Ketamine in ADNP Syndrome

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Artificial intelligence jump starts clinical trial for rare genetic disease

by Bob Shepard

May 07, 2020 | Print | Email

It was a pretty simple e-mail. Just a couple of lines. "It looks like low-dose ketamine is an up-regulator for ADNP. Do you think this makes sense for ADNP patients?"

Matt Might sent that e-mail to Matt Davis on Feb. 18, 2019. Might is the director of the Hugh Kaul Precision Medicine Institute at the University of Alabama at Birmingham School of Medicine. Davis is chief resident in the Department of Neurosurgery at UAB and the father of Benjamin, a child with a developmental delay caused by a variant in the ADNP gene.

And that e-mail was the first step toward a just-launched clinical trial that may make a world of difference for children like Benjamin.

Matt and Anna Davis, with son Benjamin
Photography: Matt Davis

Ketamine may induce ADNP expression

Cancer Therapy: Preclinical

Clinical Cancer Research

November 30, 2016;

ADNP Is a Therapeutically Inducible Repressor of WNT Signaling in Colorectal Cancer

Cristina Blaj[1], Agnes Bringmann[1], Eva Marina Schmidt[1], Manuela Urbischek[1], Sebastian Lamprecht[1], Thomas Fröhlich[2], Georg J. Arnold[2], Stefan Krebs[2], Helmut Blum[2], Heiko Hermeking[1,3,4], Andreas Jung[1,3,4], Thomas Kirchner[1,3,4], and David Horst[1,3,4]

IN VIVO AND *IN VITRO* KETAMINE EXPOSURE EXHIBITS A DOSE-DEPENDENT INDUCTION OF ACTIVITY-DEPENDENT NEUROPROTECTIVE PROTEIN IN RAT NEURONS

B. P. BROWN,[a,d] S. C. KANG,[a] K. GAWELEK,[a,b,d] R. A. ZACHARIAS,[a,c] S. R. ANDERSON,[a,c,e] C. P. TURNER[a] AND J. K. MORRIS[a,b*]

