Long-term Positive Outcome in Autism Spectrum Disorders: Predictors, Characteristics, Mechanisms

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Except: Activity Kit for Babies and Toddlers at Risk (Fein, Helt, Brennan, Barton)

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Graduate students

- First 5 years
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- Dr. Molly Helt
- Dr. Christy Irvine
- Dr. Alyssa Orinstein
- Dr. Mike Rosenthal
- Dr. Joyce Suh
- Dr. Eva Troyb
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- RA: Brittany Mills

- The basic phenomenon
- Predictors
- Characteristics
- Mechanisms (?)

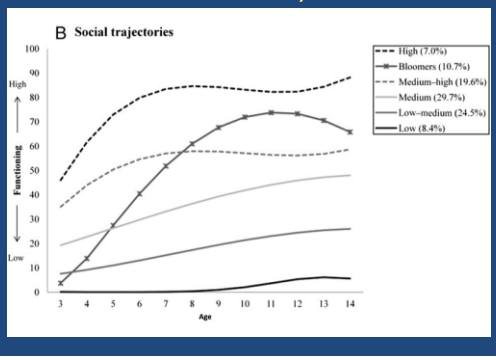
Specific Outcome: Losing Diagnosis of ASD

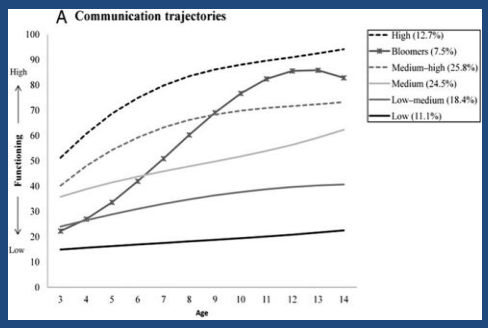
- Key recent papers:
  - Anderson, Liang, Lord (2014) followed 85 autistic children from age 2 to 19
  - 9% lost diagnosis and had normal IQ ("very positive outcome")
  - predicted in part by reductions in RRB's from age 2 to 3, hi initial IQ, and greater participation in early treatment

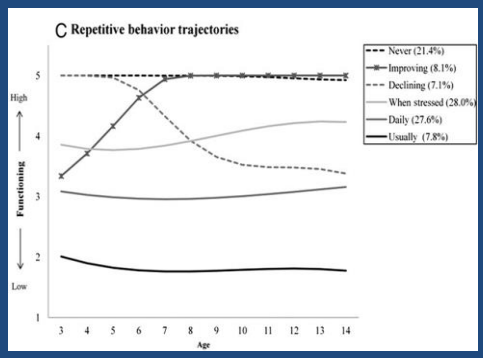
Fountain, Winter & Bearman, Pediatrics, 2012

- 6975 children aged 2 to 14 years
- 6 developmental trajectories identified
- ~10% of children experienced rapid gains ("bloomers")

Fountain et al, 2012







- In general, the 3 dimensions were associated with one another, such that children who improved on 1 dimension were likely to improve on the others.
- 'Blooming' was associated with high SES, and no ID

Rogers et al (2014) Autism treatment in the first year of life: A pilot study of Infant Start…. for symptomatic infants. JADD.

- 7 symptomatic infants aged 7-15 months had good outcomes at 36 months
- 5 of the 7 had no significant signs of autism
- 1 had average language and cognitive and PDD-NOS
- 1 had significant developmental delay and autism

MacDonald, et al, 2014 Assessing progress and outcome of EIBI for toddlers with autism.

