


M.I.N.D. INSTITUTE
UCDAVIS

New Treatments in Fragile X Syndrome

German Fragile X Association, Germany 10-1-16

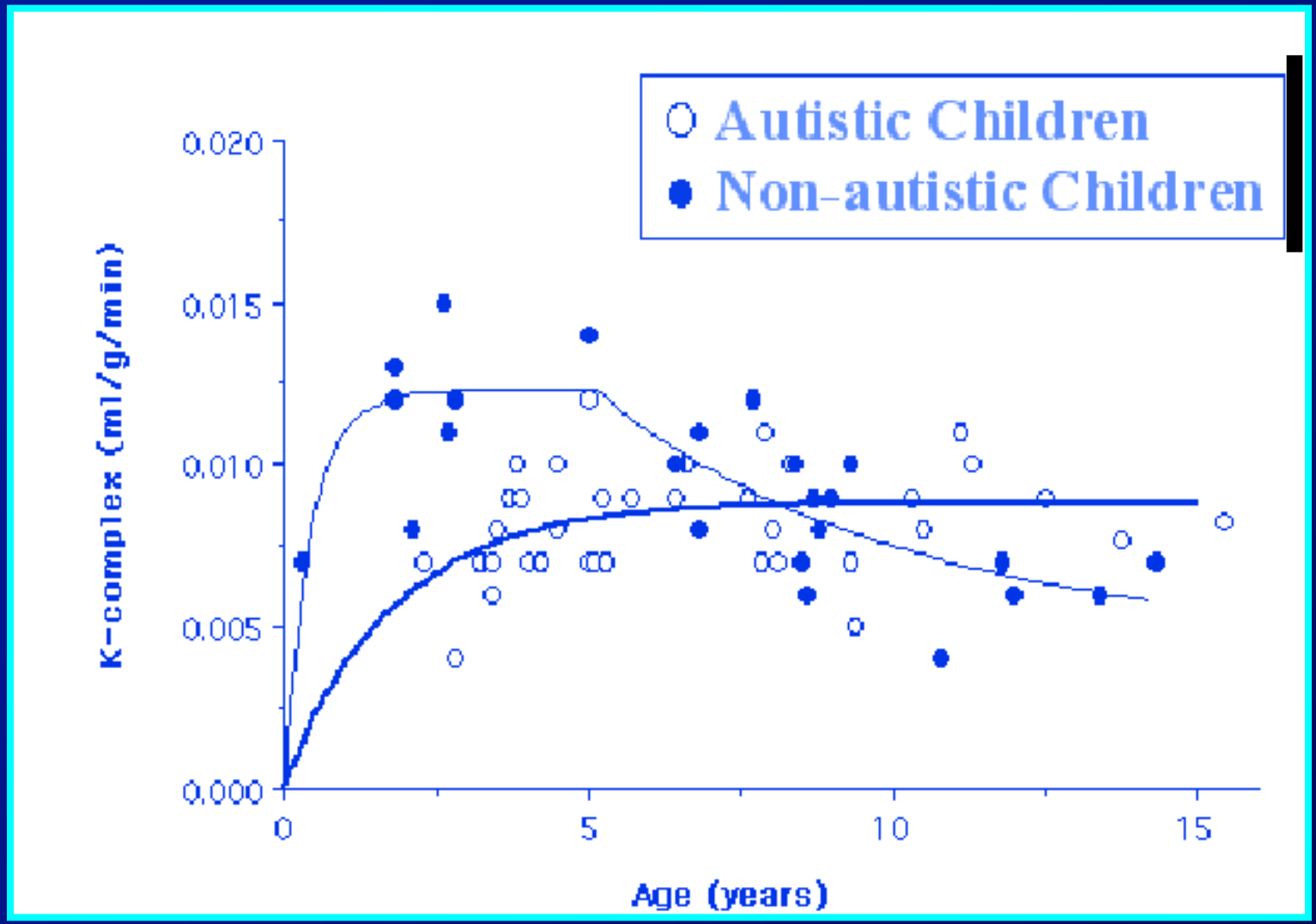
Randi Hagerman MD
Distinguished Professor of Pediatrics
Endowed Chair in Fragile X Research
MIND Institute UC Davis Medical Center

Conflicts/Funding from NICHD, Roche/ Genentech,
NFXF, Zynerba, Novartis, Neuren, Ovid, HRSA, DoD

Early in childhood may be the best time to demonstrate efficacy

- ASD studies have demonstrated this with the Early Start Denver Model (ESDM Dawson et al 2010, 2012)
- Neurochemical abnormalities can be modified before the brain infrastructure is permanently changed so ongoing development can be normalized

SEROTONIN SYNTHESIS CAPACITY:
Autistic vs. Non-autistic Children

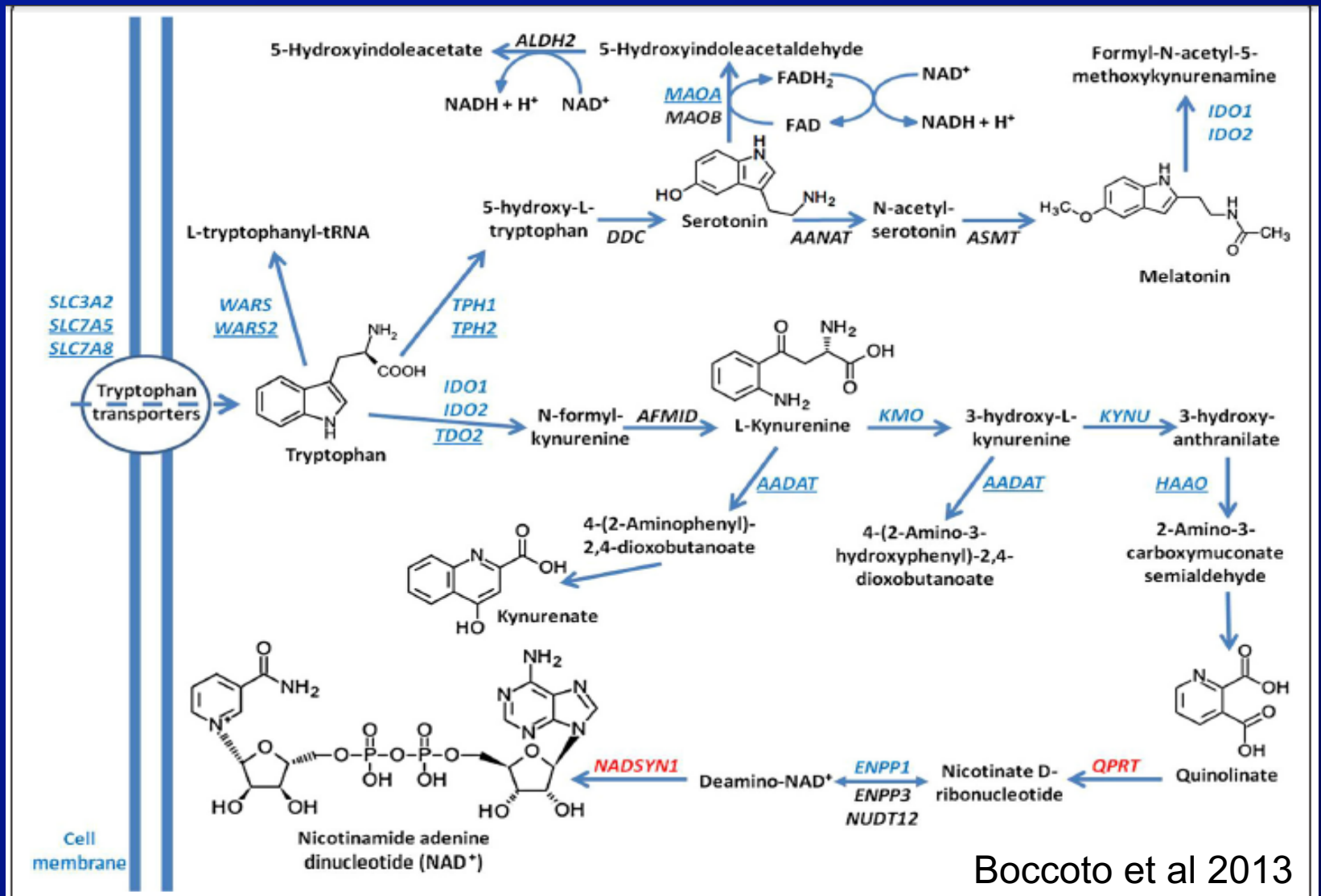


Chugani et al., 1999

Syndromic and non syndromic forms of ASD have reduced tryptophan metabolism

- Boccoto et al 2013 Mol Aut: Studied 137 lymphoblastoid cell lines of patients with neurodevelopmental disorders with (80) and without ASD and 78 controls (2.5 to 35yo)
- Metabolic profiling demonstrated deficits in tryptophan metabolism in ASD with reduced NADH, not seen in ID or schizophrenia
- Found abnormal gene expression of enzymes in tryptophan metabolism pathway

Tryptophan metabolic pathway



Boccoto et al 2013

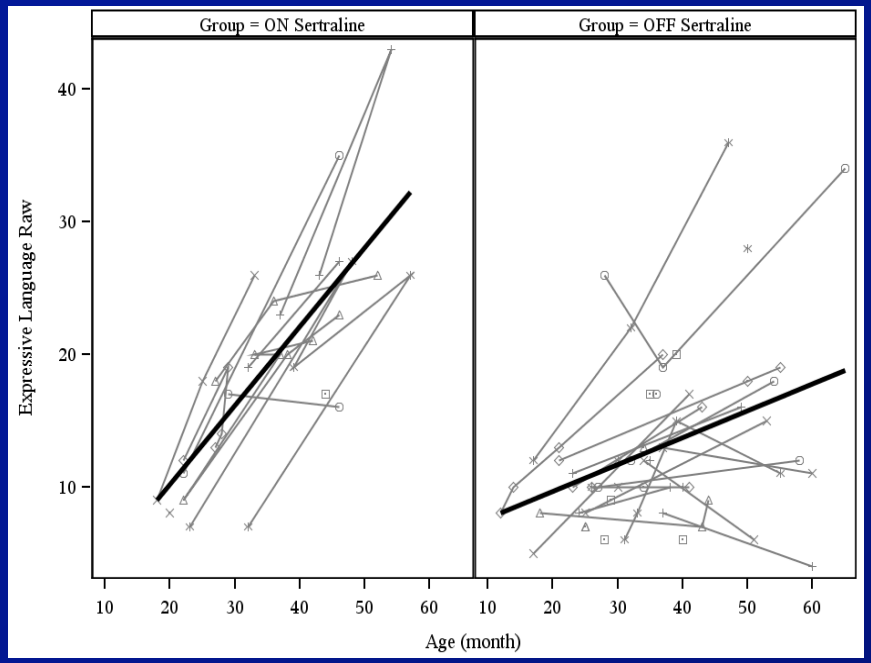
Figure 4 Tryptophan pathways. The figure illustrates the main intracellular pathways involving tryptophan. Genes with reduced expression in our microarray dataset are in blue, genes with increased expression are in red. Genes with statistically significant reduction of expression are underlined. Reactions generating NADH are indicated in the top section of the figure. FAD, flavin adenine dinucleotide.

