Current Clinical Research in PMS

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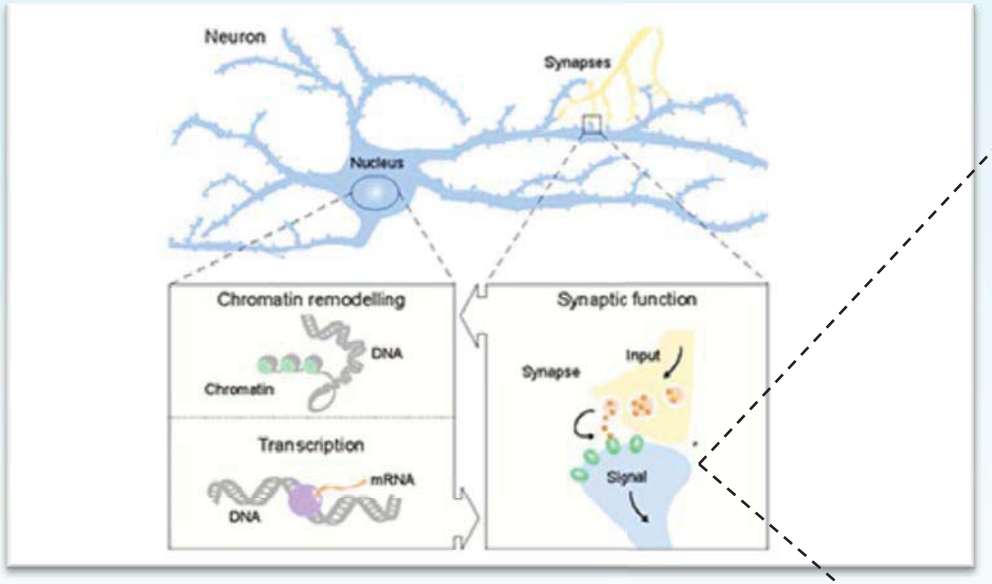
Advances in autism genetics: on the threshold of a new neurobiology

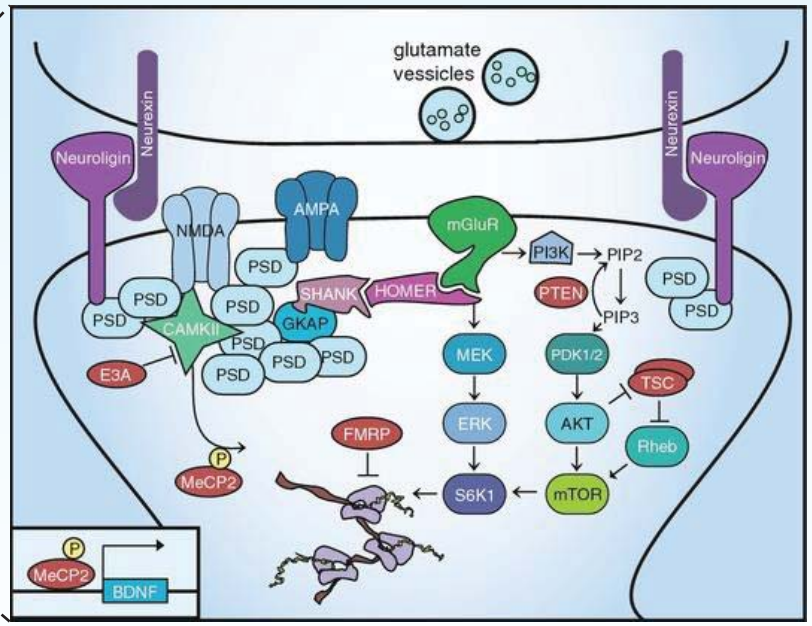
Brett S. Abrahams and Daniel H. Geschwind

Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome	Refs
15q duplication — Angelman syndrome	*UBE3A* (and others)	>40%	1–2%	101–103
16p11 deletion	Unknown	High	~1%	20, 35, 44
22q deletion	*SHANK3*	High	~1%	21, 22, 104
Cortical dysplasia-focal epilepsy syndrome	*CNTNAP2*	~70%	Rare	37
Fragile X syndrome	*FMR1*	25% of males; 6% of females	1–2%	105
Joubert syndrome	Several loci	25%	Rare	106
Potocki–Lupski syndrome	Chromosome position 17p11	~90%	Unknown	107
Smith–Lemli–Optiz syndrome	*DHCR7*	50%	Rare	108
Rett syndrome	*MECP2*	All individuals have Rett syndrome	~0.5%	109
Timothy syndrome	*CACNA1C*	60–80%	Unknown	24
Tuberous sclerosis	*TSC1* and *TSC2*	20%	~1%	110

Genomic architecture of ASD



De Rubeis et al., *Nature*, 2014



Dolen & Bear, 2009

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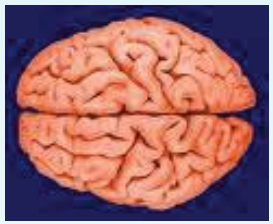
Novel Therapeutics



Disease

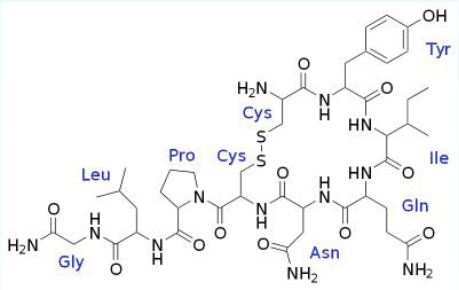
Gene Discovery

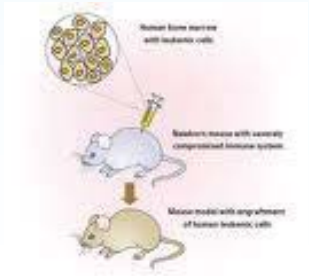
Model Systems

Pathophysiology

Drug Development

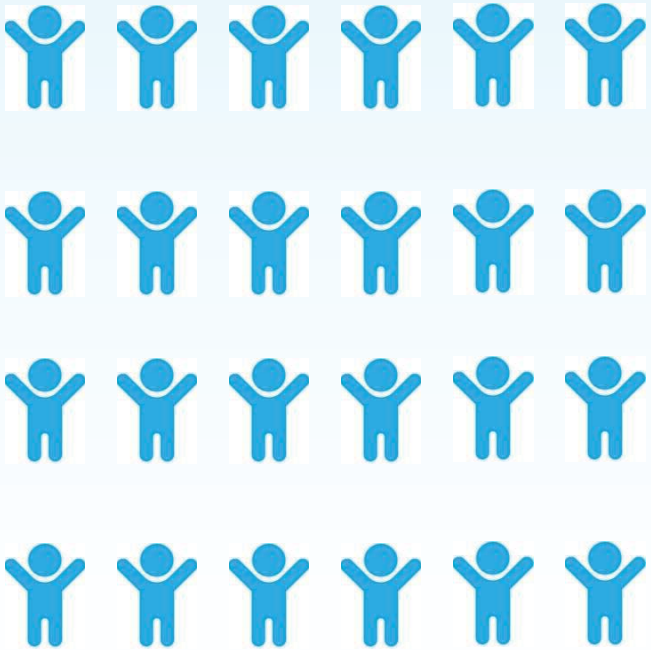
Novel Therapeutics





Implications for treatment

Before



After

Challenges for Clinical Trial Readiness

- Need validated measures specific to syndrome/phenotype
  - Comprehensively phenotype patients
  - Clarify natural history of illness to identify appropriate targets
  - Establish sensitivity to change over time
  - Validate across age groups and level of intellectual function
- Need new instruments
  - Adapt existing tools
  - Develop objective measures
- Need to focus on functional assessments
  - Motor skills
  - Language
  - Cognitive function

Clinical Outcome Assessments

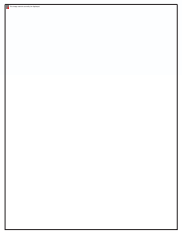
- Patient reported
- Caregiver reported
- Clinician reported
- Composite instruments
- *Objective tests*

Potential Biomarkers for Clinical Trials

- EEG: evoked and event related potentials
- Neuroimaging
- Eye tracking, pupillometry
- Sensory gating – prepulse inhibition
- Protein synthesis assays