- Followed 83 children 18-23 month olds, 24-30 month olds, and 2.5 to 3 year olds
- Treatment grains were greatest with entry into treatment before second birthday

Optimal Outcome: Background (see Helt et al, 2008 review in Neuropsychology Review)

- Most longitudinal studies report 3-25% no longer meet criteria for autism on follow-up
- Often assumed that
  - the initial diagnosis was incorrect or
  - despite improvement, the core symptoms are still present (e.g., Piven, 1996; Seltzer et al, 2004; Turner and Stone, 2007)

Pervasive Developmental Disorder Can Evolve into ADHD: 11 Case Illustrations

Deborah Fein, Ph.D.
Pamela Dixon, M.A.
Jennifer Paul, M.A.
Harriet Levin, OTR/L

Journal of Autism and Developmental Disorders, August, 2006

Case of ST

- Language lost around 15 months
- Met criteria for full autism at age 3
- Responded rapidly to intense ABA program starting at age 3
- Age 5, starting to develop more social interest; diagnosed PDD-NOS
- Age 7.5, quite social, academically and cognitively normal, attention problems, qualified for ADHD
- Age 13, socially normal, academically high achieving, good motor skills, mild attention problems, tics
- Age 18, attending a music conservatory
- Age 22, graduating from a major university, planning graduate school, close friends, romantic relationship, mild residual social anxiety

Interpretations of the autistic to ADHD clinical picture

- Comorbid ASD/ADHD; autism resolves, leaving the ADHD clinical picture
- The children are a severe subtype of ADHD that presents as autism in the early years
- Attention impairment is part of ASD; when social, behavioral, and communication impairments subside, attention impairments remain

Predictors

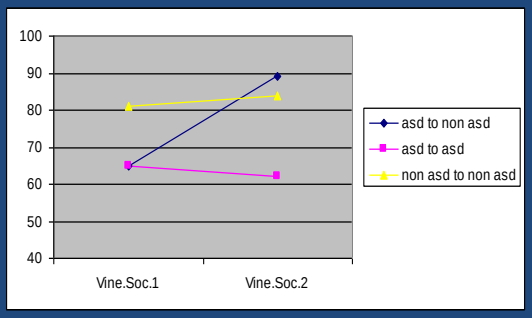
Sutera et al (2007)

- 73 children dx'd with ASD at age 2 followed to age 4
- 13 (18%) lost dx

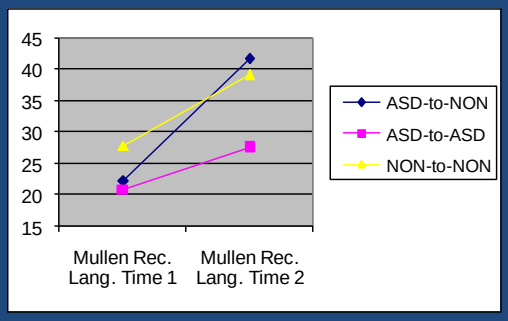
	autism age 2	no autism age 2
autism age 4	60 (49 AD 11 PDD-NOS*)	0
no autism age 4	13 (6 AD 7 PDD-NOS)	17

4 additional children moved from ASD to global developmental delay

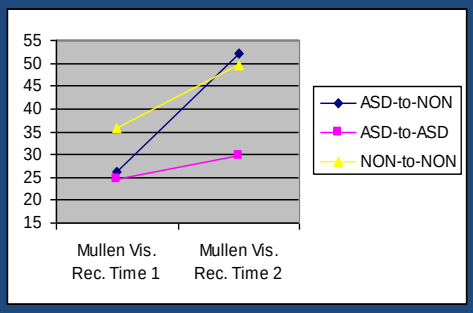
Vineland Socialization



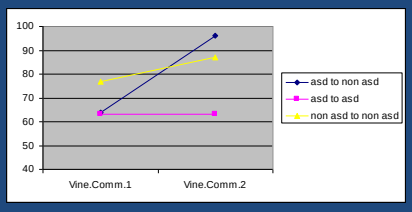
Receptive Language



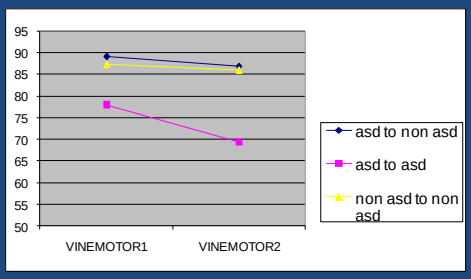
Visual Reception (nonverbal reasoning)