Sertraline is an optimal SSRI for FXS and ASD

- SSRIs stimulate neurogenesis in the mouse and in humans (Malberg et al 2004; Warner-Schmidt et al 2006)
- SSRIs stimulate BDNF levels (Bianchi et al 2010;Taler et al 2013)
- Sertraline in FXS has a calming effect to the anxiety and may directly stimulate speech or improve language as a secondary effect from less anxiety
- Sertraline is the only SSRI to stimulate dopamine levels in the striatum and nucleus accumbens (Kitaichi et al 2010)

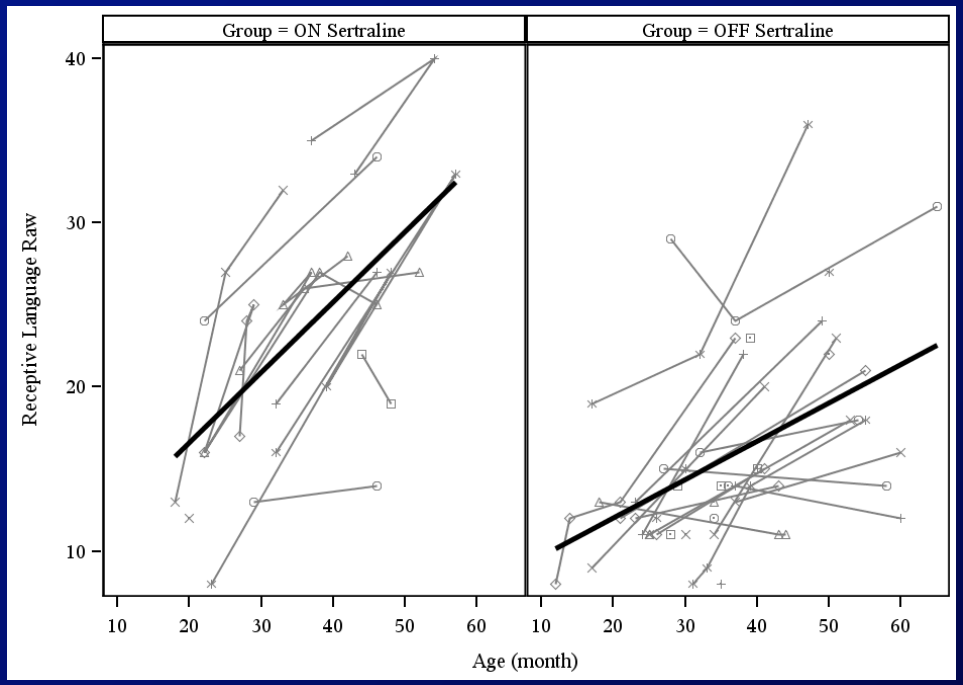
Sertraline Treatment in Early Childhood in FXS

A retrospective study of 45 children followed 12 to 50 months and 11 treated with sertraline: significant differences in expressive and receptive language in TX vs non treated (p=0.0001 and p=0.0071 respectively)



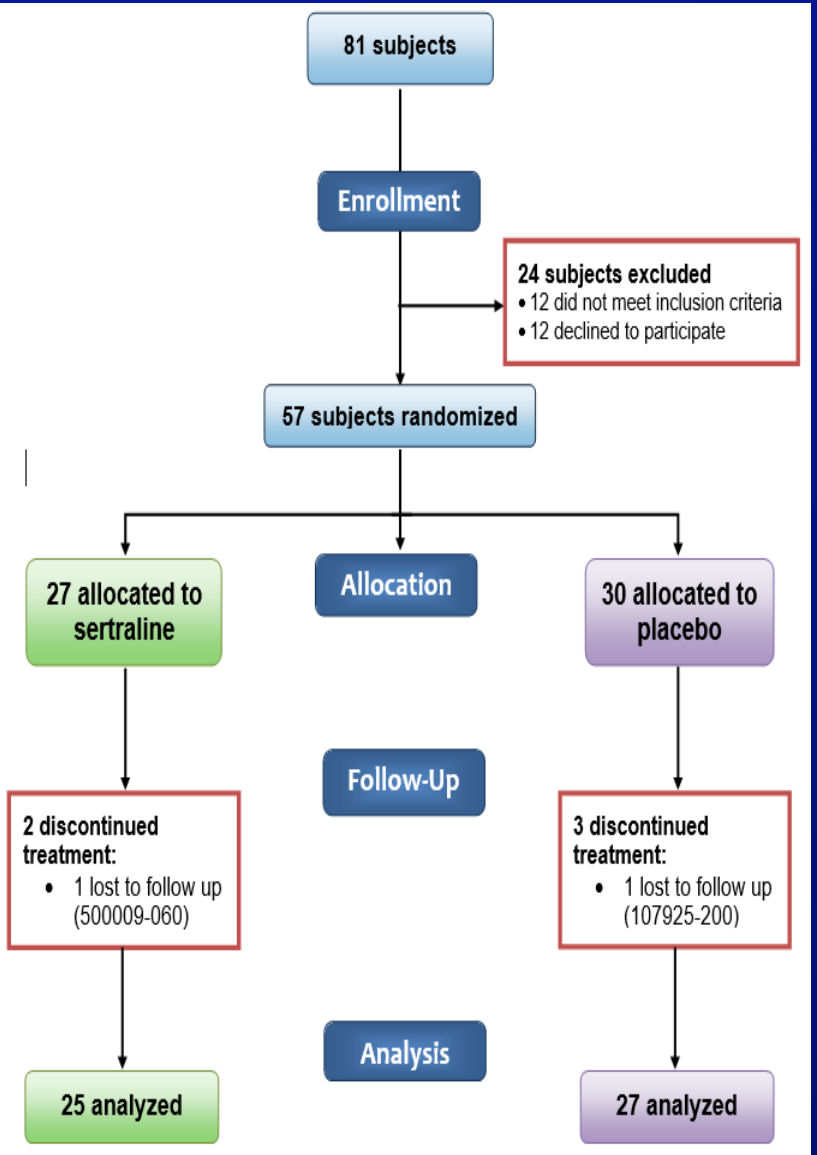
Expressive language

Receptive language



Winarni et al 2012 Autism Treatment and Re

Randomized, double blind, controlled trial of sertraline in 2 to 6yo with FXS lasting 6 months



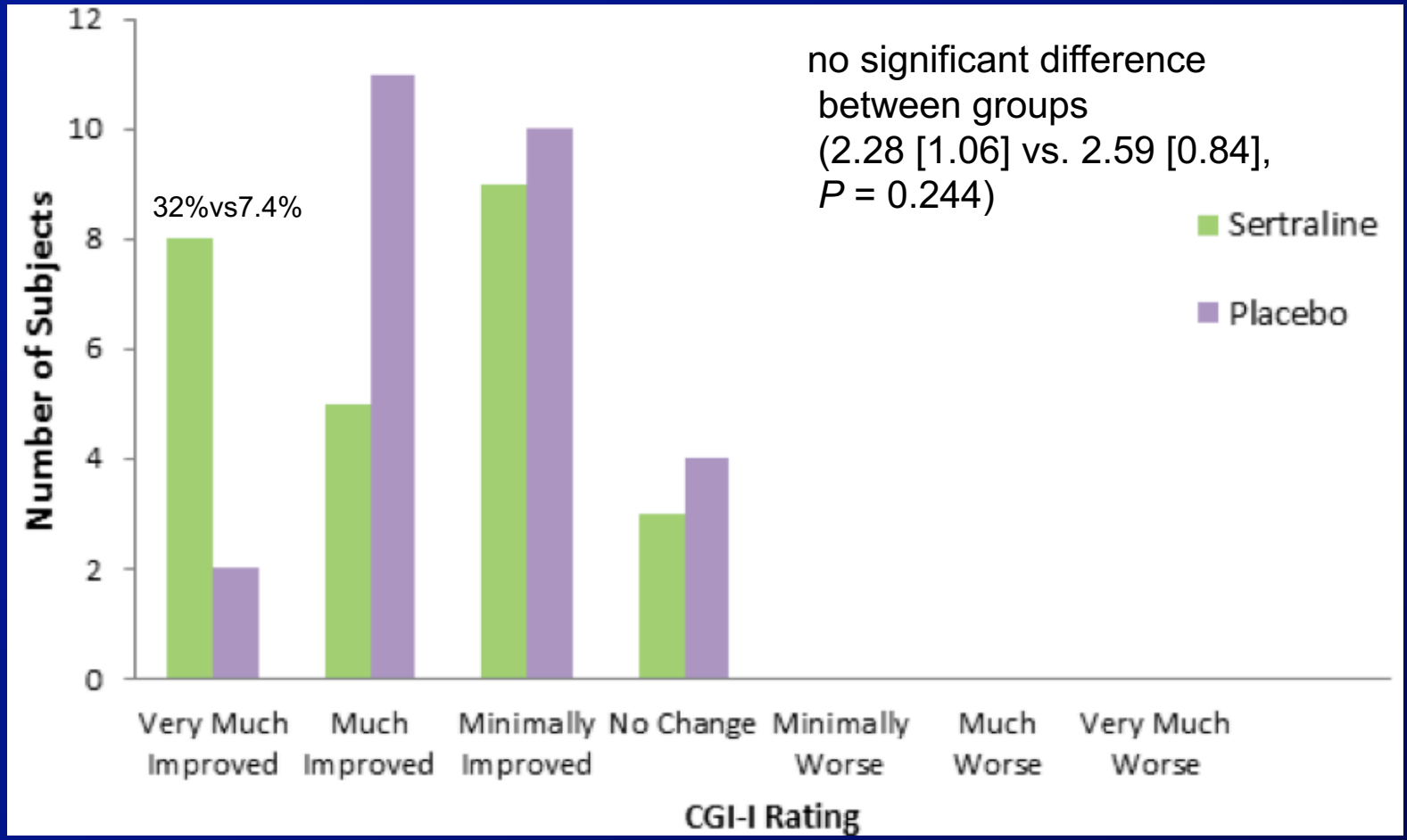
Baseline and 6 month Follow-up:
1* CGI-I, MSEL Expressive Language

