

Pathways Toward Translational Research Programs for ASD

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NJ Governor's Council
Conference

April 9, 2014



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ASD – Research History

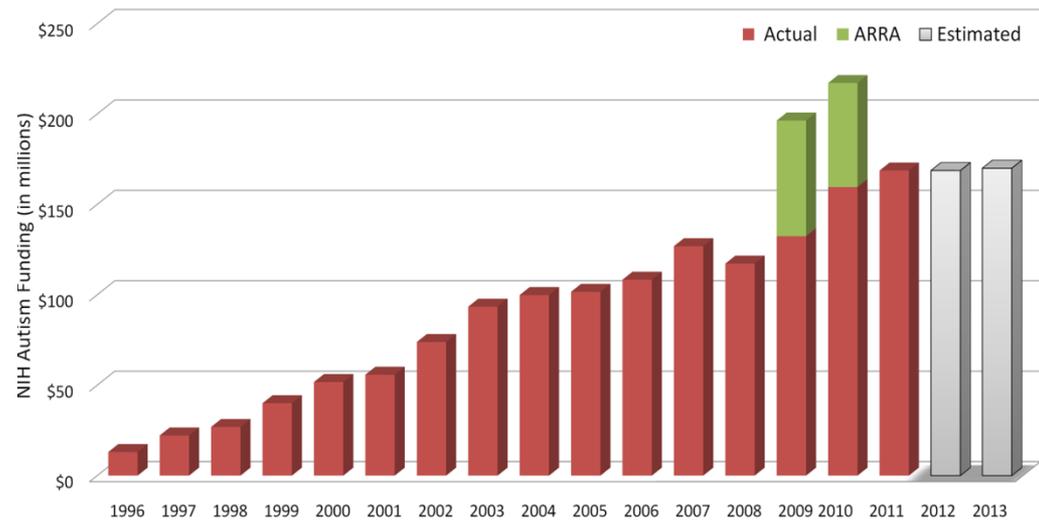
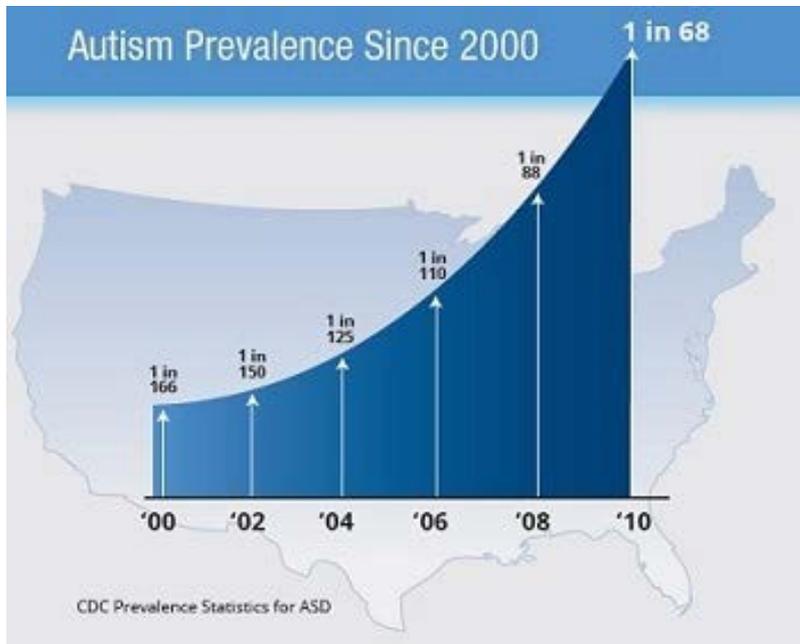
For several decades research on autism was severely limited:

- Lack of awareness (or interest)
- Funding
- Theoretical frameworks
- Tools for investigating etiology
- Tools for investigating pathophysiology and mechanisms



The Current Landscape

Radical transformations on all fronts



NIH funding for autism research has tripled in the last decade (2001-2011).



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The Urgency for New Research Agendas

- With rising prevalence rates and growing concern comes an imperative to move beyond asking *what, why and when...*
- *How can we make a difference in the lives of children with ASD?*
- The most significant research issue for families is development of new treatments



Goals for Treatment Research

- Individualized treatment
- Developmentally sensitive
- Targeted to the biological and behavioral phenotypes of each child and adult
- Produces significant changes in behavior
- Safe, few side effects



Translational Research Models

Three Pathways

1. Behavioral treatments
(Developmental science)
2. Pharmacological treatments
(Molecular biology)
3. Neurologically-based treatments
(Neural/cognitive architecture): ACE





Behavioral Treatments

- Classic ABA Model (Lovaas, 1987) – DTT
- One-size-fits-all **method** and content
- Effective approach for improving cognitive skills, but not grounded in developmental psychology
- Current best practice behavioral treatments are guided by a stronger developmental science foundation