Neuroscience 290 (2015) 31–40

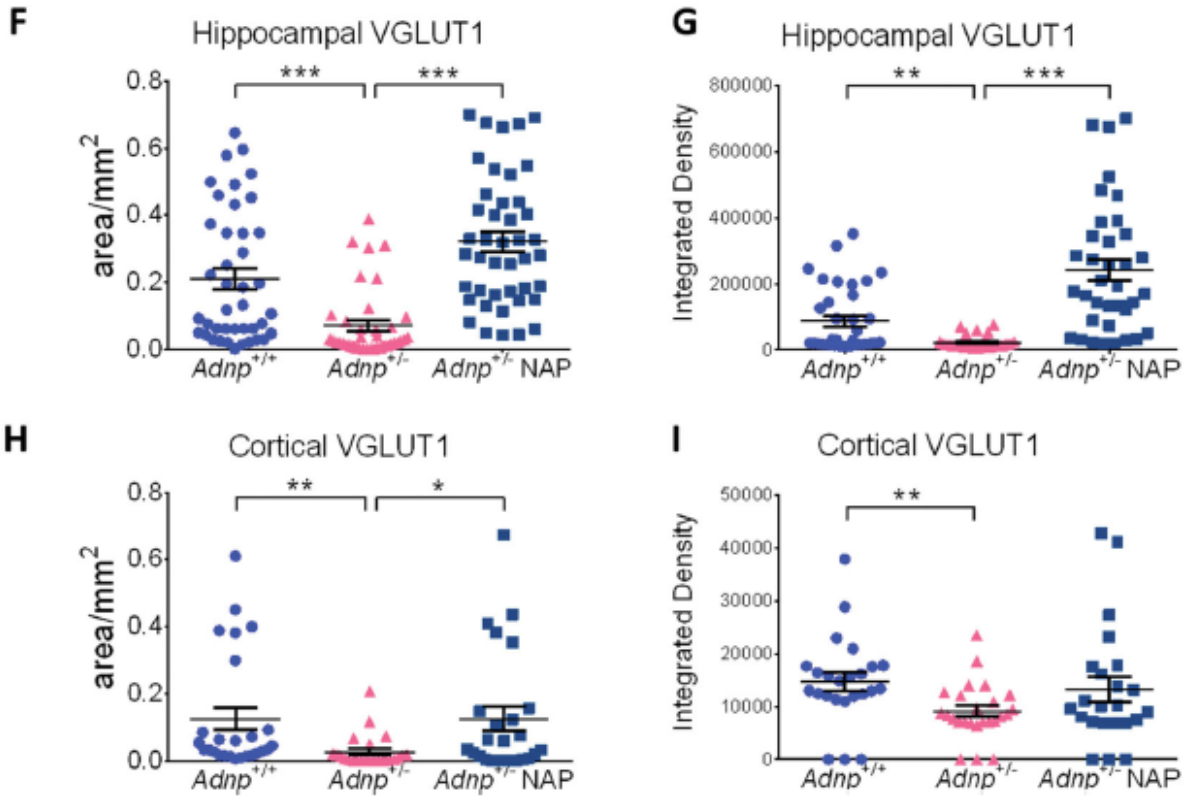
STRATEGIES TO DEFEAT KETAMINE-INDUCED NEONATAL BRAIN INJURY

Neuroscience 210 (2012) 384–392

C. P. TURNER,[a*] S. GUTIERREZ,[a] C. LIU,[a] L. MILLER,[b] J. CHOU,[b] B. FINUCANE,[a] A. CARNES,[a] J. KIM,[a] E. SHING,[a] T. HADDAD[a] AND A. PHILLIPS[a]

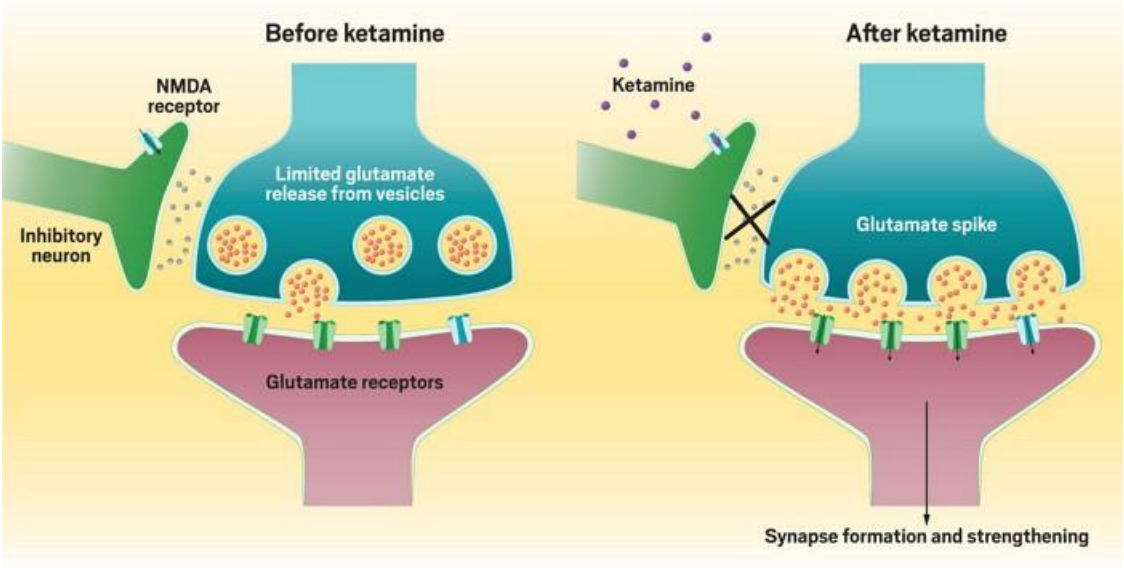
The autism/neuroprotection-linked ADNP/NAP regulate the excitatory glutamatergic synapse

Shlomo Sragovich[1], Anna Malishkevich[1], Yael Piontkewitz[2], Eliezer Giladi[1], Olga Touloumi[3], Roza Lagoudaki[3], Nikolaos Grigoriadis[3] and Illana Gozes[1]



Low-Dose Ketamine in ADNP Syndrome

- Ketamine is an N-methyl-D-aspartate (NMDA) antagonist that enhances excitatory (glutamatergic) nerve cell functioning by blocking inhibitory nerve cells (GABAergic interneurons)
- Ketamine also increases nerve cell growth factors (neurotrophins) to influence synaptic plasticity.
- While high-dose ketamine has toxic effects in animal models, these effects can be prevented by pre-treatment with low-dose ketamine.