2* MSEL: Receptive, fine motor, visual reception, Composite T score, Sensory Processing Measure-(SPM) Preschool version, Visual Analogue Scale

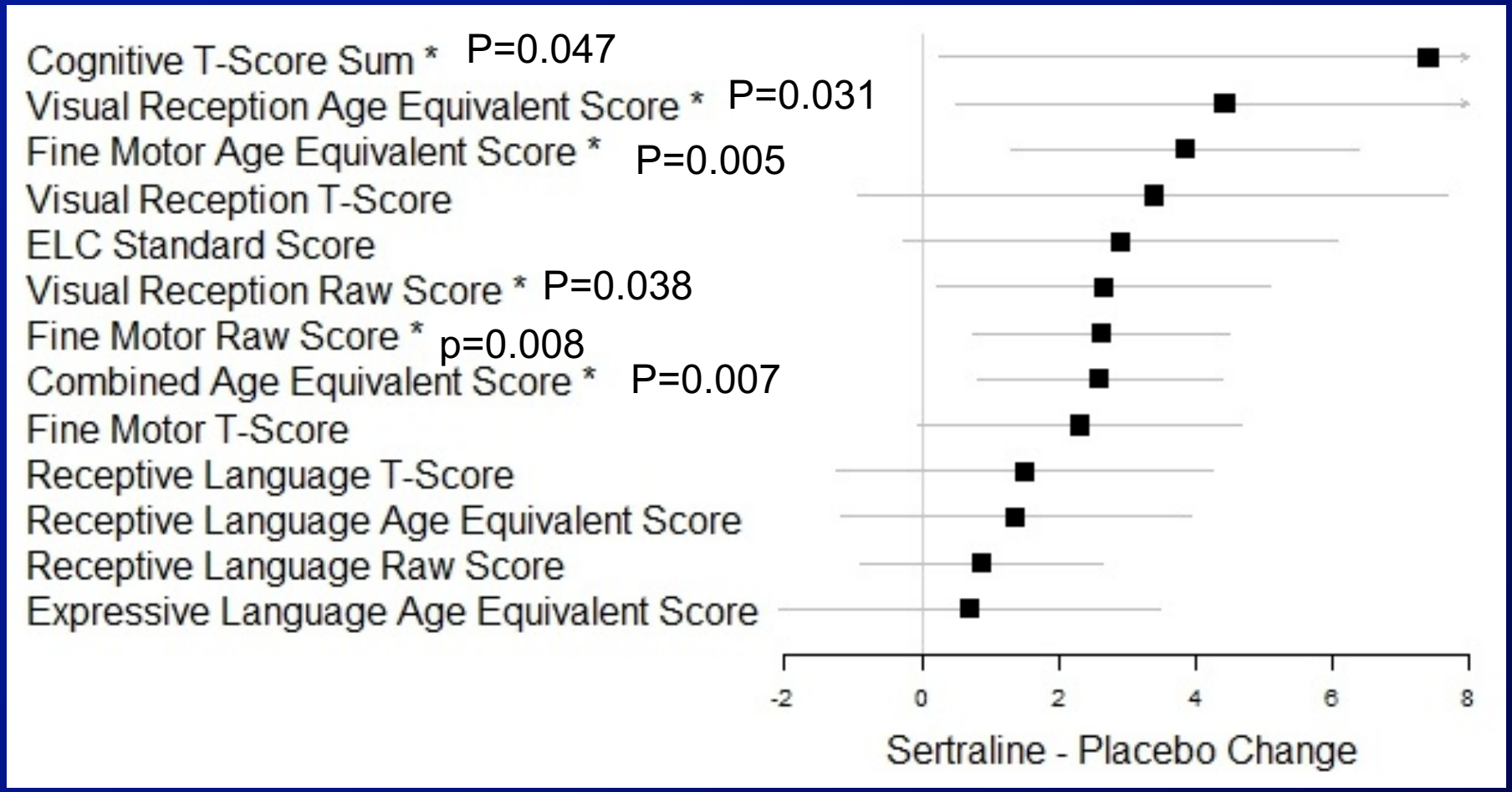
Laura Greiss Hess PhD, OTR
Kerrie Lemons Chitwood PhD, CCC
initiated study

Sarah Fitzpatrick
NFXF summer student fellow
finalized the study and data

Clinical Global Impression-Improvement (CGI-I)



Mullen Scales of Early Learning (MSEL)



Conclusions

- MSEL visual perception and fine motor subtests, the composite T score, and the combined mean of all the subtests scores were improved on sertraline vs placebo so cognitive and motor benefits and improvement in social participation on SPM-P. Those with ASD with most significant benefit and improved expressive language score. It was safe without signif AEs
- A significantly beneficial treatment by age 2 yo reinforces the need for early diagnosis and even newborn screening
- Families wanted to continue on sertraline after the study and long term follow-up is needed.
- Currently enrolling 2 to 6yo with ASD for a controlled trial of low dose sertraline

AFQ056+ PILI in 3-6yo FXS through NeuroNEXT

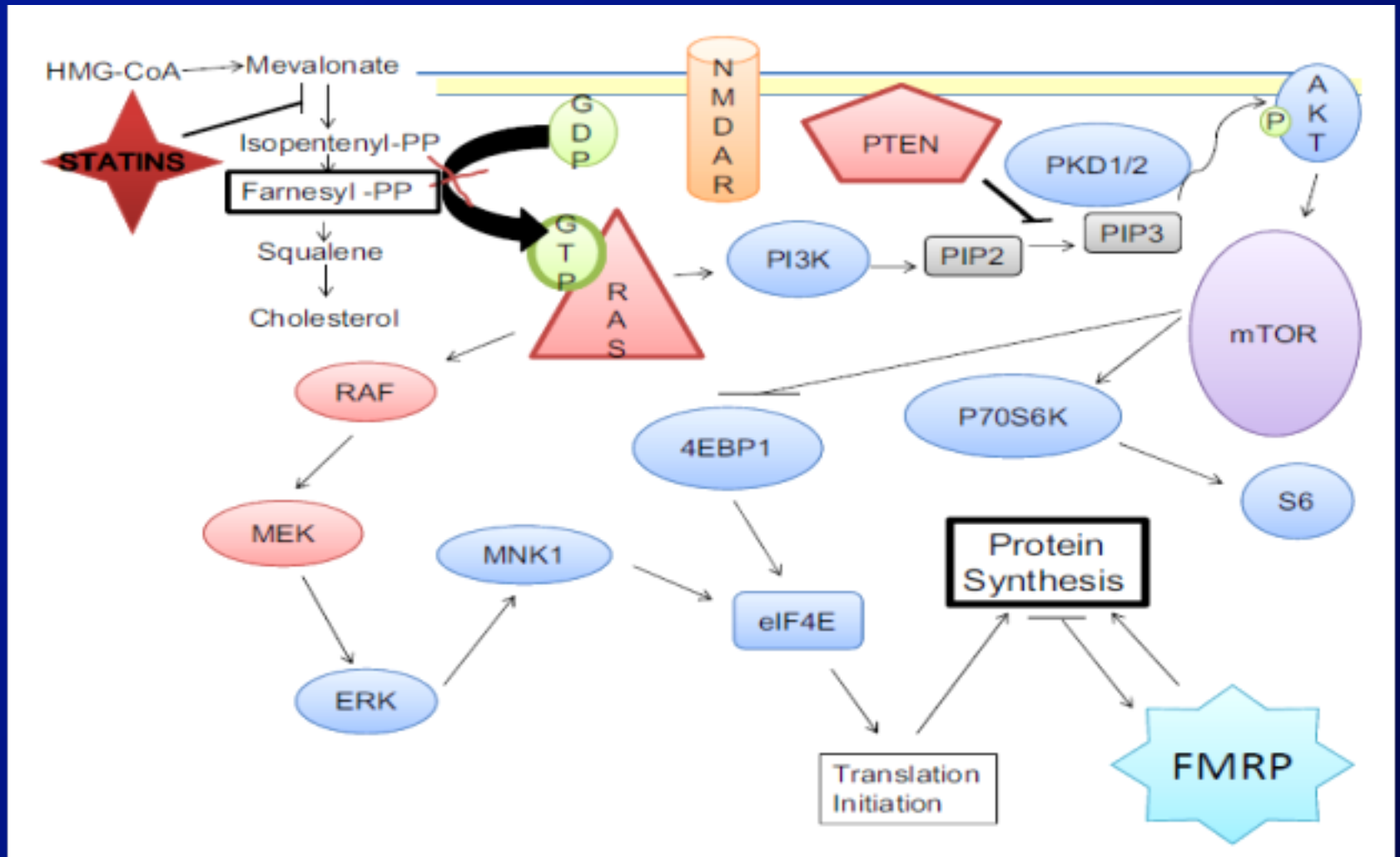
- Effects of AFQ056 on Language Learning in Young Children with FXS with lead in PILI for 6 months
- Change paradigm/create model for development of mechanism targeted pharmacotherapy in NDDs – effects of drug on plasticity
- Address many Quandries: incorporate young age (3-6y), longer trial, objective measures, learning intervention, biomarkers for target engagement
- Randomize to AFQ056 or placebo - lead-in period when adjust to best dose
- Extension for 8 months on AFQ056 for all participants

Study Team PI: Elizabeth B-Kravis; Co-PIs: Randi Hagerman, Len Abbeduto; Co-Is: Walter Kaufmann, Craig Erickson, David Hessl, Flora Tassone

Controlled trial of lovastatin in 10 to18yo combined with Parent Implemented Language Intervention (PILI)