Translating Developmental Science

- Knowledge of core developmental impairments in ASD
- Critical precursor skills for language and communication (imitation, joint attention, play, gesture)
- Active learning in social-affective contexts



RCT on Toddlers with ASD

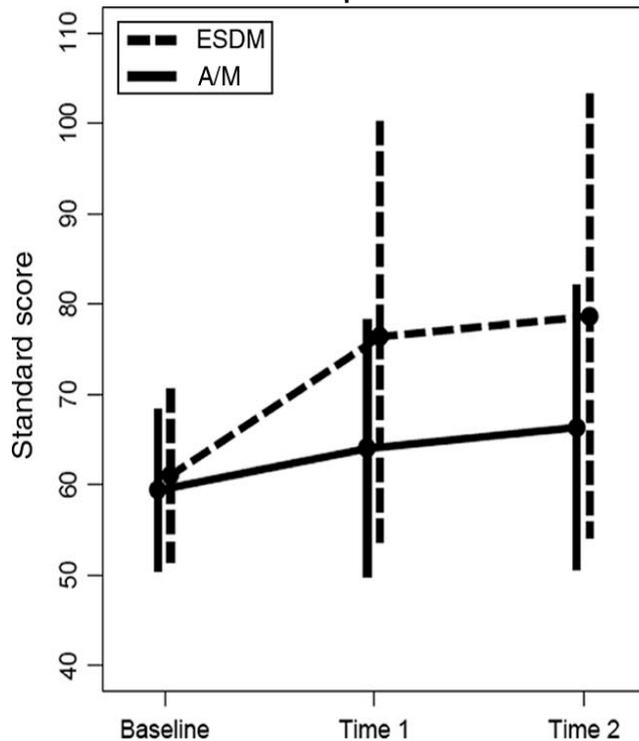
Dawson et al. (2010)

- Randomized 48 children, average age of 24 months to specialized comprehensive treatment model – ESDM (comprehensive treatment, targeting multiple core behaviors) or community control
- Provided treatment for 2 years
- Evaluated behavioral changes at 12 and 24 months
- Evaluated brain changes at 24 months

