Enhancing Neurodevelopmental Resilience from Conception to Adulthood

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Faculty Disclosure

- Grants — Curemark, Roche, Otsuka, NIH
- Advisory Board — Curemark, BioMarin, Janssen, Axial Biotherapeutics
- Honoraria/Royalties: Oxford University Press, Taylor & Francis

PRONTO Lab: Program for Research On Neurodevelopmental and Translational Outcomes

- Our mission is to build resilience in children with or at risk of neurodevelopmental disorders through innovative biomedical and grit and resilience enhancing interventions and evaluate their impact in real world settings such as schools.

PRONTO Lab

Bob Hendren, D.O.
Principal Investigator

Steve Bent, M.D.
Research Director

Felicia Widjaja, M.P.H., C.C.R.P
Clinical Research Supervisor

China Parenteau
Clinical Research Coordinator

Bushra Hossain
Clinical Research Coordinator

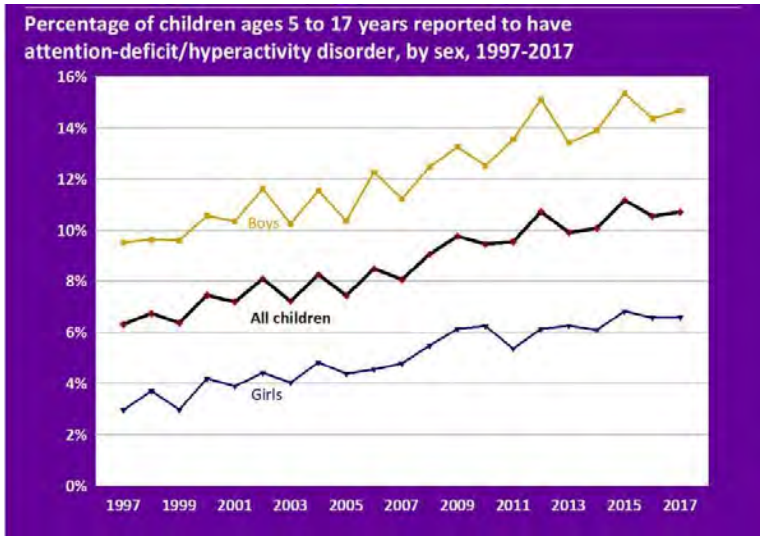
Resilience

- The capacity of a system to adapt successfully to challenges that threaten the function, survival, or future development of the system.
- Resilience is common, dynamic, generated through myriad interactions of multiple systems from the biological to the sociocultural, and mutable given strategic targeting and timing.
- Neuroscience based-interventions promote resilience by improving the executive functions (EF); inhibitory control, planning, and problem-solving skills, emotional regulation, and attentional capacities.

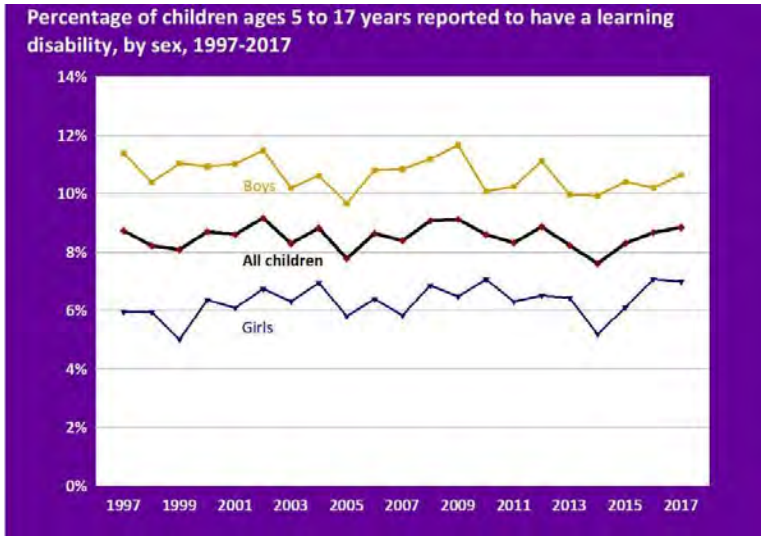
Masten, 2018; Greenberg, 2006

Increasing Prevalence of NDDs

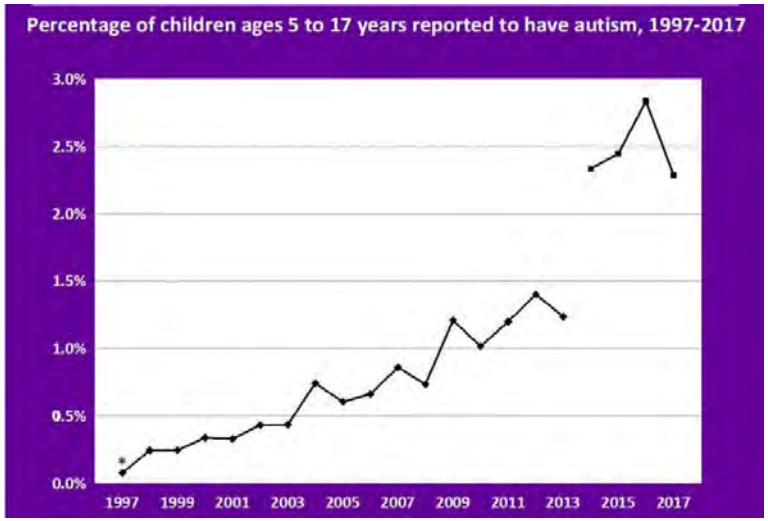
ADHD



LD



ASD



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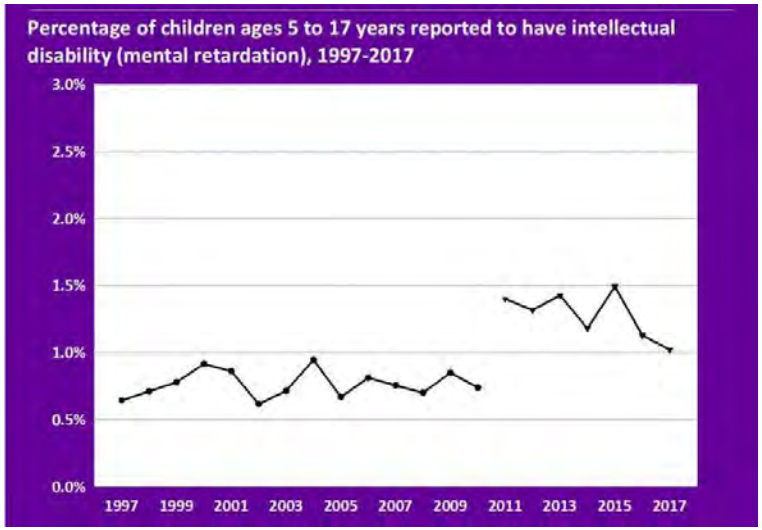