Electrophysiological Markers

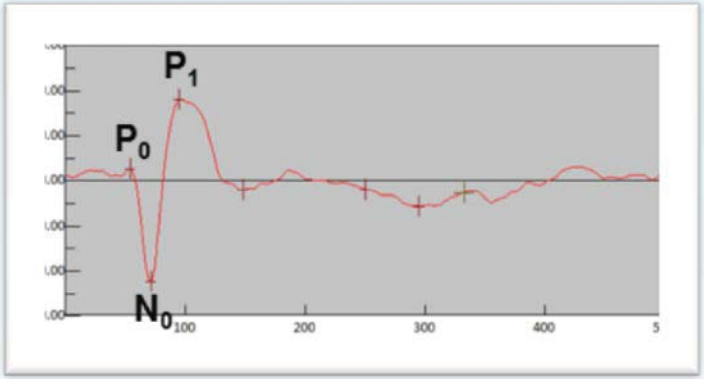
- **Identify subtypes** of neurodevelopmental disorders based on excitatory/inhibitory (E/I) profiles
- Inform **personalized treatment** approaches
- Monitor **treatment response** and determine optimal responders
- Identify associations between neurophysiological responses and **clinical outcomes**



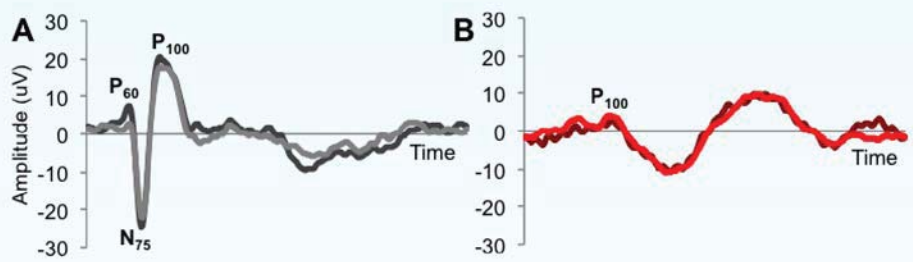
Paige Siper, PhD

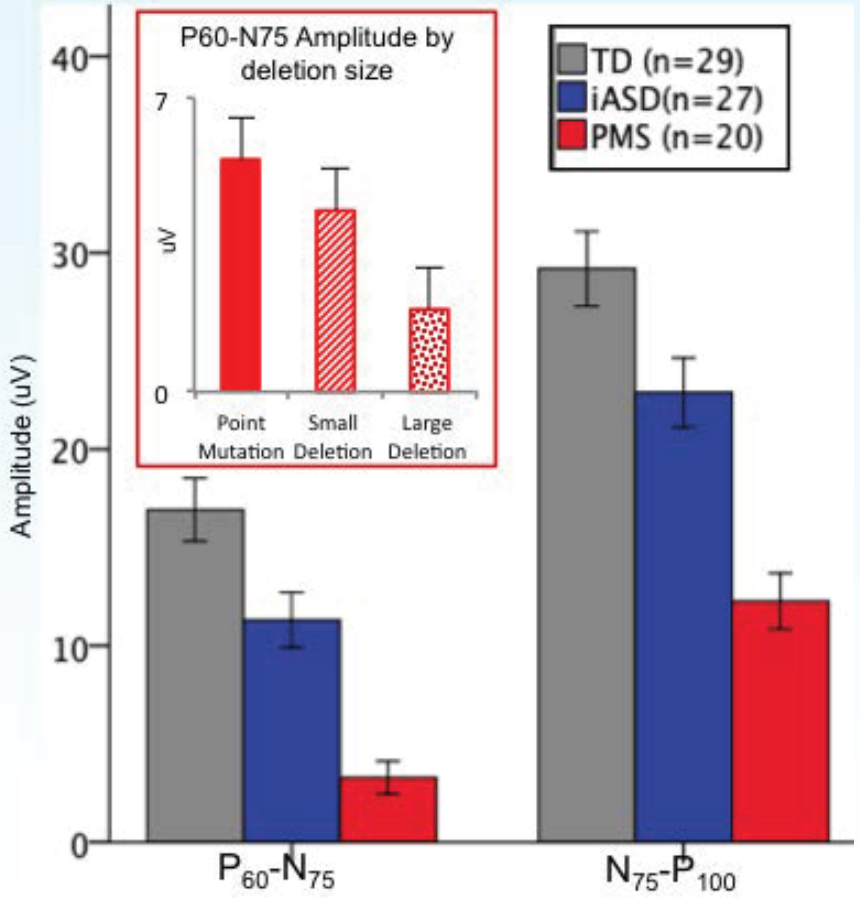
Visual Evoked Potentials

- VEPs are extracted from ongoing EEG through signal averaging
- Reflect the sum of excitatory and inhibitory postsynaptic potentials
- Three electrodes applied to the scalp with an active electrode over the visual cortex
- P_0 represents activation of the primary visual cortex from the LGN
- N_0 represents excitatory postsynaptic activity spreading to the primary visual cortex
- P_1 reflects inhibitory postsynaptic activity



Transient VEPs in PMS





Siper, PM

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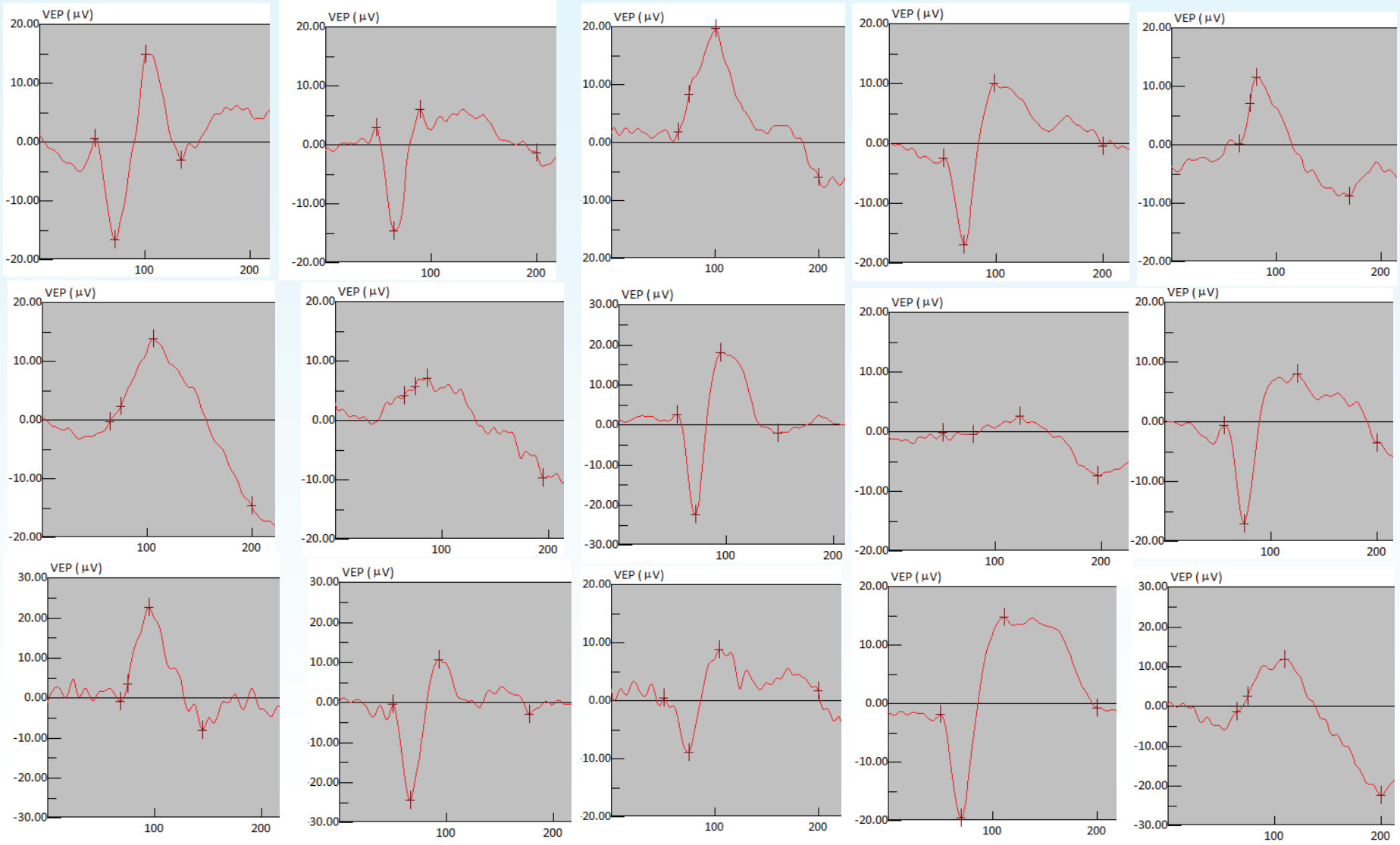
VEP Quiz