Credit: Yang H. Ku / Chemical & Engineering News

Specific Aims

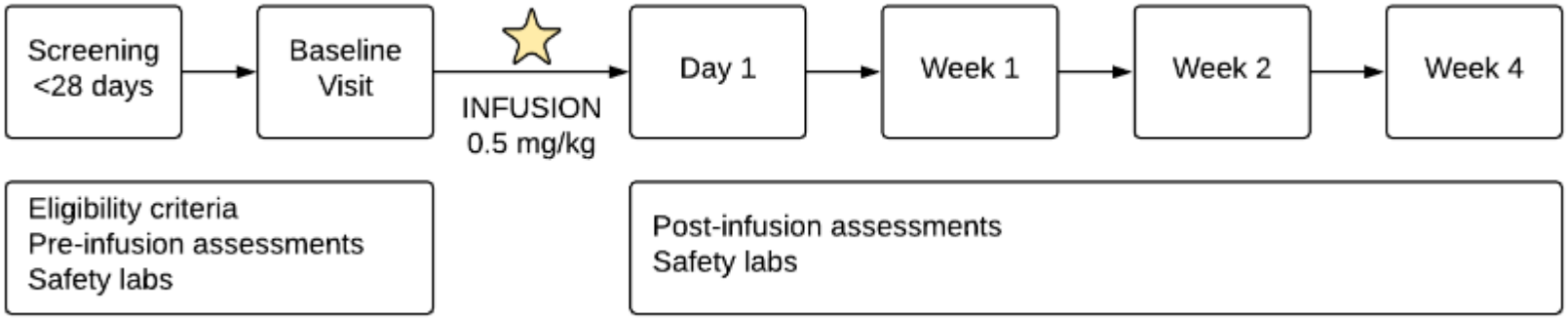
- **Aim 1.** Evaluate safety and tolerability of low dose ketamine in children with ADNP syndrome
- **Aim 2.** Evaluate efficacy targeting measures of aberrant behavior, sensory reactivity, sleep, language, and adaptive functioning
- **Aim 3.** Explore the feasibility of electrophysiological markers and computerized eye tracking
- **Aim 4.** Explore the feasibility of blood-based biological markers using RNA sequencing to measure ADNP expression and DNA methylation analysis

HGG Advances
Available online 27 August 2022, 100138
In Press, Journal Pre-proof

Article

An Open-Label Study Evaluating the Safety, Behavioral, and Electrophysiological Outcomes of Low-Dose Ketamine in Children with ADNP Syndrome

Alexander Kolevzon [1, 2, 3], Tess Levy [1, 2], Sarah Barkley [1, 2], Sandra Bedrosian-Sermone [4], Matthew Davis [4], Jennifer Foss-Feig [1, 2], Danielle Halpern [1, 2], Katherine Keller [1, 2], Ana Kostic [1, 2], Christina Layton [1, 2], Rebecca Lee [5], Bonnie Lerman [1, 2], Matthew Might [6], Sven Sandin [1, 2, 7], Paige M. Siper [1, 2], Laura G. Sloofman [1, 2], Hannah Walker [1, 2], Jessica Zweifach [1, 2], Joseph D. Buxbaum [1, 2, 8, 9]



