Bloorview RESEARCH INSTITUTE

UNIVERSITY OF TORONTO

autism RESEARCH CENTRE

Diversity of the Autistic Brain

Genes, brain, interventions, lived experiences

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Senior Clinician Scientist, Bloorview Research Institute
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Disclosures

- Funding:
  - Ontario Brain Institute, CIHR, NIH, DoD, HRSA, NCE-NeuroDevNet, Autism Speaks, Brain Canada, Azrieli Foundation, Ministry of Health
  - Pharma grant support: ROCHE
  - In kind support: AMO pharma. Simons foundation –CRA
  - Consolation: ROCHe, Quadrant, Ono,
- Patents:
  - Anxiety meter Patents #: 14/755/084, United States, Patents #: 2,895,954, Canada
- Consulting: Roche, Quadrant, Impel, ONO

Diversity in Clinical Presentations

Aggression
Irritability

Social-communication Deficits

ASD

Repetitive behaviors / restricted interests

Anxiety depression

ADHD

OCD

Intellectual Disability

Language Delay

epilepsy

Sensory-motor dysfunction

Immune differences

GI / sleep dysfunction

Congenital heart disease

Genetic syndromes associated with ASD: e.g. fragile X, Tuberous sclerosis

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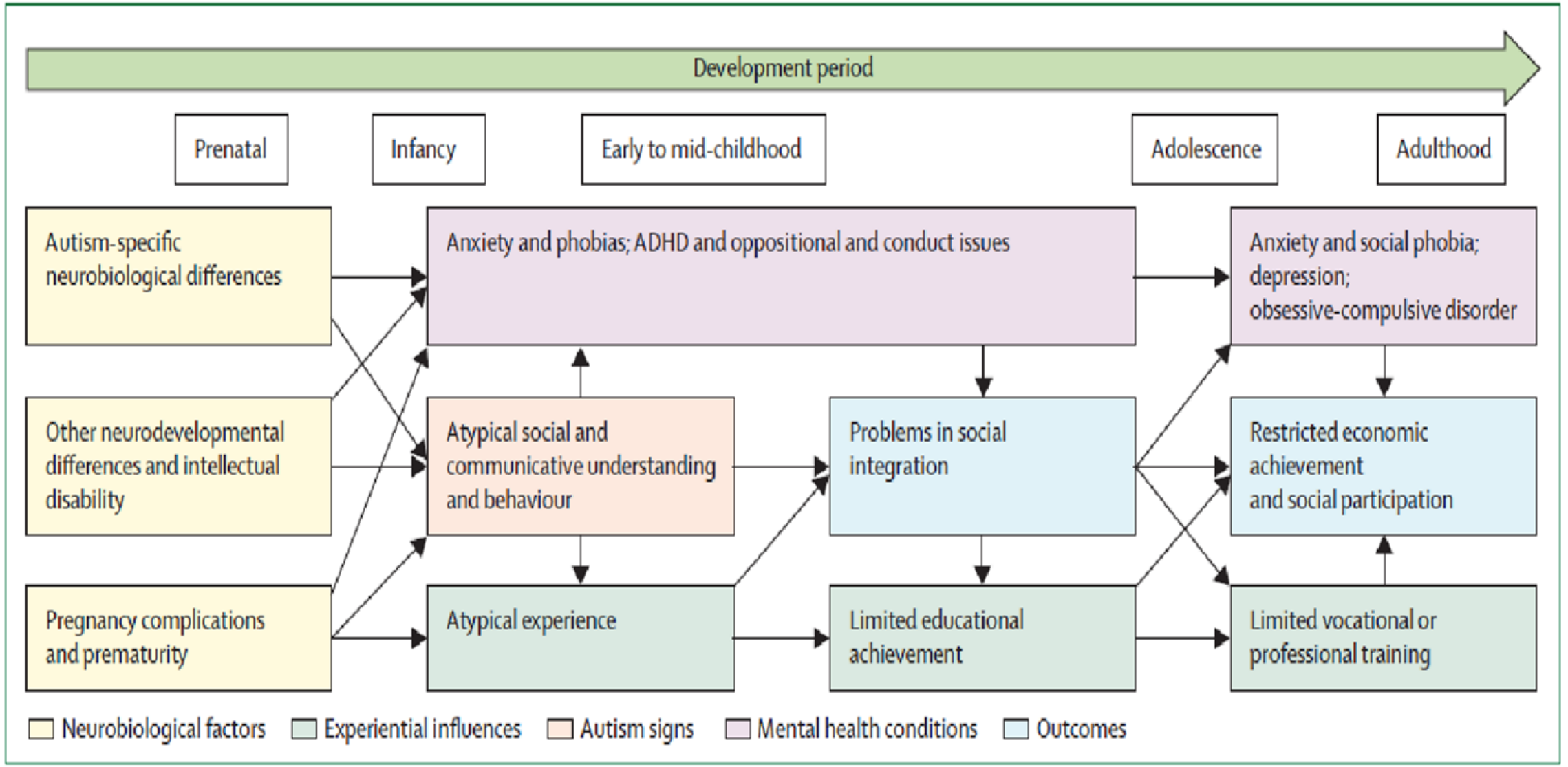
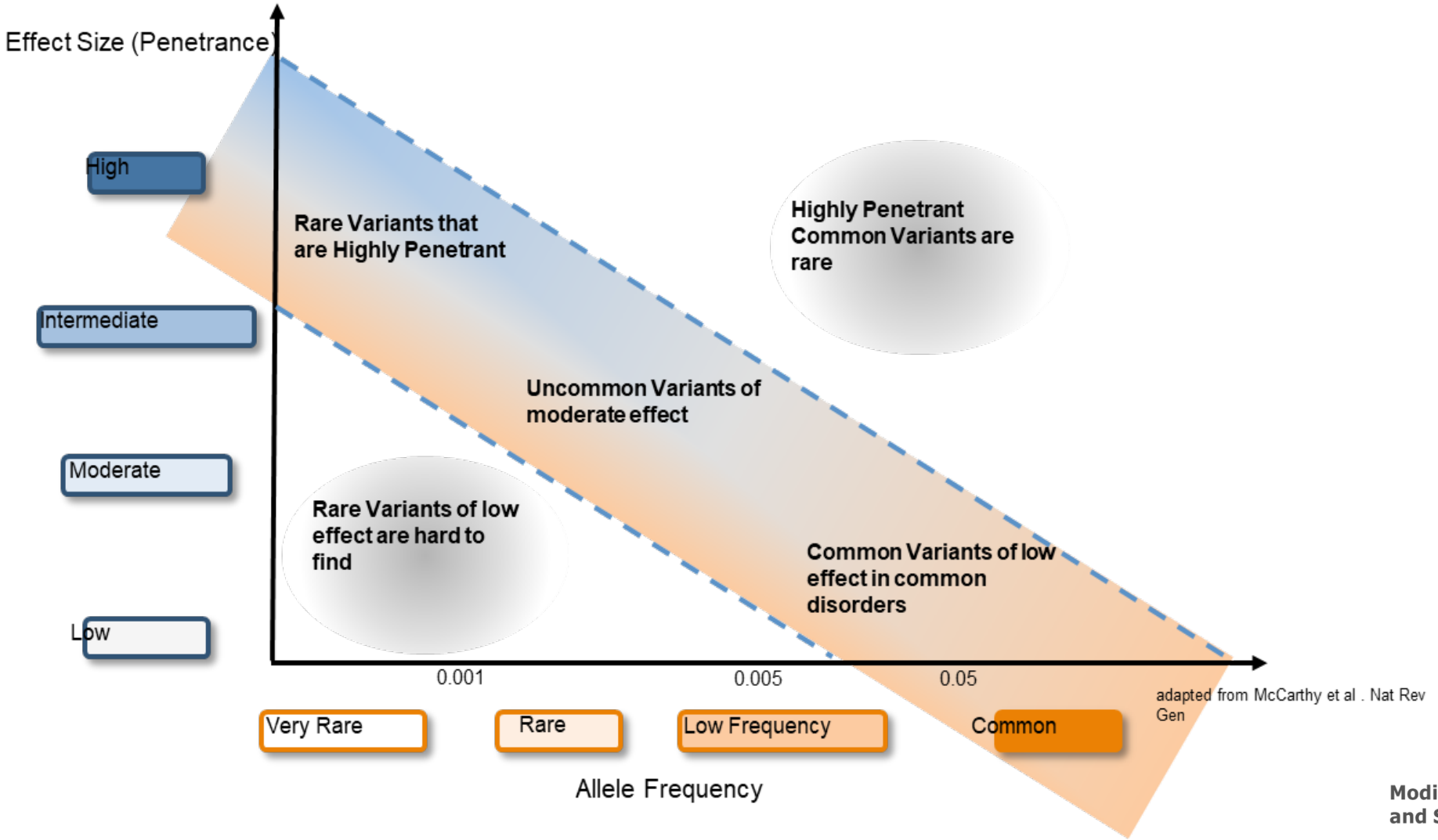
The *Lancet* Commission on the future of care and clinical research in autism

Catherine Lord, Tony Charman*, Alexandra Havdahl, Paul Carbone, Evdokia Anagnostou, Brian Boyd, Themba Carr, Petrus J de Vries, Cheryl Dissanayake, Gauri Divan, Christine M Freitag, Marina M Gotelli, Connie Kasari, Martin Knapp, Peter Mundy, Alex Plank, Lawrence Scahill, Chiara Servili, Paul Shattuck, Emily Simonoff, Alison Tepper Singer, Vicky Slonims, Paul P Wang, Maria Celica Ysrraelit, Rachel Jellett, Andrew Pickles, James Cusack, Patricia Howlin, Peter Szatmari, Alison Holbrook, Christina Toolan, James B McCauley*



Diversity in Genetic Architecture



Modified from Christian Marshall and Steve Scherer

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Cell

CellPress

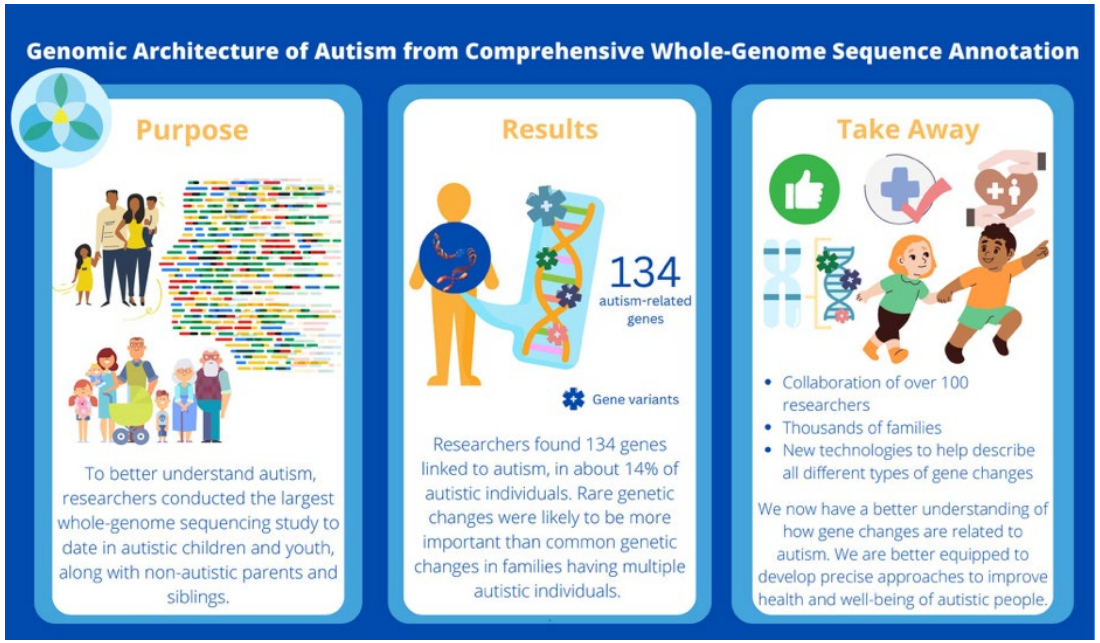
Cell *185*, 4409–4427, November 10, 2022