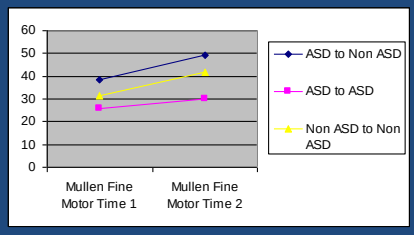
Vineland Communication



Vineland Motor



Mullen Fine Motor



Early Characteristics of Children Who Lose Their Autism Diagnosis Between Age 2 and 4 (Moulton et al, 2016)

- 207 children with ASD at age two who were reevaluated at age four
- "optimal outcome" defined more strictly
- 83% (171) retained an ASD diagnosis
- 9% (19) showed clear ASD at age two but no ASD at age four, with average cognition, language, communication and social skills

Non-predictors

- age at dx (all detected thru screening)
- sex
- maternal education
- ethnicity
- cognitive function (except for low MA)

Significant Predictors

- initial diagnosis
  - 16% of PDD-NOS,
  - 8% of AD,
  - 0% of ASD low MA)
- milder symptoms in social communication, stereotypies and sensory abnormalities
- higher adaptive function

What about predictors of low-mental age ASD to intellectual disability?

- Hinnebusch, A. J., Miller, L. E., & Fein, D. A. (2017). Autism spectrum disorders and low mental age: Diagnostic stability and developmental outcomes in early childhood. Journal of Autism and Developmental Disorders. 47(12): 3967–3982.

Diagnostic Stability

Time 1 Diagnosis	Time 2 Diagnosis				
	ASD	Non-ASD	x^2	p	Φ (Phi)
Autistic Disorder	96 (86.5%)	15 (13.5%)	9.34	.009	.207
PDD-NOS	60 (73.5%)	22 (26.8%)			
ASD Low-MA	24 (96.0%)	1 (4.0%)			

Developmental Growth between Ages 2 and 4 (Hinnebusch, Miller and Fein 2017)

	AD	PDD-NOS	ASD-low MA	*p*
MSEL visual reception	0.86	0.99	0.48	0.002
MSEL fine motor	0.69	0.74	0.27	<0.0005
MSEL receptive language	0.77	0.85	0.35	<0.0005
MSEL expressive language	0.88	0.99	0.34	0.015
VABS receptive language	0.80	0.76	0.24	0.075
VABS expressive language	0.77	0.91	0.41	0.01
VABS interpersonal relationships	0.54	0.66	0.13	0.001
VABS play and leisure	0.46	0.47	0.14	0.049
VABS coping	0.50	0.82	0.06	<0.0005

Characteristics

Inclusion Criteria

3 groups:
- HFA (high functioning autism)
- TD (typical)
- OO (optimal outcome)

All groups:
- age 8-21
- VIQ, PIQ, and FSIQ in the normal range

Typical controls:
- no history of ASD
- no first degree relatives with ASD
- Vineland Commun. And Social. >70

HFA:
- ASD as per ADOS and clinical judgment

Inclusion criteria for optimal outcome group

HISTORY
- ASD diagnosis made by a specialist before the age of 5
- Early language delay
- Early report reviewed by Dr. Barton blind to group, mixed in with foils

CURRENT
- No current ASD as per ADOS and clinical judgment
- Vineland Communication and Socialization >77
- Full inclusion in regular education with no aide, no social skills services

Exclusion criteria for all groups

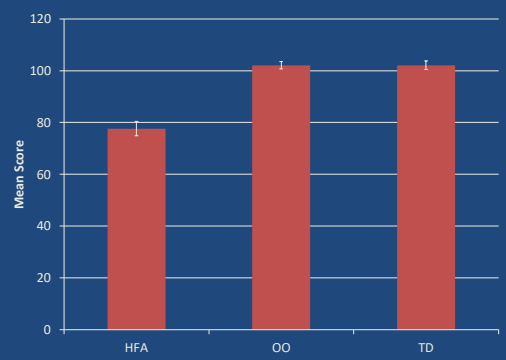
- Active psychosis
- Severe uncorrected visual, hearing or motor deficit
- TBI with any loss of consciosness
- Seizure disorder
- Fragile (X)