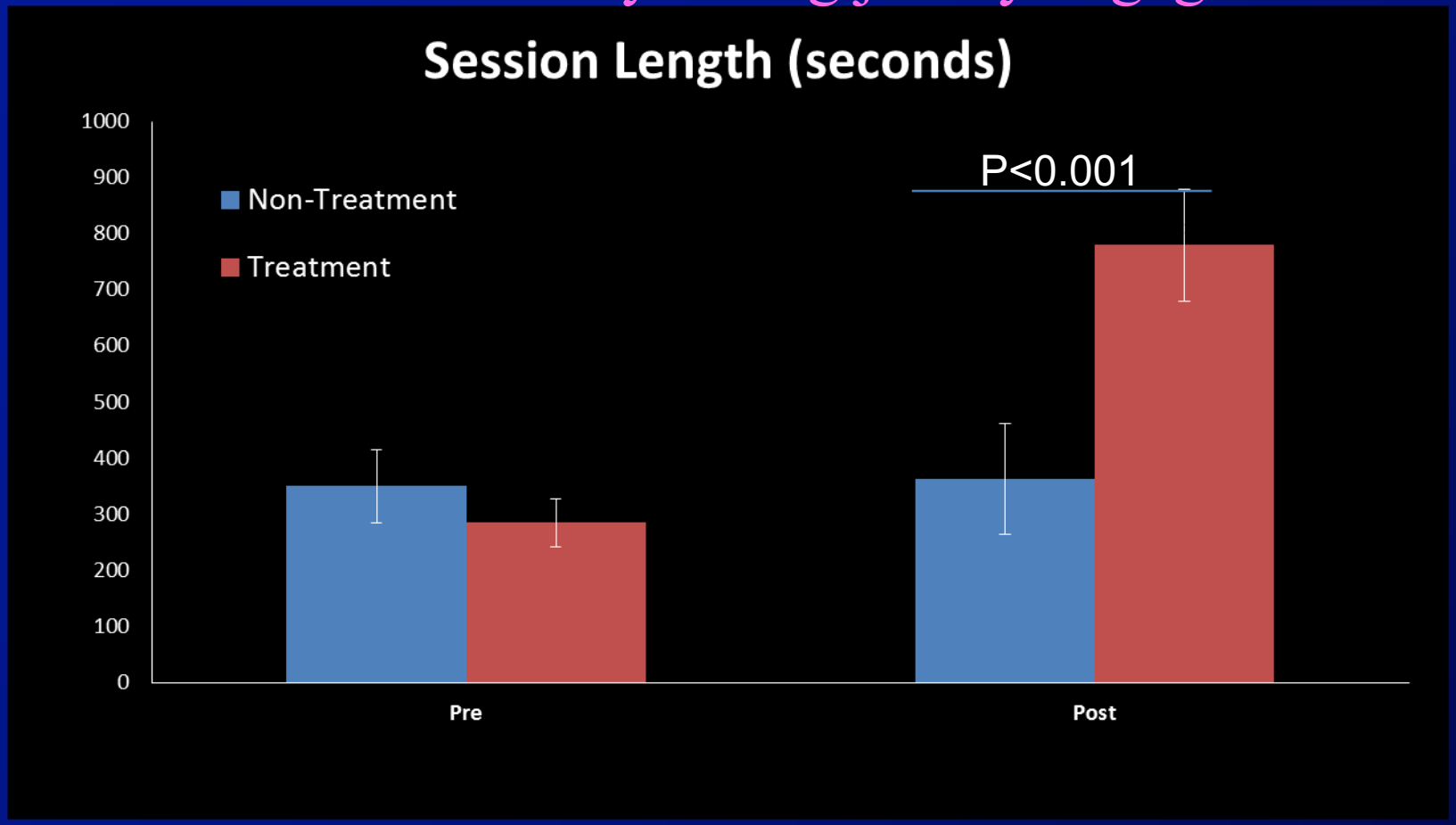
- **Lovastatin** is an inhibitor of the rate-limiting enzyme in cholesterol biosynthesis and an FDA-approved treatment for hyperlipidemia (Acosta et al 2011).
- Lovastatin down-regulates the RAS-ERK1/2 pathway and lowers the excessive protein synthesis in FXS
- In FX KO mice lovastatin rescues seizures and lowers excess protein production in KO mouse (Osterweil et al 2013)
- Lovastatin was beneficial in open label trial in FXS
- Lovastatin has anti-inflammatory effects

lovastatin inhibits Ras farnesylation by targeting the upstream mevalonate pathway and thereby downregulates ERK1/2 activation



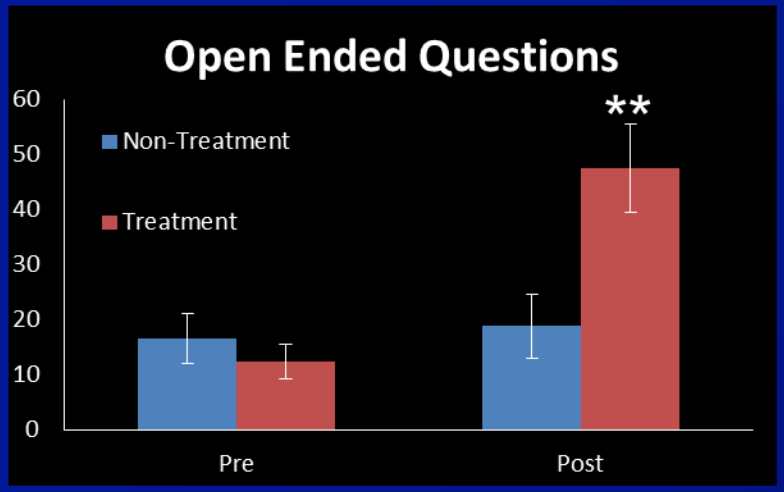
PILI has demonstrated efficacy in FXS (n=10 in Rx and n=9 in controls over 20 weeks)

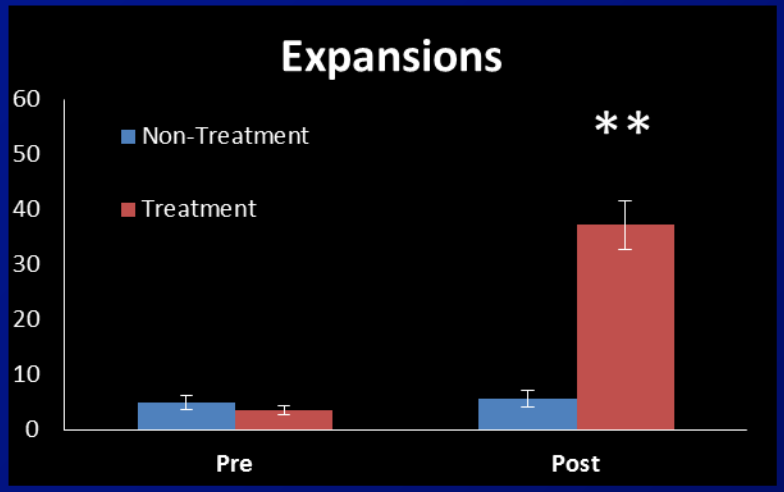
time in shared story telling jointly engaged

