard Scores	0.51	0.08	**0.51*****		
ADOS-2 SA CSS	-1.77	0.45	**-0.31*****		
Step 3				0.461	**0.068*****
PLS-4 Total Standard Scores	0.49	0.07	**0.49*****		
ADOS-2 SA CSS	-2.18	0.44	**-0.38*****		
ADOS-2 RRB CSS	1.92	0.54	**0.27*****		
***p<0.001					
Observations	104				
R^2 / R^2 adjusted	0.461 / 0.445				

Total PLS-4 score was the most dominant predictor, explaining 30% of the variance in age of diagnosis, followed by ADOS-2 SA CSS and ADOS-2 RRB CSS that explained an additional 9.3% and 6.8% of the variance, respectively.

This analysis highlights the strong and unique relationship between severity of language delays and age of diagnosis.

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Conclusions

- While ASD is not a language disorder, clear language delays were apparent in the vast majority of children diagnosed with ASD. Moreover, children with more severe language delays were diagnosed earlier and PLS-4 scores were the strongest predictor of diagnosis age (explaining ~30% of the variance across children). This emphasizes the importance of fast referral of children with language delays to further screening for ASD symptoms to improve early ASD diagnosis in the community.
- Age of ASD diagnosis was negatively correlated with social symptom severity and positively correlated with RRB symptom severity. Hence, the two core ASD symptoms have opposite association with the age of diagnosis, demonstrating that children diagnosed early often have relatively strong social symptoms and relatively weak RRB symptoms.