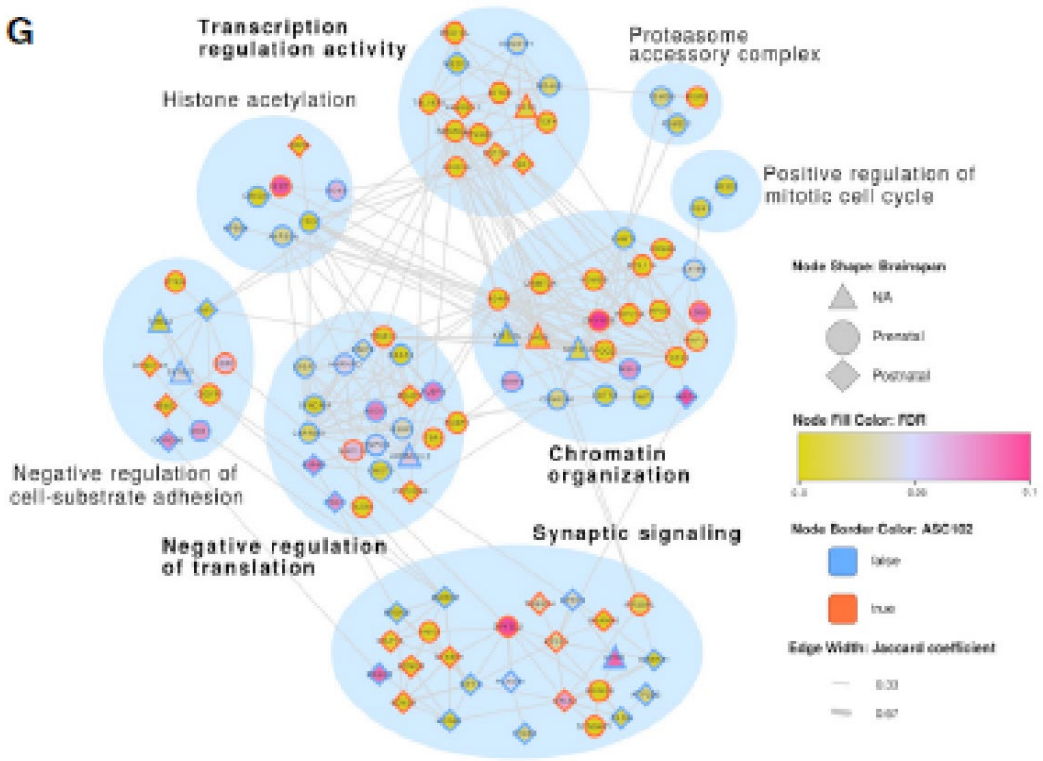
Resource

Genomic architecture of autism from comprehensive whole-genome sequence annotation

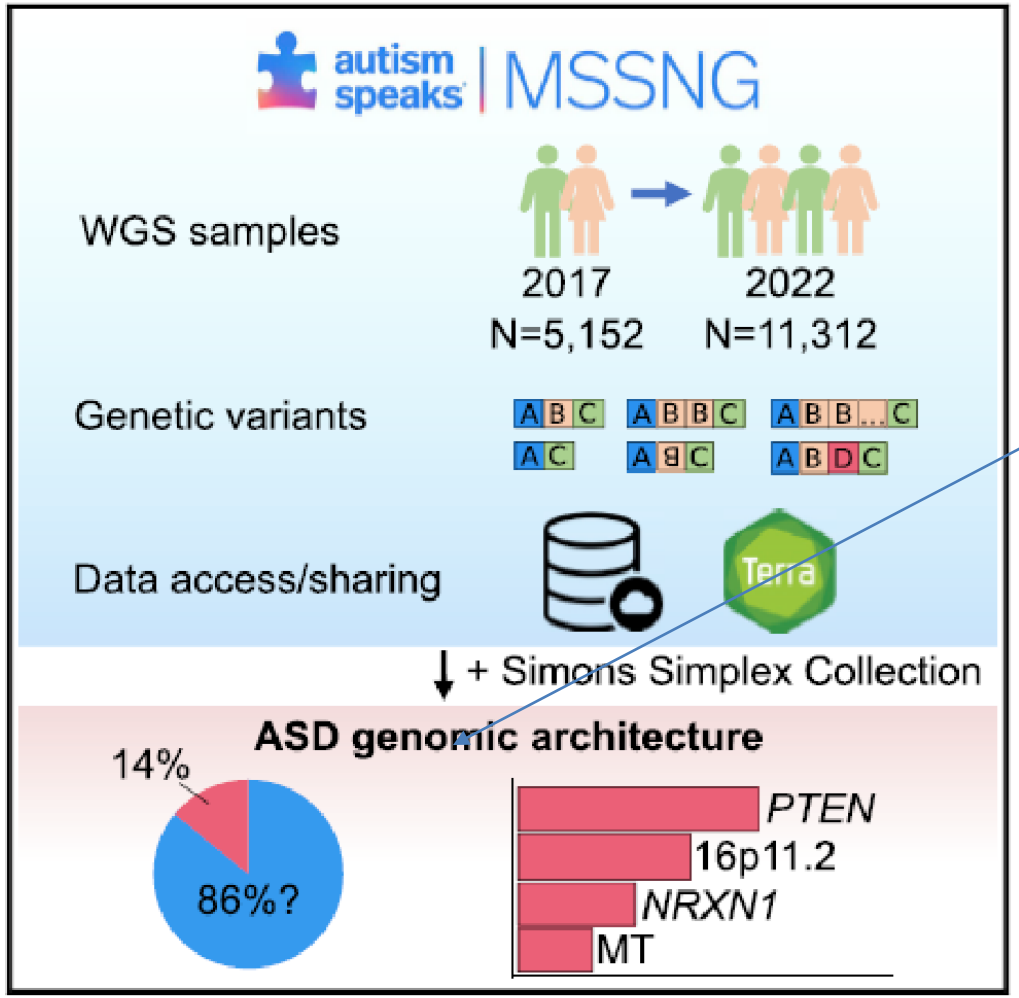
Brett Trost,[1,2] Bhooma Thiruvahindrapuram,[1] Ada J.S. Chan,[1,2] Worrawat Engchuan,[1,2] Edward J. Higginbotham,[1,2] Jennifer L. Howe,[1] Livia O. Loureiro,[1,2] Miriam S. Reuter,[1,2,3] Delnaz Roshandel,[2] Joe Whitney,[1] Mehdi Zarrei,[1,2] Matthew Bookman,[4] Cherith Somerville,[5] Rulan Shaath,[1] Mona Abdi,[6,7] Elbay Aliyev,[6] Rohan V. Patel,[1] Thomas Nalpathamkalam,[1] Giovanna Pellecchia,[1] Omar Hamdan,[1] Gaganjot Kaur,[1] Zhuozhi Wang,[1] Jeffrey R. MacDonald,[1] John Wei,[1] Wilson W.L. Sung,[1] Sylvia Lamoureux,[1] Ny Hoang,[2,8,9,10] Thanuja Selvanayagam,[2,8,10] Nicole Deflaux,[4] Melissa Geng,[2,8] Siavash Ghaffari,[1,2] John Bates,[4] Edwin J. Young,[11,12] Qiliang Ding,[5] Carole Shum,[1,2] Lia D'Abate,[1,2] Clarrisa A. Bradley,[2,13] Annabel Rutherford,[1,2,9] Vernie Aguda,[1] Beverly Apresto,[1] Nan Chen,[1] Sachin Desai,[1] Xiaoyan Du,[1] Matthew L.Y. Fong,[1] Sanjeev Pullenayegum,[1] Kozue Samler,[1] Ting Wang,[1] Karen Ho,[1] Tara Paton,[1] Sergio L. Pereira,[1] Jo-Anne Herbrick,[1] Richard F. Wintle,[1] Jonathan Fuerth,[14] Juti Noppornpitak,[14]

(Author list continued on next page)





Summary: Genetic Diversity



Is Genomics on its own adequate to understand the diversity of clinical presentations and needs?

Important but not enough

- Brain structure and function
- Body systems: e.g. gut, immune
- **Epigenetics**
- Omics markers

Holland Bloorview Kids Rehabilitation Hospital

McMaster University

LAWSON HEALTH RESEARCH INSTITUTE

SickKids

Queen's University

University of Toronto

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

ONTARIO BRAIN INSTITUTE

>30 Investigators

Patient advisory Committee

Youth advisory Commitee

Holland Bloorview Kids Rehabilitation Hospital

AI

Biostatistics

Genomics

Behaviour

Cognition

Epigenetics

Imaging

Immune

Endocrine

Clinical Trials

IPS Cells

Mouse Models

Knowledge Translation

3500 participants

Kushki et al. *Translational Psychiatry* (2019)9:318
https://doi.org/10.1038/s41398-019-0631-2

Translational Psychiatry

ARTICLE Open Access

Examining overlap and homogeneity in ASD, ADHD, and OCD: a data-driven, diagnosis-agnostic approach

Azadeh Kushki[1,2], Evdokia Anagnostou[1,3], Christopher Hammill[4], Pierre Duez[5], Jessica Brian[1,3], Alana Iaboni[1], Russell Schachar[6,7], Jennifer Crosbie[6,7], Paul Arnold[8] and Jason P. Lerch[4,9,10]

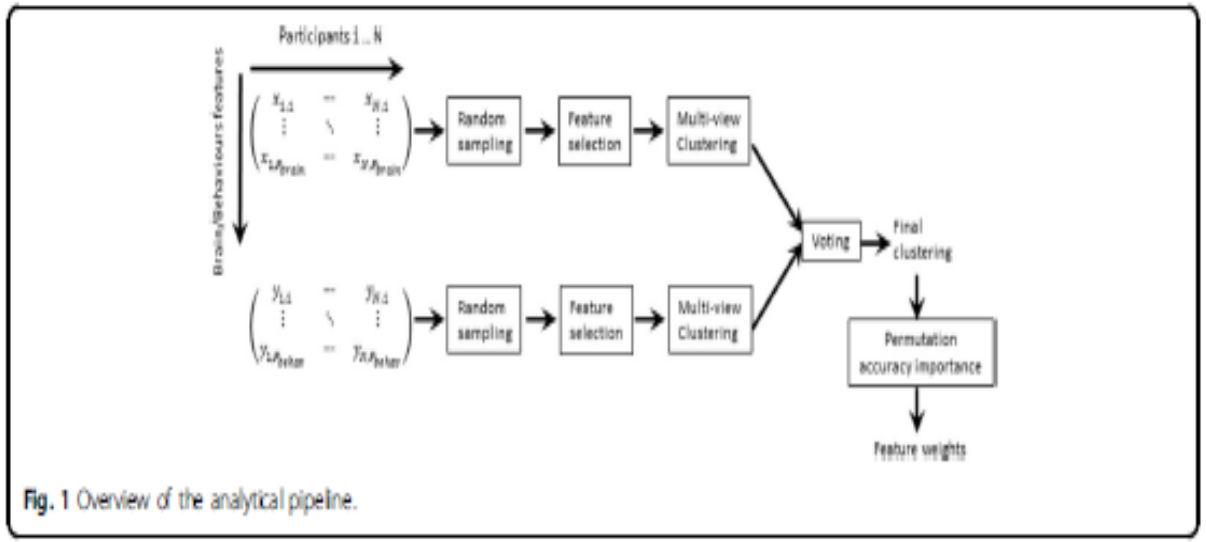


Fig. 1 Overview of the analytical pipeline.

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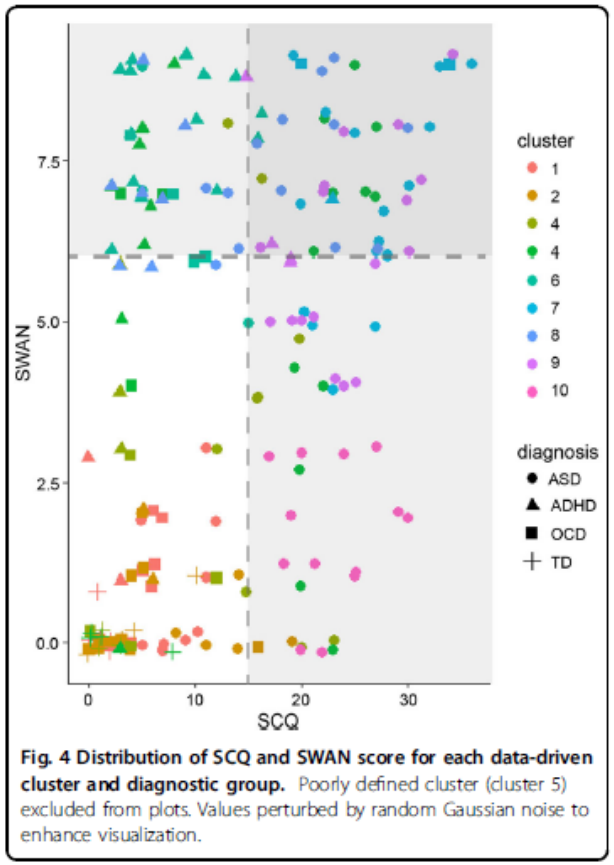
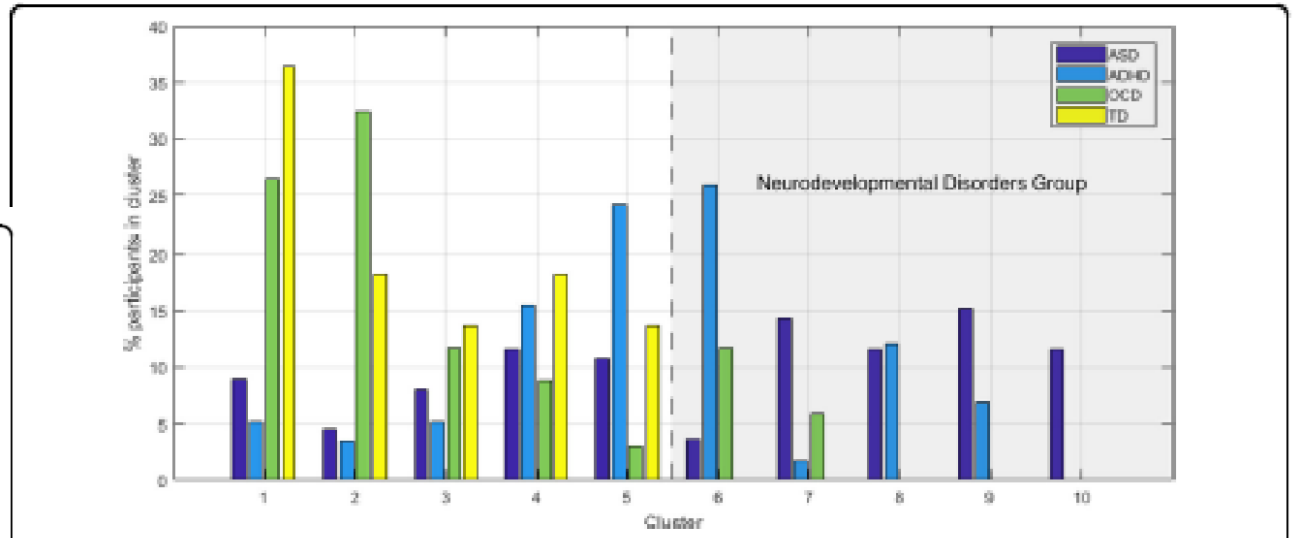


Fig. 4 Distribution of SCQ and SWAN score for each data-driven cluster and diagnostic group. Poorly defined cluster (cluster 5) excluded from plots. Values perturbed by random Gaussian noise to enhance visualization.



ig. 3 Percentage of participants from the four diagnostic categories in each cluster.