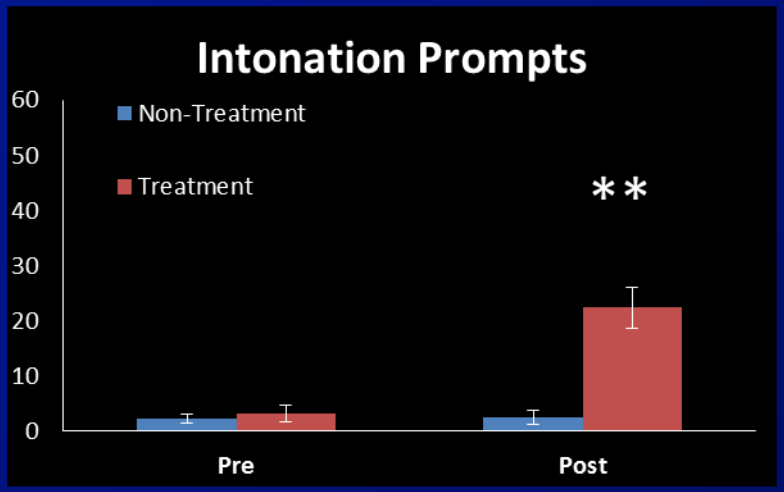


Data from McDuffie and Abbeduto 2016

Maternal Use of Intervention Strategies were significantly improved with PILI







Data from McDuffie et al 2016

Every one gets PILI intervention

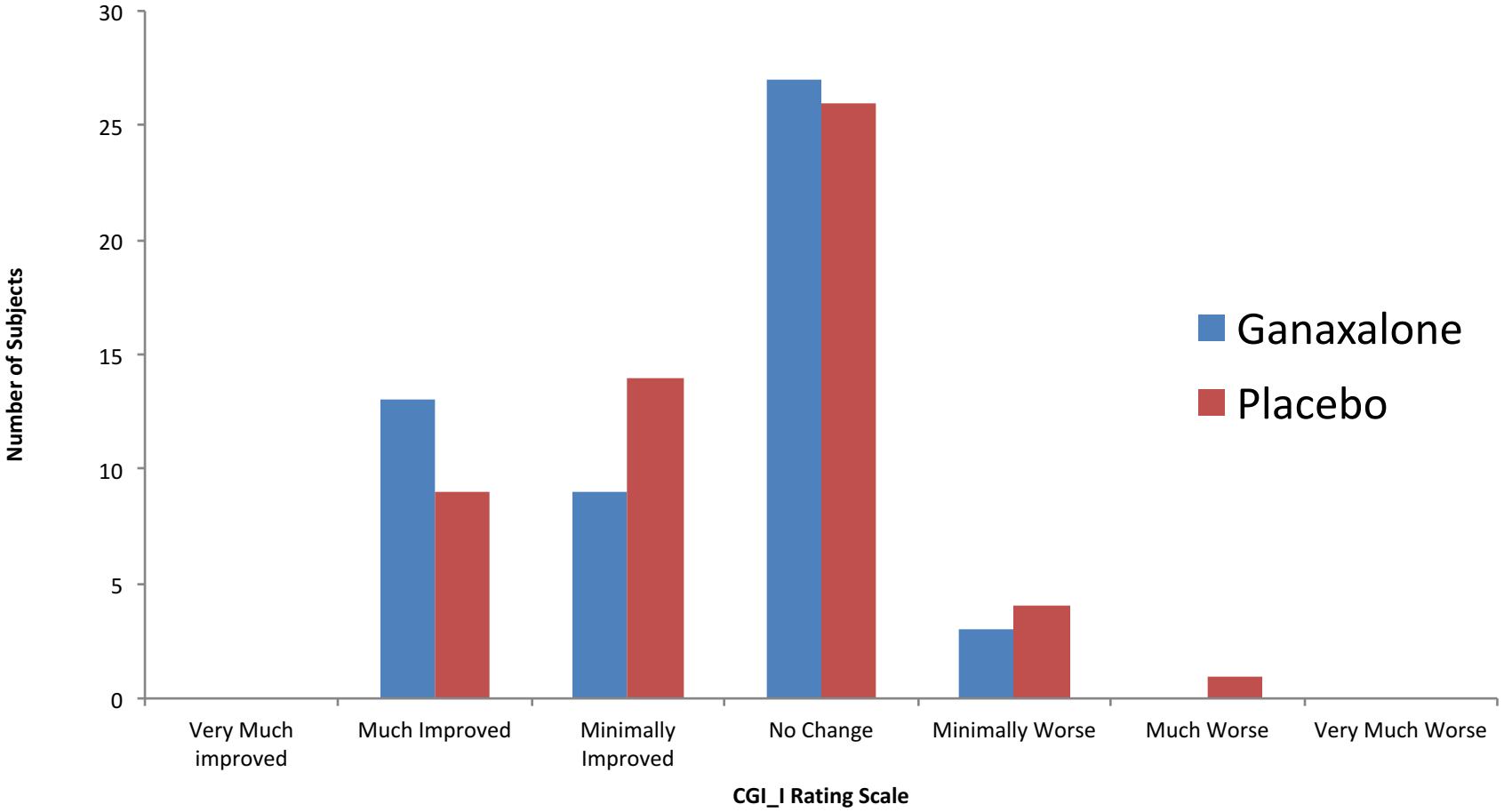
- PILI is twice a week with S and L therapist and with behavior interventionist on skype in your home
- Controlled trial of lovastatin increasing from 10 mg gradually up to 40 mg if tolerated
- Total trial lasting 18 weeks ages 10 to 18yo
- Contact Erika Bickel (esbickel@ucdavis.edu) at the MIND institute or rjhagerman@ucdavis.edu

$GABA_A$ receptor expression is down-regulated in FXS

- $GABA_A$ expression is down- regulated in the KO mouse (D'Hulst et al 2007; Kooy et al 2005)
- $GABA_A$ agonists: Ganaxolone
  - Investigational medication with efficacy in infantile spasms and other types of epilepsy: A controlled double blind cross-over trial (each arm 7 weeks) in children with FXS (6 -18y) funded by DOD is finished. Marinus supplied the ganaxolone; Ligsay et al 2016
  - Targeting improvement in anxiety and behavior
  - Frank Kooy has studied 11 patients in Belgium and we studied 48 patients at the MIND: total 59 in study

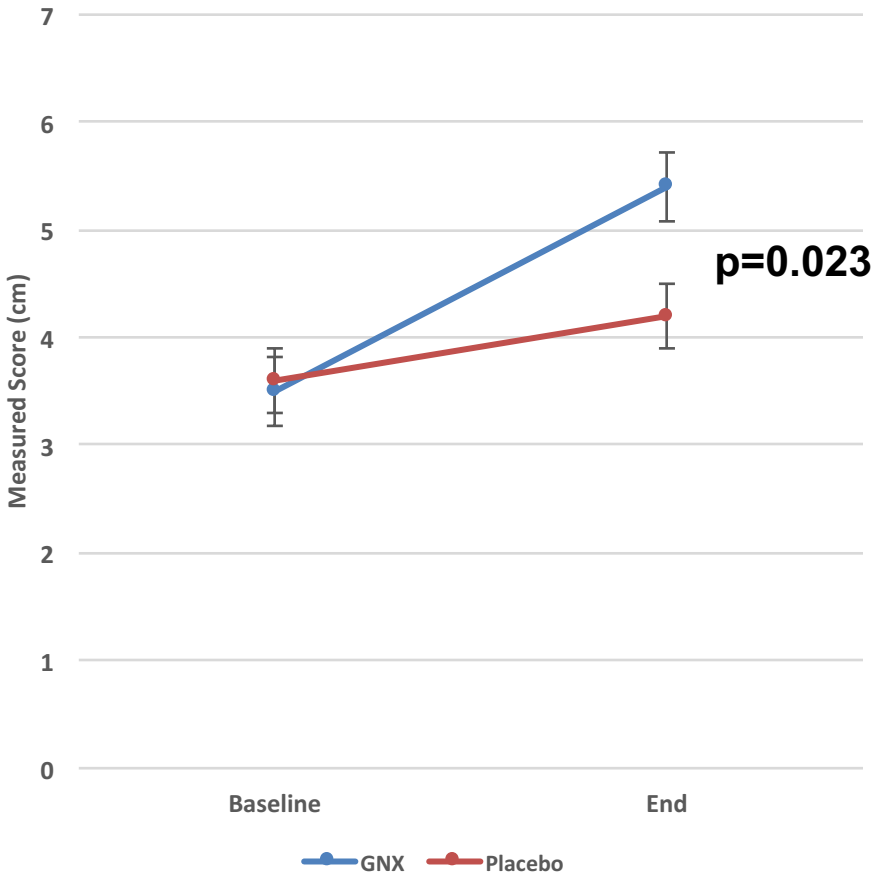
Primary Outcome Measures with no significant efficacy: CGI-I

p = 0.448

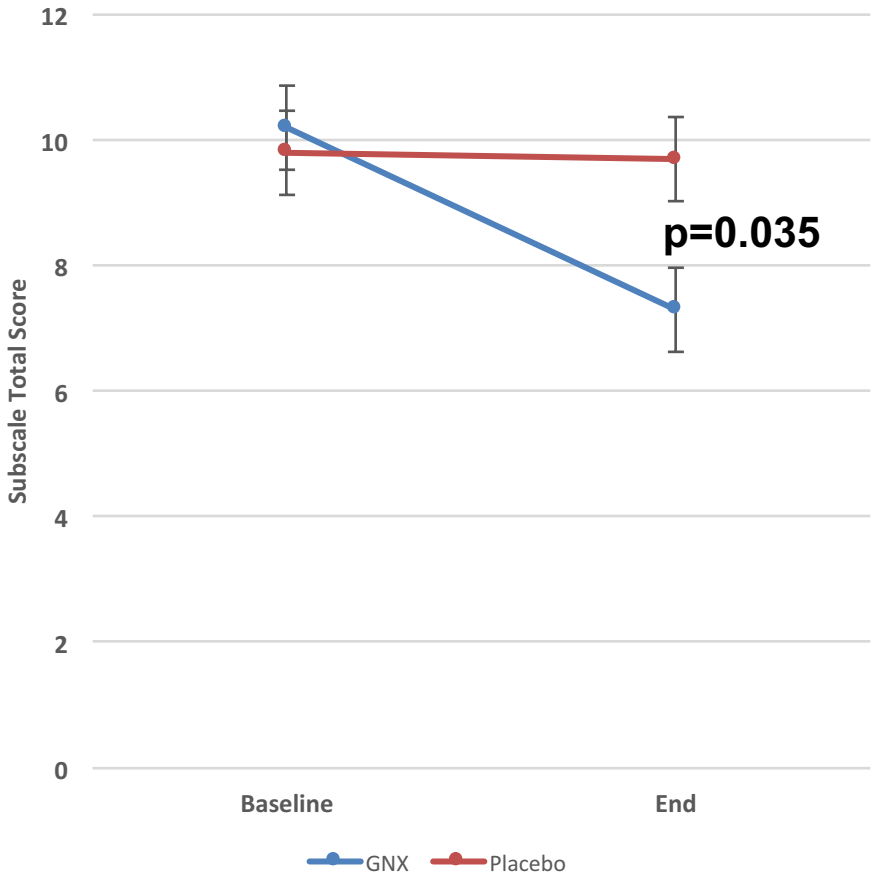


Post-hoc: High Anxiety (PARS) Significant efficacy

VAS-Anxiety



ADAMS-General Anxiety



Adverse events and plans

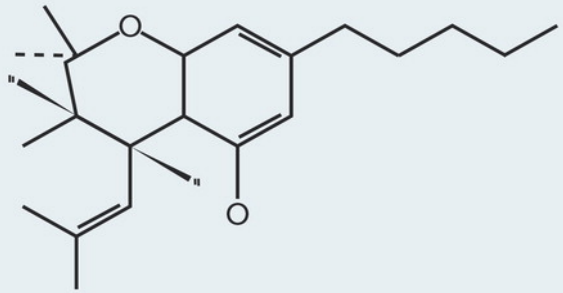
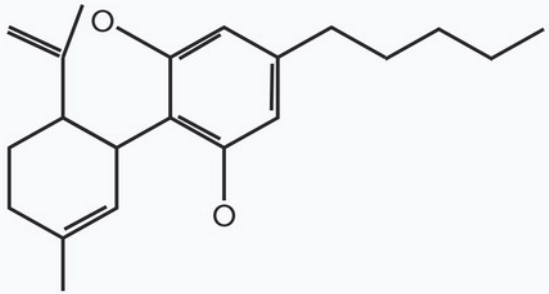
- Ganaxolone was generally safe, although some experienced sedation which was the main adverse event
- Data shows those with high anxiety ie PARS above 13 demonstrated the best efficacy
- Additional studies are warranted for this subgroup of patients with FXS

Additional $GABA_A$ agonists in FXS

- Alphaxolone improved anxiety and seizures in KO mouse (Huelens et al 2012)
- Gaboxadol normalized neuronal hyperactivity in amygdala and PPI in KO mouse (Olmos-Serrano 2010;2011)
- Ovid announced plans to carry out controlled trial of gaboxadol in Angelman syndrome and in FXS
- Could allopregnanolone be helpful in FXS?

Yoga and Mindfulness Meditation improves GABA inhibition

Cannabinoid Structures: Cannabidiol (CBD) is not psychotropic.