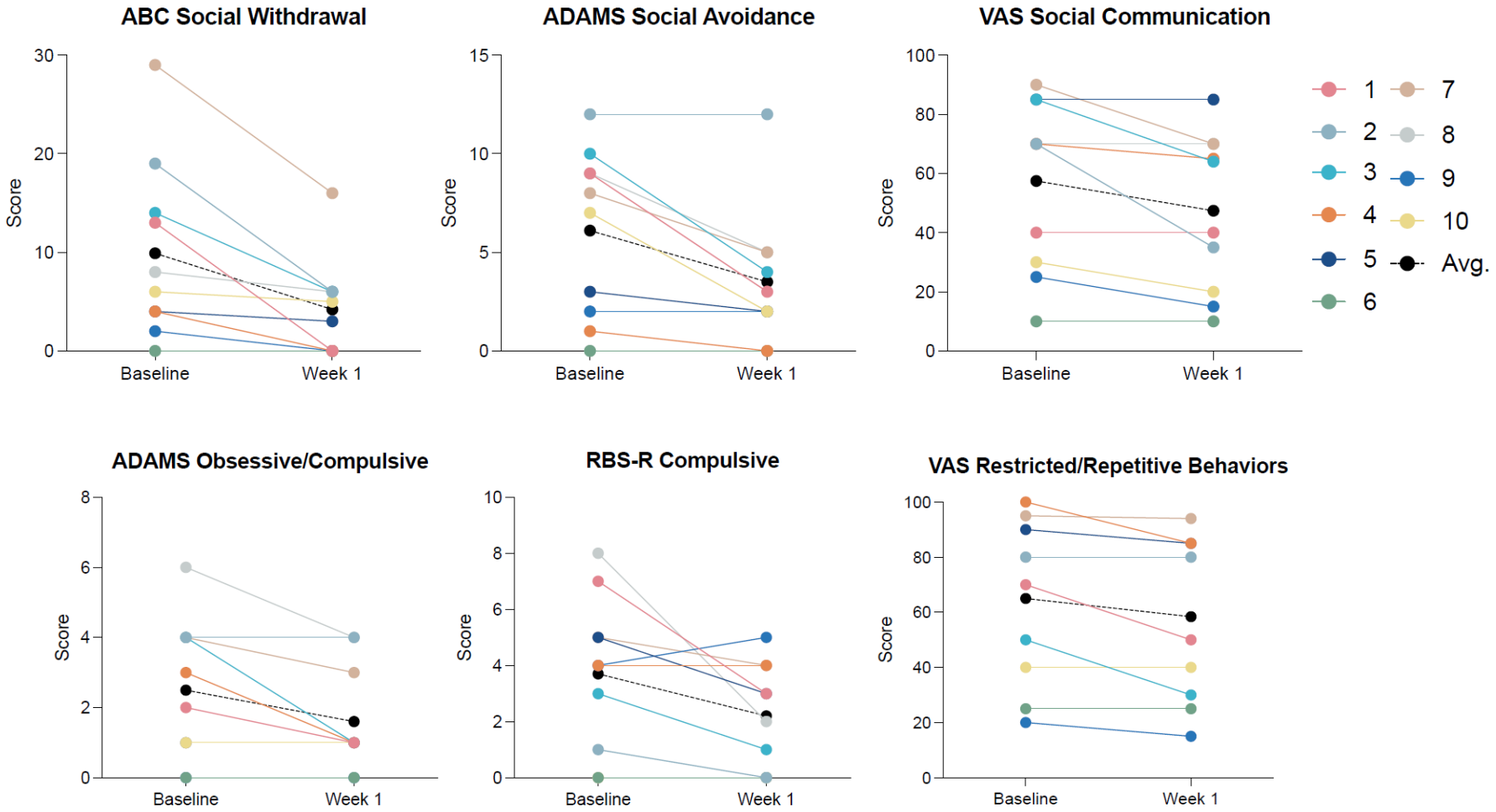
Participant Characteristics

Demographic Categories	Proportion or Mean (SD)	Range
Total Sample	10	
Sex		
Female	3/10	
Male	7/10	
Age: years	9.50 (2.30)	6.35–12.85
Developmental Quotient		
Verbal	26.71 (15.33)	5.65–52.48
Nonverbal	31.28 (16.13)	8.87–58.42
Full Scale	28.81 (15.42)	7.26–54.5
ASD	4/10	
ADHD	7/10	
Genetic Mutation		
Frameshift	6/10	
Nonsense	4/10	
Race and Ethnicity		
Hispanic/Latino	2/10	
White	8/10	