Basic Functioning

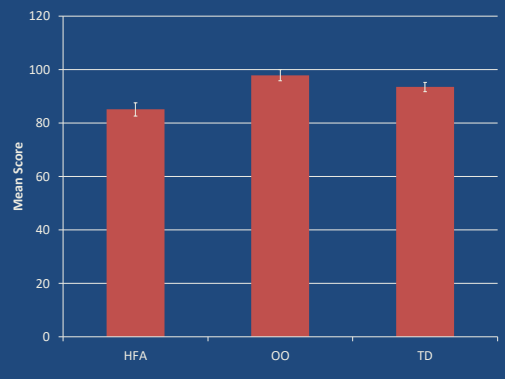
Fein et al (2013) J. Child Psychol. and Psychiat.

	HFA (n=44)	OO (n=34)	TD (n=34)	p
Sex	40 M; 4 F	27 M; 7 F	31 M; 3 F	.23
Age (8-21)	13.9 (2.7)	12.8 (3.5)	13.9 (2.6)	.20
VIQ	105.4 (14.4)	112.7 (13.7)	112.0 (11.2)	.03
NVIQ	110.2 (12.8)	110.3 (15.1)	112.8 (11.3)	.64

Vineland Socialization



Vineland Communication



Troyb et al (2014) Restricted and repetitive behaviors in individuals with a history of ASDs who have achieved optimal outcomes. JADD, 44:3168–3184

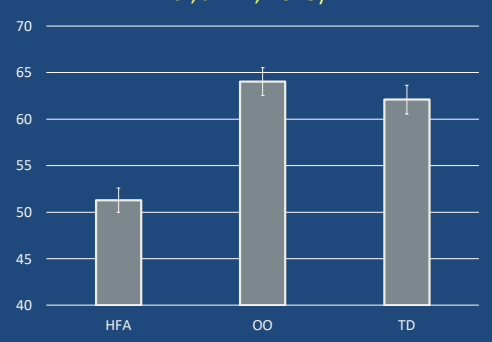
RRB's are often noted to be harder to remediate than social and language deficits

Measures and Results

- ADI-R and ADOS, Yale Special Interests Survey, Repetitive Behavior Scale-R
- Past behavior:
  - HFA and OO groups did not differ on any scale or most items.
  - HFA group was sig. more severe on sensitivity to noise and distress to minor changes in routine
- Current behavior:
  - HFA group had persistent sensory and motor abnormalities, circumscribed interests, and rituals
  - OO group did not differ from TD on almost all items. Mild routines on sleeping and meals

Let's looks at a few more subtle markers…

Modified Reysen Likeability Scale (Orinstein et al, JADD, 2015)



Uh, Um, and Autism: Filler Disfluencies as Pragmatic Markers (Irvine et al, JADD, 2016)

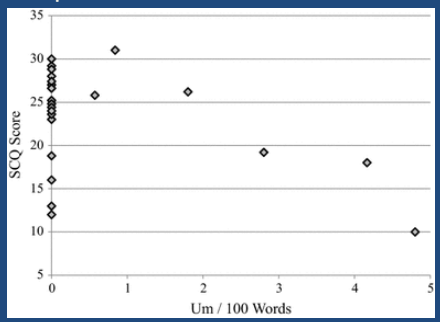
- Filler dysfluencies such as 'um' and 'uh' serve different communicative functions
- In English, 'uh' may be more inner-directed, priming word-finding
- 'Um' may be more social, communicating word-finding difficulty and holding the floor

- Participants described 6 paintings while tapping the right index finger
- Descriptions were transcribed and coded for 'um' and 'uh' per 100 words
- Nonparametric analyses found no group differences in rates of 'uh' (p=.23)
- Group differences in 'um' were found:
  OO = TD > HFA, with medium effects