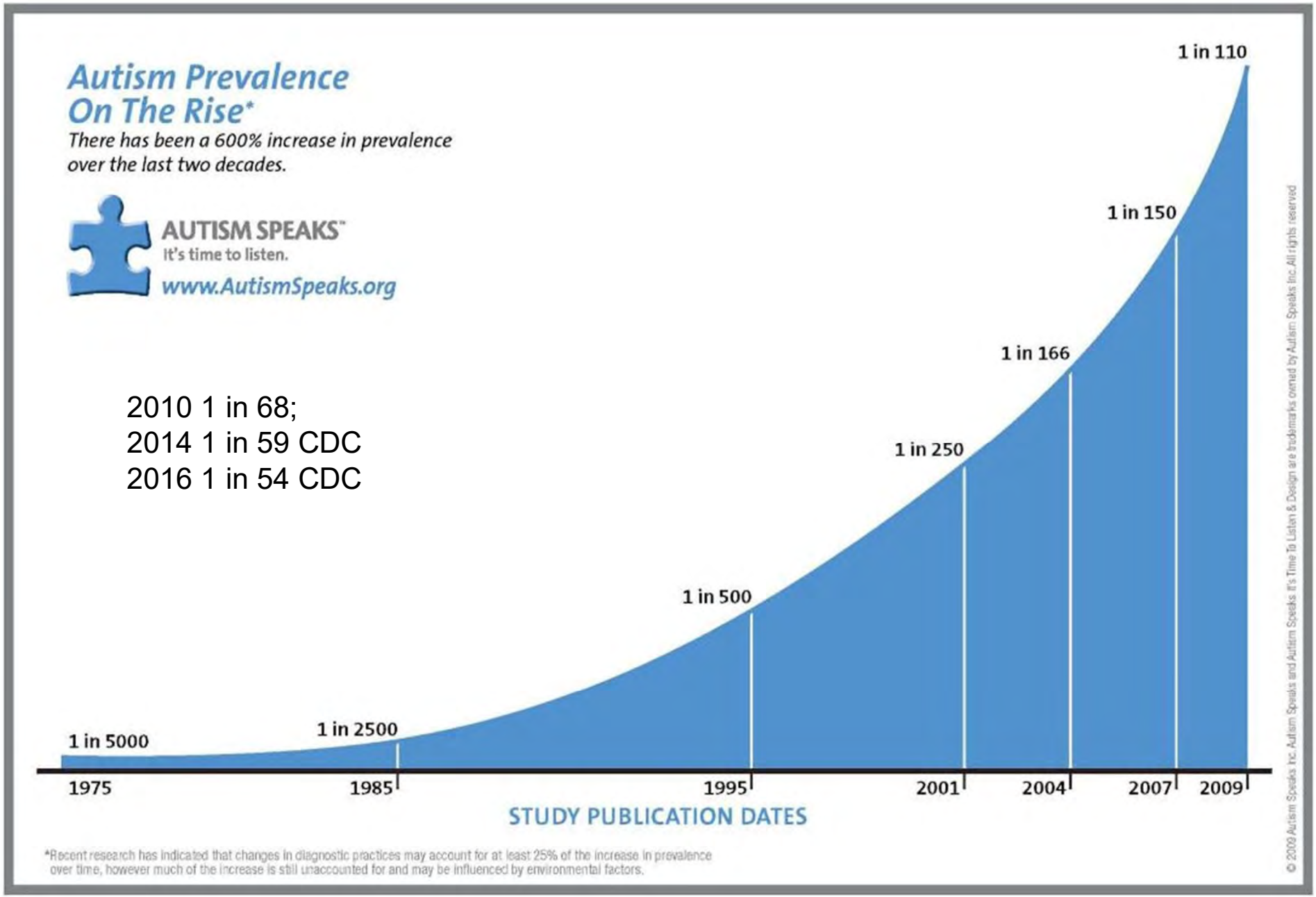
Autism Prevalence
On The Rise*
There has been a 600% increase in prevalence over the last two decades.
AUTISM SPEAKS™
It's time to listen.
www.AutismSpeaks.org
2010 1 in 68;
2014 1 in 59 CDC
2016 1 in 54 CDC
1 in 5000
1 in 2500
1 in 500
1 in 250
1 in 166
1 in 150
1 in 110
1975
1985
1995
2001
2004
2007
2009
STUDY PUBLICATION DATES
*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.
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Prevalence of NDD

- Possible explanations include
  - Diagnostic expansion and substitution
  - Better reporting
  - Increased recognition
  - Increasing acceptability
  - Immigration for services
  - Environmental toxins
  - Infectious and immune vulnerability
  - Epigenetic processes

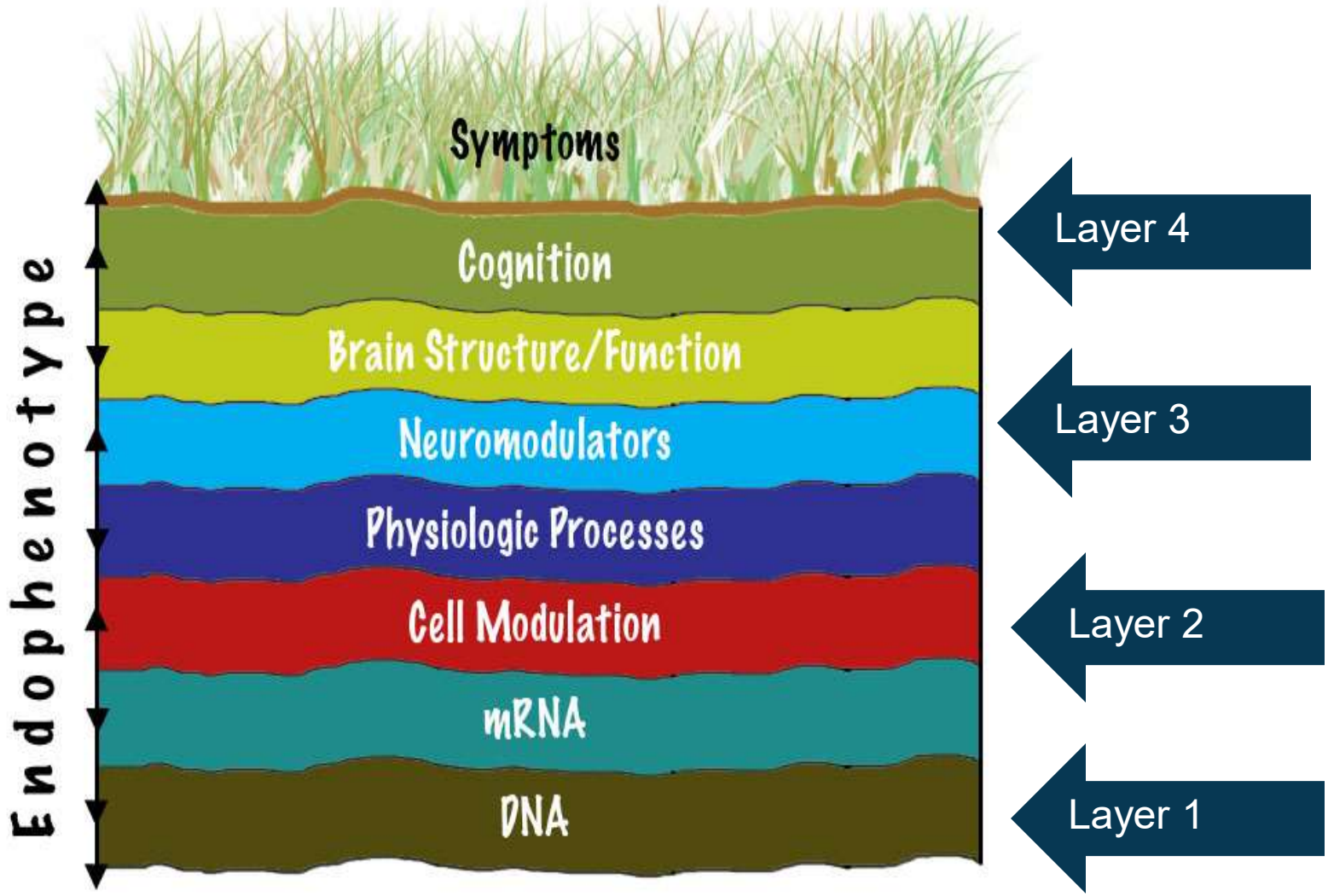
Rutter M. *Acta Pediatr*. 2005;94(1):2-15. Centers for Disease Control and Prevention. Autism Spectrum Disorders. www.cdc.gov/ncbddd/autism. Accessed June 16, 2015. Hagerman R, Hendren RL (Eds). *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms*. Oxford University Press; 2014.

Model for Neurodevelopmental Disorder (NDD) Etiology

- First hit – Genetic neurodevelopmental vulnerability
- Second hit – Environmental "stressor" and interaction between the two
- Third hit – Restricted development

Translating from “Terroir”: Model

Epigenetic Layer to Targeted Treatment



Hagerman R, Hendren RL (Eds). *Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms*. Oxford University Press; 2014.

IACAPAP
International Association for Child and Adolescent Psychiatry and Allied Professions

Layer-Based Interventions

Layer 4 – Behavioral interventions, family support, structure

Layer 3-4 – Speech and language, OT, therapy, CBT

Layer 2-3 – Pharmacotherapy

Layer 2 – Biomedical/epigenetic

Layer 1 – Gene modification

CBT = cognitive-behavioral therapy; OT = occupational therapy.

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Enhancing Perinatal
Neurodevelopment

Brain Growth and Development

- Parental history and early developmental experiences also exert effects through epigenetic information not contained in the DNA sequence, which cause changes in gene expression
  - methylation and chromatin patterning
  - Histone acetylation
  - noncoding RNAs and mitochondria

- Transgenerational epigenetic effects interact with conditions at conception to program the developmental trajectory of the embryo and fetus, ultimately affecting the lifetime health of the child

Wells et al, 2016; Lane M, et al. *Science*. 2014;345(6198):756-760.

Medical Hypotheses 127 (2019) 26–33

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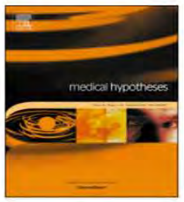
journal homepage: www.elsevier.com/locate/mehy



Improving autism perinatal risk factors: A systematic review

Jenna Cheng[a], Brenda Eskenazi[b], Felicia Widjaja[c], José F. Cordero[d], Robert L. Hendren[e,*]

- MEDLINE search for studies between January 1, 2005 and July 1, 2018 for perinatal risk factors and autism, risk factors such as infections, medications, and environmental factors including non-chemical stressors, chemical and nutritional factors. Then, we searched for interventions that may improve neurodevelopmental outcome including nutritional supplements during pregnancy, breastfeeding, and postpartum stress reduction.