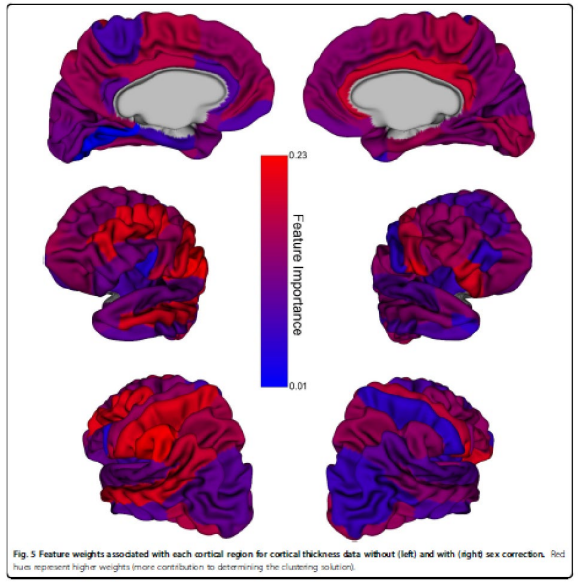
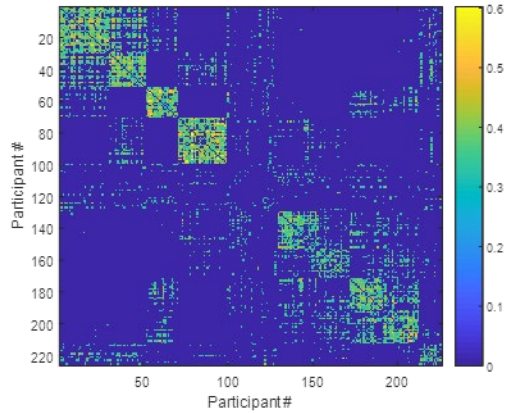


Fig. 5 Feature weights associated with each cortical region for cortical thickness data without (left) and with (right) sex correction. Red hues represent higher weights (more contribution to determining the clustering solution).



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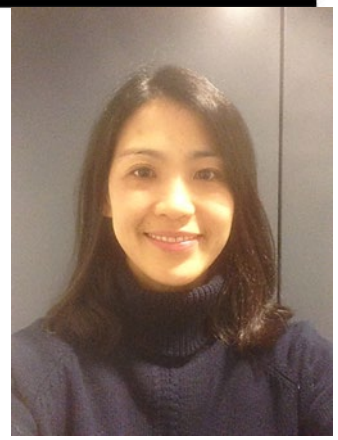
NeuroImage: Clinical 28 (2020) 102476

Contents lists available at ScienceDirect

NeuroImage: Clinical

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



Beyond diagnosis: Cross-diagnostic features in canonical resting-state networks in children with neurodevelopmental disorders

Eun Jung Choi [a,b,*], Marlee M. Vandewouw [a,b,c,d], Margot J. Taylor [b,c,e], Paul D. Arnold [f], Jessica Brian [a,g], Jennifer Crosbie [b,h], Elizabeth Kelley [i], Meng-Chuan Lai [b,h,j,k,l], Xudong Liu [m], Russell J. Schachar [b,h], Jason P. Lerch [n,o,p], Evdokia Anagnostou [a,g]

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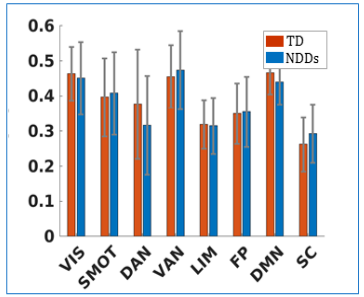
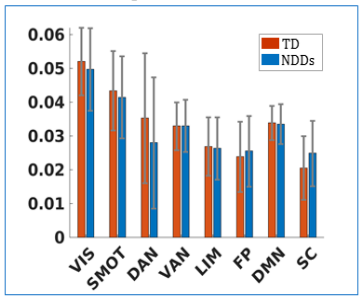
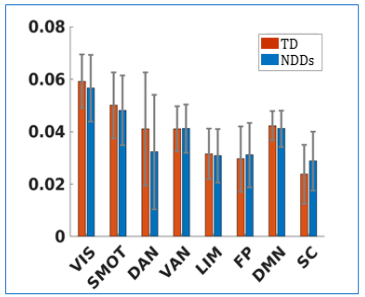
1A. Degree in NDDs vs. TD



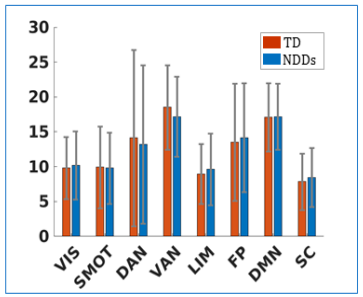
1B. Clustering coefficient in NDDs vs. TD



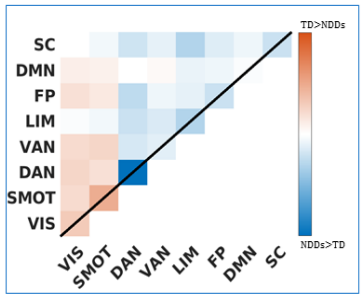
1C. Local efficiency in NDDs vs. TD



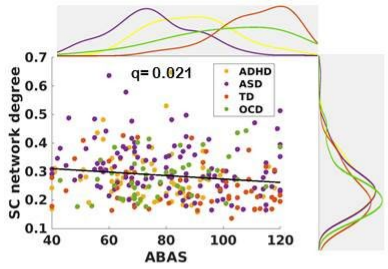
1D. Betweenness centrality in NDDs vs. TD



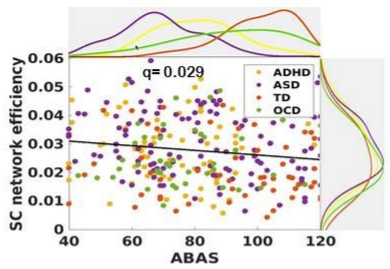
1E. Density in NDDs vs. TD



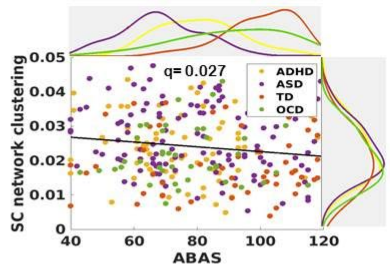
3A. SC network degree and ABAS



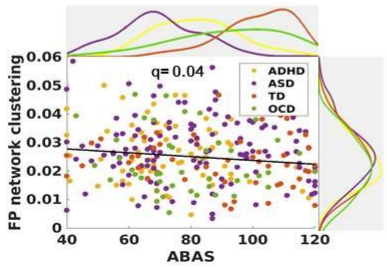
3B. SC network efficiency and ABAS



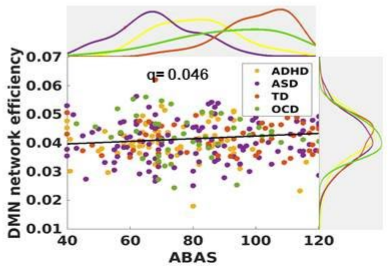
3C. SC network clustering coefficient and ABAS



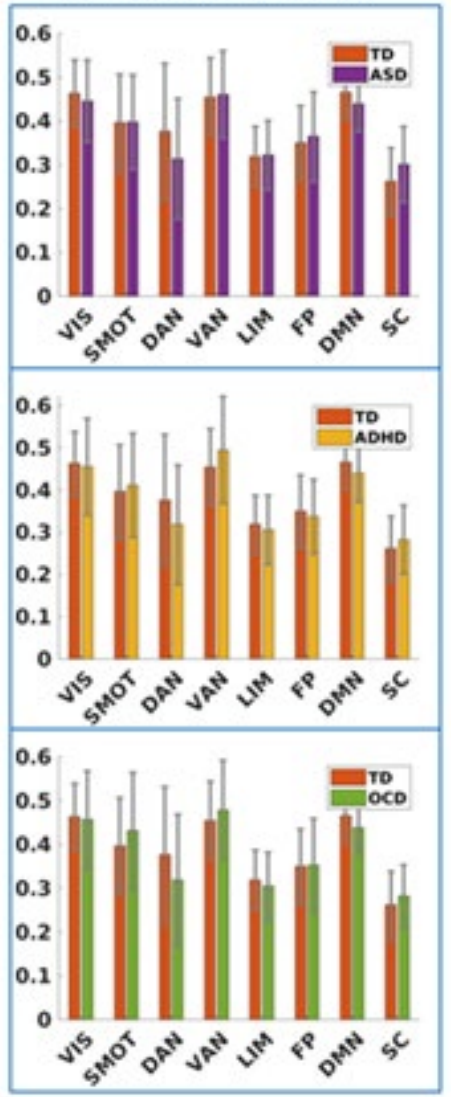
3D. FP network clustering coefficient and ABAS



3E. DMN efficiency and ABAS



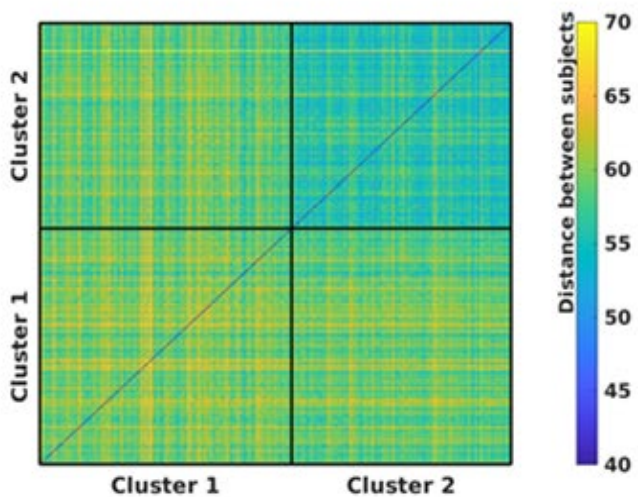
2A. Degree in each NDD vs. TD



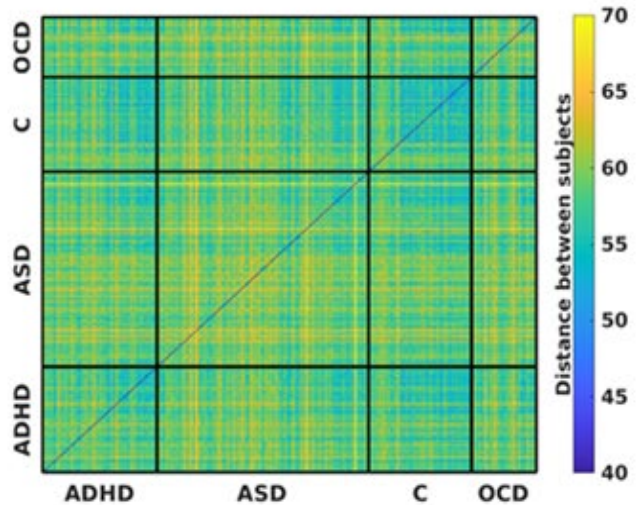
4A. Diagnostic distribution in each data-driven cluster

	Cluster 1	Cluster 2	Total
ASD	97 (55.4%)	78 (44.6%)	175 (100.0%)
ADHD	70 (75.3%)	23 (24.7%)	93 (100.0%)
OCD	11 (20.0%)	44 (80.0%)	55 (100.0%)
TD	39 (46.4%)	45 (53.6%)	84 (100.0%)

4B. Distance between each pairs of participants grouped by data-driven clusters



4C. Distance between each pairs of participants grouped by diagnoses



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POND

Marlee Vandewouw

HBN

	POND	HBN
Initial sample	*N*=763 (212 ADHD, 327 ASD, 70 OCD, 154 TD)	*N*=966 (672 ADHD, 111 ASD, 12 OCD, 171 TD)
Post-QC	*N*=592 (173 ADHD, 235 ASD, 66 OCD, 118 TD)	*N*=756 (513 ADHD, 87 ASD, 11 OCD, 145 TD)
Propensity matching	*N*=551 (164 ADHD, 217 ASD, 60 OCD, 110 TD)	*N*=551 (374 ADHD, 66 ASD, 11 OCD, 100 TD)