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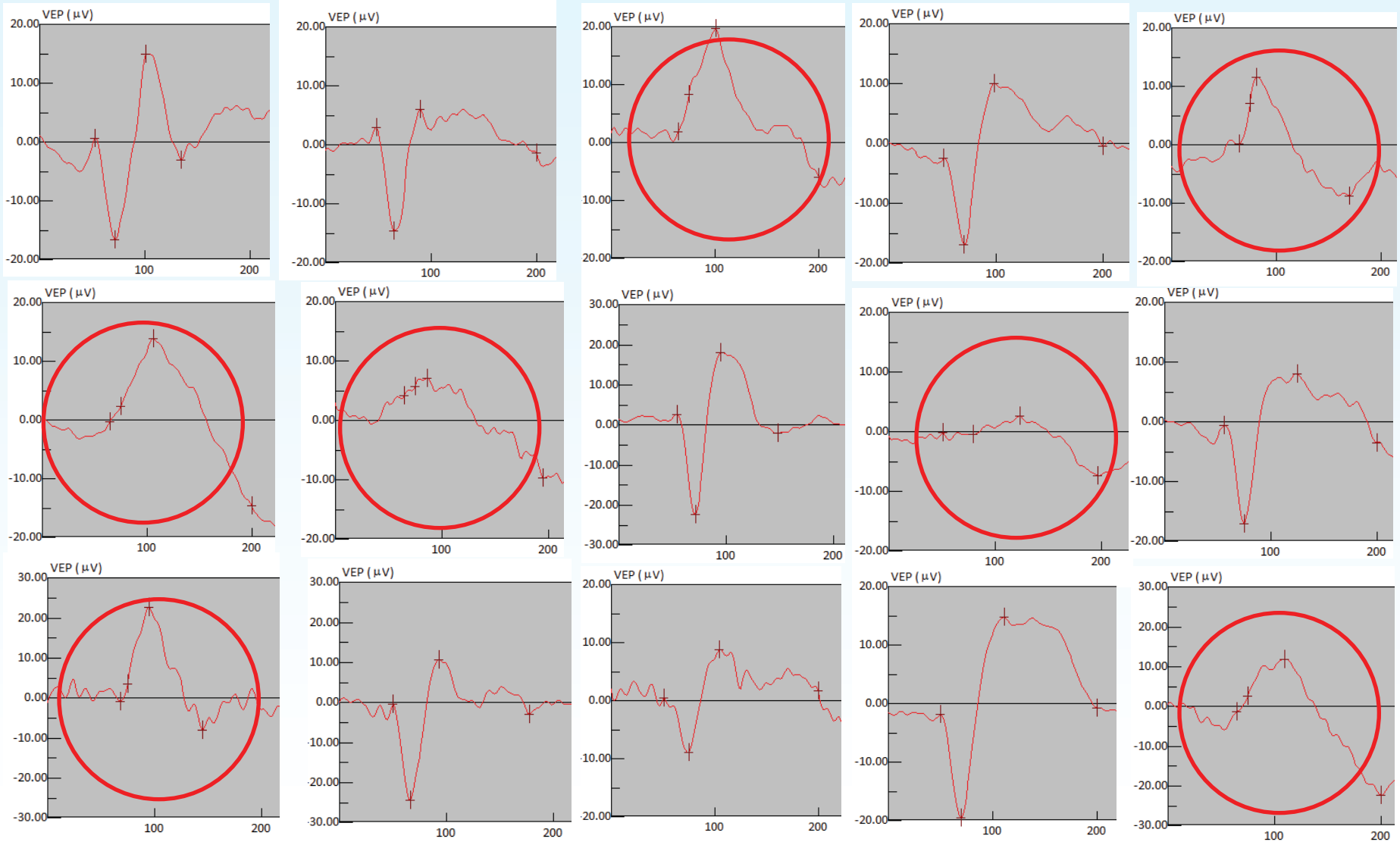
VEP Quiz



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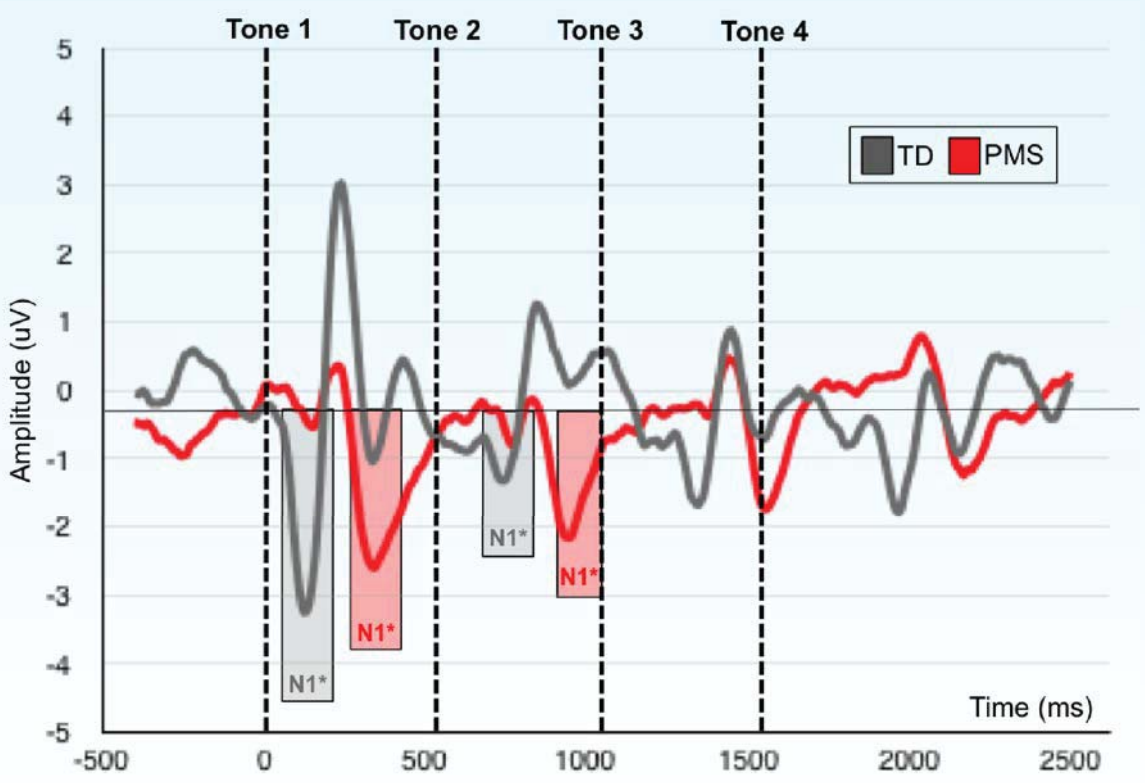
Auditory Event Related Potentials



Jennifer Foss-Feig, PhD

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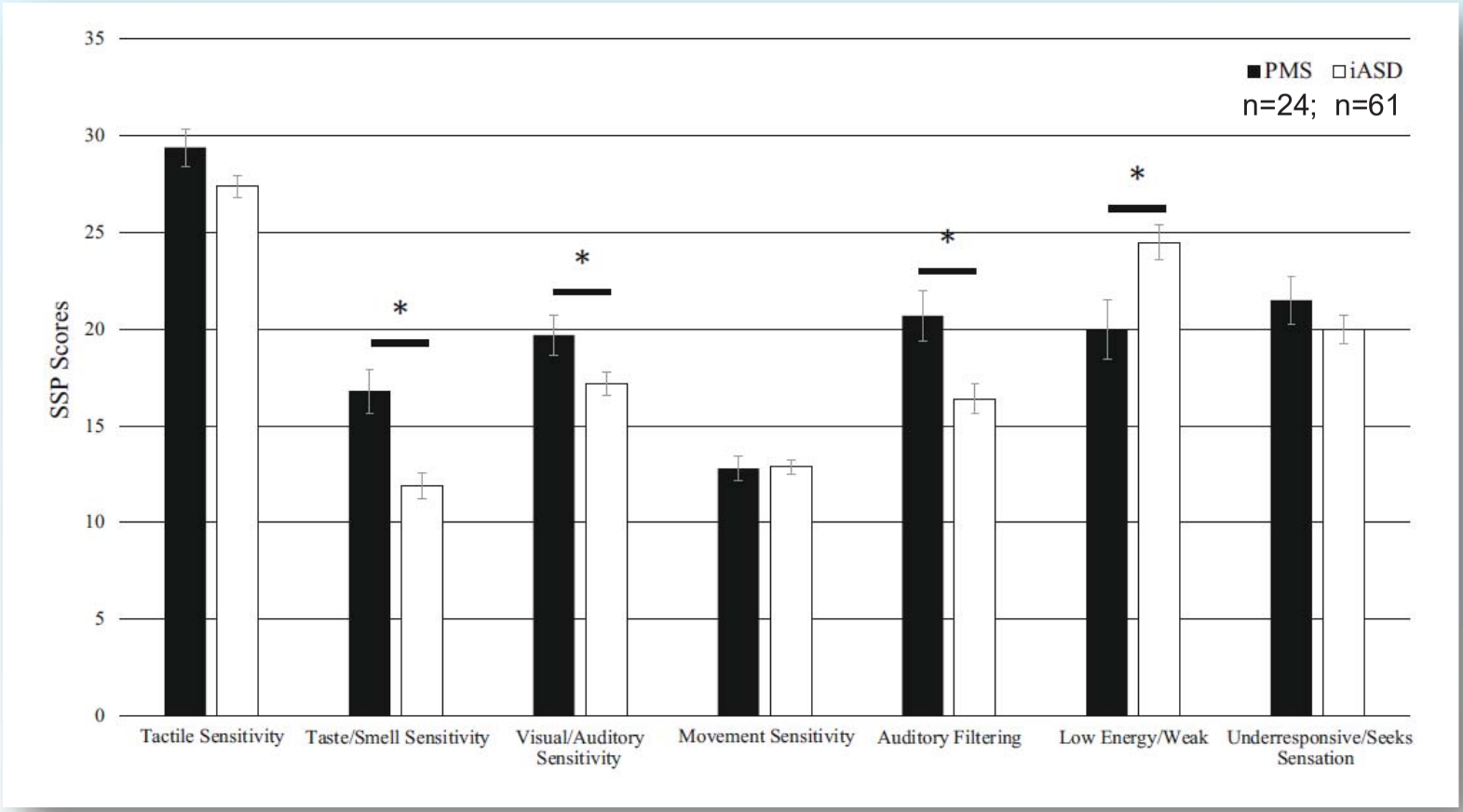
Sensory Reactivity in PMS (Short Sensory Profile)