Results: Safety

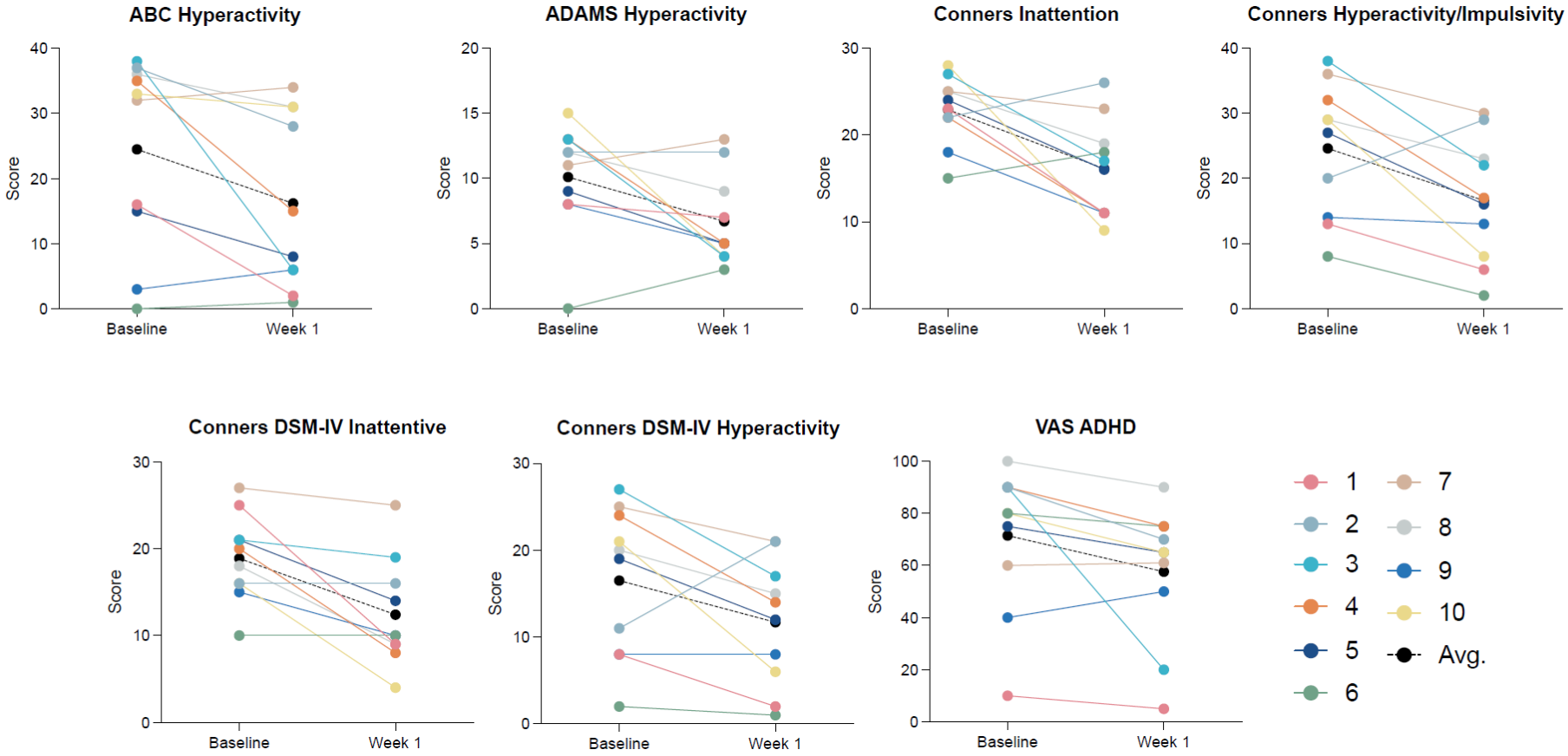
Adverse event type	N (%)
Elated / silly	5 (50)
Aggression	4 (40)
Fatigue	4 (40)
Decreased appetite	3 (30)
Anxiety	3 (30)
Restless	2 (20)
Increased fluid intake	2 (20)
Nausea/vomiting	2 (20)
Moody / irritable	2 (20)
Self-injury	1 (10)
Gagging / reflux	1 (10)
Dry mouth	1 (10)
Loose stool	1 (10)
Increased appetite	1 (10)
Difficulty falling asleep	1 (10)
Limping with possible pain	1 (10)
Early morning wakening	1 (10)
Decreased fluid intake	1 (10)
Distractibility	1 (10)
Constipation	1 (10)
Increased frustration	1 (10)
Oppositional	1 (10)
Upper respiratory tract infection	1 (10)
Agitation	1 (10)

Results: Efficacy



ABC = Aberrant Behavior Checklist; ADAMS = Anxiety, Depression, and Mood Scale; RBS-R = Repetitive Behavior Scale; VAS = Visual Analog Scale