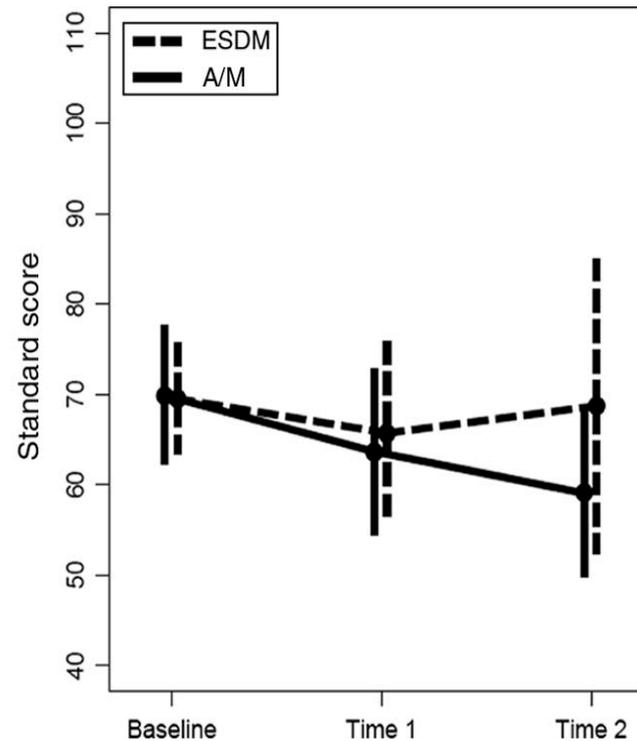


Changes in IQ/Language and Adaptive Functioning

Changes in IQ 20 points

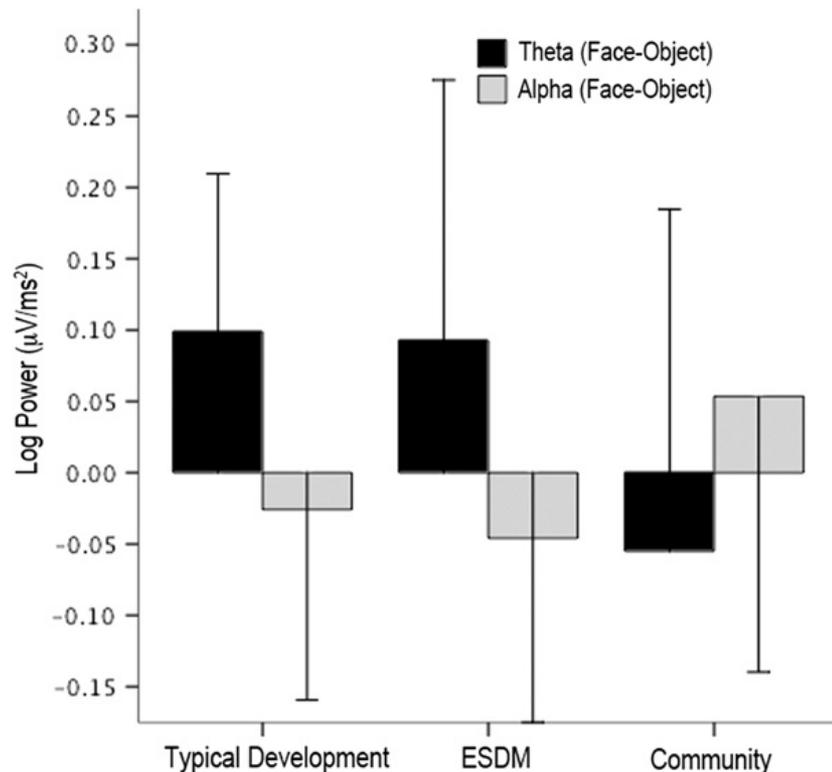
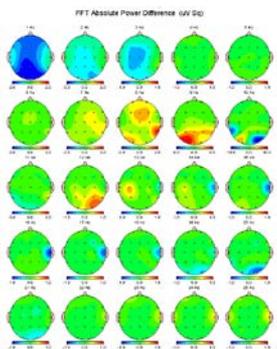
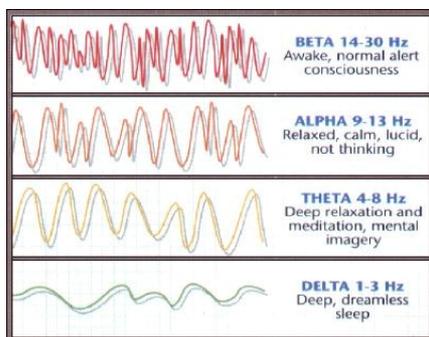


Changes on Vineland prevents loss of skills



Changes in Brain Activity

Behavioral treatment led to normalized brain functioning in toddlers



Targeting Core Symptoms

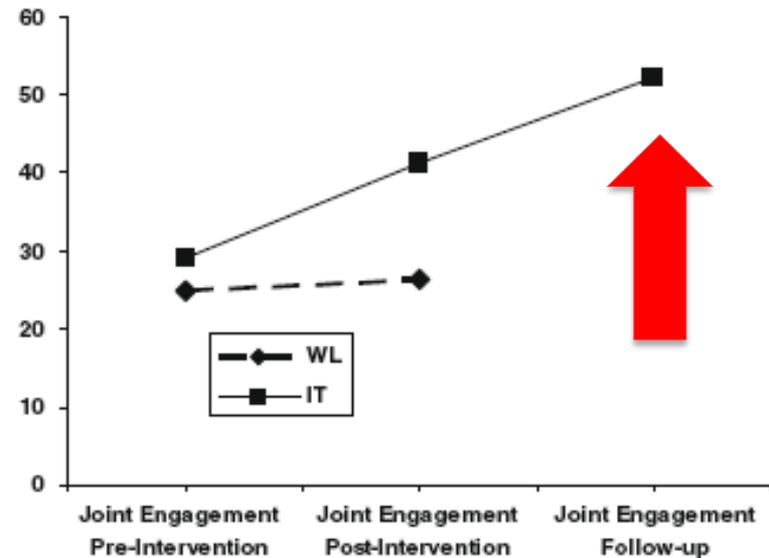
Kasari et al. (2010)