Mieses et al., 2016

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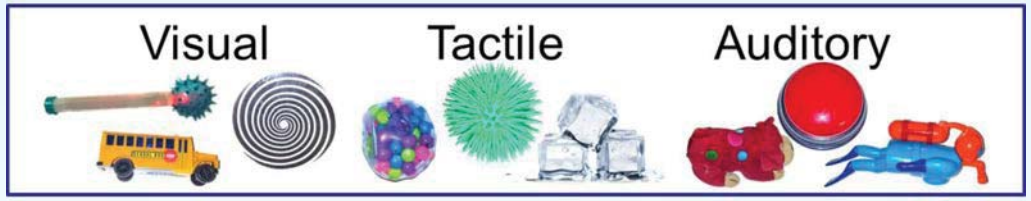
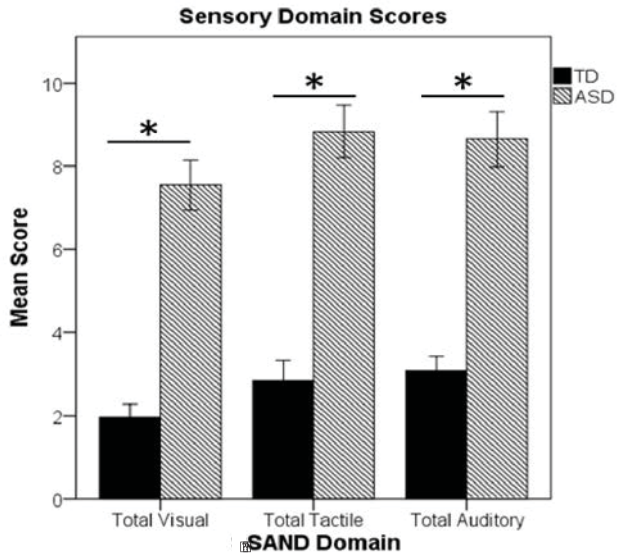
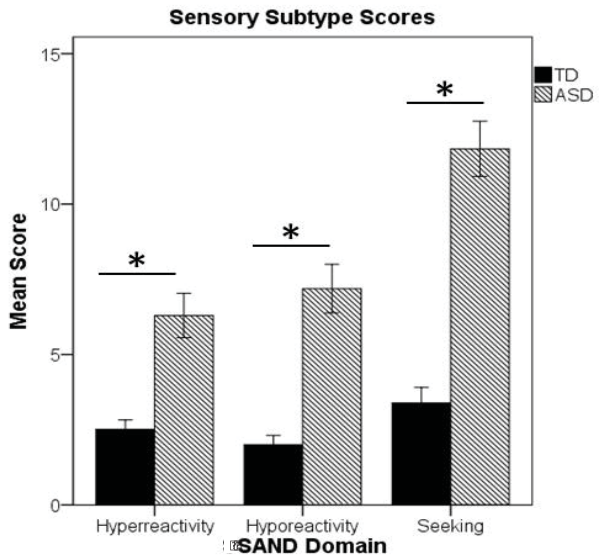
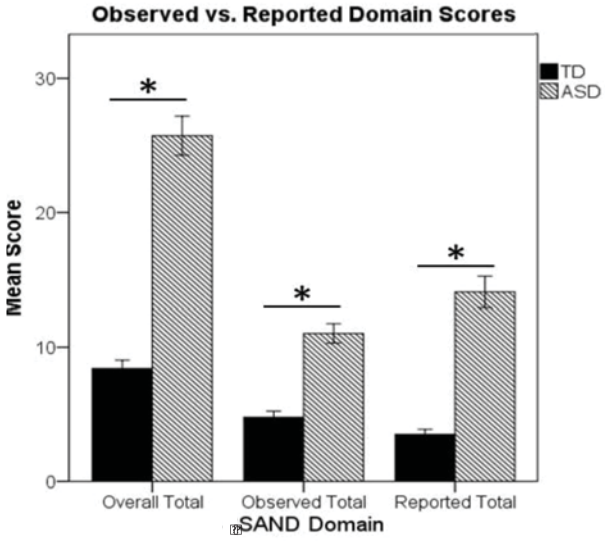
Sensory Assessment for Neurodevelopmental Disorders (SAND)

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









Siper, PM et al., 2017

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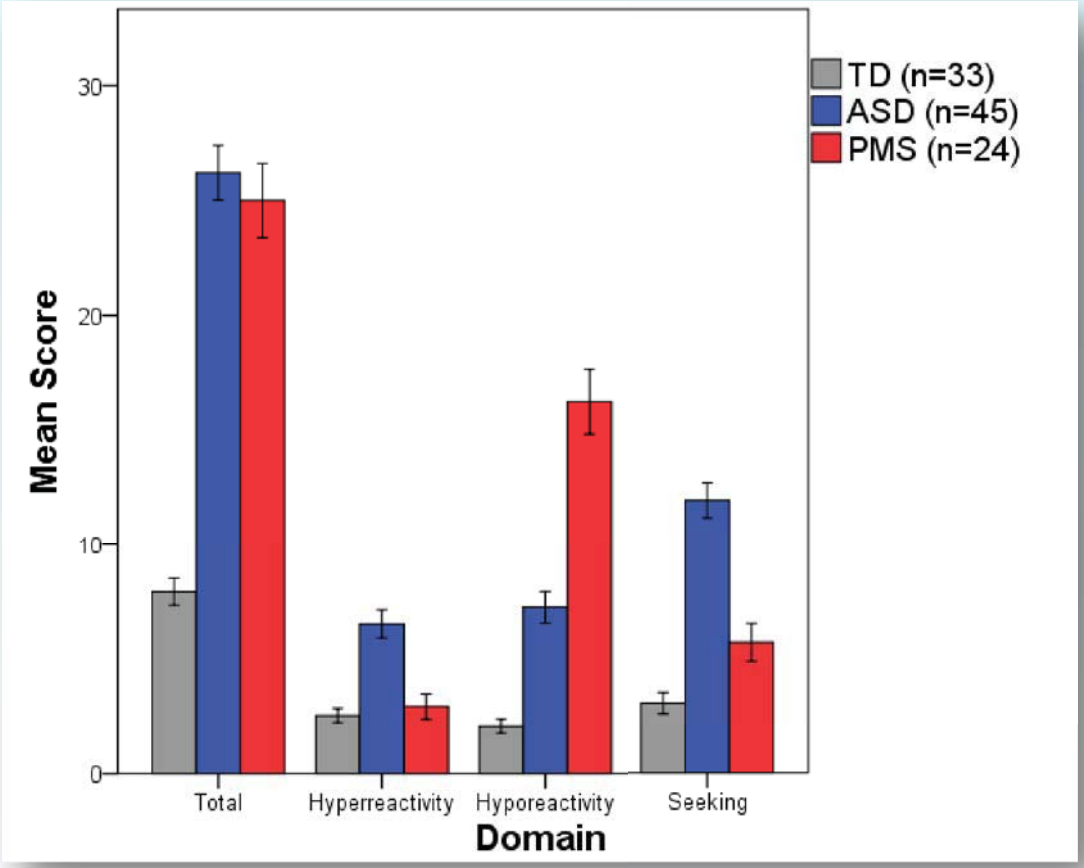
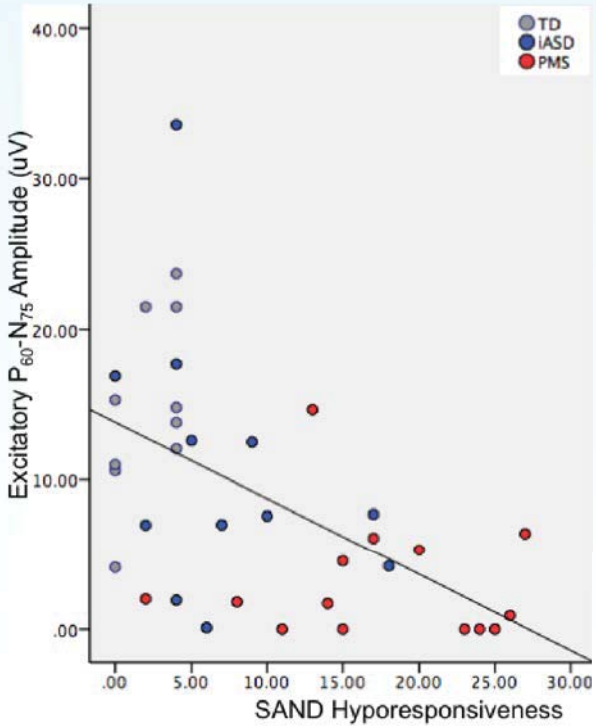
Sensory Reactivity in PMS – SAND