- Conclusions: Studies of individual components for improving pregnancy outcomes and several uncontrolled preconception to infancy medical practices suggest that multiple interventions might improve the outcomes of pregnancies where there is risk for developing ASD.

Cheng…Hendren, Medical Hypothesis, 127 (2019) 26-33
Hertz-Picciotto et al, 2018, Wang et al, 2017, Getahun et al., 2017, Hisle-Gorman et al., 2018

Pregnancy NDD Risk (Grade B Mod)

- Maternal Infection and Inflammation (congenital rubella)
- Environmental Toxicants (methylmercury, PCBs, Toluene, Arsenic)
- Air Pollution
- Pesticides
- Bisphenols and Phthalates
- Valproic Acid
- Thalidomide
- SSRIs
- Acetaminophen
- Heavy Metals

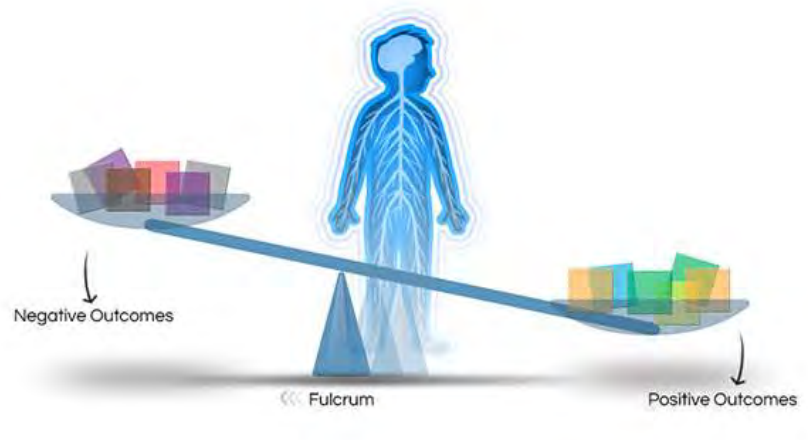
Atladottir et al., 2010; Ornoy et al, 2016; Muzhe & Chou, 2017; Eskenazi et al, 2008; Kondolot et al, 2016; Christensen et al. 2013; Croen et al, 2011; Bourkhris et al, 2016; Avella-Garcia CB et al, 2016; Kern 2016

Can NDDs be Prevented? (Grade C Mod)

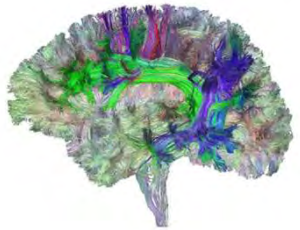
- Folic Acid and multivitamin Supplements before and during pregnancy associated with reduced risk of ASD (45,300 children; P<.001)
- Omega-3 Polyunsaturated Fatty Acid
- Vitamin D
- Antioxidants
- Iron
- Choline/phosphatidylcholine
- One practice minimized toxicant exposure; maximized breastfeeding; probiotics, nutritional counseling; limited antibiotics; minimized acetaminophen
  - Out of 294 general pediatric patients followed since 2005 there were 0 new cases of autism

Levine SZ et al., 2018; Suren et al., 2013; Morgese & Trabace, 2016; Stubbs et al., 2016; Zhang et al, 2015; Schmidt et al., 2014; Ross et al, 2016; Mumper E. *North American Journal of Medicine and Science*. 2013;6(3):134-144

Targeting Neurodevelopmental Resilience



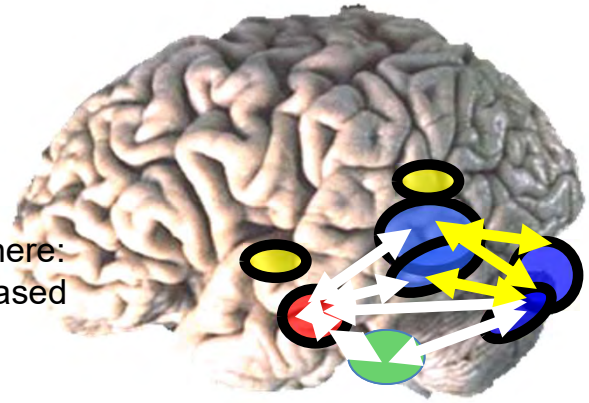
UCSF Dyslexia Center

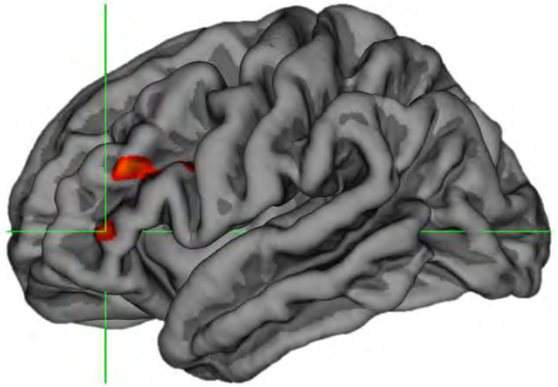


- Our vision is to demonstrate more clearly how neuroscience research can impact education, with a focus on personalized learning.
- *Phenotyping Project*: Neuroscience based evaluation- Marilu Gorno Tempini, MD, PhD
- *School Outcome project*: Hendren PRONTO lab

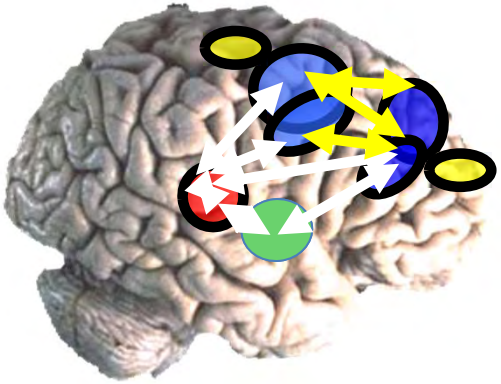
Neural Networks and Biology

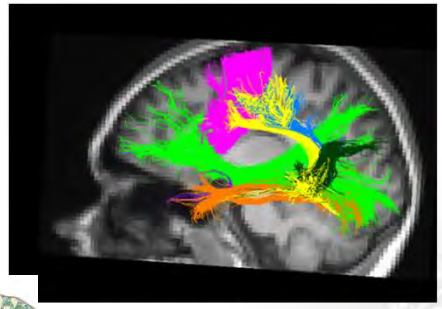
Left hemisphere:
Language-based
Symbolic

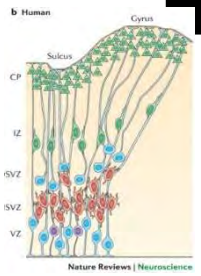




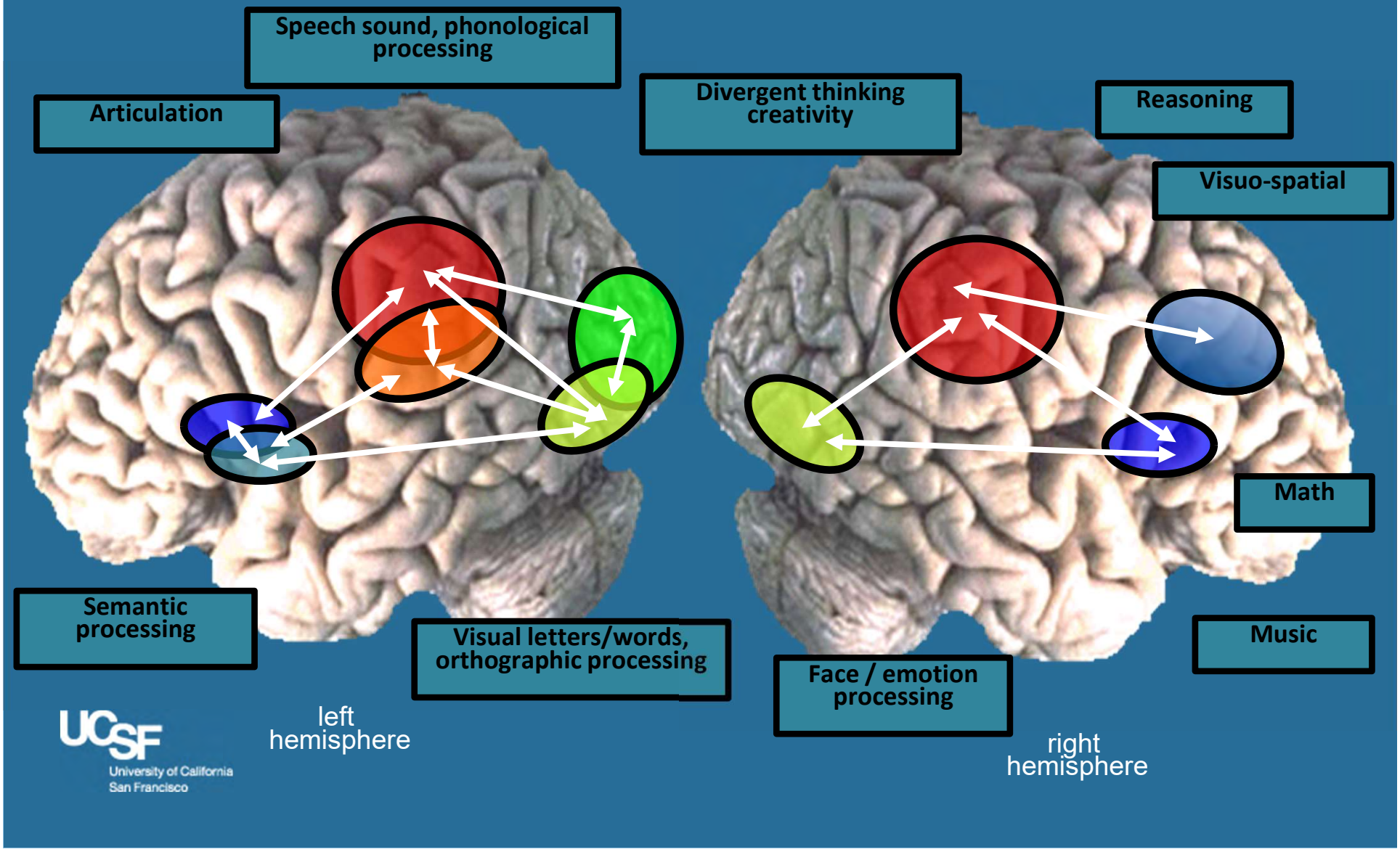
Right hemisphere:
Visuo-spatial-based
Social