Parent training for increasing joint engagement

20 sessions/30 minutes



Increased Joint Engagement



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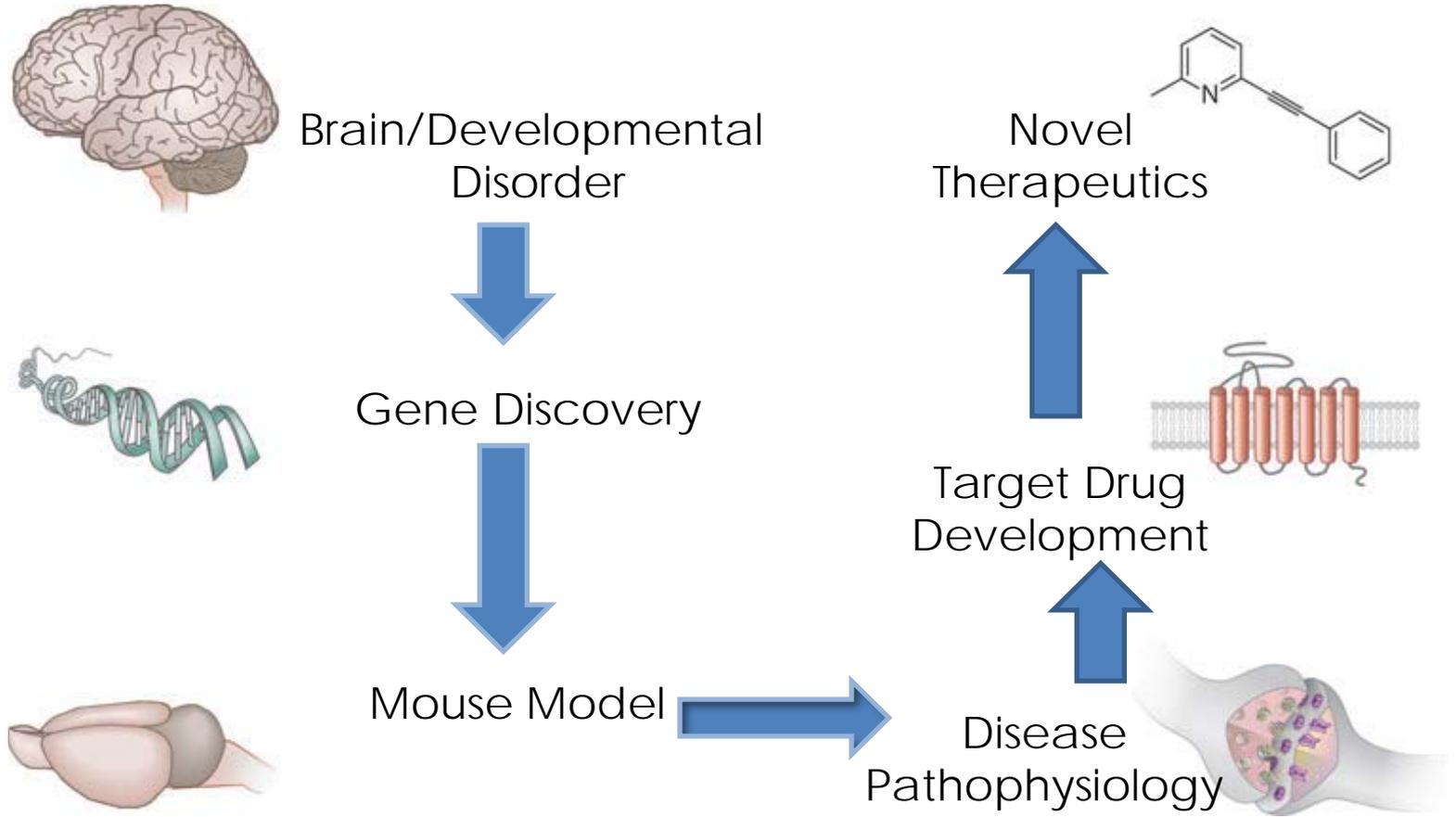
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2. Pharmacological Treatments

- Current medications target co-morbid behaviors (aggression; anxiety; mood) but not core symptoms
- Few RCTs even for current medications routinely prescribed for children and adults with ASD
- Many individuals take multiple medications for behavioral problems



Translational Model: From Bench to Bedside



The Story of Fragile X Syndrome

Physical Features

Long face; large prominent ears; extendable finger joints; soft skin; flat feet; large testicles; growth issues

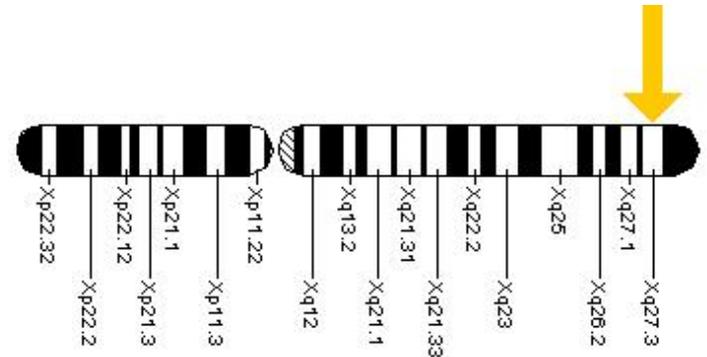
Cognition/Behavior

ID; speech and language problems; anxiety; perseveration; impulsive/hyperactive; hypersensitive; avoid eye contact; **40% meet criteria for ASD**

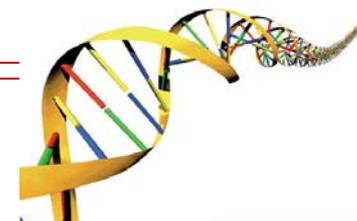
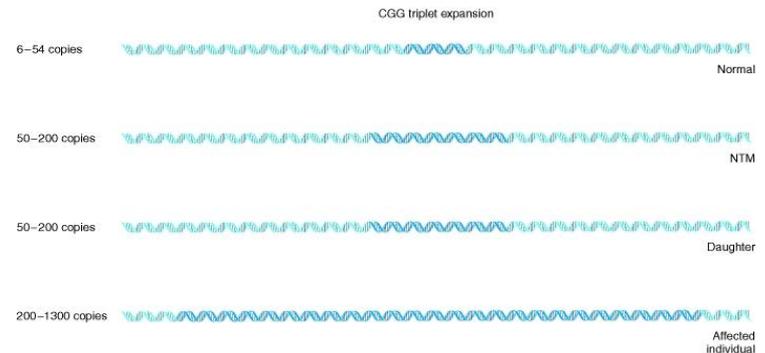