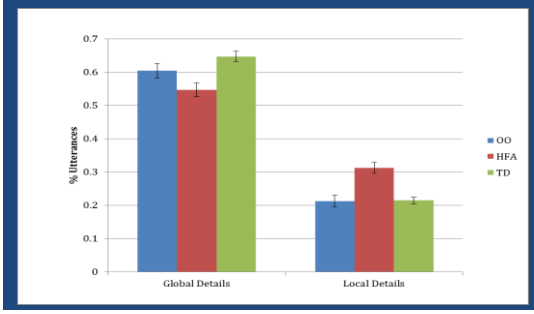
Furthermore…

- 'Uh' rates were not correlated with any social or language measure for any group
- 'Um' rates were not correlated with any social or language measure for OO or TD groups
- For HFA group, 'Um' rate was correlated with Social Communication Questionnaire, $r = -.45$, $p < .05$, such that lower *um* rate was associated with greater ASD symptomatology.

Six of the 24 HFA participants produced at least one 'um'



Fitch, A., et al. (2015). Detail and gestalt focus in individuals with optimal outcomes from ASD. J Autism Dev Disord. 45: 1887-96. Main result: Global/local composite OO=TD>HFA



Orinstein et al (2015) Psychiatric symptoms in youth with a history of autism and optimal outcome. JADD

- Background:
  - 70 % of early adolescents with HFA meet criteria for at least one comorbid psychiatric disorder; 41% have two or more
  - Most common: social and other anxiety, ADHD, oppositional defiant disorder (Simonoff et al, 2008; Levy et al, 2010)
  - Adults with HFA: Anxiety, obsessive–compulsive behavior, tics, and ADHD (Burd et al, 2002)

Past Internalizing Disorders

	TD (N=34)	OO (N=33)	HFA (N=42)	*p*	Post-Hoc
Panic disorder	0	0	0	NA	
Specific phobia	2	8	6	.11	OO>TD
Separation anxiety	0	0	3	.085	
Social phobia	0	0	2	.20	
Generalized anxiety	0	0	3	.085	
OCD	1	0	4	.13	
PTSD	0	0	2	.20	
Major depression	1	1	8	.018	HFA>TD,OO
Bipolar I or II	0	0	0	NA	

Past Externalizing and Other Disorders

	TD (N=34)	OO (N=33)	HFA (N=42)	*p*	Post-Hoc
ADHD	1	13	22	<.001	OO,HFA>TD
Conduct disorder	0	0	1	.45	
Oppositional defiant disorder	2	1	8	.045	HFA>OO
Anorexia nervosa	0	0	0	NA	
Bulimia nervosa	0	0	0	NA	
Encopresis	0	0	2	.20	
Enuresis	2	2	4	.79	
Tic disorders	0	4	7	.05	OO,HFA>TD

Current Internalizing Disorders

	TD (N=34)	OO (N=33)	HFA (N=42)	*p*	Post-Hoc
Panic disorder	0	0	0	N/A	
Specific phobia	0	5	6	.062	OO,HFA>TD
Separation anxiety	0	0	0	N/A	
Social phobia	0	0	2	.20	
Generalized anxiety	0	0	2	.20	
OCD	1	0	4	.13	
PTSD	0	0	0	N/A	
Major depression	0	1	3	.25	
Bipolar I or II	0	0	0	N/A	

Current Externalizing and Other Disorders

	TD (N=34)	OO (N=33)	HFA (N=42)	*p*	Post-Hoc
ADHD	1	8	14	**.005**	OO,HFA>TD
Conduct disorder	0	0	2	.20	
Oppositional defiant disorder	3	1	1	.36	
Anorexia nervosa	0	0	0	N/A	
Bulimia nervosa	0	0	0	N/A	
Encopresis	0	0	1	.45	
Enuresis	0	0	1	.45	
Tic disorders	0	0	5	**.015**	HFA>TD,OO

Specific Phobias

- HFA: crowds, babies crying, dogs,
- OO: dark, stink bugs, ants and bees, loud noises, crowds, elevators, ketchup, germs, dogs, babies crying, boats/water, heights
- TD: dogs, forests, snakes

Conclusions

- HFA individuals had the highest level of current and past comorbid psychiatric disorders
- OO psychiatric symptoms abated over time
- Most frequent: phobias, ADHD
- Also: tics, depression, ODD
- HFA group also had generalized anxiety and social phobia