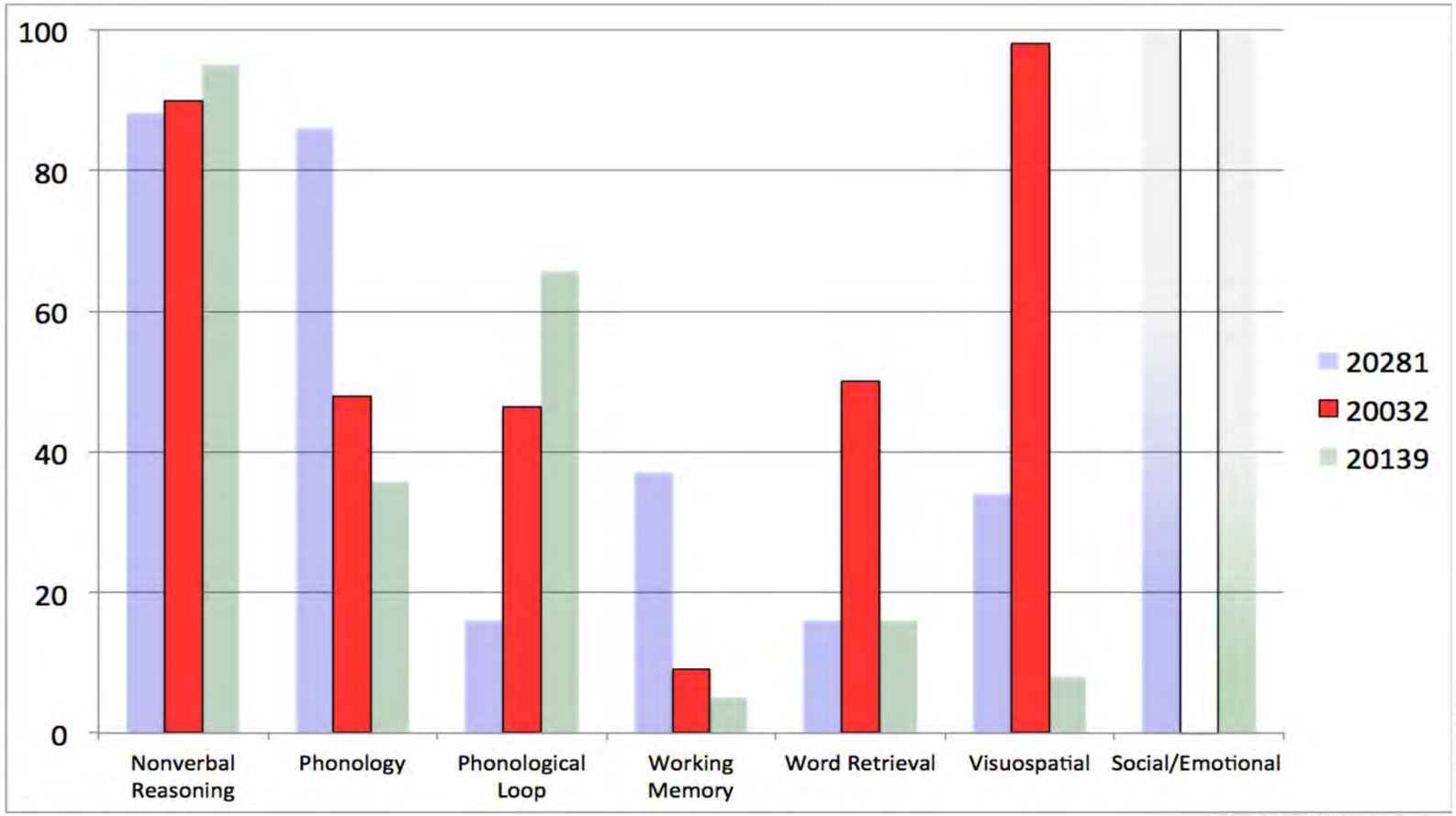




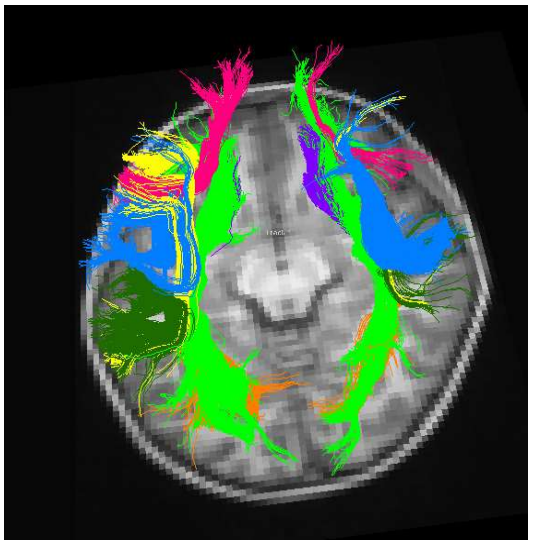
Many brain networks are involved in dyslexia



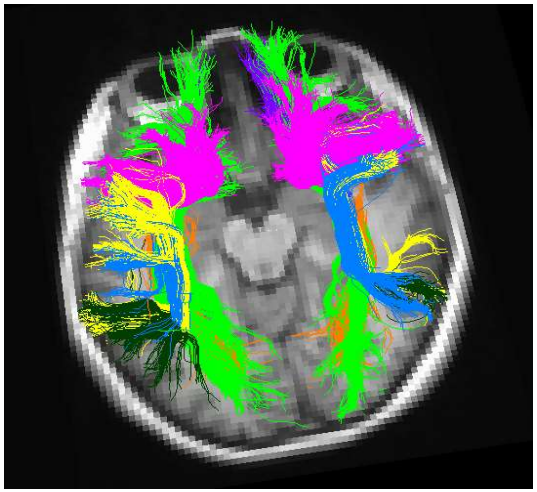
Cognitive Testing Overview (three cases)



Three dyslexia cognitive/neural phenotypes

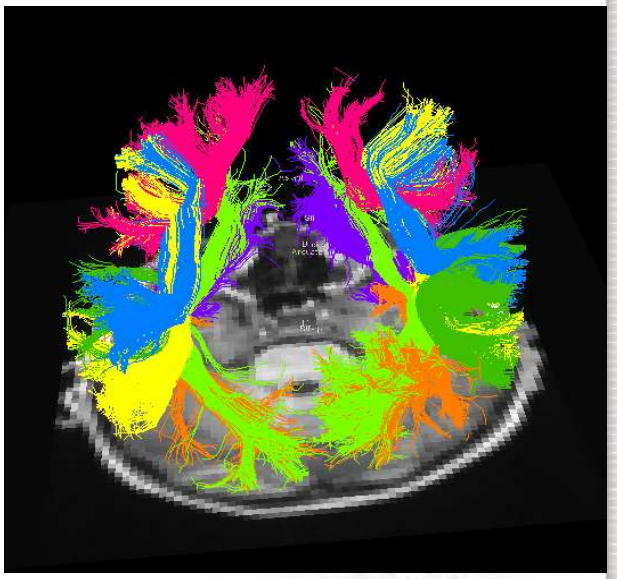


Visuo-spatial/social



Working memory
Insight

Visuo-phonology



Developing a Collaborative School Based Outcome System for Youth with Dyslexia:

Charles Armstrong School, Athena Academy, Chartwell School & UCSF Dyslexia Center

UCSF Dyslexia Center

Anxiety and Academic Performance in RD

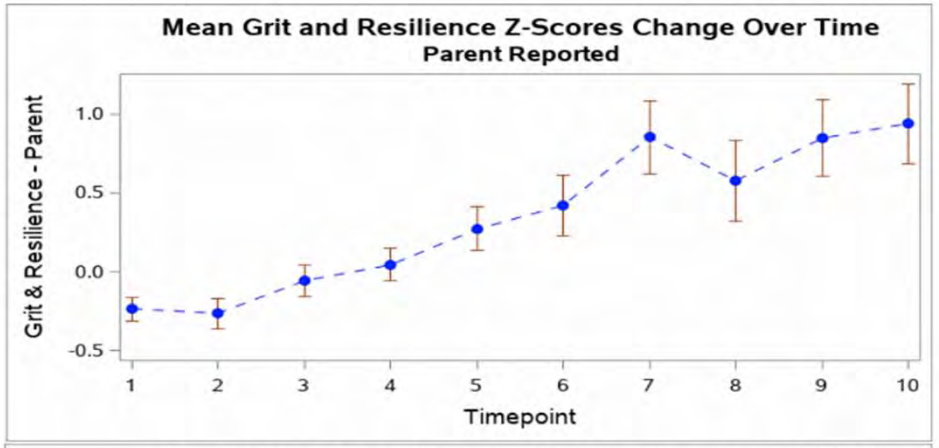
- Anxiety is significantly associated with academic performance in children with RD
    - At each cross-sectional timepoint
        - Those with higher anxiety tend to have poorer academic performance
    - Within an individual over time
        - As a child's anxiety increases over time, their academic performance decreases

- Significance remains even after adjusting for age, sex and ADHD

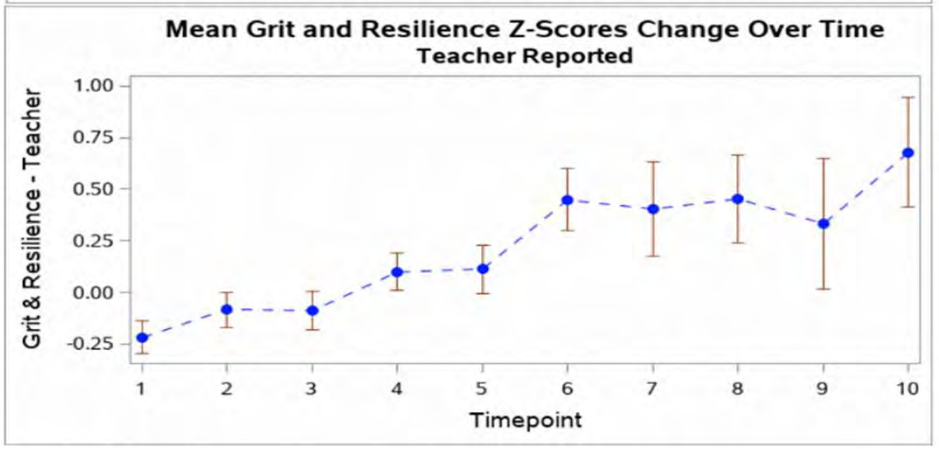
Grit & Resilience in RD

- On average, grit and resilience improves over time
- Grit and resilience is significantly associated with all outcomes in children with RD
- Significance remains even after adjusting for age and sex

a



b



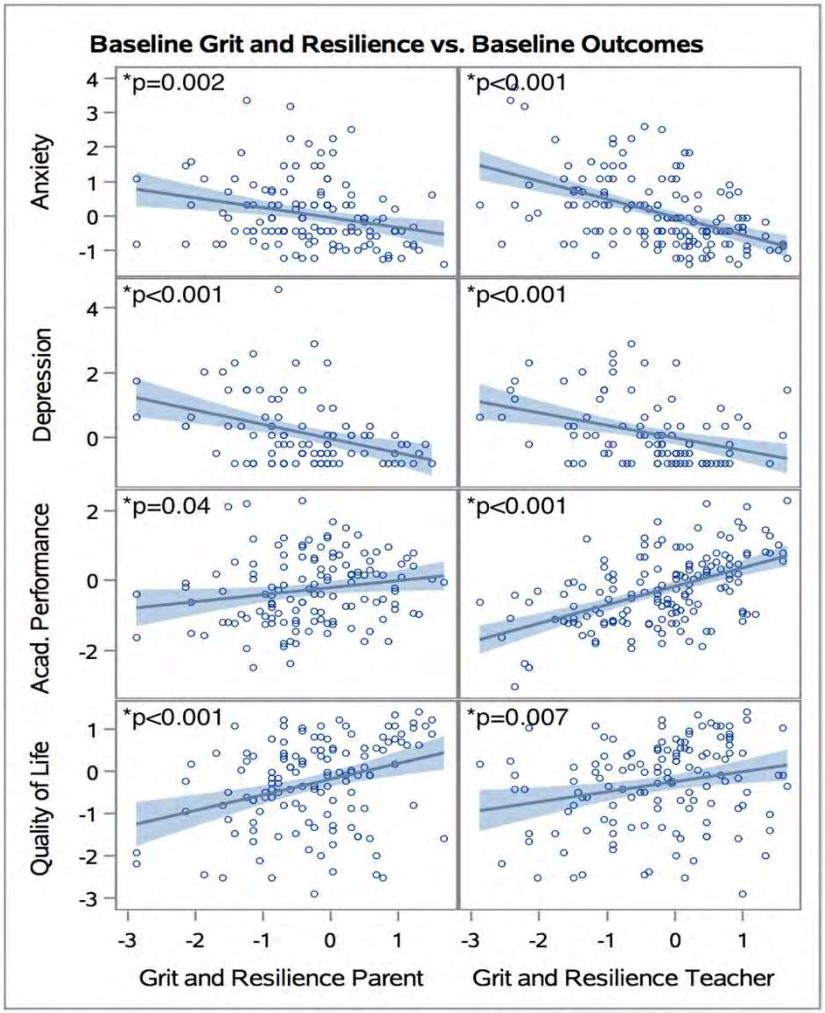
Grit & Resilience in RD

At baseline

- Those with higher grit and resilience tend to have
  - Lower anxiety symptoms
  - Lower depression symptoms
  - Better academic performance
  - Better quality of life

Within an individual over time

- As a child's grit and resilience increases over time, their
  - anxiety decreases
  - depression decreases
  - academic performance improves
  - quality of life improves



"Training for Awareness, Resilience, and Action" (TARA)

- The TARA model takes into consideration the developmental limitation in top-down cognitive control in adolescence and promotes bottom-up strategies such as vagal afference to decrease limbic hyperactivation and its secondary effects.
- Informed by mindfulness-based therapy and yoga, as well as modern psychotherapeutic techniques.
- Semi-manualized, progressive, and applied in a module-based approach designed for a 12 week group
- R61 to determine the neural mechanism by which meditation exerts its positive effect on emotional health of adolescents.
- Ho that structural connectivity of the putamen with other brain regions will positively affect emotional health.

Henje Blom E, Front Hum Neurosci. 2014 Aug 19;8:630; Pis Tymofiyeva & Yang

Biomedical CIM Interventions (Layer 2)

CAM/CIM/Biomedical and NDD

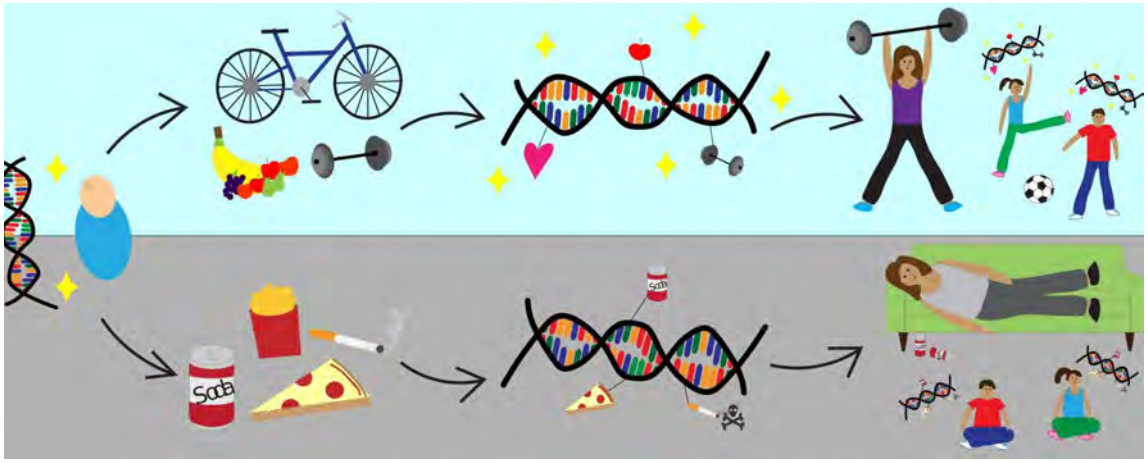
- National Center for Complementary and Alternative Medicine defines CAM as “a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine”
- Seventy-five percent of children with ASD consumed supplements with multivitamins (77.8%), vitamin D (44.9%), omega 3 (42.5%), probiotics (36.5%), and magnesium (28.1%) as the most prevalent.
- The main reasons for choosing CAM were related to concerns with the safety and adverse effects of prescribed medications
- Physicians not perceived as a knowledgeable resource

Birdee GS, et al. *Pediatrics*. 2010;125(2):249-256. Trudeau MS et al. Nutrients 2019; 11(8):1783; Huang A, et al. *J Altern Complement Med*. 2013;19(9):746-750. Hanson E, et al. *J Autism Dev Disord*. 2007;37(4):628-636.