ADHD: HBN > POND
ASD: POND > HBN
OCD: POND > HBN
FSIQ: POND > HBN
SCQ: POND > HBN
SWAN-I: POND > HBN

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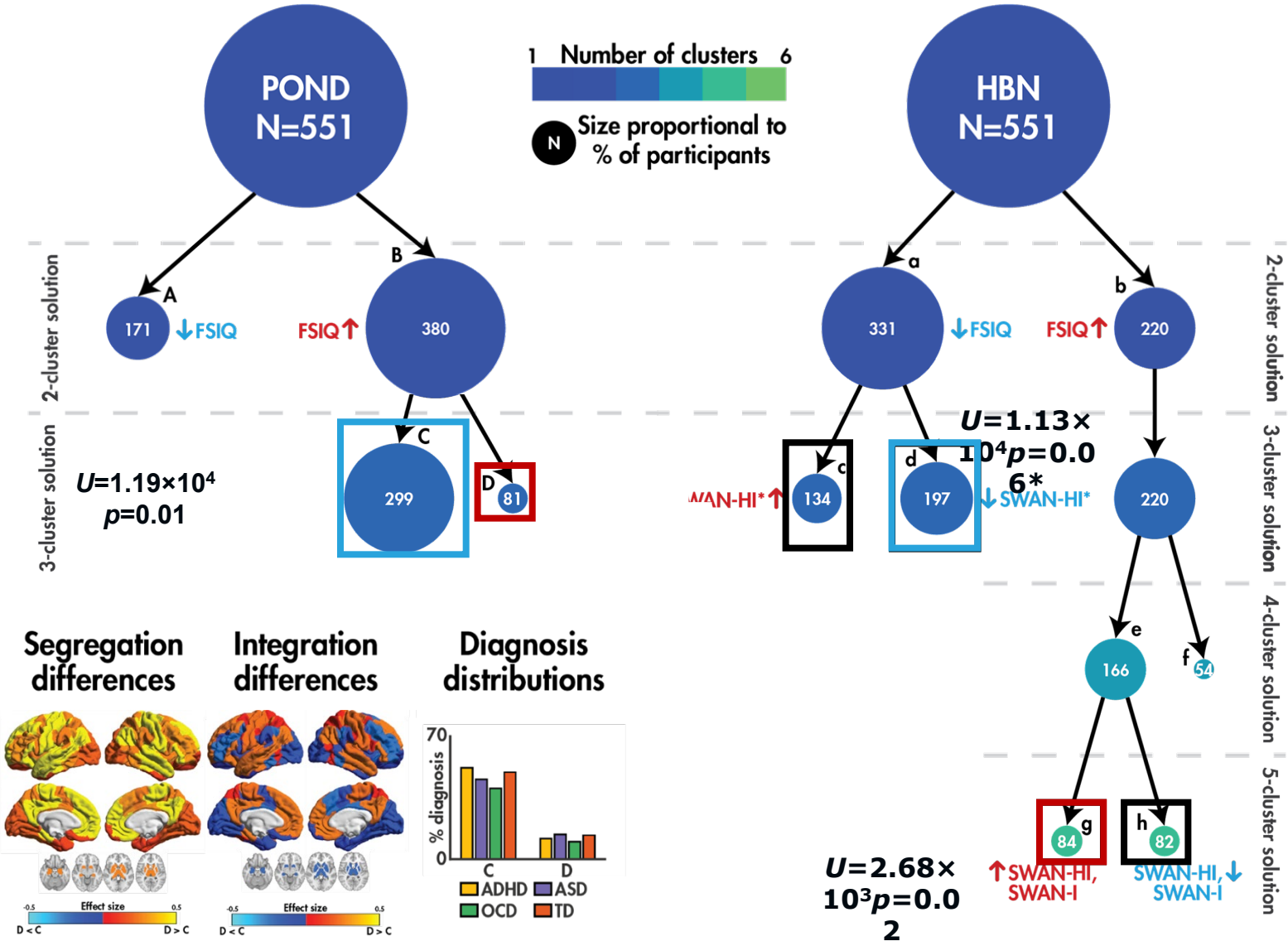
Cognition, thinking skills

ADHD symptoms



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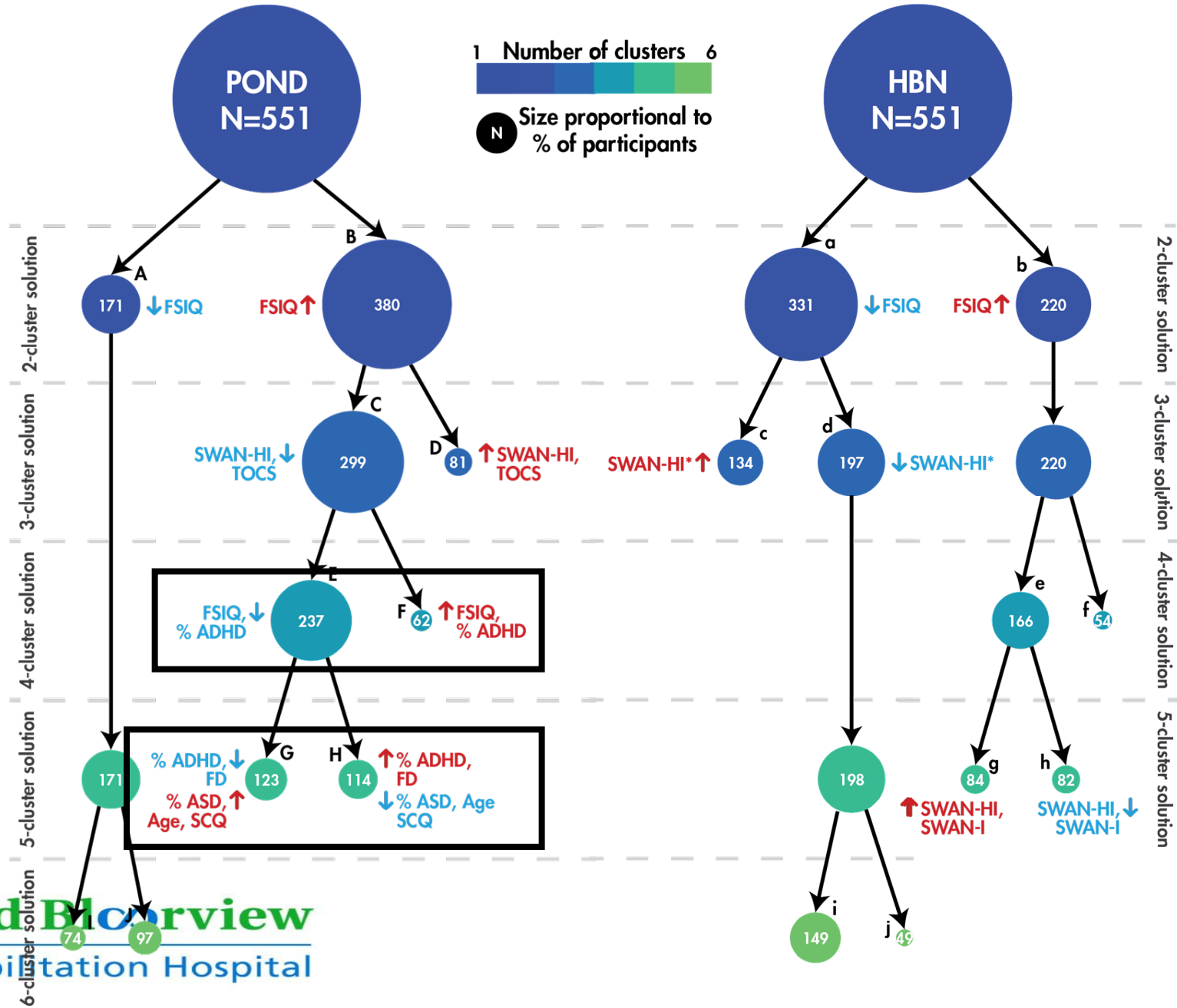
Hierarchical clustering dendrogram



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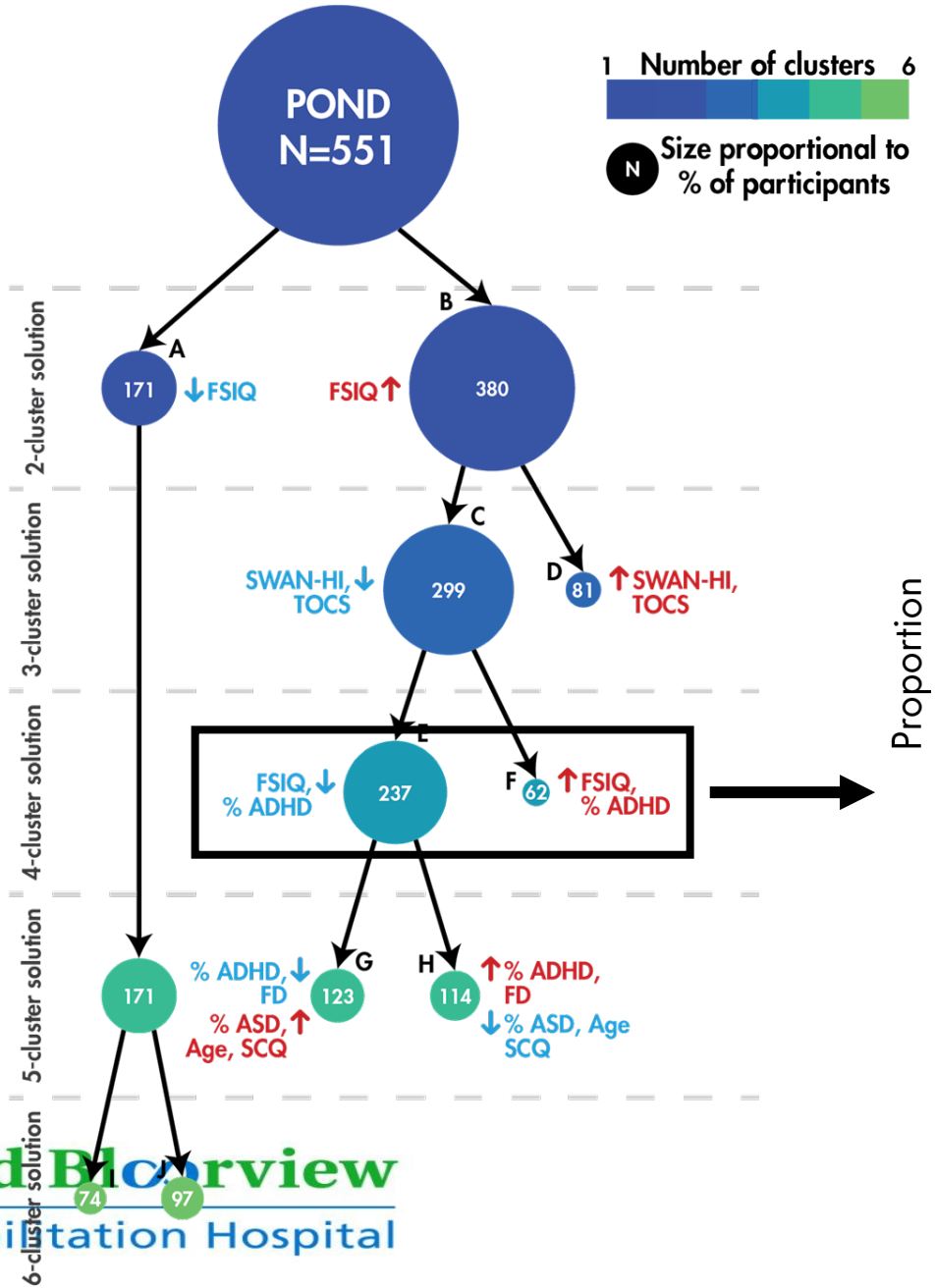
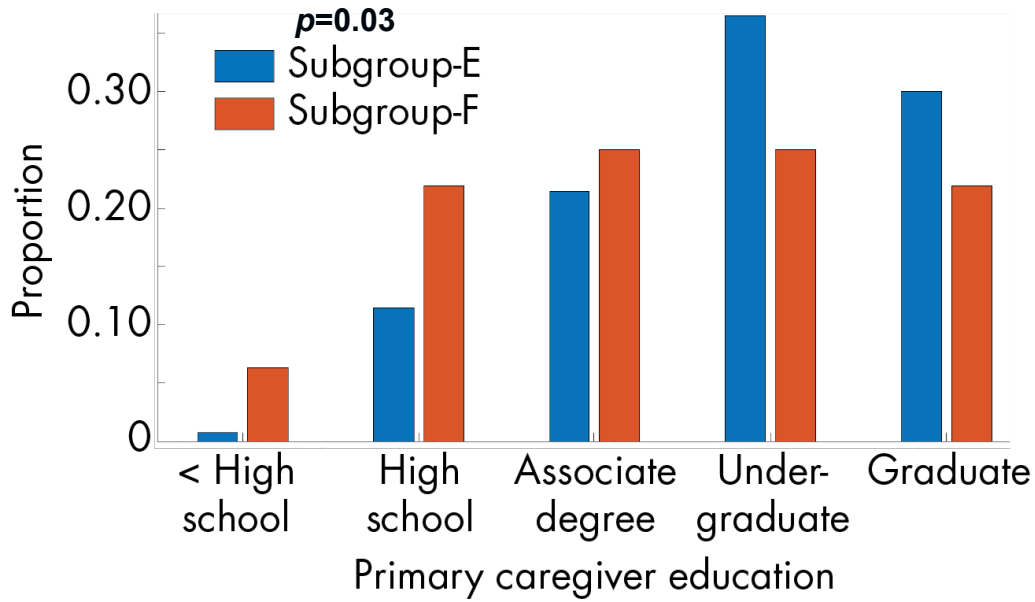
Hierarchical clustering dendrogram



12/13 rare variants in group E



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Aging brain

Very early days - diversity

Aging in Autism Spectrum Disorders: Changes in Brain Structure and Function

Principal Investigator:

Dr. Evdokia Anagnostou

CONTACT INFORMATION:

TO ASK QUESTIONS OR TO SIGN UP, PLEASE CONTACT:
Daman Rehal, 416-425-6220 ex. 3740 or drehal@hollandbloorview.ca

Date Posted:

Version Date: [V.3] Mar 17 2022

Are you an autistic adult/adult with Autism Spectrum Disorder (ASD)? Consider participating in our study.