Mutation Patterns in FMR1 Gene

- On the FMR1 gene (X chromosome) CGG repeat pattern:
 - Normal = 6-54 repeats
 - Pre-mutation carriers = ~50-200
 - Full mutation = 200+
- Mutation silences the production of FMR protein (found in all cells)
- Absence of FMRP *causes* Fragile X syndrome

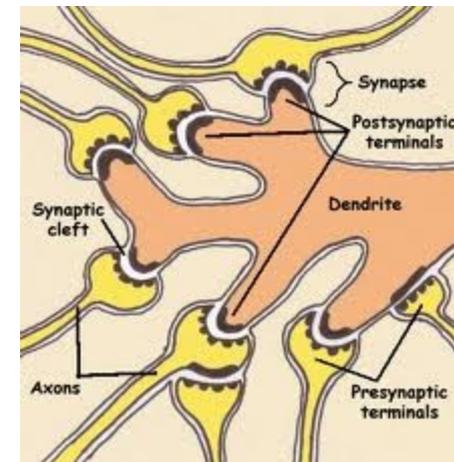
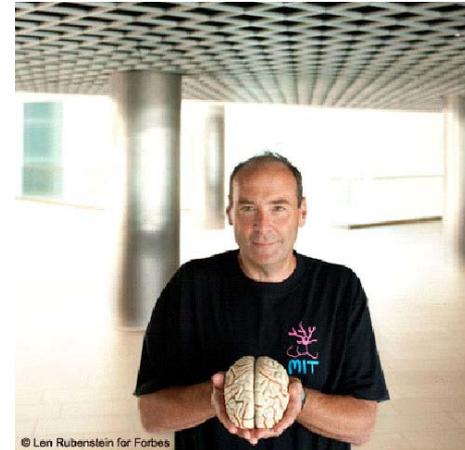


CGG: cytosine-guanine-guanine



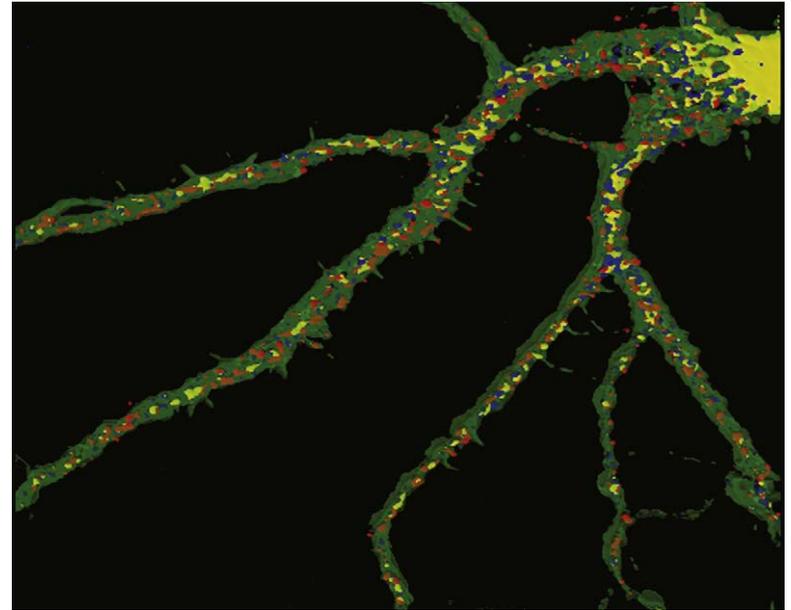
From Mouse to Man – Mark Bear

Mouse models (knock-out the Fmr1 gene) led to important discoveries about role of FMRP in transporting mRNAs to dendrites and synapses - leading to altered brain plasticity, and affecting capacity to learn