"I'm afraid you've had a paradigm shift."

Epigenetic Processes

- Phenotypes represent the full picture of the expression of an individual's genes given the environment.
- Epigenetics is the study of how the environment can influence gene expression and even pass it along through generations without altering the gene structure.
- Process through which an environmental stimulus during development alters epigenetic marks (e.g. DNA methylation, histone modifications, etc) and thus gene expression altering developmental trajectory and phenotypic expression.
- These alterations are potentially reversible and preventable



Gottesman II, Gould TD. *Am J Psychiatry*. 2003;160:636-645.; Kofink, 2013; El-Sayed, et al. 2013; McKinney BC, *AM J Psychiatry; 2017, 174:12*.

Gene-Environment Interactions and Endophenotype (Terroir Layer 2; Evidence Levels 2 & 3)

- Immune abnormalities/inflammation
- Oxidative stress
- Disturbed methylation
- Mitochondrial dysfunction
- Free fatty acid metabolism
- Excitatory/inhibitory imbalance
- Hormonal effects
- Microglia

Goines P, et al. *Curr Opin Neurol*. 2010;23(2):111-117. James SJ, et al. *Am J Clin Nutr*. 2009;89(1):425-430. Frye RE, et al. *Pediatr Res*. 2011;69(5 Pt 2):41R-47R. Manji H, et al. *Nat Rev Neurosci*. 2012;13(5):293-307. Bell JG, et al. *Br J Nutr*. 2010;103(8):1160-1167. Rubenstein JL. *Curr Opin Neurol*. 2010;23(2):118-123. Harony H, et al. *Neurosignals*. 2010;18(2):82-97. Cunningham CL. *J Neurosci*. 2013;33(10):4216-4233.

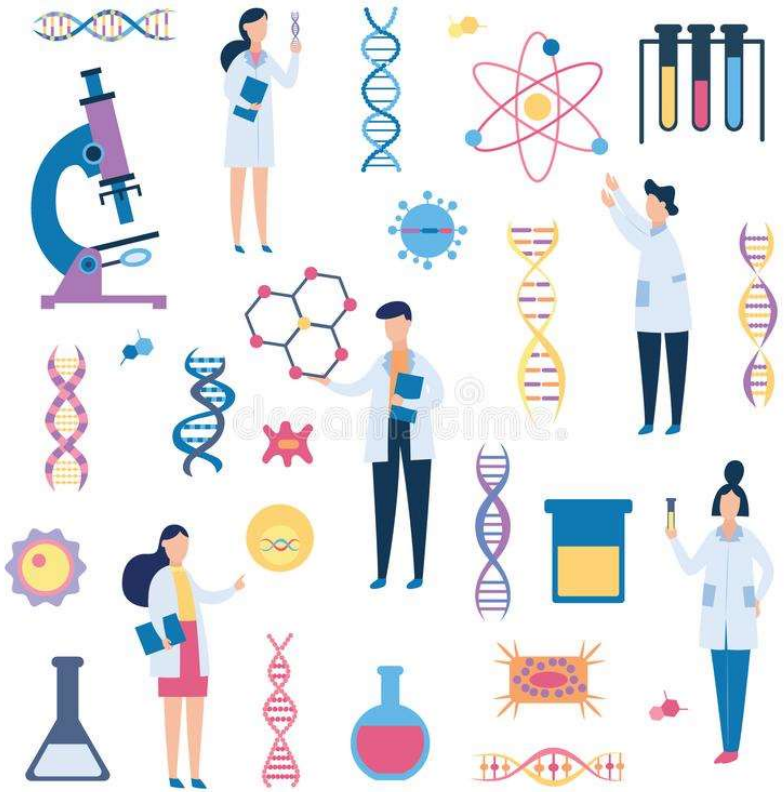
A New Paradigm (Grade C Mod; Neutral)

- Significant subsets of people with NDD have intestinal inflammation, digestive enzyme abnormalities, metabolic impairments, oxidative stress, mitochondrial dysfunction, and immune problems that range from immune deficiency to hypersensitivity to autoimmunity
- In many cases, improvement of NDD symptoms is achieved by a combination of nutritional recommendations, prescription medications, and addressing the underlying medical conditions seen in these individuals

Mumper E. *North American Journal of Medicine and Science*. 2012;5(3):180-184.

BioMedical/CIM Treatments

- Melatonin
- Omega-3
- Vitamin D3
- NAC
- Methyl B12
- Vitamin/Mineral Supplements
- Diet
- Microbiome
- Pancreatic Digestive Enzymes
- CBD/THC
- Probiotics



Over the Counter (OTC)

Amino acids	**Fatty Acids (Omega 3)**	**Methyl B12**	**Vitamin A**
Antifungals	Folic/ folinic acid	**N-acetylcysteine (NAC)**	Vitamin B3
Antivirals	Glutathione	Oxytocin	Vitamin B6/ Magnesium
Cholestyramine	5-Hydroxytryptophan (5-HTP)	Probiotics	Vitamin C, D
CoQ10	Iron supplement	Pyridoxal-5´-phosphate (P5P)	Zinc
Curcumin	1-Carnosine	Ribose and NADH	**Sulforaphane** McGuinness, 2020
Digestive enzymes	Magnesium	S-adenosyl-l-methionine (SAMe)	**Micronutrients** Adams, 2018
Dimethylglycine (DMG, TMG)	Melatonin	St. John's Wort	

US Preventive Services Task Force evidence review criteria for Grade of net benefit of A (high certainty of benefit), B (moderate certainty of benefit), C (net benefit small), D (no benefit or harms outweigh benefit), I (evidence lacking or conflicting), followed by Levels of grade certainty of Low, Moderate, High, followed by recommendation for practice.

Popular Biomedical/CAM Treatments with Insufficient/Negative Evidence

- Chelation (Grade D)
- HBOT (Grade D)
- IVIG (Grade I)
- Secretin (Grade D)
- Memantine (failed trials)
- Arbaclofen (failed trial)
- Vasopressin (failed trials)

Challenges of CAM/Biomedical Research

- Sample size for effect size
- Heterogeneity of ASD
- Duration of trial
- Biomarker for inclusion
- Holding other treatments constant
- Blinding
- Formulation variability
- IRB issues
- Ethical issues

Bent S, et al. *Neurotherapeutics*. 2010;7(3):232-240.

Targeting Shared Mechanisms

Immune/Inflammation

- Melatonin (Grade B Mod; Rec)
- IV/IG (Grade D Low; Poor)
- Corticosteroids (Grade D Low; Poor)
- Celecoxib plus risperidone: RCT for irritability, withdrawal, and stereotypy (Grade I Low; Poor)
- Vitamin D (Grade B Mod; Rec)

Mitochondrial Function

- Carnitine (Grade C Low; Insuff)
- CoQ10 (Grade C Low; Insuff)
- L-carnosine (Grade C Low; Insuff)

Asadabadi M, et al. *Psychopharmacology*. 2013;225(1):51-59. Suren P, et al. *JAMA*. 2013;309(6):570-577. Rossignol DA, et al. *Mol Psychiatry*. 2012;17(4):389-401. Delhey LM et al. J Clin Med, 2017

Melatonin (Grade B; Mod; rec)

- Endogenous neurohormone causes drowsiness, establishes circadian rhythms and synchronization of peripheral oscillators, and is produced from serotonin
- Review and meta-analysis of 35 studies reported that of 18 treatment studies, there were 5 RCTs (N = 61, 2 to 10 mg/day) where sleep duration (44 min, ES = .93) was increased, sleep onset latency was decreased (39 min, ES = 1.28), but nighttime awakenings were unchanged
- Adverse effects were minimal to none
- May also benefit social communication impairments and stereotyped behaviors or interests
- Prolonged release efficacious

Tordjman S, et al. *Int J Mol Sci*. 2013;14(10):20508-20542. Rossignol DA, et al. *Dev Med Child Neurol*. 2011;53(9):783-792. Gringras et al; JAACAP, 2017

Vitamin D (Grade B Mod; rec)

- "Ecological Evidence" – Northern latitudes, rainfall, skin pigment. Low levels of vitamin D reported
- Vitamin D activates serotonin-synthesizing gene
- Vitamin D is a "potent neurosteroid"

- 57% of the 122 pts had vitamin D deficiency, and 30% had vitamin D insufficiency. Mean 25-OHD levels in pts with severe autism were significantly lower than those in pts with mild/moderate autism. Vitamin D3 (300 IU/kg/day not to exceed 5000 IU/day) given for 3 months. 83 ss completed 3 months of treatment. Collectively, 80.72% (67/83) had significantly improved CARS and ABC outcomes.