What is this study about?
This study will help us develop a better understanding of autistic adults/adults with ASD. We will explore aging and brain function amongst autistic adults/adults with ASD.

Who can participate?
We are looking for adults:

- 40 years and older
- Have an ASD diagnosis or are Neurotypical
- With normal or corrected-to-normal vision and hearing
- Individuals who are neurotypical would have:
  - No history of severe mental health disorders or developmental disorders
  - No first-degree family members with Autism Spectrum Disorder
  - Taking no psychotropic medications

What's involved?

- You will be asked to answer questionnaires, undergo cognitive assessments, and have brain scans
- Participation involves two sessions- one initial session and another after 4 years
- You may also provide a blood sample for genetic analysis (optional)
- Each session will take approximately 2 days.

What are the benefits of participating?
Not enough is known about the aging process in those with ASD. By participating you will help us understand how aging happens so that we can develop better supports for autistic adults.

Participants will receive $100 per study session as reimbursement. You can also request the results of your testing.

Bloorview RESEARCH INSTITUTE
Canada's Only Hospital-Based Childhood Disability Research Institute
Holland Bloorview Kids Rehabilitation Hospital

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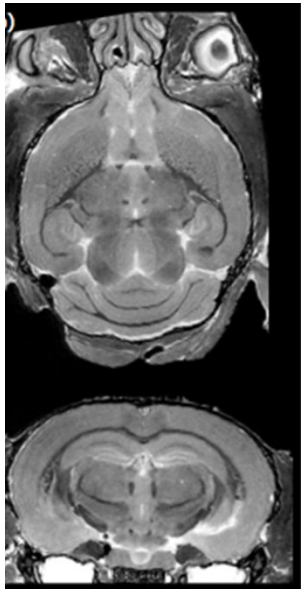
Mouse models of autism

- Start with human genetics
- Knock out or modify identified genes
- Phenotype for brain and behaviour
- >1500 mice
- >60 Genotypes



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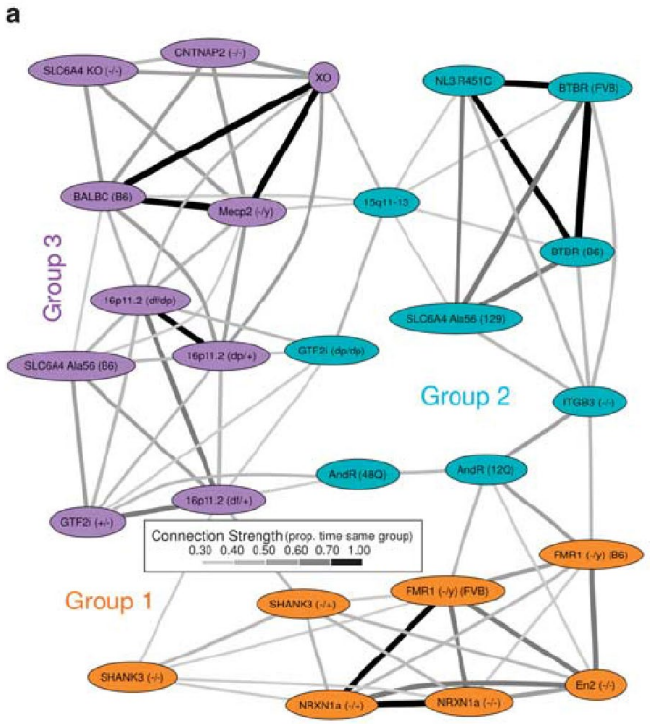
Molecular Psychiatry (2015) 20, 118–125

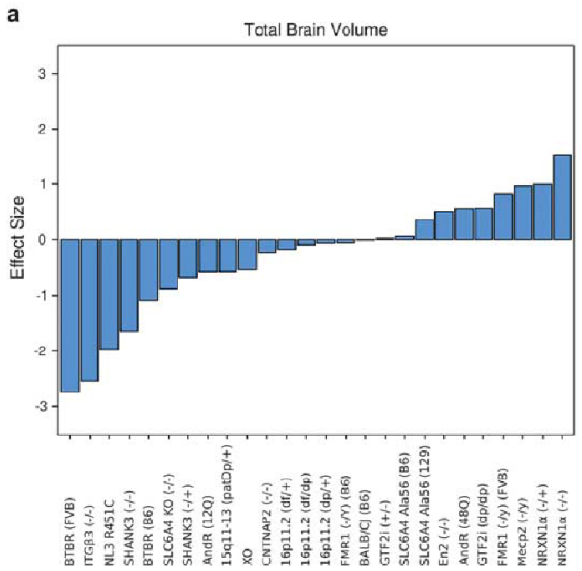
www.nature.com/mp

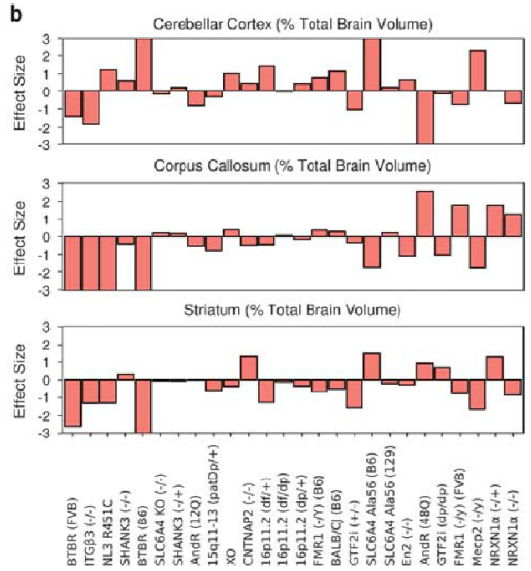

ORIGINAL ARTICLE

Clustering autism: using neuroanatomical differences in 26 mouse models to gain insight into the heterogeneity

J Ellegood[1], E Anagnostou[2], BA Babineau[3], JN Crawley[3,4], L Lin[5], M Genestine[5], E DiCicco-Bloom[5], JKY Lai[6], JA Foster[6], O Peñagarikano[7], DH Geschwind[7], LK Pacey[8], DR Hampson[8], CL Laliberté[1], AA Mills[9], E Tam[10], LR Osborne[10], M Kouser[11], F Espinosa-Becerra[11], Z Xuan[11], CM Powell[11], A Raznahan[12], DM Robins[13], N Nakai[14], J Nakatani[14], T Takumi[14], MC van Eede[1], TM Kerr[15], C Muller[15], RD Blakely[15], J Veenstra-VanderWeele[15], RM Henkelman[1,16] and JP Lerch[1,16]







Holla
Kids Re

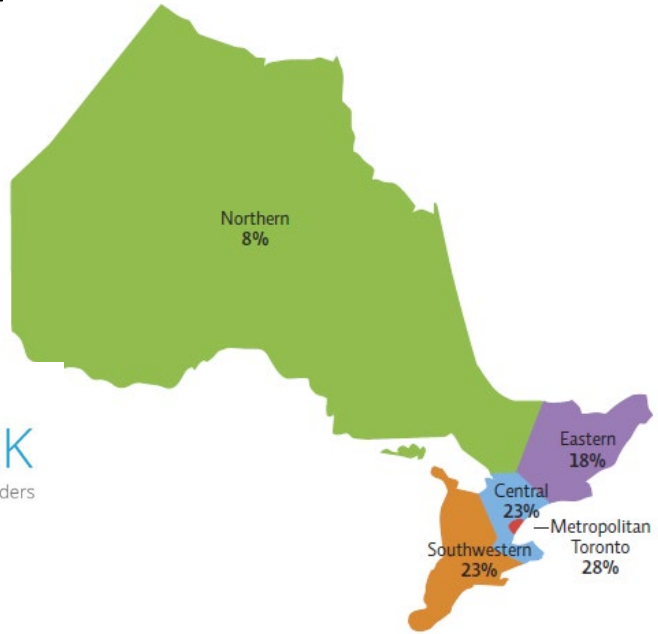
Summary: Brain Diversity

- Many different brains both in terms of structure and function within Autism
- No specific brain differences to ASD; overlap with other neurodevelopmental conditions
- Thinking skills, hyperactivity, attention, and repetitive behaviors more likely to have shared brain signatures
- The differences in brain development seem to map to specific pathways predicted by rare genetic variants

Diversity
Partner experiences

Canadian JLA initiative on Research priorities of neurodivergent individuals

- JLA initiative



POND NETWORK
Province of Ontario Neurodevelopmental Disorders

The Top 10

The Top 10 research priorities from the neurodevelopmental disorder community are:

1. What are the most effective treatment options/plans (e.g., timing, frequency, duration, type, intensity or dosage) for individuals with neurodevelopmental disorders for both short and long-term benefits?
2. How can system navigation be organized in a manner that enables coordinated services and supports across the lifespan for individuals with neurodevelopmental disorders and their families??
3. Which biological treatments (including medications, gene therapy, stem cell therapy, etc.) are effective for neurodevelopmental disorders and associated symptoms?
4. Which child and family-centered interventions or approaches promote optimal individual and family functioning?
5. Which interventions best help individuals with neurodevelopmental disorders develop emotional and behavioural regulation (including increasing impulse control and reducing compulsive behaviour)?
6. Which resources are needed to more effectively address the health, social and emotional needs of families or caregivers of individuals with neurodevelopmental disorders?
7. How can treatment decisions for individuals with neurodevelopmental disorders be more precise (i.e., based on the diagnosis, age, functional need of the individual)?
8. Which are the most effective pharmacological and non-pharmacological treatments for aggressive and self-injurious behaviour in individuals with neurodevelopmental disorders?
9. Which are the most effective pharmacological and non-pharmacological intervention(s) to reduce anxiety in individuals with neurodevelopmental disorders?
10. Which interventions are most effective to help individuals with neurodevelopmental disorders improve their social skills and develop and maintain social relationships?

James Lind Alliance Research priority setting partnerships

Ontario Canada

The Top 10

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10. Which interventions are most effective to help individuals with neurodevelopmental disorders improve their social skills and develop and maintain social relationships?

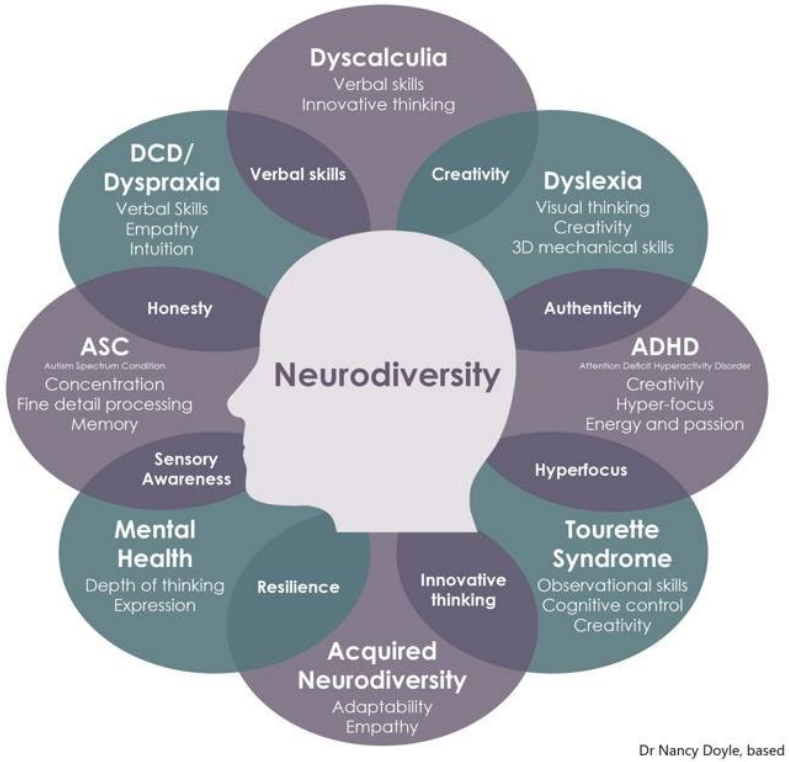
UK

1. Which interventions improve mental health or reduce mental health problems in autistic people? How should mental health interventions be adapted for the needs of autistic people?
2. Which interventions are effective in the development of communication/language skills in autism?
3. What are the most effective ways to support/provide social care for autistic adults?
4. Which interventions reduce anxiety in autistic people?
5. Which environments/supports are most appropriate in terms of achieving the best education/ life/ social skills outcomes in autistic people?
6. How can parents and family members be supported/educated to care for and better understand an autistic relative?
7. How can autism diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately diagnosed?
8. How can we encourage employers to apply person-centred interventions & support to help autistic people maximize their potential and performance in the workplace?
9. How can sensory processing in autism be better understood?
10. How should service delivery for autistic people be improved and adapted in order to meet their needs?