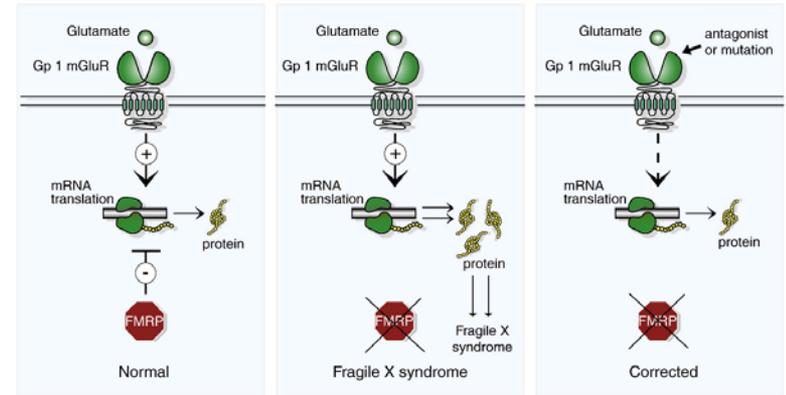
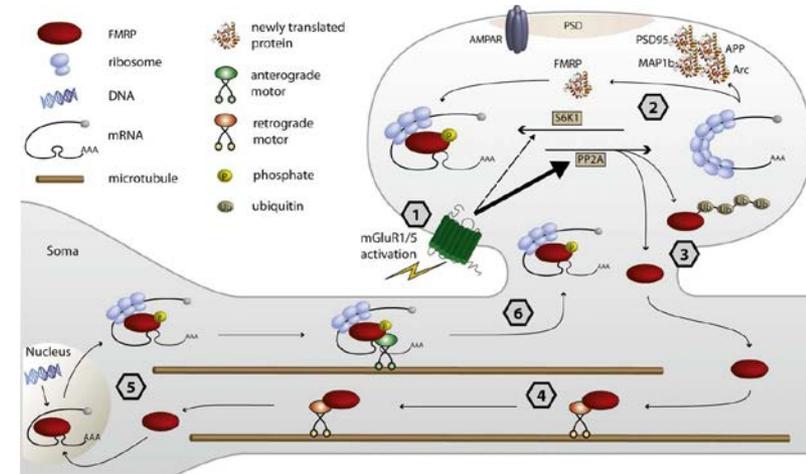
Effects on the Brain

- Key area – synapse: effects on growth of spines on dendrites
- Direct correlation between immaturity of dendritic spines and cognitive impairment
- FMR1 also regulates expression of other genes disrupting brain development



Molecular Pathways

- Immature dendritic spines affect transduction of signal at the synapse
- FMRP is important in a neural pathway – a chain of key proteins that influence synaptic transmission
- One element affected by absent FMRP is **mGluR5** which is important in cortical pathways (normally modulated by FMRP)



Drug Treatments Based on mGluR5 Theory

- Without FMRP, mGluR5 is not modulated at the synapse
- Therapy: Apply mGluR agonists to “rescue” the excessive expression of mRNA at the synapse
- Potential drugs are already on the chemist’s shelf (e.g., arbaclofen, STX107)
- When given to mice, these drugs alter course of brain development and functioning



Clinical Trials in People

- Several randomized double-blind controlled clinical trials completed and some (for newer drugs) underway
- Targeting children and adults; FRX and ASD
- Results have been disappointing.....
- After more than 5 years, still no treatment approved by FDA



The Challenges

- Outcome measures
- Placebo effects swamp the ability to detect unique signal from drugs
- Can the drugs reverse brain damage that begins prenatally?
- Will a person require life-long medications?
- Ethical issues



3. Neurologically-Based Treatments

- Targeted treatment, based on understanding of neural-cognitive architecture underlying ASD-related deficits
- Primary method – behavioral treatment that changes brain/behavior mechanisms



BU Autism Center of Excellence

Central question

Why do ~25% children with ASD fail to acquire spoken language?



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Conceptual Framework

- Deficits in speech and language are related to impairments in neural connectivity. The neural architecture for language closely linked to motor systems; language and music share neural substrates
- Test several hypotheses about specific neurocognitive mechanisms that underlie speech/language deficits in this population
- Potential mechanisms are tested in the context of an intervention study - explore developmental plasticity in children



The Intervention



Auditory-Motor Mapping Training (AMMT)

- Based on interventions developed for aphasic patients (MIT)
- Trains association between sounds and articulatory actions to facilitate speech output
- Combined intonation (song) and use of pair of tuned drums to facilitate auditory-motor mapping
- Engaging: draws on relative strengths of children with ASD and enjoyable activities
- Delivered in structured (ABA), socially engaging context