Jia et al. Pediatrics, 2014; Patrick RP, et al. *FASEB J*. 2014;28(6):2398-2413. McGrath J, et al. *Trends Neurosci*. 2001;24(10):570-572. Saad K, J Child Psychol Psychiatry. 2016

Targeting Shared Mechanisms

Oxidative Stress

- Glutathione (Grade I Low; insuff)
- Methyl B12 (Grade B Mod; neutral)
- Curcumin – anti-inflammatory and antioxidant activity (Grade I Low; insuff)
- NAC (Grade B Mod; rec)

Neurotransmitter Production

- Tetrahydrobiopterin (Grade I Low; insuff)
- Rivastigmine & donepezil– parasympathomimetic or cholinergic agent (Grade I Mod; insuff)
- Galantamine – acetylcholinesterase inhibitor (Grade I Mod; insuff)

NMDA = N-methyl-D-aspartate

GABA

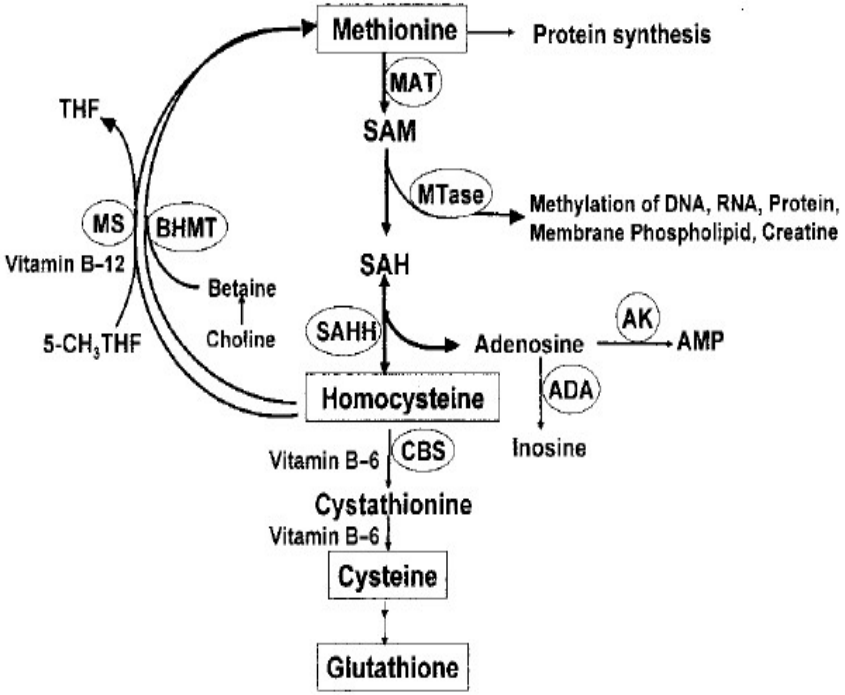
- Arbaclofen (STX209) (Grade D Mod; ineff)
- Bumetanide – diuretic (Grade I Mod; Low)

Glutamate

- Riluzole – used to treat amyotrophic lateral sclerosis (Grade I Mod; insuff)
- D-cycloserine – partial agonist of the neuronal NMDA receptor (Grade B Mod; insuff)

Kern JK, et al. *Med Sci Monit*. 2011;17(12):CR677-CR682. Bertoglio K, et al. *J Altern Complement Med*. 2010;16(5):555-560. Darvesh AS, et al. *Expert Opin Investig Drugs*. 2012;21:1123-1140. Frye RE, et al. *Transl Psychiatry*. 2013:e237. Chez MG, et al. *J Child Neurol*. 2004;19(3):165-169. Nicolson R, et al. *J Child Adolesc Psychopharmacol*. 2006;16(5):621-629. Wang P, et al. Presented at: International Society for Autism Research; May 14, 2011; San Diego, CA. Abstract 8281. Hadjikhani N, et al. *Autism*. 2013;Epub ahead of print. Wink LK, et al. *J Child Adolesc Psychopharmacol*. 2011;21(4):375-379. Posey DJ, et al. *Am J Psychiatry*. 2004;161(11):2115-2117.

Metabolic Biomarkers of Increased Oxidative Stress and Impaired Methylation Capacity in Children with Autism



Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children[1]

	Control children ($n = 33$)	Autistic children ($n = 20$)
Methionine (μmol/L)	31.5 ± 5.7 (23–48)	19.3 ± 9.7 (15–25)[2]
SAM (nmol/L)	96.9 ± 12 (77–127)	75.8 ± 16.2 (68–100)[3]
SAH (nmol/L)	19.4 ± 3.4 (16–27)	28.9 ± 7.2 (14–41)[2]
SAM:SAH	5.2 ± 1.3 (4–8)	2.9 ± 0.8 (2–4)[2]
Adenosine (μmol/L)	0.27 ± 0.1 (0.1–0.4)	0.39 ± 0.2 (0.17–0.83)[4]
Homocysteine (μmol/L)	6.4 ± 1.3 (4.3–9.0)	5.8 ± 1.0 (4.0–5.8)[3]
Cystathionine (μmol/L)	0.17 ± 0.05 (0.1–0.27)	0.14 ± 0.06 (0.04–0.2)[5]
Cysteine (μmol/L)	202 ± 17 (172–252)	163 ± 15 (133–189)[2]
tGSH (μmol/L)	7.6 ± 1.4 (3.8–9.2)	4.1 ± 0.5 (3.3–5.2)[2]
Oxidized glutathione (nmol/L)	0.32 ± 0.1 (0.11–0.43)	0.55 ± 0.2 (0.29–0.97)[2]
tGSH:GSSG	25.5 ± 8.9 (13–49)	8.6 ± 3.5 (4–11)[2]

[1] All values are $\bar{x}$ ± SD; range in parentheses. SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

[2–5] Significantly different from control children: [2] $P < 0.001$, [3] $P < 0.01$, [4] $P < 0.05$, [5] $P < 0.002$.

James SJ, et al. *Am J Clin Nutr*. 2004;80(6):1611-1617.

Methyl B12 Study (Grade B Mod; insuff)
UCSF (Autism Speaks)

- 53 children between the ages of 3 and 7 years enrolled in study at UCSF funded by Autism Speaks
- Eligible children randomly assigned to 8 weeks of treatment with methyl B12 at 75 ug/kg given SubQ every 3 days
- Primary outcome measure CGI-I and the mean at 8 weeks was significantly better (lower) in the methyl B12 group (2.4) compared to the placebo group (3.1) (95% CI 1.2 to 0.2, *P* = .005
- Clinical improvement in CGI-I was significantly correlated with methionine (*P* = .05), decreases in SAH (*P* = .007), and improvements in SAM/SAH (*P* = .007)

Hendren RL, et al. Journal of Child and Adolescent Psychopharmacology (2016) . ClinicalTrials.gov Identifier: NCT01039792.

NAC in Children with Autism (Grade B Mod; rec)

- NAC is a glutamatergic modulator and an antioxidant
- 12-week, double-blind, randomized, placebo-controlled study of NAC in children with autistic disorder
- NAC was initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks, and 900 mg 3 times daily for 4 weeks
- 33 patients (31 male, 2 female; aged 3.2 to 10.7 years) were randomized
- Oral NAC was well tolerated with limited adverse effects
- Compared with placebo, NAC resulted in significant improvements on ABC-I ($F = 6.80$; $P < .001$; $d = .96$)

Hardan AY, et al. *Biol Psychiatry*. 2012;71(11):956-961.

Metabolic/Amino Acids/Nutrient

- Omega 3 (Grade B Mod; rec)
- B6/Magnesium (Grade I Mod; insuff)
- Folic acid (Grade I Mod; insuff)
- Iron (Grade A Low; rec if indicated)
- Ascorbic acid (Grade I Low; insuff)
- Zinc and copper (Grade I Low- insuff)
- Inositol (Grade I low; insuff)
- Diet (Grade I low; insuff)
- Oxytocin (Grade C Mod; insuff)

Microbiome

- Probiotics (Grade B Mod; insuff)
- Pancreatic Digestive Enzymes (Grade C Mod; insuff)

Cheng JX, et al. *Adolesc Med State Art Rev*. 2013;24(2):446-464. Lofthouse N, et al. *Autism Res Treat*. 2012;2012:870391.