Siper, PM

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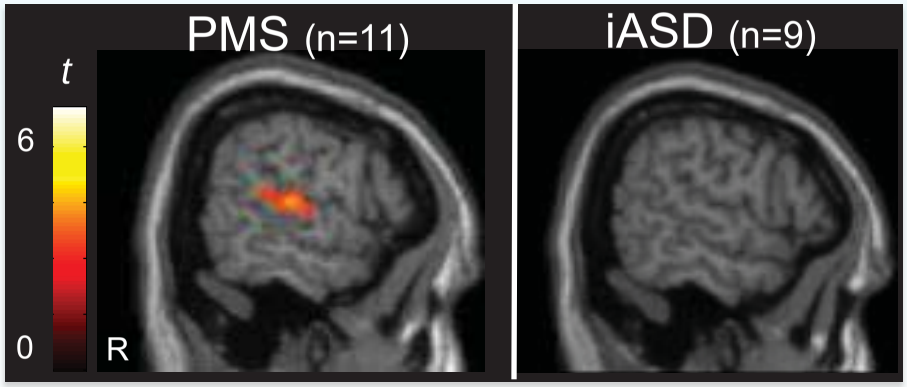
Neural selectivity for communicative auditory signals in Phelan-McDermid syndrome

A. Ting Wang[1,2,3,4*], Teresa Lim[5], Jesslyn Jamison[1,2], Lauren Bush[6], Latha V. Soorya[7], Teresa Tavassoli[1,2], Paige M. Siper[1,2], Joseph D. Buxbaum[1,2,3,4,8,9] and Alexander Kolevzon[1,2,4,9,10]

Journal of Neurodevelopmental Disorders (2016) 8:5



Communicative vocal sounds elicited greater activation in right superior temporal gyrus (STG) compared to non-communicative vocal sounds in the PMS but not idiopathic ASD group.

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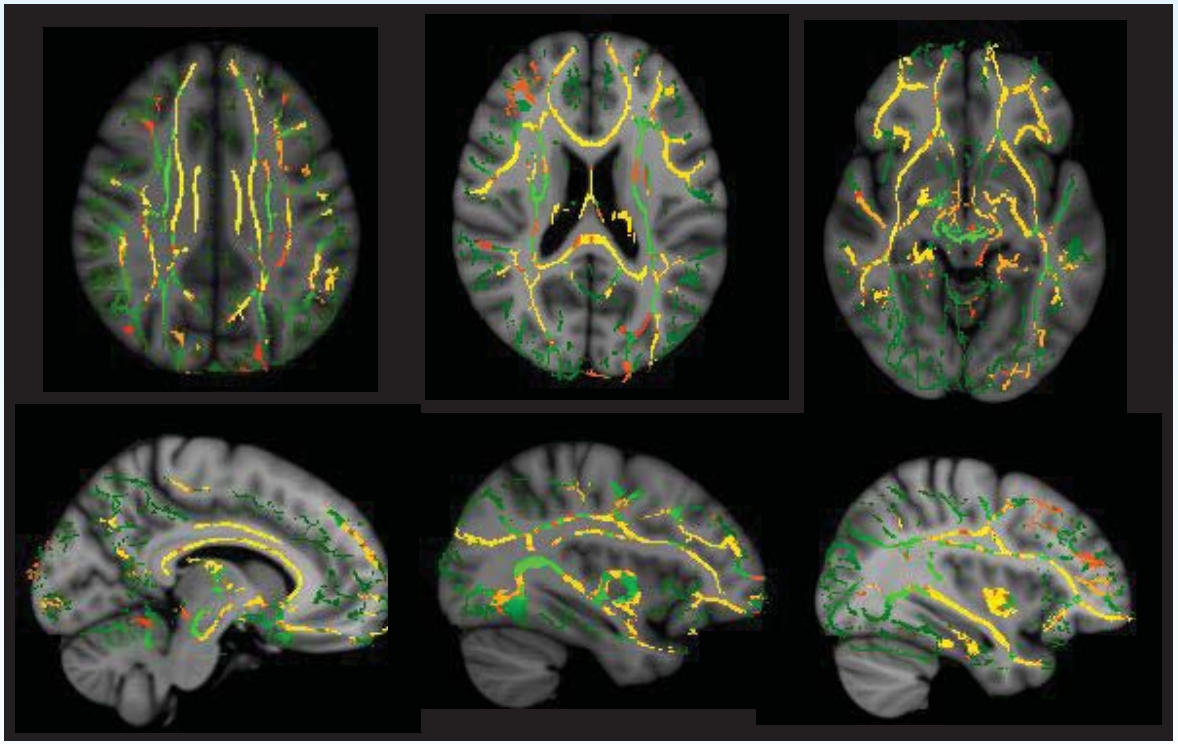
Diffusion Tensor Imaging



Tracts with reduced FA in the PMS group relative to idiopathic ASD in red-yellow (yellow = higher statistical significance; green = not significantly different between groups). No regions of increased FA in PMS group.