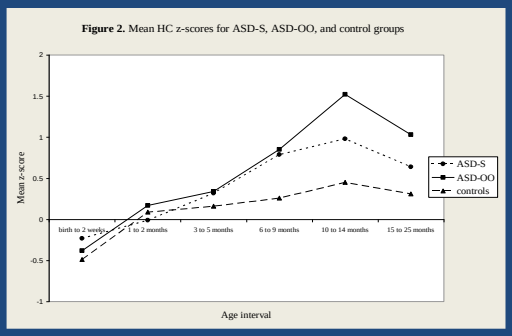
Suggested Mechanisms of Co-Morbidity

- Reactive disorder because of social stress
- Behaviorally similar symptoms with different causes
- Common underlying pathophysiology
- Misdiagnosis (avoidant anxious children may meet ADOS criteria for ASD)
- Subtypes of ASD that include other symptoms

Mechanisms

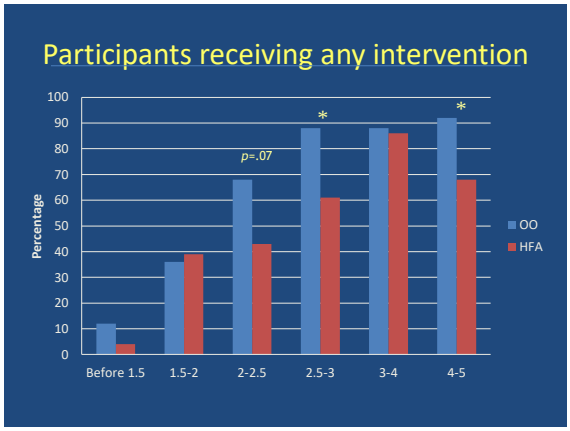
- Head circumference
- Intervention
- fMRI

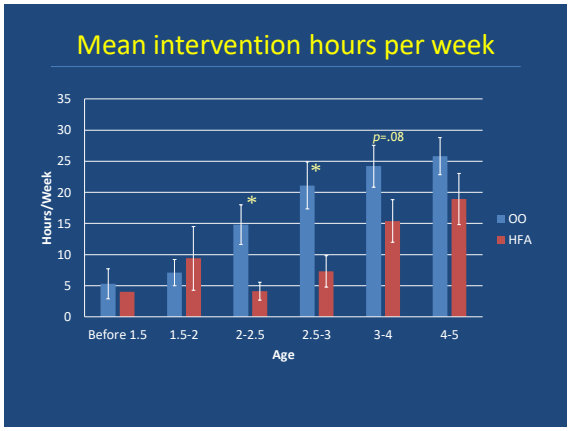
Mean Head Circumference (Mraz et al, 2009)

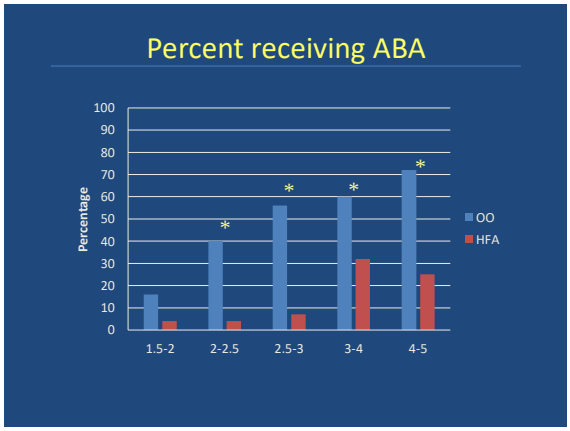


Group differences at 6-9 (.05), 10-14 (.01) and 15-25 (.07)

Intervention for Optimal Outcome in Children and Adolescents with a History of Autism (Orinstein et al, J. Dev Behav Pediatr, 2014)


Participants receiving any intervention
Percentage
100
90
80
70
60
50
40
30
20
10
0
p=.07
*
*
Before 1.5
1.5-2
2-2.5
2.5-3
3-4
4-5
OO
HFA