Folinic acid improves verbal communication in children with autism and language impairment

(Grade B Mod; insuff)

- Forty-eight children (mean age 7 years 4 months; 82% male) with ASD and language impairment were randomized to receive 12 weeks of high-dose folinic acid (2 mg kg − 1 per day, maximum 50 mg per day; n = 23) or placebo (n= 25).
- Improvement in verbal communication, as measured by a ability-appropriate standardized instrument, was significantly greater in participants receiving folinic acid as compared with those receiving placebo, resulting in an effect of 5.7 (1.0,10.4) standardized points with a medium-to-large effect size (Cohen's d = 0.70).
- Folate receptor-α autoantibody (FRAA) status was predictive of response to treatment.

Frye RE et al., Molecular Psychiatry, 2016

Microbiota Modulate Behavioral and Physiological Abnormalities Associated With Neurodevelopmental Disorders (Grade C Mod)

- Demonstrate GI barrier defects and microbiota alterations in the MIA mouse model that is known to display features of ASD
- Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like, and sensorimotor behaviors
- Microbiota Transfer Therapy

MIA = maternal immune activation.

Hsiao EY, et al. *Cell*. 2013;155(7):1451-1463; Buffington SA et al, 2016; Kang et al. 2017.

Pancreatic Digestive Enzymes (Grade I Mod; insuff)

- Enzyme deficiencies in children with autism result in an inability to digest protein
- The inability to digest protein affects the production of amino acids essential for brain function
- RCT completed but not published
- Biomarker – fecal chymotrypsin

ClinicalTrials.gov Identifier: NCT00881452, NCT00912691.

Other Considerations

- Medical marijuana/THC/CBD and the endocannabinoid systems (Level 4)
- GABA-A (Level 3)
- Vitamins and Mineral Supplements (Level 2)
  - Relatively high doses of Vitamins B1, B2, B3, B5, B6, B12, biotin, folate, C, D, and K
  - Folate instead of folic acid
  - MSM (a good source of sulfate which is low in many ASD)
  - Low-dose lithium (more than 100× below the levels when it is used as a psychiatric medication

THC = tetrahydrocannabinol; CBD = cannabidiol.

Hollander E, et al. *Am J Psychiatry*. 2012;169(3):292-299. Krueger DD, et al. *Neuron*. 2013;78(3):408-410. Han S, et al. *Nature*. 2012;489(7416):385-390; Adams JB et al., *Nutrients*, 2018; 10(3):369

Oak Hill serves a heterogeneous population of children, adolescents, and young adults, all of whom have autism spectrum disorder (ASD) or other neurologically-based disorders of relating and communicating. Students receive special education instruction and customized on-site clinical programs which may include speech/language pathology, occupational therapy, and group and individual psychotherapy. A portion of students have received recent functional behavior analyses (FBAs), with school staff implementing positive behavior intervention programs. The school also offers arts-based therapies and adaptive arts instruction.

Dang, K., Bent, S., Lawton, B., Warren, T., Widjaja, F., McDonald, M. G., Breard, M., O'Keefe, W., Hendren, R. L. (2017)
Integrating autism care through a school-based intervention model: A pilot study. *Journal of Clinical Medicine*.

UCSF & OAK HILL SCHOOL

INTEGRATING MEDICINE AND EDUCATION

Optimize children's internal environment to best utilize educational, social, and life skills interventions by:

- Enhancing biomedical resilience
- Creating a Medical Home
- Measuring effects of interventions
  - behavioral, academic, social, physiological
- Identifying educational and treatment targets
- Developing new effective treatments

Supported by J. S. Foundation

Sulforaphane trial at Oak Hill School

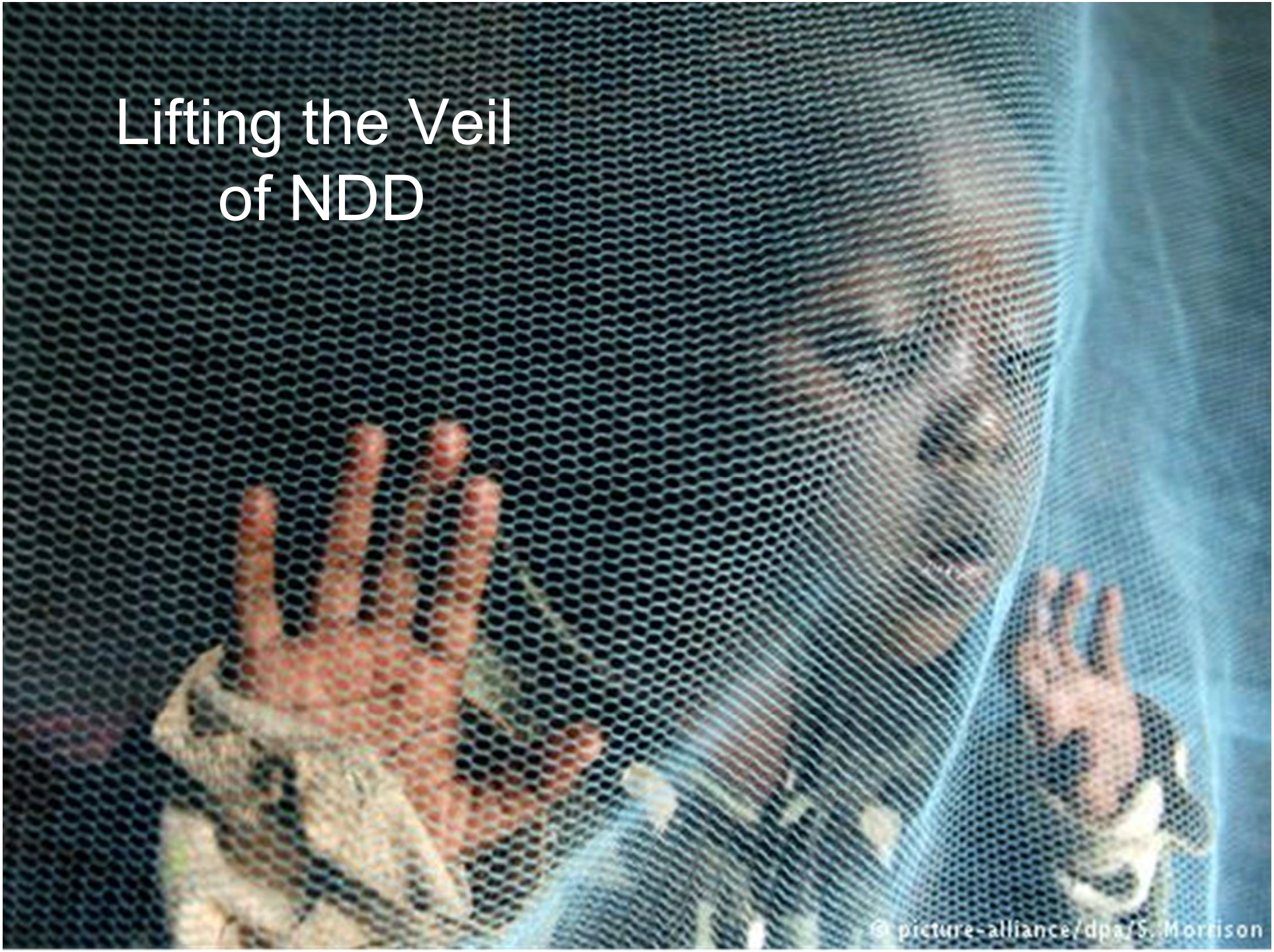
Methods

- 15 subjects, ages 5-22 (mean age 14.7), with ASD diagnoses, attending Oak Hill School (San Anselmo, CA)
- Open-label, 12-week study
- Daily, weight-based dose of sulforaphane
- Baseline and final ABC, SRS, and urine sample

Results

- ABC improved -7.1 points (95% CI: -17.4 to 3.2).
- SRS improved significantly -9.7 points (95% CI: -18.7 to -0.8).
- 77 urinary metabolites were correlated with changes in symptoms, clustered into the following pathways:
  - Oxidative stress
  - Amino acid/gut microbiome
  - Neurotransmitters
  - Hormones
  - Sphingomyelin metabolism

Bent …Hendren, Molecular Autism 2019


Lifting the Veil
of NDD
© picture-alliance/dpa/S. Morrison

Integrated Whole Body Approach to Enhancing Neurodevelopmental Resilience

- Medical – genetic, neurology, GI, other medical symptoms
- Ancillary – meditation, speech, OT
- Behavioral
- Treat associated symptoms – pharmacology
- Biomedical assessment and treatments
- **Building personal relationships and resilience are all encompassing**