https://braininstitute.ca/resources/pond-youth-digital-stories

https://www.youtube.com/watch?v=2eF7Fj7CV4E

Neurodiversity



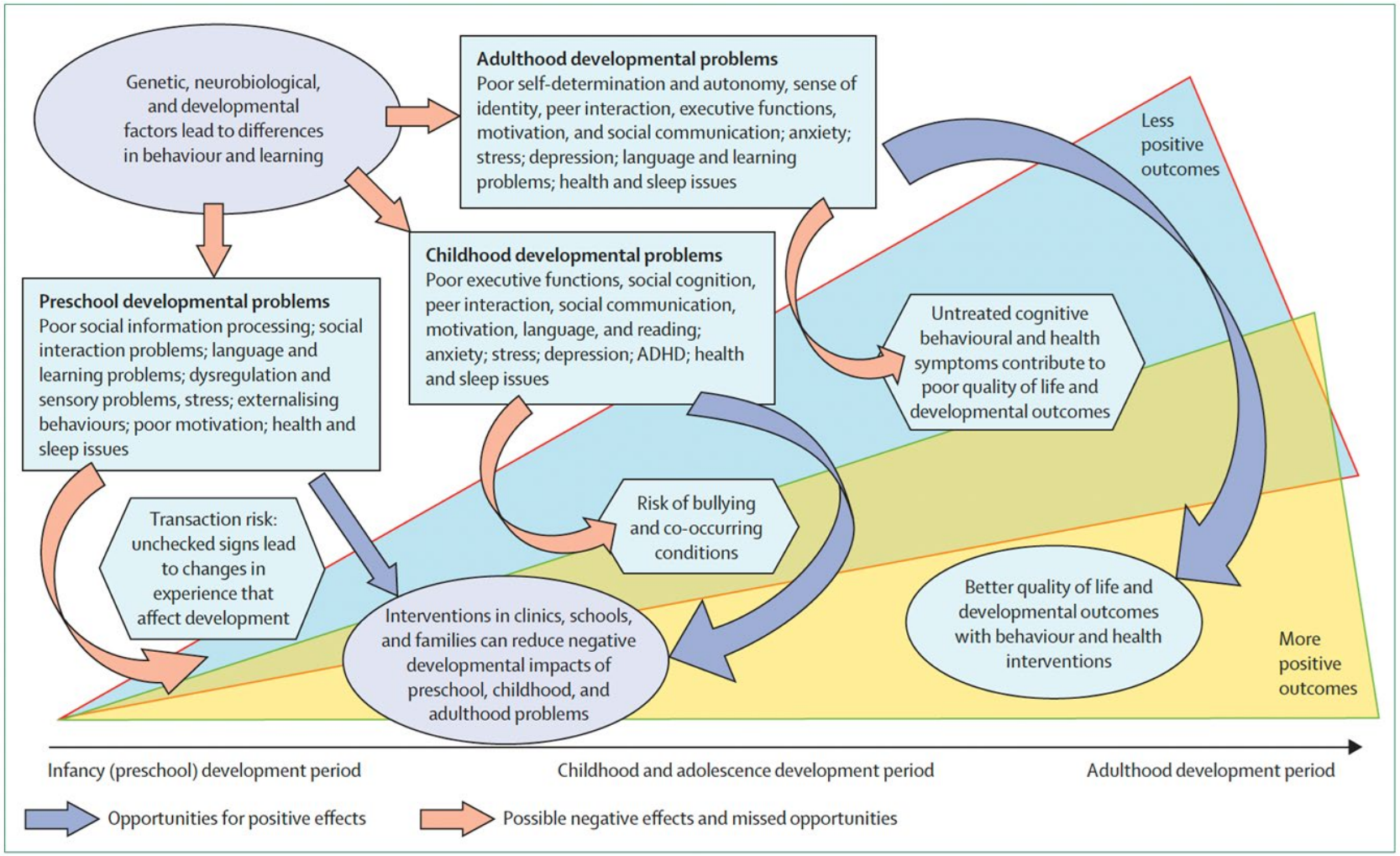
Dr Nancy Doyle, based on the work of Mary Colley

by Ariela Paulsen

Diversity Interventions

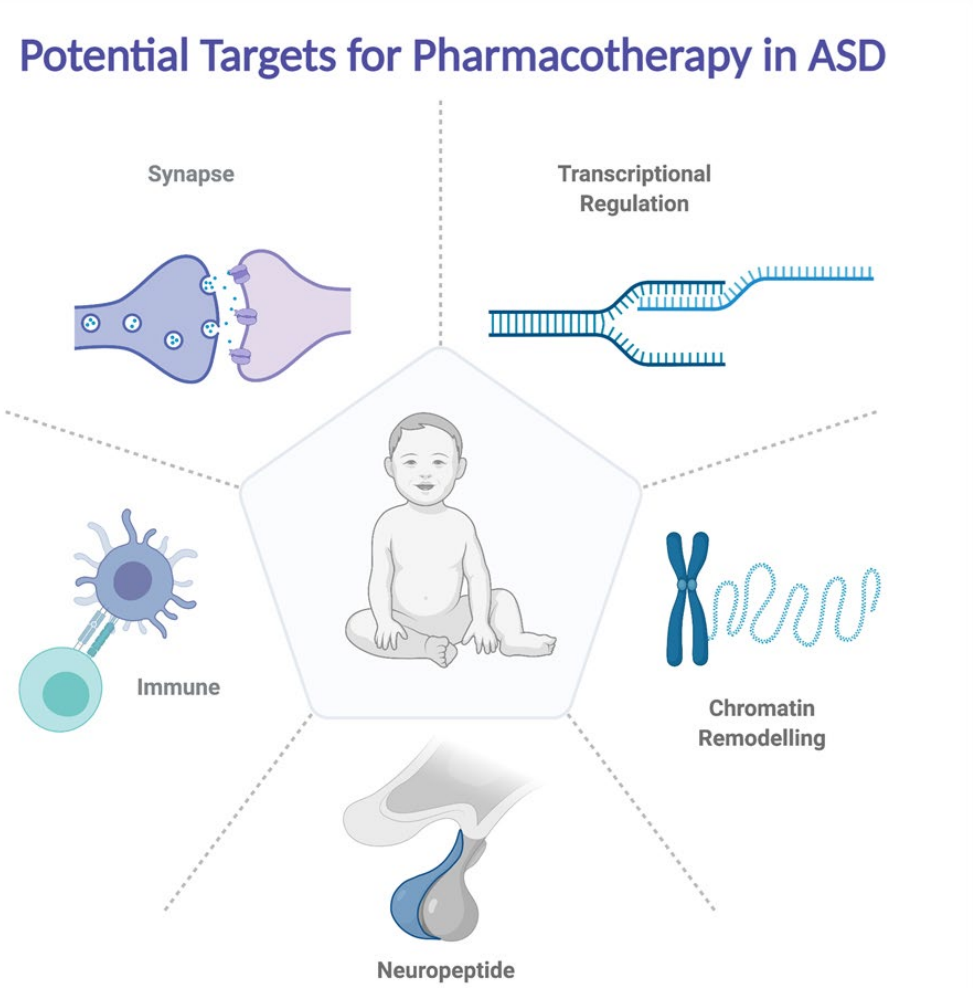
The *Lancet* Commission on the future of care and clinical research in autism

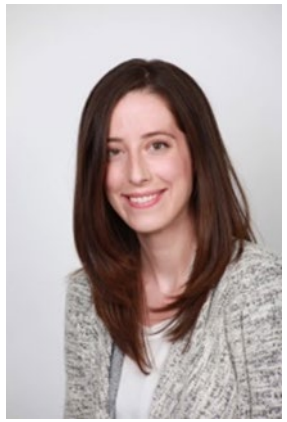
Catherine Lord, Tony Charman*, Alexandra Havdahl, Paul Carbone, Evdokia Anagnostou, Brian Boyd, Themba Carr, Petrus J de Vries, Cheryl Dissanayake, Gauri Divan, Christine M Freitag, Marina M Gotelli, Connie Kasari, Martin Knapp, Peter Mundy, Alex Plank, Lawrence Scahill, Chiara Servili, Paul Shattuck, Emily Simonoff, Alison Tepper Singer, Vicky Slonims, Paul P Wang, Maria Celica Ysrraelit, Rachel Jellett, Andrew Pickles, James Cusack, Patricia Howlin, Peter Szatmari, Alison Holbrook, Christina Toolan, James B McCauley*