Cannabinoid	Structure
Δ^9-Tetrahydrocannabinol	
Cannabidiol	

Friedman D, Devinsky O. N Engl J Med 2015;373:1048-1058.

The NEW ENGLAND JOURNAL of MEDICINE

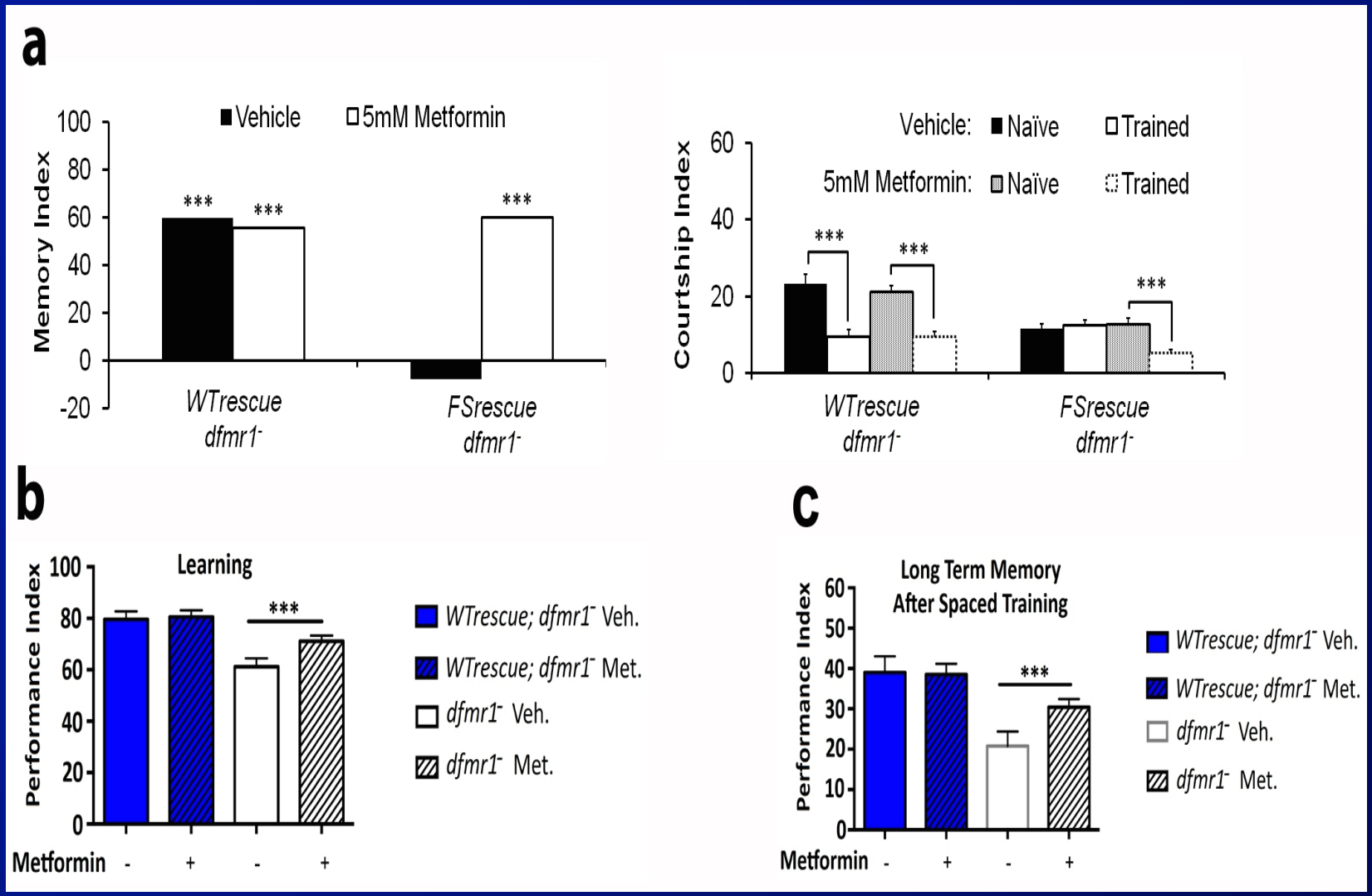
Cannabidiol (CBD)

- The lack of FMRP in FXS leads to a reduction of endocannabinoid system and lowering of endogenous ligands of CB1 and CB2 receptors, 2 arachidonoylclycerol (2AG) and anandamide (AEA)
- CBD increases 2AG and AEA and indirectly a GABA agonist effect
- 2 companies interested in CBD trials in FXS: GW pharmaceuticals and Zynerba
- Anecdotal evidence of improvements with CBD in individual cases and maybe helpful for carriers too, so parents have mentioned

Metformin a type 2 diabetes med

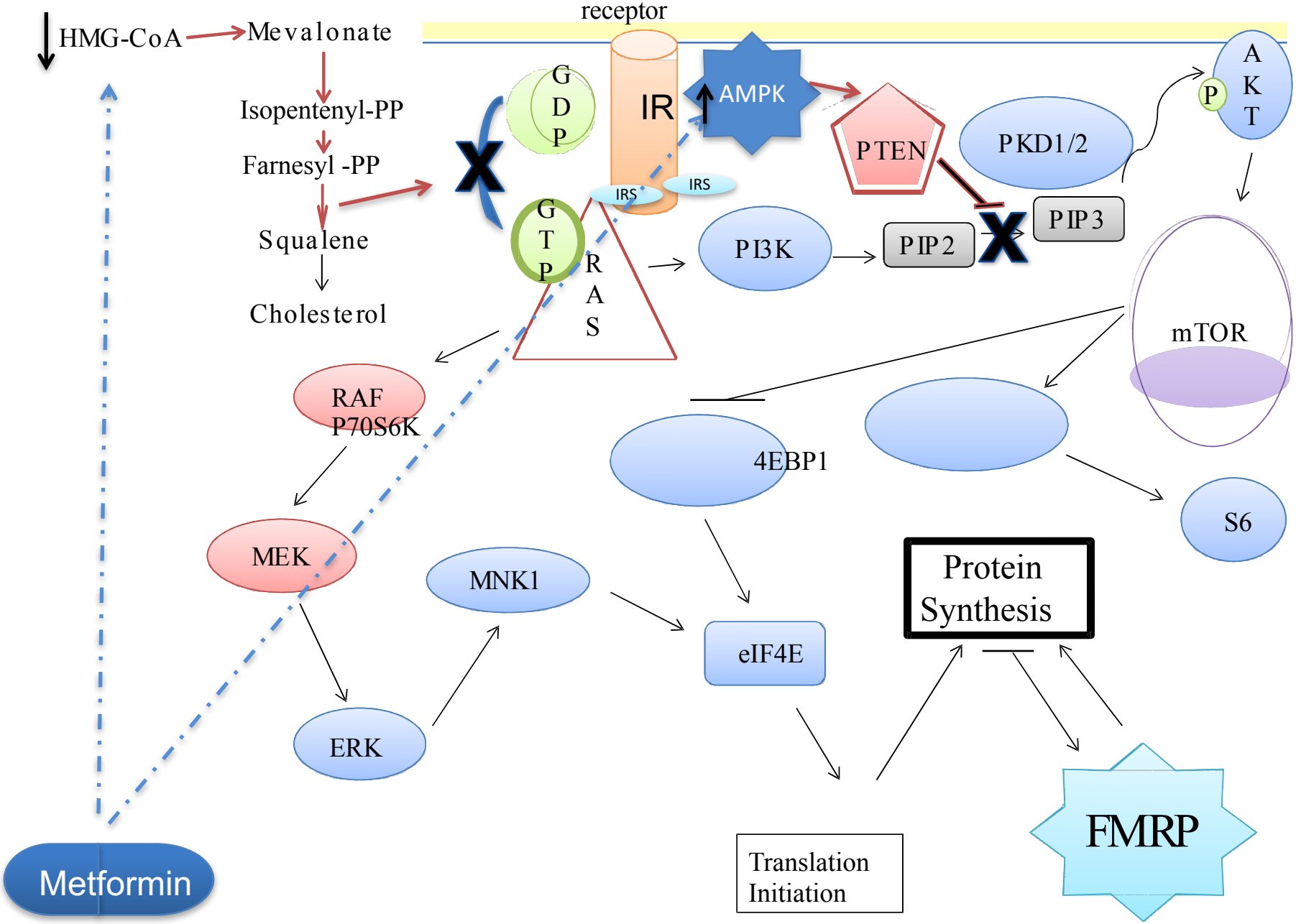
- Known to help overeating and obesity
- Can prevent cognitive deficits in diabetics
- Helpful in several patients with Prader-Willi Phenotype of FXS (obesity and hyperphagia), present in less than 10% of FXS
- Drosophila FX model: insulin-like peptide 2 (dilp2) in insulin-producing cells elevated insulin signaling via PI3K/Akt/mTOR pathway (Monyak et al 2016)
- Defect in **circadian rhythm** and short and long-term **memory improves in FX fly with metformin**

Defects in FX fly improved with metformin



(Monyak, et al., 2016)