AMMT

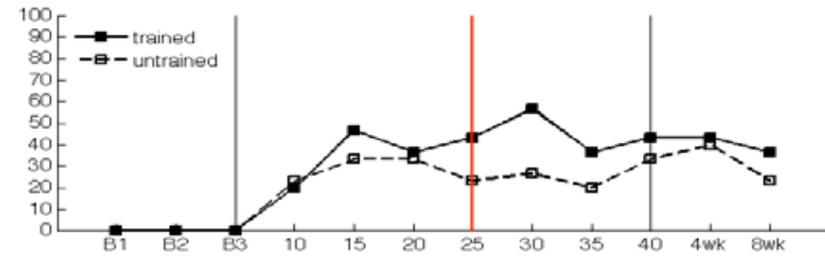
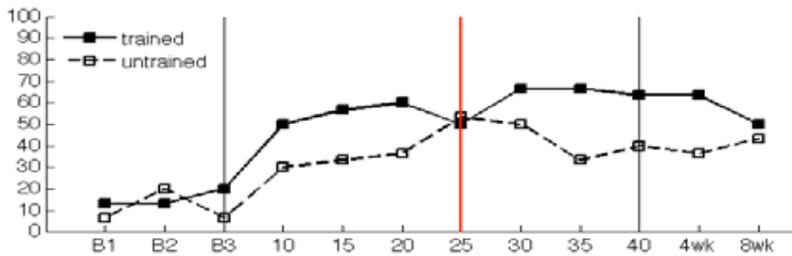
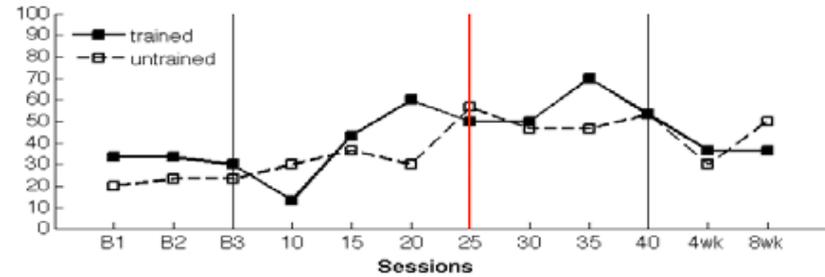
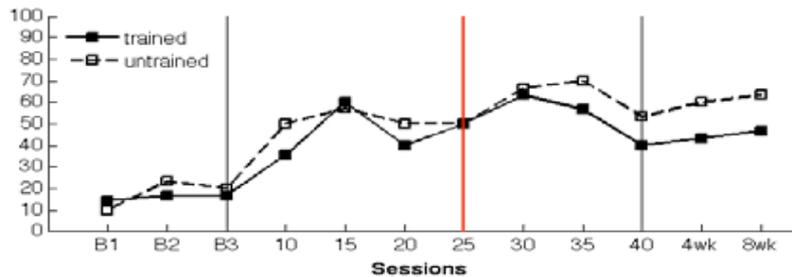
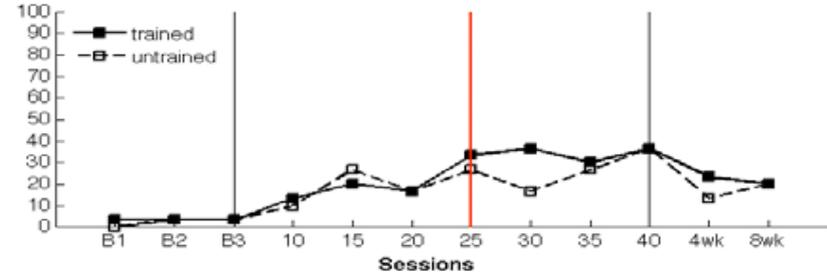
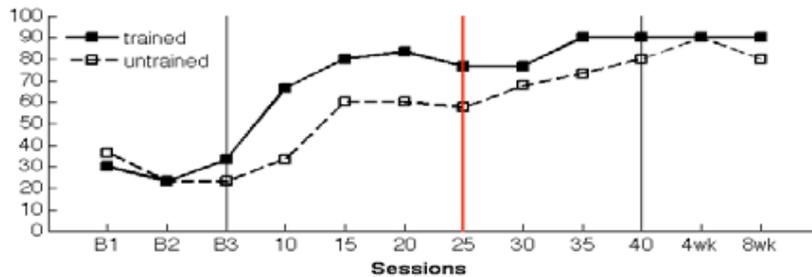


Potential Critical Components

1. Intonation – singing engages bilateral frontal-temporal network (bias to right hemisphere); slowed presentation rate; phonemes isolated and therefore easier to process
2. Imitation – through repetitive training
3. Hand-motor activities – tapping drums while intonating words; may engage a sensori-motor network that controls both hands and articulatory initiations



6 Minimally Verbal Children (5-9)



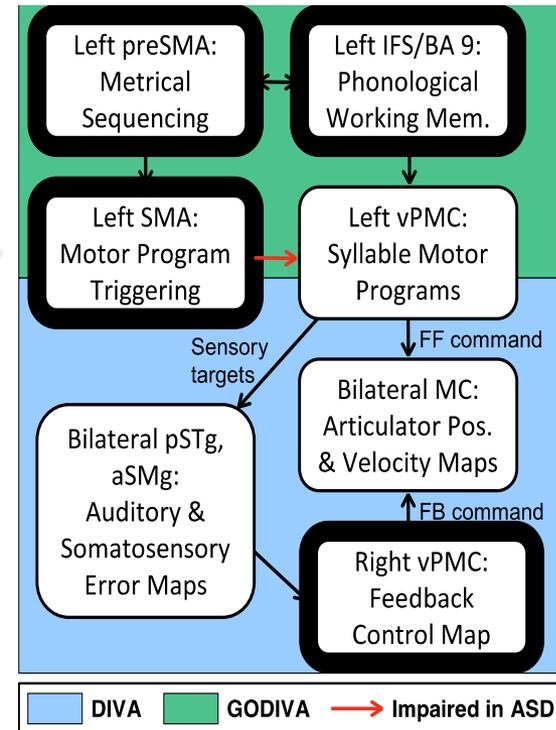
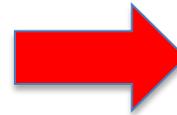
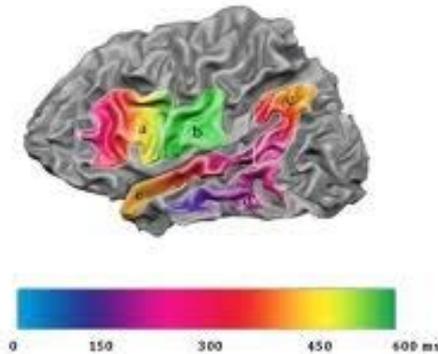
Speech Initiation