Wang, AT

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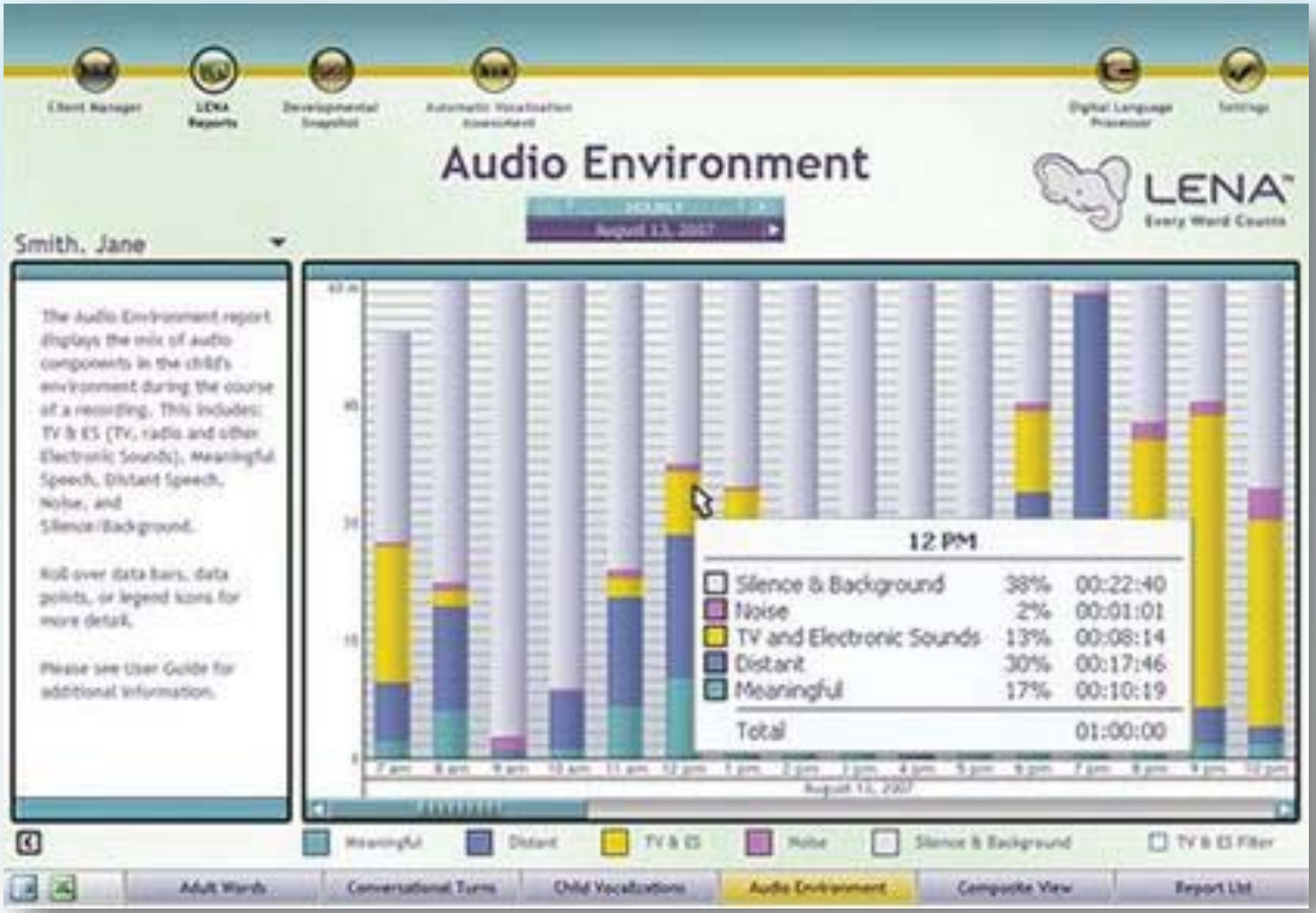
Language ENvironment Analysis (LENA) in Phelan-McDermid Syndrome: Validity and Suggestions for Use in Minimally Verbal Children with Autism Spectrum Disorder

Jacquelin Rankine[1] · Erin Li[1] · Stacey Lurie[1,8] · Hillary Rieger[1] · Emily Fourie[1] · Paige M. Siper[1,2] · A. Ting Wang[1,2,4,6] · Joseph D. Buxbaum[1,2,4,5,6,7] · Alexander Kolevzon[1,2,3,4,5]

J Autism Dev Disord (2017) 47:1605–1617

- 18 subjects with PMS underwent comprehensive evaluations.
- Over 542 hours of audio recording from the home environment was collected using LENA.
- 3 hours of audio was randomly selected for each participant and analyzed by human transcribers

LENA Output



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Findings

How accurately does LENA distinguish the Key Child from all others?

Human Transcriber	LENA System: Key Child	LENA System: All Other Sound Sources
Key Child	12,229 (40%)	18,127 (60%)
All Other Sound Sources	2,662 (3%)	86,942 (97%)

k = 0.449 (p <.001), 95% CI (0.443, 0.455).

Rankine et al., 2017

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Findings

How accurately does LENA distinguish Key Child speech-related vocalizations from non-speech sounds?

Human Transcriber	LENA System: Child Vocalizations	LENA System: Child Non-Speech Sounds
Child Vocalizations	6,800 (84%)	1,313 (16%)
Child Non-Speech Sounds	1,609 (39%)	2,507 (61%)

k = 0.455 (p <.001), 95% CI (0.437, 0.473).

Rankine et al., 2017

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Findings

What factors impact LENA performance?

	Key Child Inter-rater Agreement	Child Vocalization Inter-rater Agreement
Age		
Pearson Correlation	-.618 *	-.577 *
Sig. (2-tailed)	.006	.012
ADOS-2 Total Score		
Pearson Correlation	.125	-.134
Sig. (2-tailed)	.620	.596
ABC Inappropriate Speech Subscale Score		
Pearson Correlation	-.247	-.567 *
Sig. (2-tailed)	.323	.014
RBS Total Score		
Pearson Correlation	-.140	-.242
Sig. (2-tailed)	.581	.333

Rankine et al., 2017

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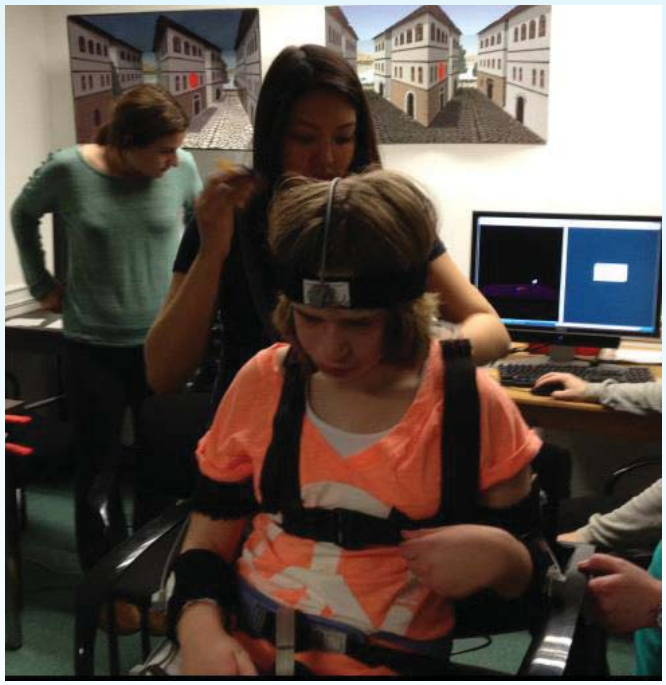
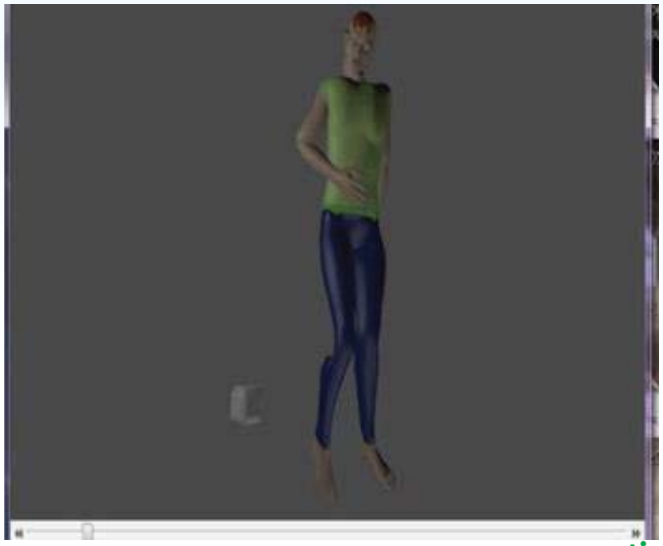
Gait Analysis

Performed in real time and captured at 240 Hz using 16 electro-magnetic sensors

All output kinematic features of movement trajectories are analyzed from the head and upper/lower extremities.

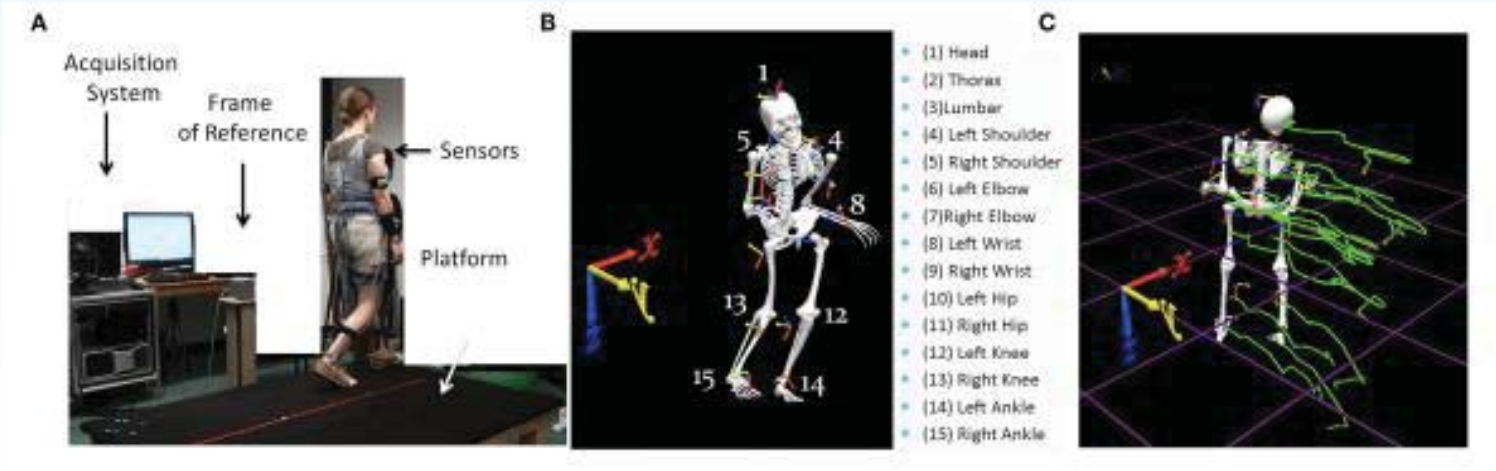
Gait is measured during two exercises: 1) walking spontaneously along a six foot marked path; 2) walking along the identical path circumventing a waist-high obstacle.