Results: Efficacy



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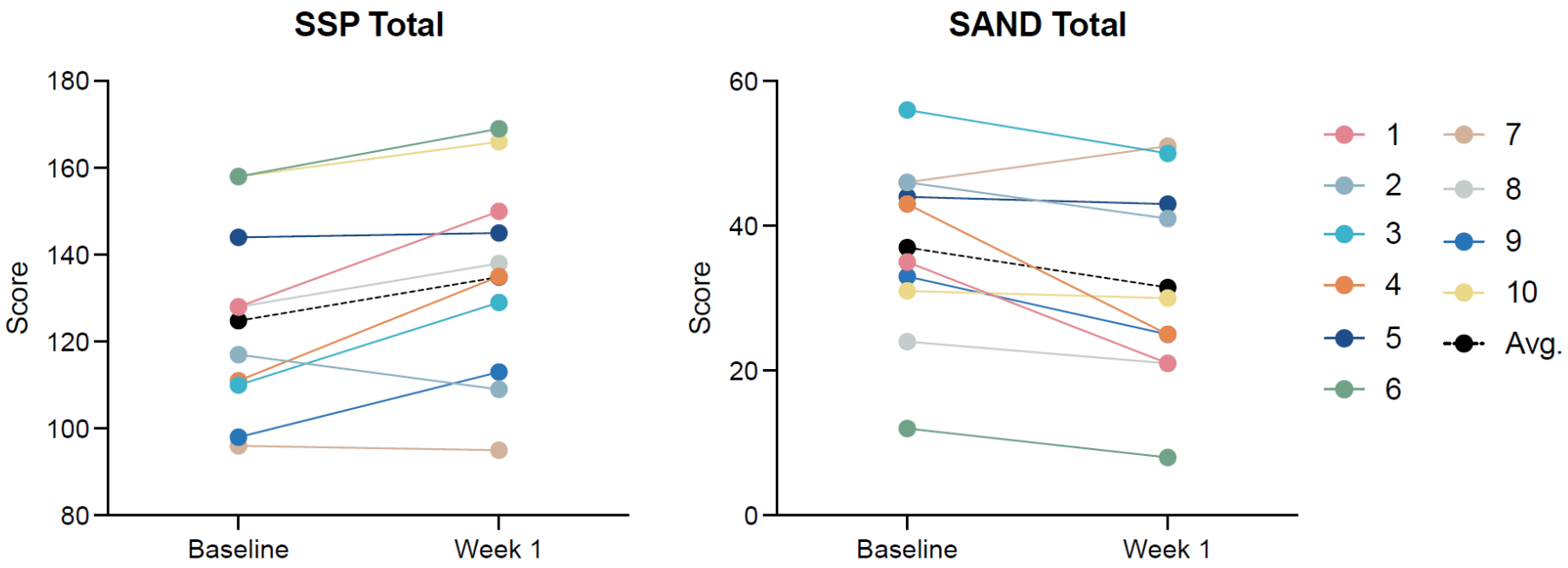

SSP = Short Sensory Profile; SAND = Sensory Assessment for Neurodevelopmental Disorders

Challenges for Clinical Trial Readiness

Clinical Outcome Assessments

- Patient reported
- Caregiver reported
- Clinician reported
- Composite instruments
- Objective tests

NEW METHOD Open Access

Development of an adapted Clinical Global Impression scale for use in Angelman syndrome

Alexander Kolevzon[1], Pamela Ventola[2,3], Christopher J. Keary[4,5], Gali Heimer[6], Jeffrey L. Neul[7], Mathews Adera[8] and Judith Jaeger[9,10*]

Kolevzon *et al. Journal of Neurodevelopmental Disorders* (2021) 13:3
https://doi.org/10.1186/s11689-020-09349-8

Abstract

Background: The Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I) scales are widely accepted tools that measure overall disease severity and change, synthesizing the clinician's impression of the global state of an individual. Frequently employed in clinical trials for neuropsychiatric disorders, the CGI scales are typically used in conjunction with disease-specific rating scales. When no disease-specific rating scale is available, the CGI scales can be adapted to reflect the specific symptom domains that are relevant to the disorder. Angelman syndrome (AS) is a rare, clinically heterogeneous condition for which there is no disease-specific rating scale. This paper describes efforts to develop standardized, adapted CGI scales specific to AS for use in clinical trials.

Methods: In order to develop adapted CGI scales specific to AS, we (1) reviewed literature and interviewed caregivers and clinicians to determine the most impactful symptoms, (2) engaged expert panels to define and

Results: The resulting CGI-S/I-AS scales capture six critical domains (behavior, gross and fine motor function, expressive and receptive communication, and sleep) defined by caregivers and expert clinicians as the most challenging for patients with AS and their families.