Mean intervention hours per week
Hours/Week
35
30
25
20
15
10
5
0
p=.08
*
*
Before 1.5
1.5-2
2-2.5
2.5-3
3-4
4-5
Age
OO
HFA


Percent receiving ABA
Percentage
100
90
80
70
60
50
40
30
20
10
0
*
*
*
*
1.5-2
2-2.5
2.5-3
3-4
4-5
OO
HFA

Eigsti, et al (2016) Language comprehension and brain function in individuals with an optimal outcome from autism. NeuroImage: Clinical, Vol 10, pp 182-191

fMRI questions

- To what degree does normal language performance in OO reflect normalized brain function?
- Mundy and Crowson (1999) suggest 'neural normalization' with successful, early treatment of autism
- Dawson et al (2012) reported normalized EEG (ERP's and spectral power) to faces vs. objects in toddlers treated for 2 years with Early Start Denver Model
- Other conditions (e.g., treated dyslexia, healthy aging) suggest a combination of normalization and compensation underlie successful functioning (e.g., Eden et al, 2004)

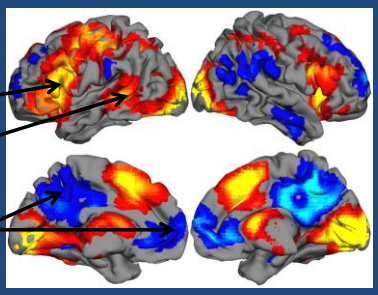
Task and Imaging

- Reading comprehension task adapted from Kana, Minshew, Just et al. (2006)
- T-F judgments on sentences (no group differences on accuracy or RT)
- Looked for brain areas in OO showing
  - Normalized activity (OO = TD ≠ HFA)
  - Compensatory activity (OO > TD and HFA)
  - Residual ASD activity (OO = HFA ≠ TD)

Reading Comprehension Activation (orange) and Deactivation (blue) across groups

A broad bi-hemispheric network including Broca's and Wernicke's areas

Deactivated the default mode network



Brain areas showing 'residual ASD' pattern in OO group

Left

- dorsolateral prefrontal cortex
- inferior parietal lobule (supramarginal gyrus)
- posterior cingulate gyrus

Right

- superior/middle temporal gyri

Brain areas showing 'compensatory' activation in OO group

Left

- precentral gyrus
- inferior temporal gyrus
- superior temporal gyrus
- precuneus
- middle occipital gyrus
- anterior and posterior cerebellum

Right

- motor and supplementary motor regions
- middle and superior frontal gyri
- supramarginal gyrus
- superior temporal gyrus
- parahippocampal gyrus
- anterior and posterior cerebellum

Brain areas showing normalized functioning in OO group

Left	Right
None	None

How Can OO Happen: Suggested Mechanisms for Losing a Neurodevelopmental Disorder

- The clinical picture represented a transient developmental delay
- Treatment bypasses abnormal motivation system(s)
- Neurologically based deficit in social orienting and joint attention is prevented from disrupting further neurological development (Mundy & Crowson, 1999)
- Pairing social contact with primary reinforcers results in social contact developing secondary reinforcing value (Geri Dawson) (how does the connection become autonomous?)
- Suppressing interfering behaviors, especially "self-stimulatory" and repetitive behaviors, that represent internal focus of attention
- Forcing attention to the environment rather than the internal world over many hours a week

Most suggested mechanisms are consistent with Menon's (2011) view of dysfunctional network connections in autism

- The **social network** does not appropriately activate the **reward network**, leading to a deficit in primary social motivation
- The **salience network** does not appropriately disengage the **default mode network**, leading to an inward focus of attention

Future Directions for Optimal Outcome Research

- How many have this potential?
- What are individual patterns of behavioral recovery (e.g., does social interaction always normalize first)?
- What are biological characteristics of OO children (genetic, structural, functional, networks not highly connected or interacting properly)? (new 5-year study)
- What is development into young adulthood like (new 5-year study)
- Is intense intervention always necessary (new 5-year study)

THANK YOU!