- Computational model of speech production – DIVA
- Hypothesis: Specific connection in the network for initiation of output is impaired
- Does AMMT increase this connectivity?



The Model

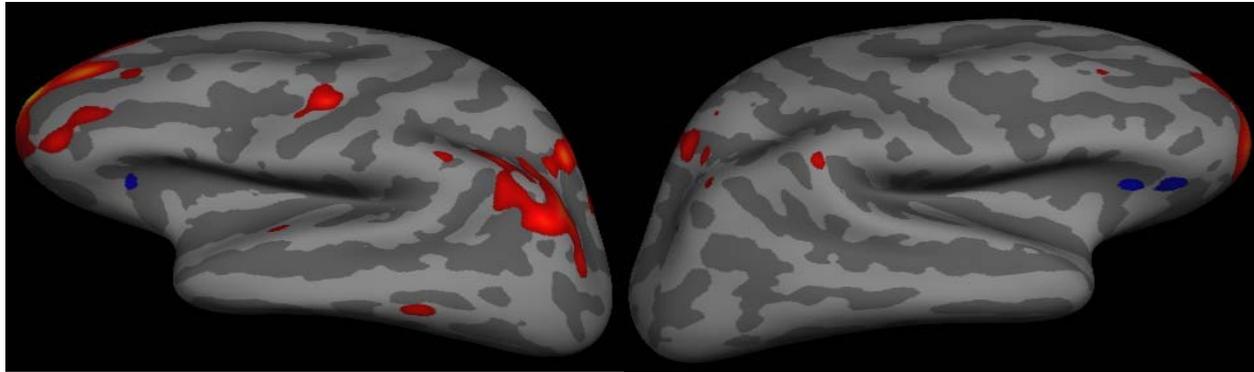




Pilot data

A: ~200 controls (resting state fcMRI); B: ASD participant

Lower FA
In ASD –
vPMC diffs



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Auditory Processing

- Auditory input is organized into 'scenes'
- Hypothesis: Failure to process sounds this way is related to speech/language deficits in ASD
- Will AMMT influence auditory processing of speech?



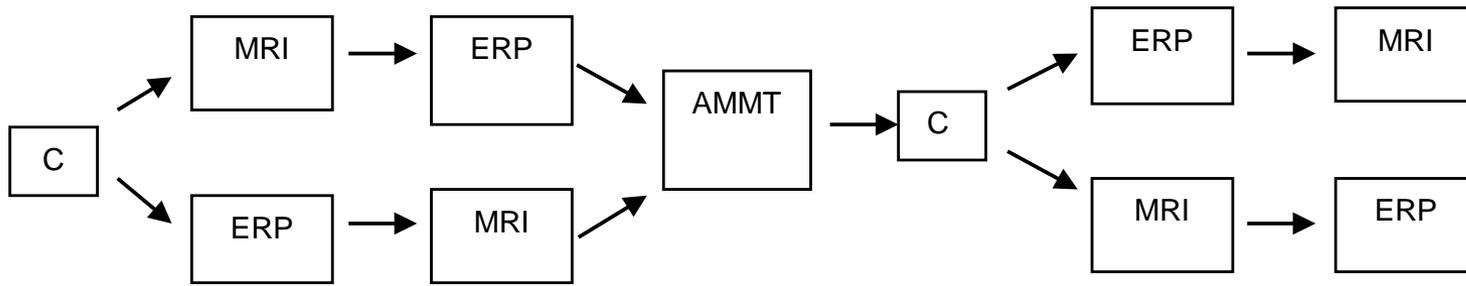
streaming object
grouping selection
object formation
understanding
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Flow Through ACE



C=Diagnostic and Behavioral Assessment Pre and Post Treatment



Translating Basic Sciences into Meaningful Change

- Scientific knowledge of ASD has advanced exponentially
- Now ready to integrate and identify novel treatment approaches and paradigms – crossing across levels from biology to behavior



Final Comments

- The landscape of research on ASD has changed radically over last two decades
- Much of this change has been driven by the families directly affected – who created new funding for research (foundations) and prompted the federal (and state) governments to increase support at all levels
- We owe these families the opportunity to participate now in the next generation of translational research programs



THANK YOU!



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