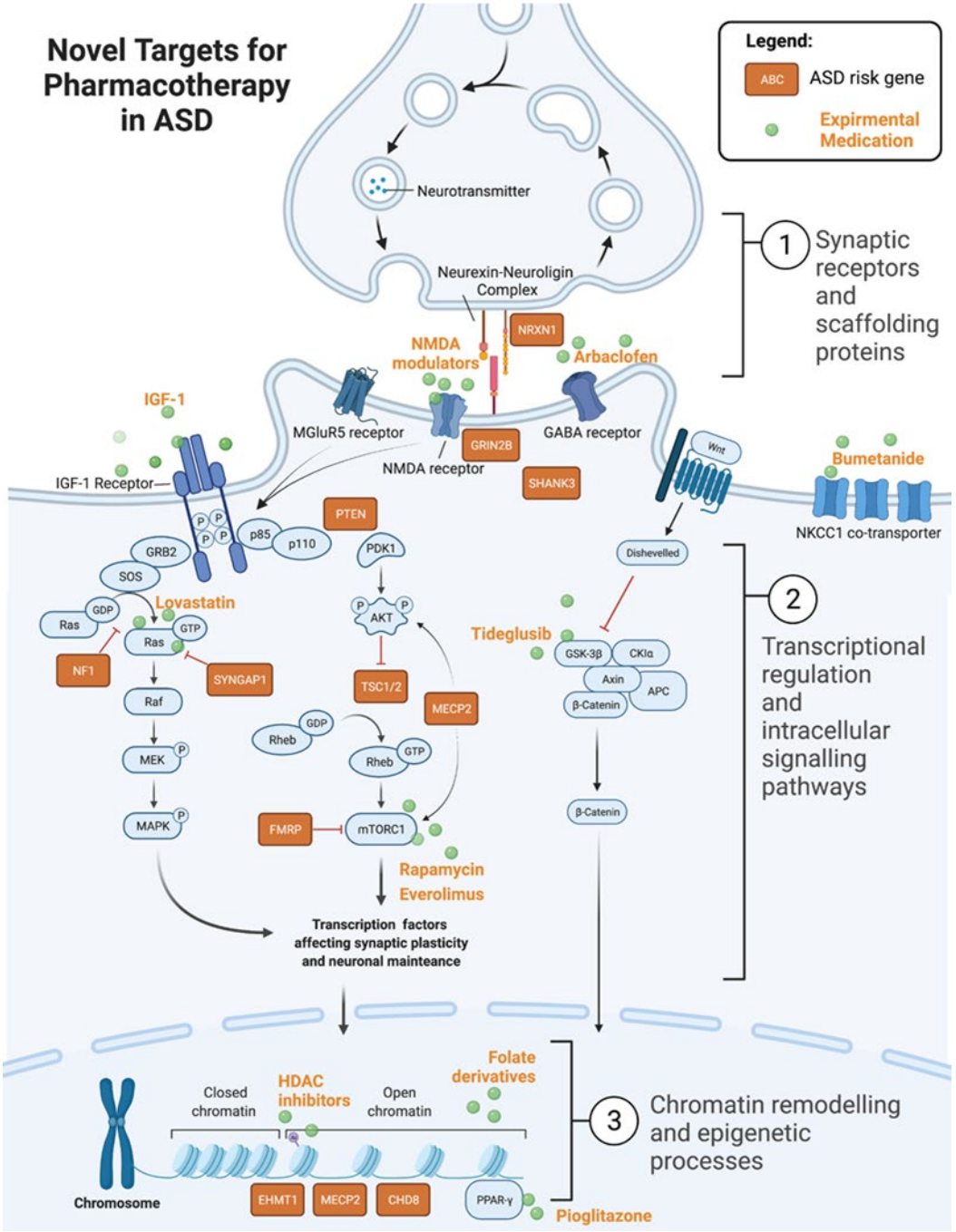


Experimental therapeutics

Baribeau et al Pharmacol Reviews, 2022



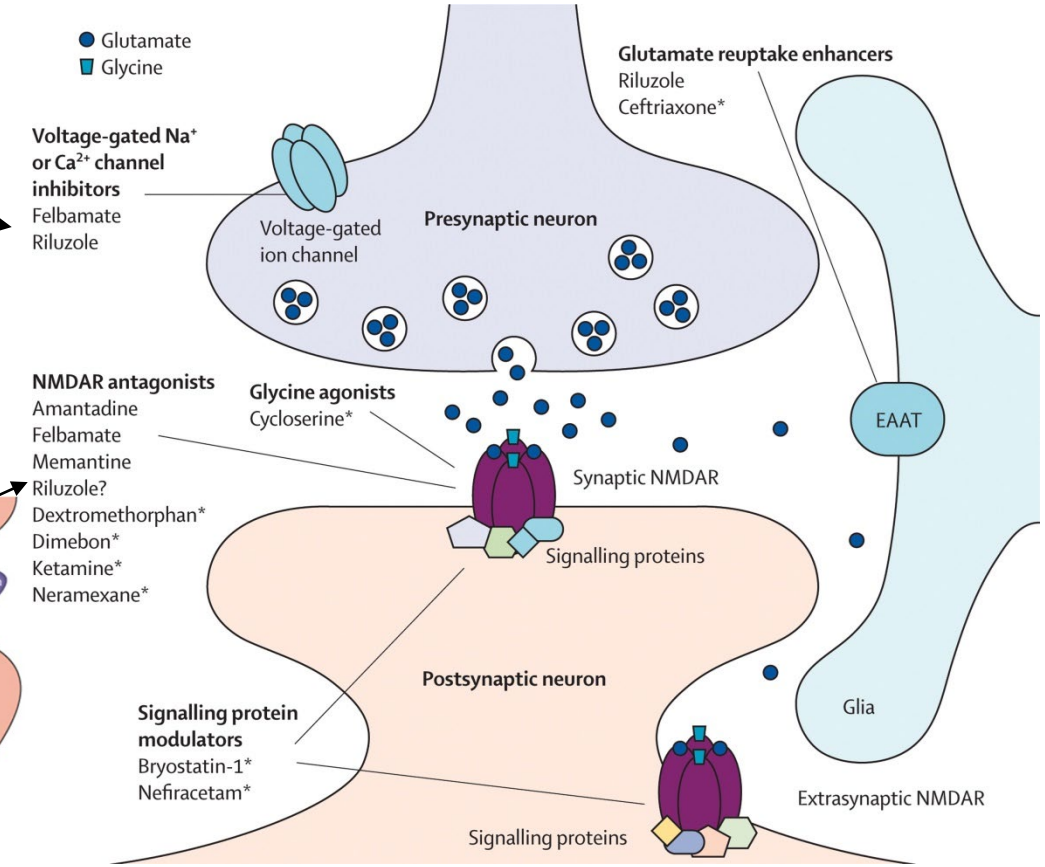


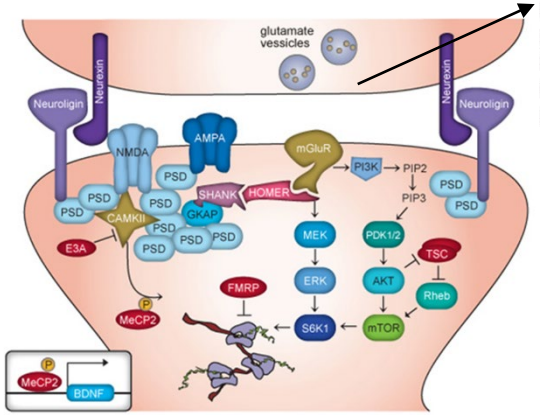


Riluzole vs placebo in autism

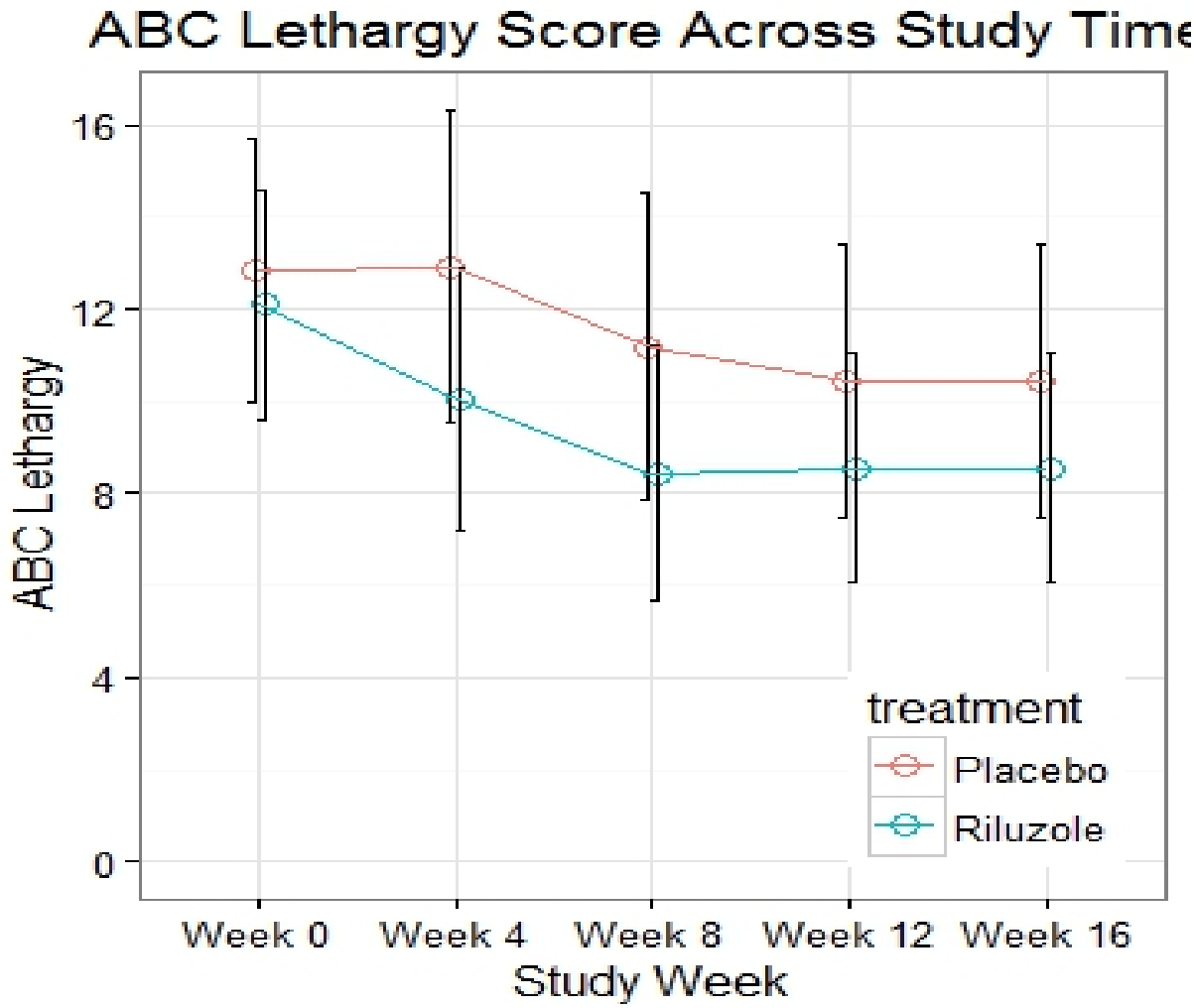
(co-Pis: Rob Nicolson, Terry Bennet)

60 Children and youth
1:1 randomization
Age-7-17



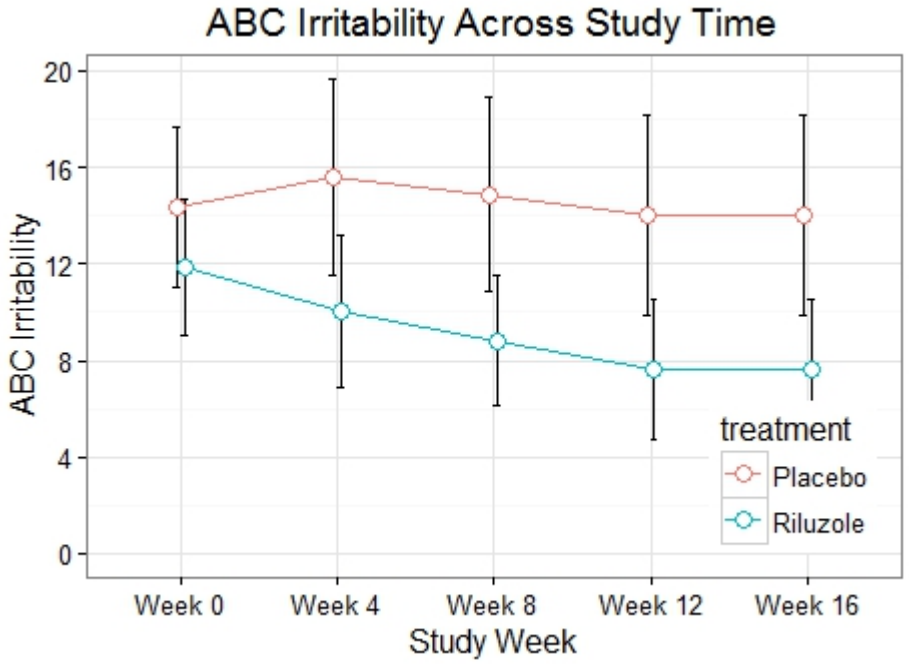


Rilise – Social Withdrawal

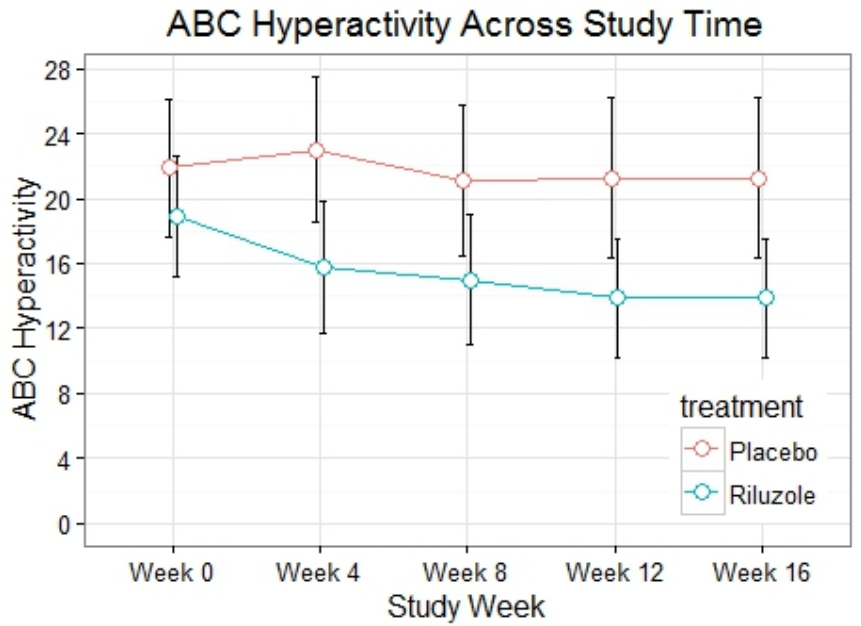


Holland Bloorview
Kids Rehabilitation Hospital

Externalizing Behaviors



p= 0.02; d= 0.45,
coeff estimate for riluzole: -4.56

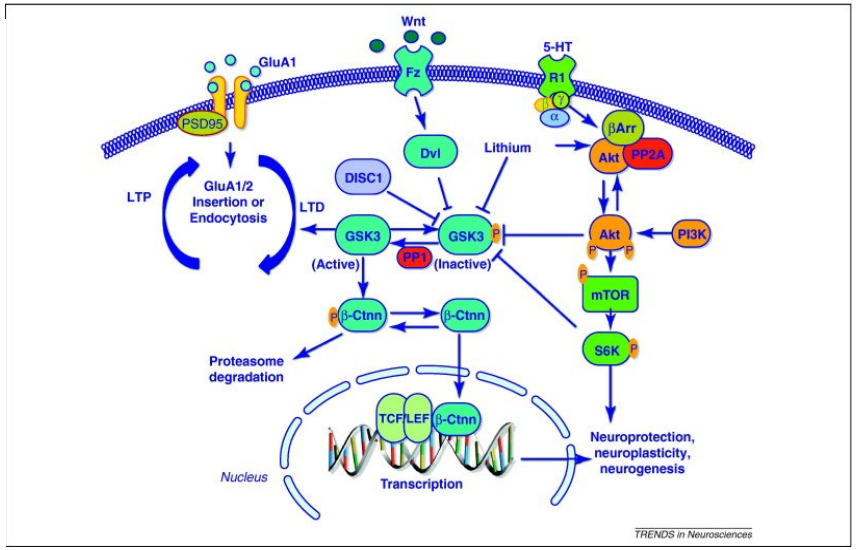


P=0.02; d=0.4
Coeff estimate for riluzole: -5.24

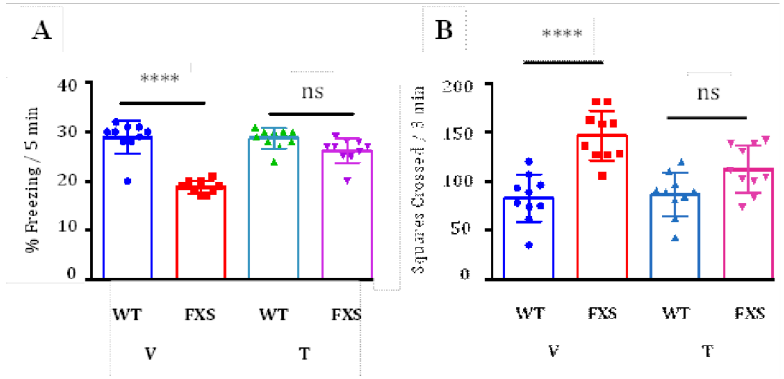
Holland Bloorview
Kids Rehabilitation Hospital

TIDE: RCT of Tideglusib vs placebo in autistic adolescents

- Regulates circadian clock
- Regulates inflammatory response (reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines)
- Regulates neurogenesis/cell differentiation
- Phosphorylates histone deacetylase 3
- Key role in synaptic plasticity (via NMDA mediated LTD).