Characterization of the Statistical Signatures of Micro-Movements Underlying Natural Gait Patterns in Children with Phelan McDermid Syndrome: Towards Precision-Phenotyping of Behavior in ASD

Elizabeth B. Torres[1], Jillian Nguyen[2], Sejal Mistry[3], Caroline Whyatt[4], Vilelmini Kalampratsidou[5] and Alexander Kolevzon[6]*



n = 16 PMS; 11 controls

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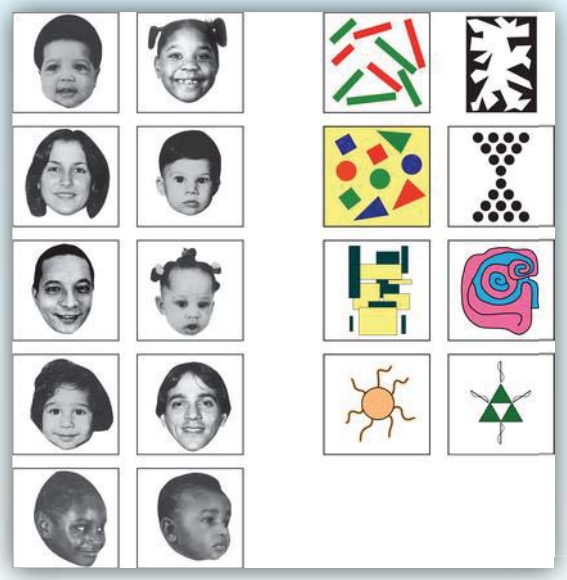
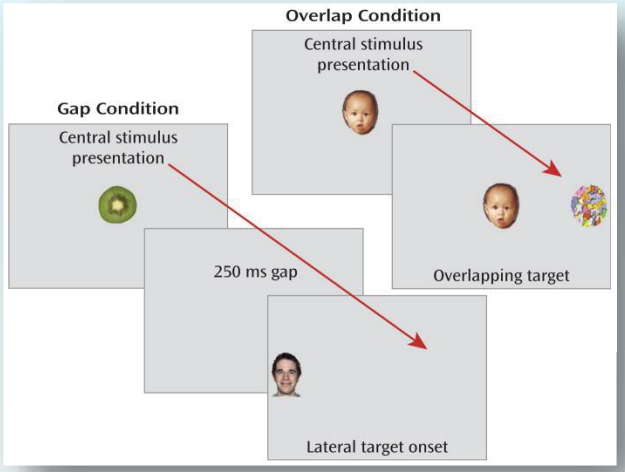
Eye Tracking in PMS



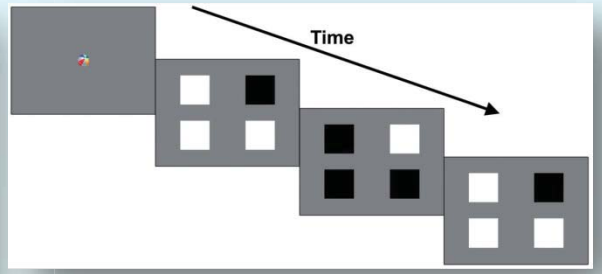
Visual Paired Comparison

Rose et al, 2013



Gap-Overlap Task

Elison et al, 2013



Flicker Detection

Farzin et al, 2011

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Pilar Trelles, MD

Dose-dependent effect of risperidone treatment in a case of 22q13.3 deletion syndrome

Augusto Pasini *, Elisa D'Agati, Livia Casarelli, Paolo Curatolo

Brain & Development (2009)

Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports

Sylvie Serret*, Susanne Thümmler, Emmanuelle Dor, Stephanie Vesperini, Andreia Santos and Florence Askenazy

BMC Psychiatry (2015) 15:107

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon[1,2,3,4,5,10*], Lauren Bush[1,4,10], A Ting Wang[1,2,4,6,10], Danielle Halpern[1,4,10], Yitzchak Frank[1,4,5,7,10], David Grodberg[1,4,10], Robert Rapaport[5,9,10], Teresa Tavassoli[1,4,10], William Chaplin[11], Latha Soorya[12] and Joseph D Buxbaum[1,2,3,4,6,8,10]

Molecular Autism 2014, 5:54

Is there an effect of intranasal insulin on development and behaviour in Phelan-McDermid syndrome? A randomized, double-blind, placebo-controlled trial

Renée J Zwanenburg[1], Gianni Bocca[2], Selma AJ Ruiter[3], Jan H Dillingh[4], Boudien CT Flapper[2], Edwin R van den Heuvel[5] and Conny MA van Ravenswaaij-Arts*[,1]

European Journal of Human Genetics (2016), 1–6

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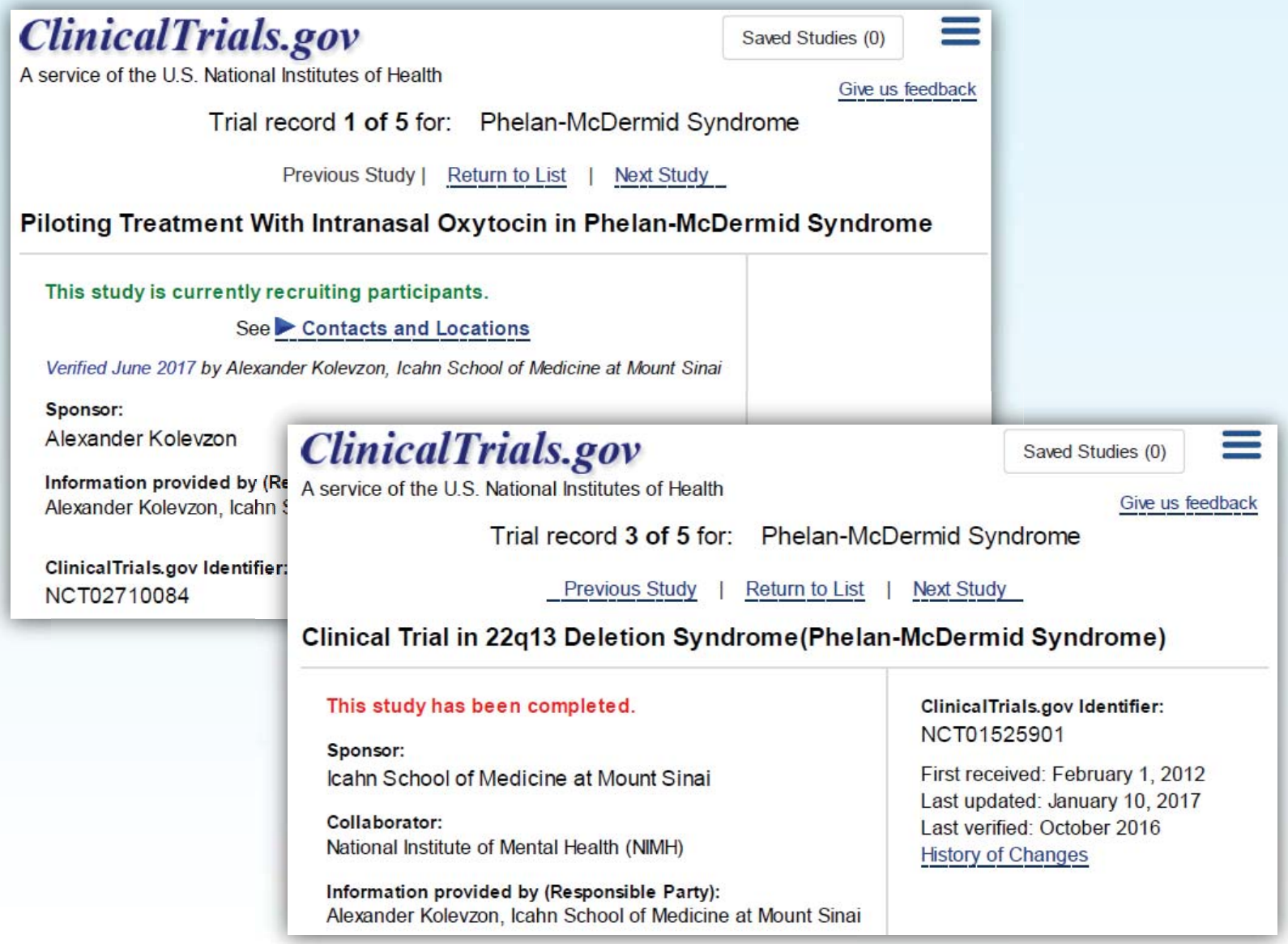

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Saved Studies (0)

Give us feedback

Trial record **1 of 5** for: Phelan-McDermid Syndrome

Previous Study | Return to List | Next Study

Piloting Treatment With Intranasal Oxytocin in Phelan-McDermid Syndrome

This study is currently recruiting participants.