Metformin

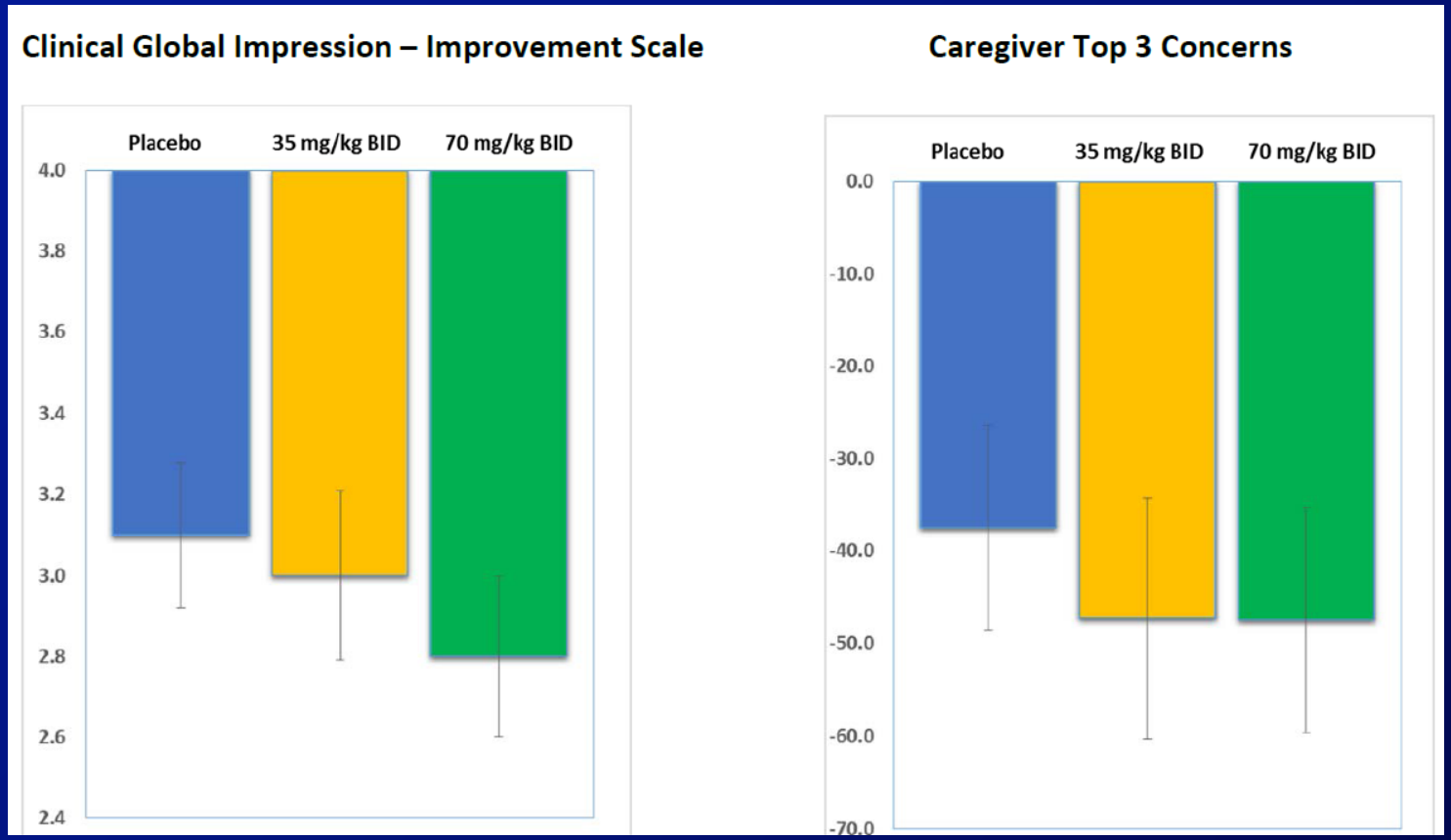


Muzar et al 2016

Age/Sex	Diagnosis	Concerns
18yo Male	FXS ID ASD, ADHD Overweight	Aggression Picking/scratching Hyperactivity Perseveration Hyperphagia
13yo Male	FXS:PWP ASD, ID OSA, Type II DM HgbA1c7.7 Glucose 174	Anxiety Perseveration Hand flapping Poor eye contact Hyperphagia
19yo Male	FXS:PWP ASD, ADHD, ID Obese	Behavioral outbursts Speaking in short phrases but not sentences Hyperphagia
60yo Female	FXS, ID HTN Obese	Memory Agitation and anxiety Hyperphagia

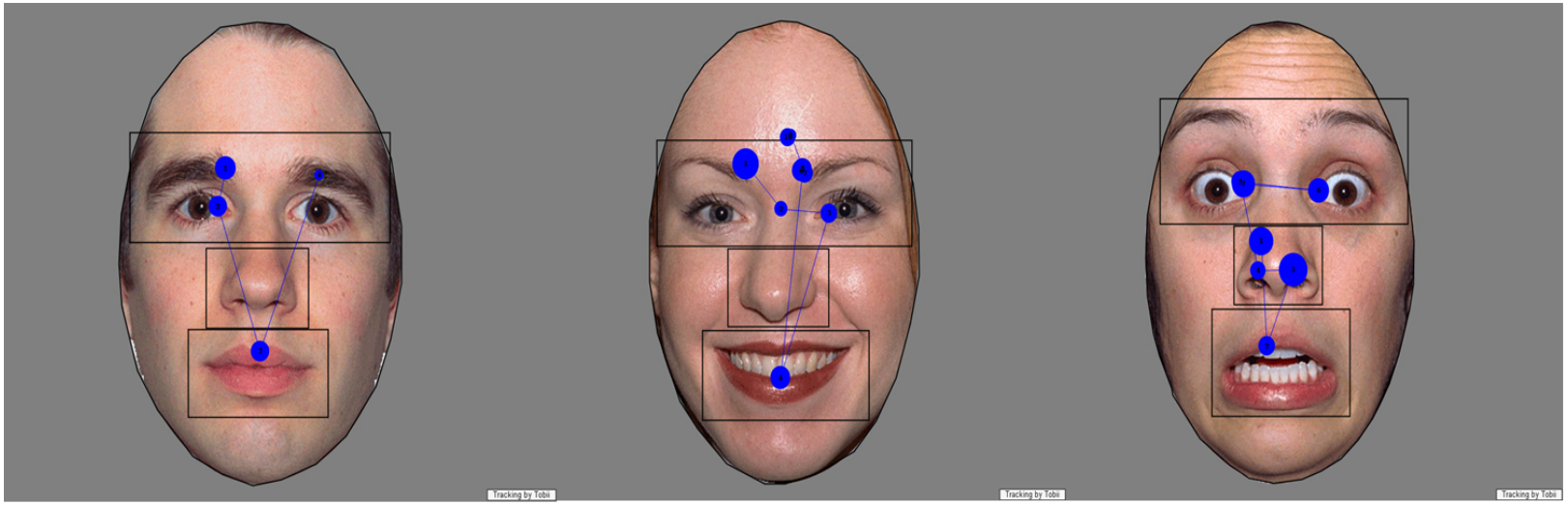
Neuren Phase 2 placebo controlled trial with IGF1 analogue

- Safe in males14-40 yo with FXS over 42 days of treatment carried out at 5 US centers. Highest dose was most effective

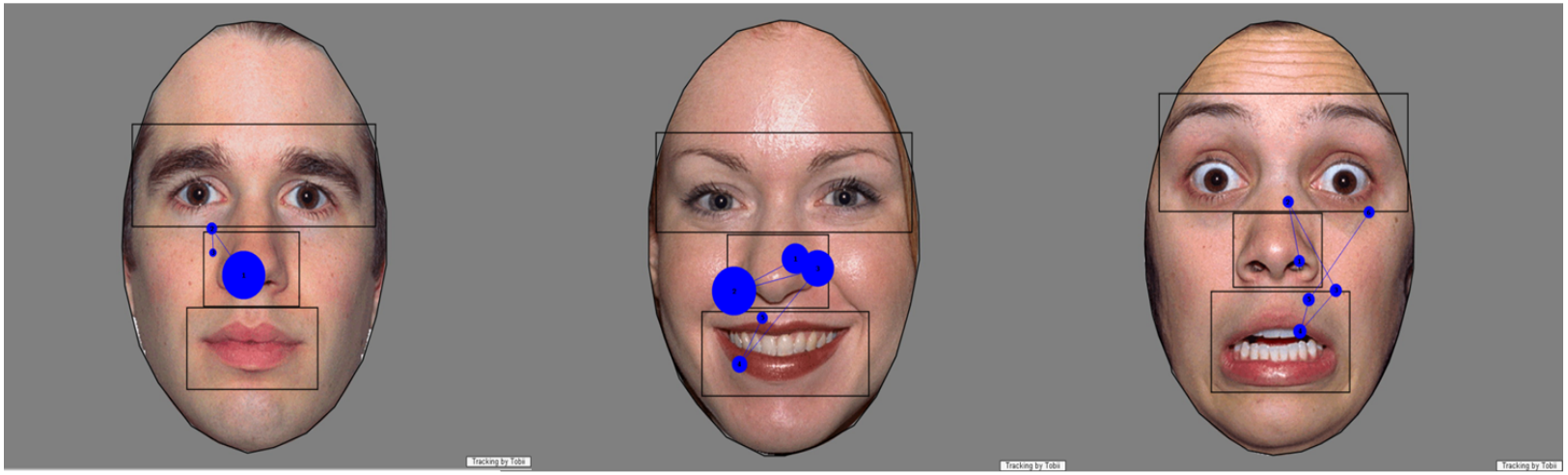


Eye Tracking in FXS As Outcome

TD:

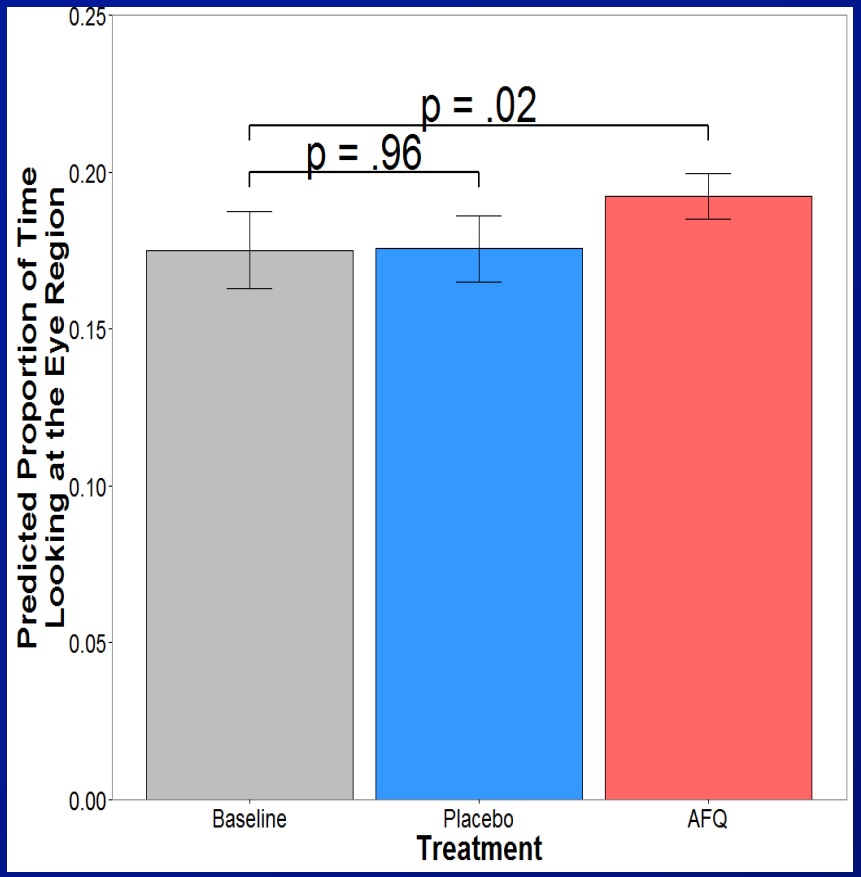


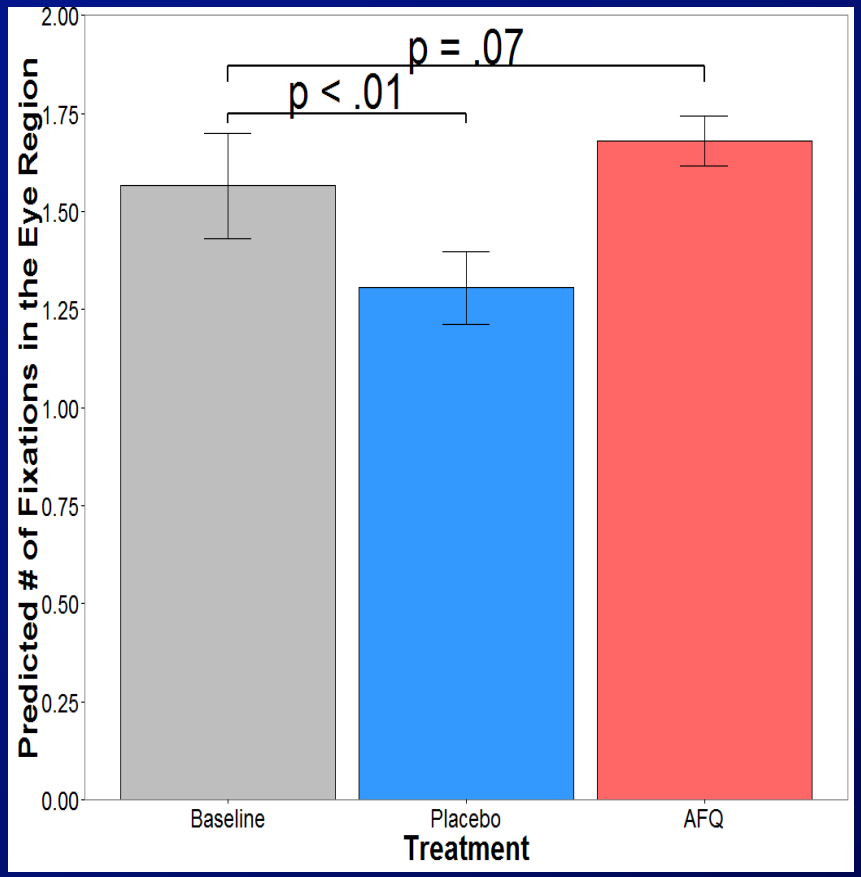
FXS:



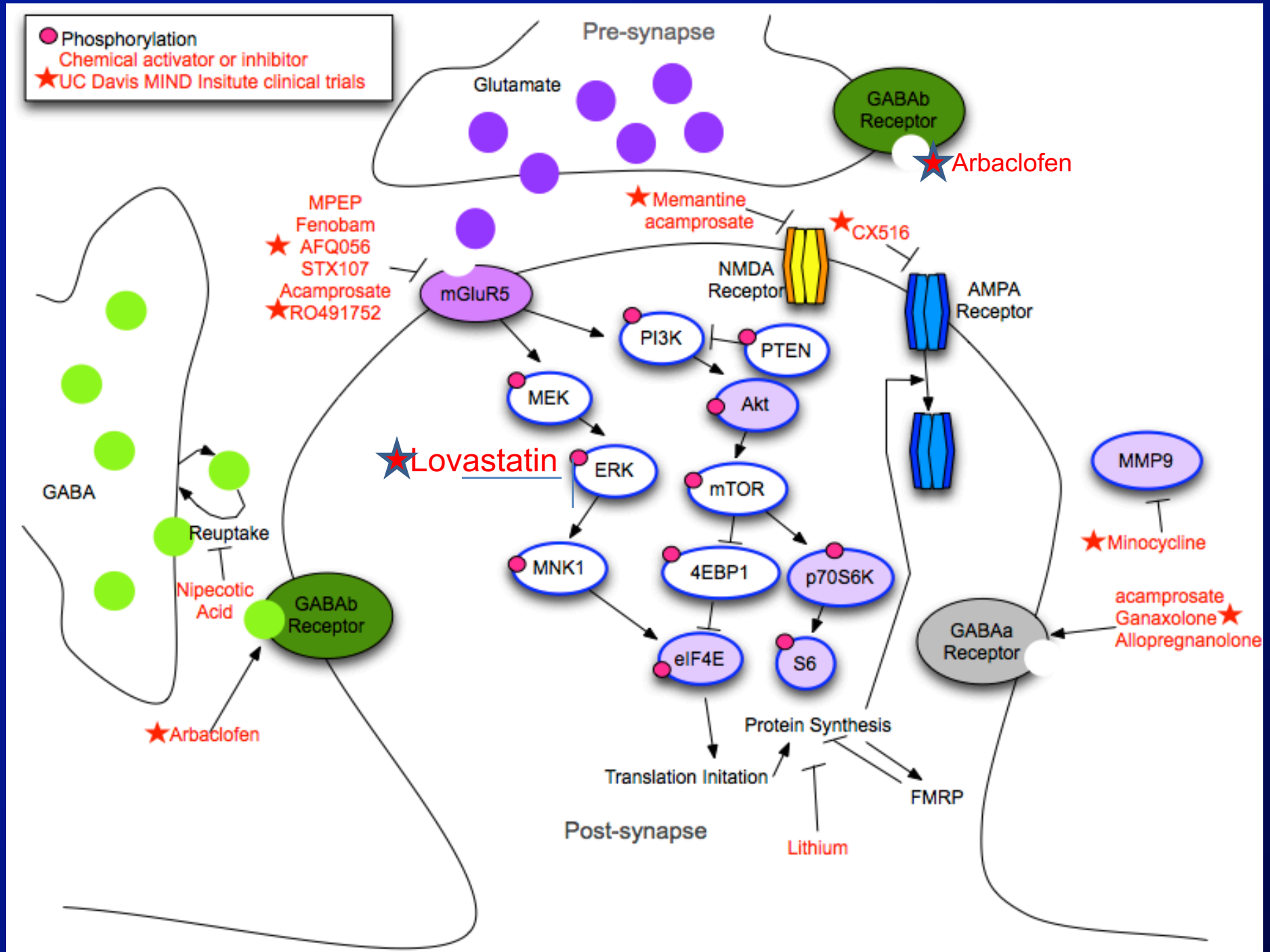
Calm Happy Fear

Eye Tracking as Outcome in AFQ056





Sansone et al 2016 Gaitlinberg


Phosphorylation
Chemical activator or inhibitor
UC Davis MIND Insitute clinical trials
Pre-synapse
Glutamate
GABAb Receptor
Arbaclofen
MPEP
Fenobam
AFQ056
STX107
Acamprosate
RO491752
Memantine
acamprosate
CX516
NMDA Receptor
AMPA Receptor
mGluR5
PI3K
PTEN
MEK
Akt
Lovastatin
ERK
mTOR
MMP9
Minocycline
GABA
Reuptake
Nipecotic Acid
MNK1
4EBP1
p70S6K
GABAb Receptor
GABAa Receptor
acamprosate
Ganaxolone
Allopregnanolone
eIF4E
S6
Arbaclofen
Protein Synthesis
Translation Initation
FMRP
Post-synapse
Lithium

Longitudinal open label AFQ056 study

- AFQ056 was well tolerated although more side effects in the 100 mg bid dose
- Gradual improvement in symptoms with the ABC-C$_{FX}$ but not more remarkable than placebo in the controlled trial. No learning paradigm or cognitive outcome measure
- AFQ056 may be helpful in young children and this will be assessed in a study of 3 to 6 yo with FXS in combination with intensive language training (NeuroNext multicenter trial funded by NIH)

Targeted Treatments must be combined with innovative educational programs

- If synaptic connections are improved with targeted treatment we must enhance these connections with educational interventions
- Combine treatment trials with educational interventions, digital programs such as CogMed, Headsprout for reading, AT devices, iPAD apps

FX tracking game

iPAD apps

Co-Writer and write out loud

Collaborators

UC Davis School of Medicine

MIND Institute
- Norman Brule
- Lauren Plummer
- Kathy Angkustsiri
- David Hessl
- Susan Rivera
- Andrea Schneider
- Mary Jae Leigh
- Sarah Fitzpatrick
- Michele Ono
- Patrick Adams
- Aisha Lott
- Erika Bickel
- Reymundo Lozano
- Lindsey Partington
- Jen Cogswell
- Maria Diez
- Len Abbeduto

Dept. Radiology
- James Brunberg

NTRI Researchers
- Isaac Pessah
- Rob Williamson
- Rob Berman

Dept. Neurology
- Lin Zhang
- John Olichney
- Ricardo Maselli
- Mike Rogawski

Dept of Psychiatry
- Andreea Seritan

Dept. Biochem & Molec. Medicine
- Paul Hagerman
- Flora Tassone
- Anna Ludwig
- Greg Mayeur
- Chris Raske

Dept. Biostatistics now at UC Irvine
- Danh Nguyen

Department of Pathology
- Claudia Greco

Department of Rehabilitation
- Veronica Martinez-Cerdeno

University of Colorado Health Sciences Center (Denver)

Nicole Tartaglia Maureen Leehey James Grigsby ; Karen Riley at DU

RUSH-Presbyterian-St. Luke's Medical Center (Chicago)

Elizabeth Berry-Kravis Deb Hall Christopher Goetz

Latrobe University, Melbourne Australia

Danuta Loesch Richard Huggins

Support: NICHD, HRSA, DOD, NIA, NFXF, CDC, NFXF, Alcobra Neuren, Roche, Novartis, Seaside Therapeutics