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Conclusions: Rigorous training and careful calibration for clinicians will allow the CGI-S/-I-AS scales to be reliable in the context of randomized controlled trials. The CGI-S/-I-AS scales are being utilized in a Phase 3 trial of gaboxadol for the treatment of AS.

Sensory Assessment for Neurodevelopmental Disorders (SAND)

Clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with neurodevelopmental disorders

Tavassoli et al., 2015
Siper et al., 2017
Siper et al, 2021

P. Siper, PhD

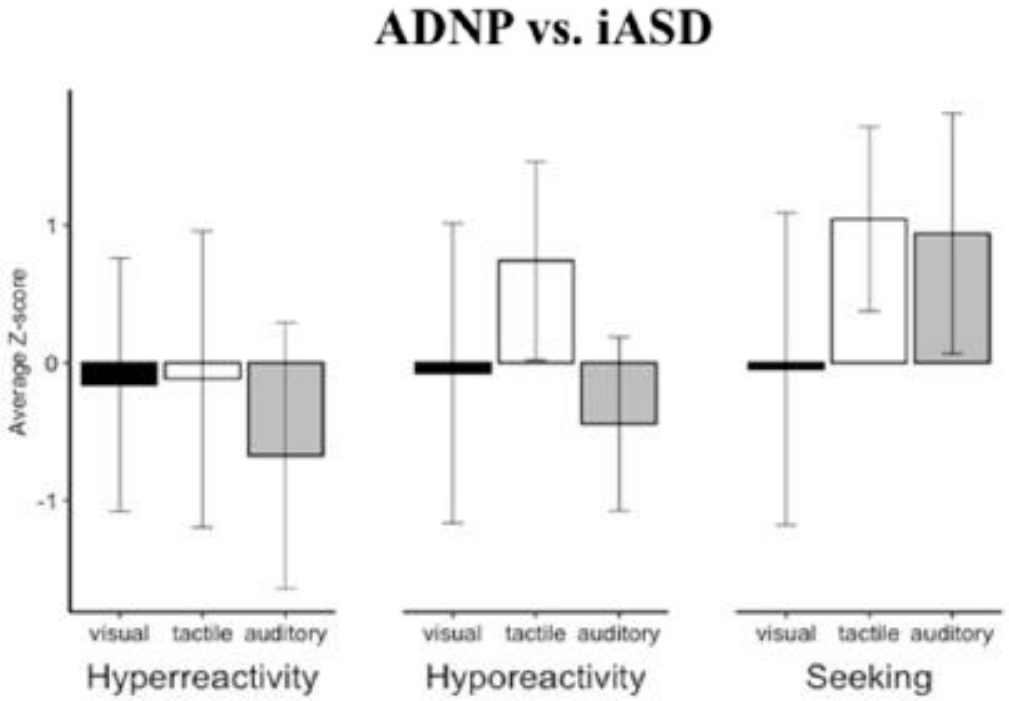
genes

MDPI

Article

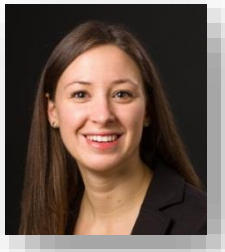
Sensory Reactivity Symptoms Are a Core Feature of ADNP Syndrome Irrespective of Autism Diagnosis

Paige M. Siper [1,2,3,*], Christina Layton [1,2], Tess Levy [1,2], Stacey Lurie [1,4], Nurit Benrey [1,4], Jessica Zweifach [1,2], Mikaela Rowe [5], Lara Tang [6], Sylvia Guillory [1,2], Danielle Halpern [1,2], Ivy Giserman-Kiss [7], Maria Del Pilar Trelles [1,2,3], Jennifer H. Foss-Feig [1,2], Silvia De Rubeis [1,2,3,8], Teresa Tavassoli [9], Joseph D. Buxbaum [1,2,3,8,10,11] and Alexander Kolevzon [1,2,3,12]