See Contacts and Locations

Verified June 2017 by Alexander Kolevzon, Icahn School of Medicine at Mount Sinai

Sponsor:
Alexander Kolevzon

Information provided by (Re
Alexander Kolevzon, Icahn S

ClinicalTrials.gov Identifier:
NCT02710084

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Saved Studies (0)

Give us feedback

Trial record **3 of 5** for: Phelan-McDermid Syndrome

Previous Study | Return to List | Next Study

Clinical Trial in 22q13 Deletion Syndrome(Phelan-McDermid Syndrome)

This study has been completed.

Sponsor:
Icahn School of Medicine at Mount Sinai

Collaborator:
National Institute of Mental Health (NIMH)

Information provided by (Responsible Party):
Alexander Kolevzon, Icahn School of Medicine at Mount Sinai

ClinicalTrials.gov Identifier:
NCT01525901

First received: February 1, 2012
Last updated: January 10, 2017
Last verified: October 2016
History of Changes

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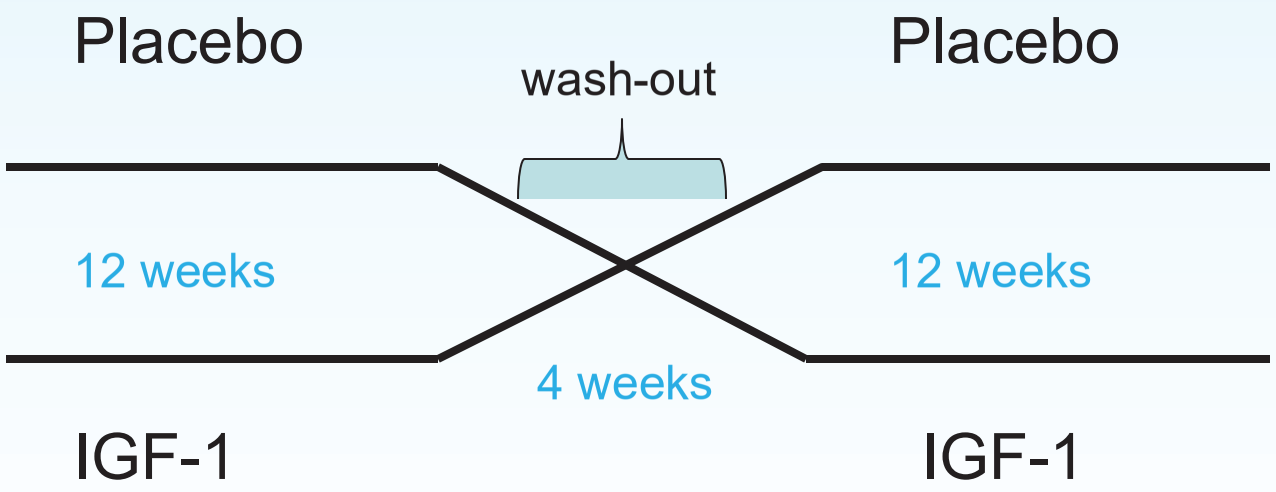
A Double-Blind Placebo-Controlled Crossover Trial of IGF-1



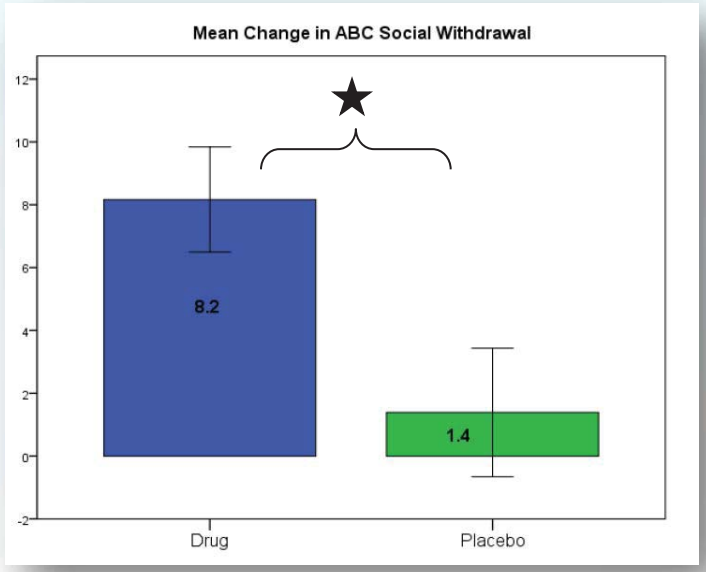
Kolevzon *et al. Molecular Autism* 2014, **5**:54
http://www.molecularautism.com/content/5/1/54

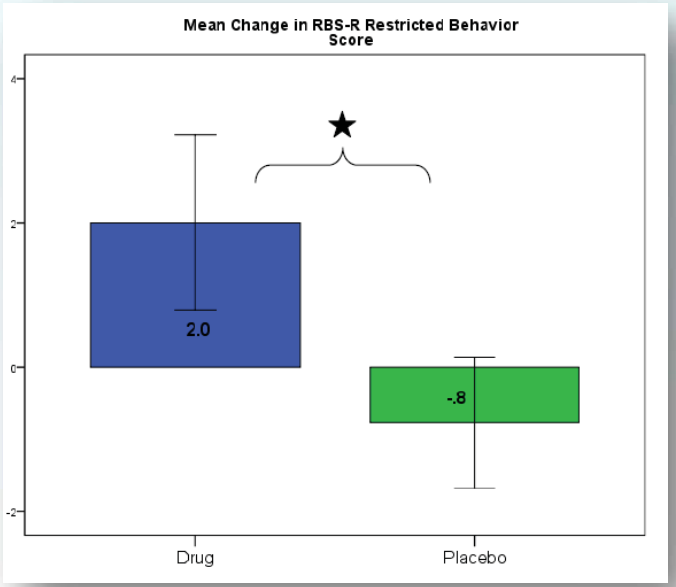
Molecular Autism

RESEARCH Open Access

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

Alexander Kolevzon[1,2,3,4,5,10*], Lauren Bush[1,4,10], A Ting Wang[1,2,4,6,10], Danielle Halpern[1,4,10], Yitzchak Frank[1,4,5,7,10], David Grodberg[1,4,10], Robert Rapaport[5,9,10], Teresa Tavassoli[1,4,10], William Chaplin[11], Latha Soorya[12] and Joseph D Buxbaum[1,2,3,4,6,8,10]





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AARTS
CENTER AT RUSH

RUSH UNIVERSITY MEDICAL CENTER

Can we use telehealth platforms to increase access to high quality behavioral/communication interventions for children with rare neurodevelopmental diseases?

- Surmount barriers to care
- Increase parent knowledge and efficacy
- <u>Use as a platform for studying integrated treatments</u>

Allison Wainer, PhD

1. Training in rare disease research and assessment/treatment
2. Examine current "landscape" of behavioral/communication interventions for individuals with PMS
   - Literature review; Archival data analysis; Descriptive data collection to inform telehealth intervention development
3. Develop & pilot an integrated intervention
4. Conduct a larger trial of the integrated intervention

Stages of PMSF Fellowship

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Stage #2: Community Based Participatory Research (in progress)

Complete a series of questionnaires related to perceptions about early intervention and parent-mediated intervention

→

Watch short clips about existing telehealth interventions and progress monitoring tools

↓

Data will then be used to select and adapt the most acceptable & appropriate telehealth intervention

→

The adapted intervention will serve as the behavioral approach for the multi-modal intervention in Stages 3 & 4

Allison Wainer, PhD

Acknowledgments*

Seaver Center Team
- Joseph Buxbaum
- Paige Siper
- Danielle Halpern
- Ting Wang
- Michelle Gorenstein
- Jennifer Foss-Feig
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*Dr. Buxbaum and Mount Sinai hold a shared patent for the use of IGF-1 in PMS

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