Computerized Eye Tracking

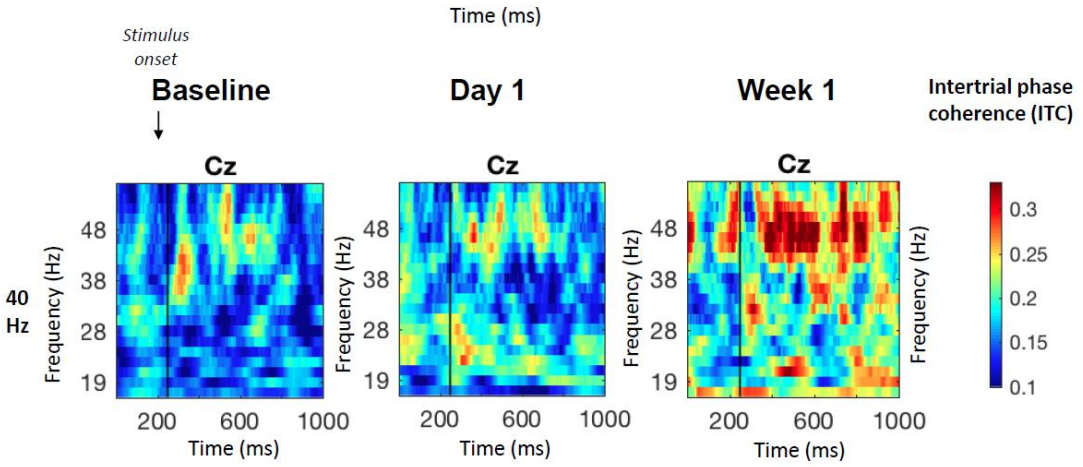
- The Gap Overlap task measures engagement and dis-engagement of visual attention to social (e.g., child faces) and non-social (e.g., objects like a ball) stimuli.
- The Joint Attention task measures ability to follow eye gaze of another person looking at objects versus a distractor.
- Results suggest this tool may be a useful marker of change in social attention with ketamine.

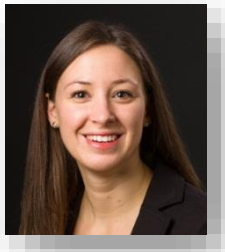


J. Foss-Feig, PhD

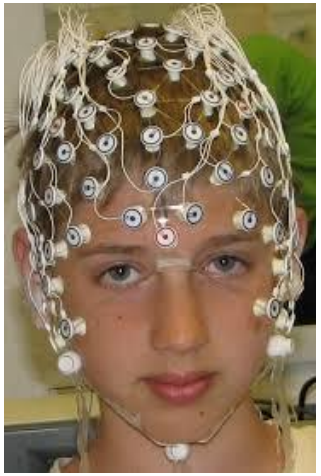
EEG Biomarkers: Auditory Steady State Response

- Participants hear a series of clicks at a stimulation rate of 40 Hz.
- Auditory Steady State Response (ASSR) is recorded with EEG nets where the coherence between trials of clicks is measured using time-frequency analysis and reflects synchrony between nerve cells.
- ASSR is considered a measure of the balance between excitatory (glutamatergic) and inhibitory (GABAergic) neural systems.
- Results suggest that ASSR may be a useful marker of change with ketamine and may also be associated with sensory symptoms.





J. Foss-Feig, PhD

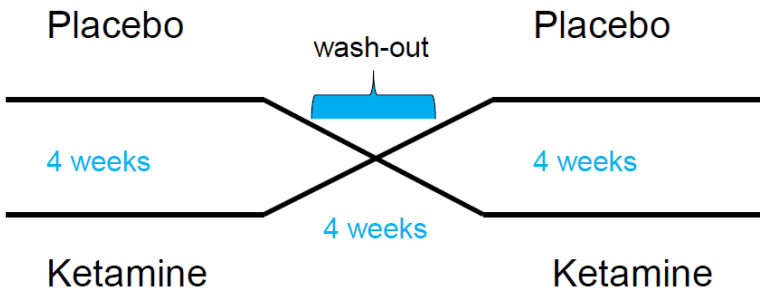


Summary

- ADNP syndrome offers a unique opportunity to study a specific genetic cause of ASD in which the neuropathology is better understood and can more readily be targeted for treatment
- Studies still need to carefully phenotype and select for target symptom/s of interest
- Need improved clinical outcome assessments specific to ADNP syndrome
- Need to develop/validate biomarkers
- Eventually, treatments in ADNP syndrome may inform treatment development in subsets of people with ASD more broadly

Future Directions

- Design a placebo-controlled treatment trial using low-dose ketamine
- Likely switch to intramuscular administration (vs. intravenous) for better ease of use
- Treatment will consist of 8 doses over at least 4 weeks likely using a crossover design
- Obtain investigational new drug application (IND) from FDA to conduct research studies
- Select additional sites to reduce travel burden on families



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