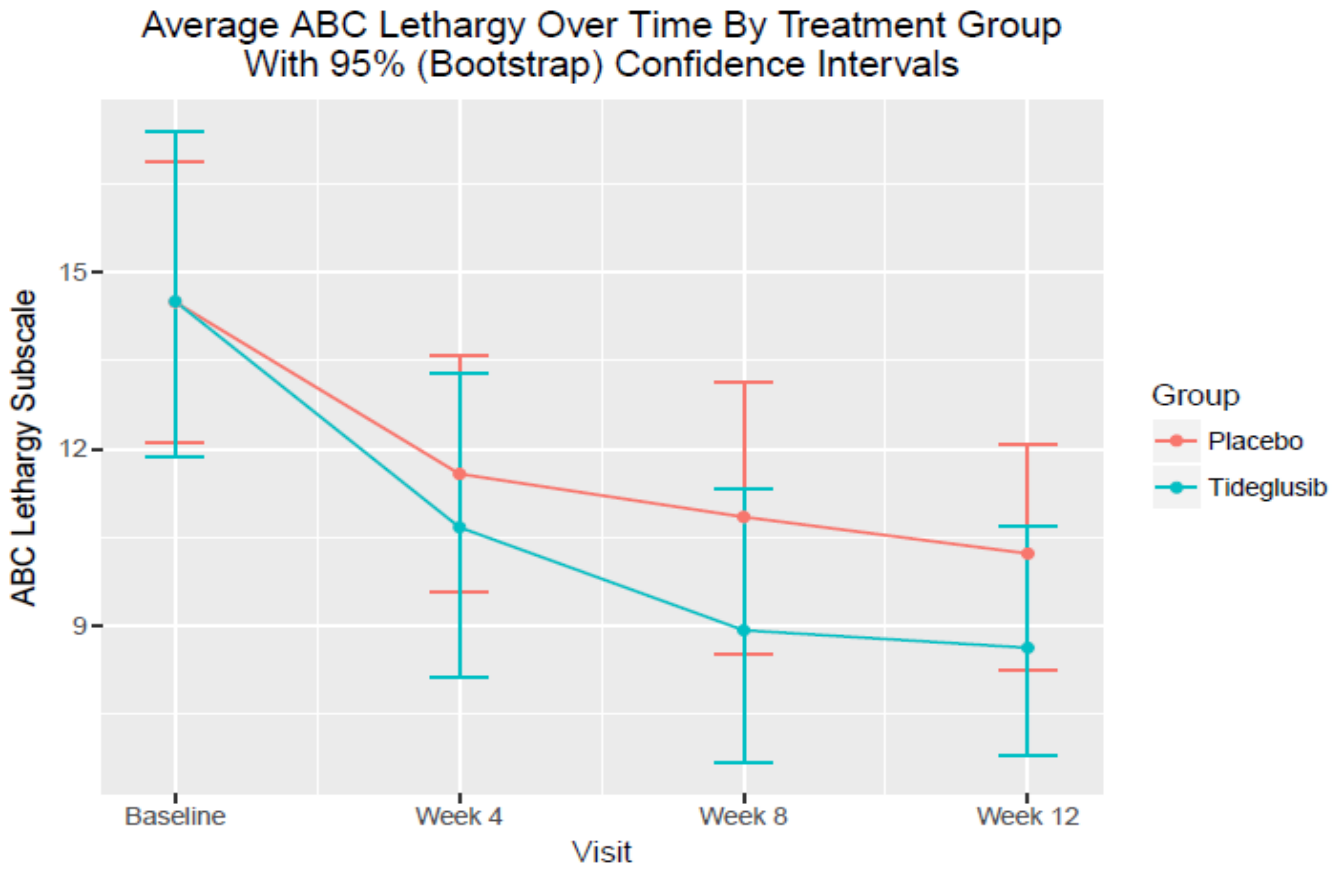


Pharmacological agents that can deplete GSK-3β such as Tideglusib have been shown to rescue the phenotype of the Fragile X – FMR1 knockout transgenic mouse. Rescued or improved domains included learning and memory, hyperactivity, anxiety and fear conditioning, as well as repetitive behaviors (Franklin et al., 2013, Figure 2).

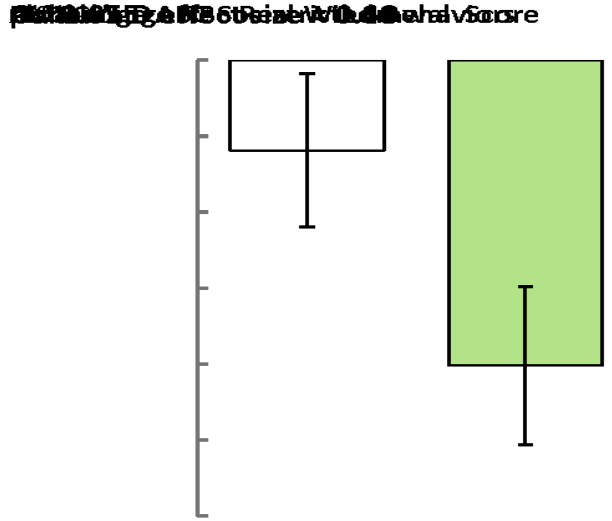


Holland Bloorview
Kids Rehabilitation Hospital

Results: Primary Analysis

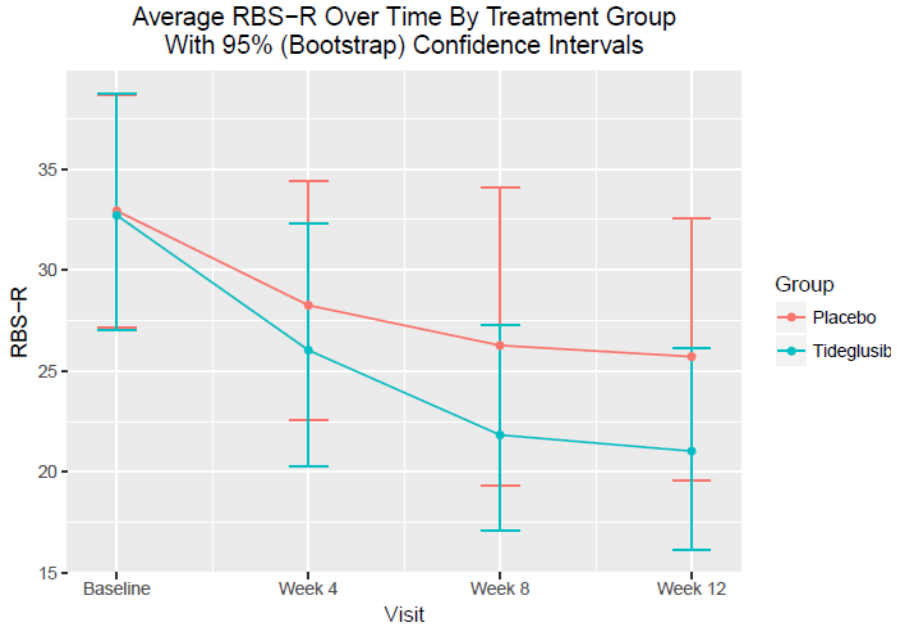


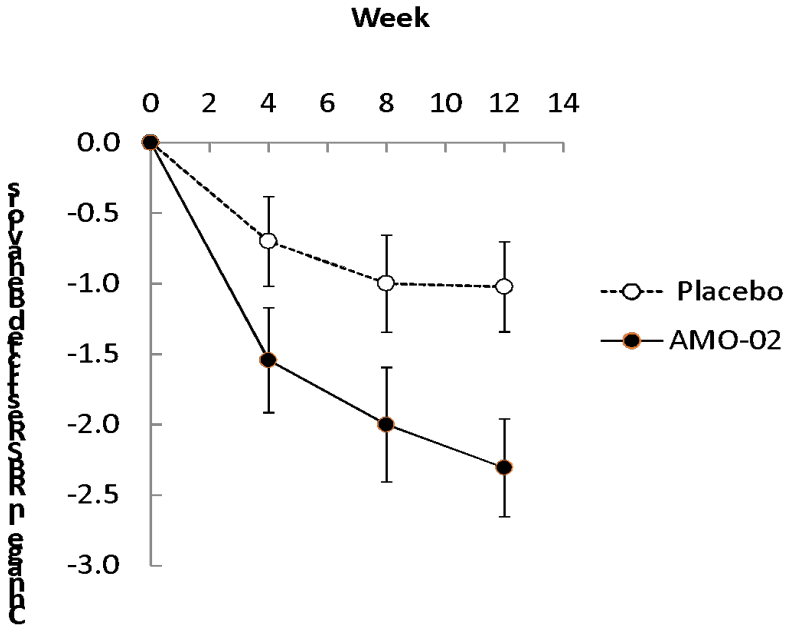
90 youth
1:1 randomization
12-18 years

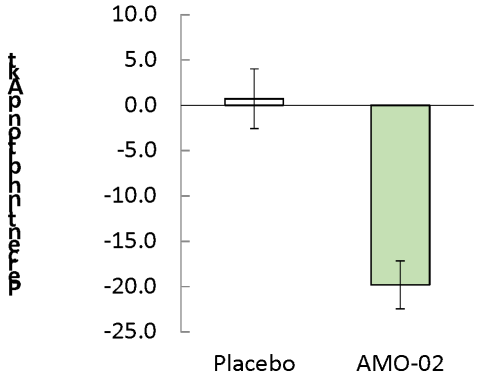


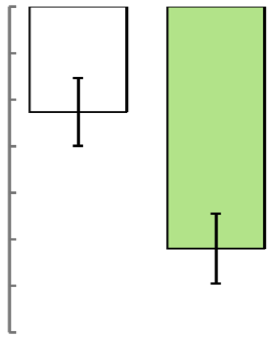
Holland Bloorview
Kids Rehabilitation Hospital

Secondary Analysis









Holland Bloorview
Kids Rehabilitation Hospital

RCT of oxytocin vs placebo in youth with autism

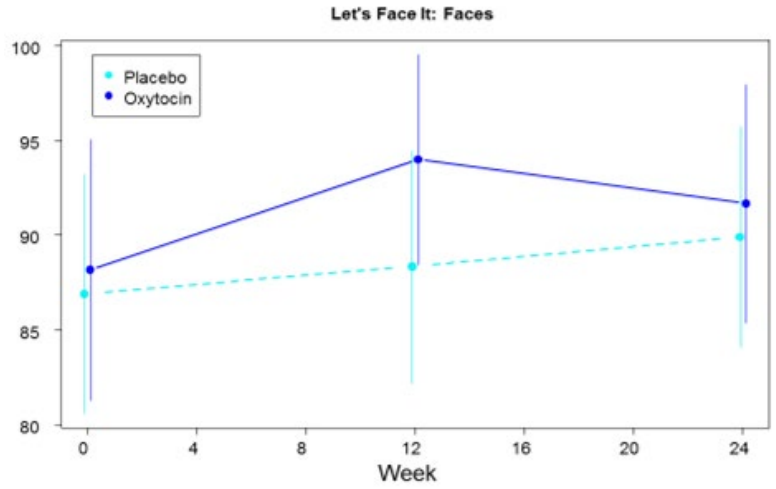
- 60 youth randomized, 1:1
  - Holland Bloorview, University of Toronto
  - University of Minnesota – Dr Jacob

- 12 weeks exposure
- Follow-up at 24 weeks

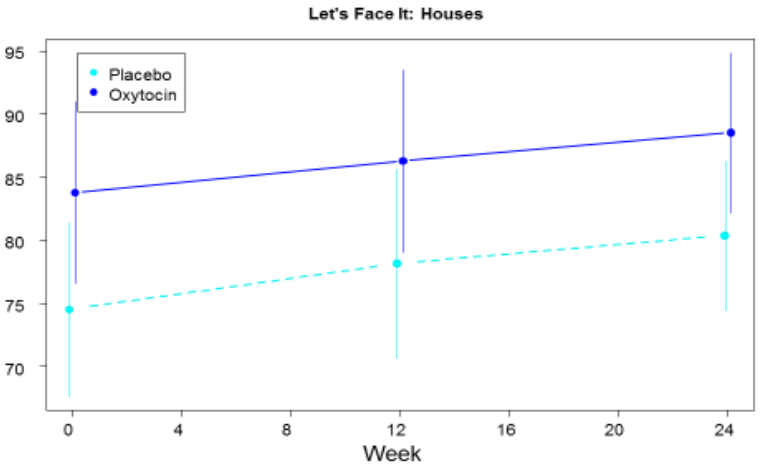
- Dose: 0.4IU/kg/ dose, 2 doses a day, 8 +/- 2 hours apart

Holland Bloorview
Kids Rehabilitation Hospital

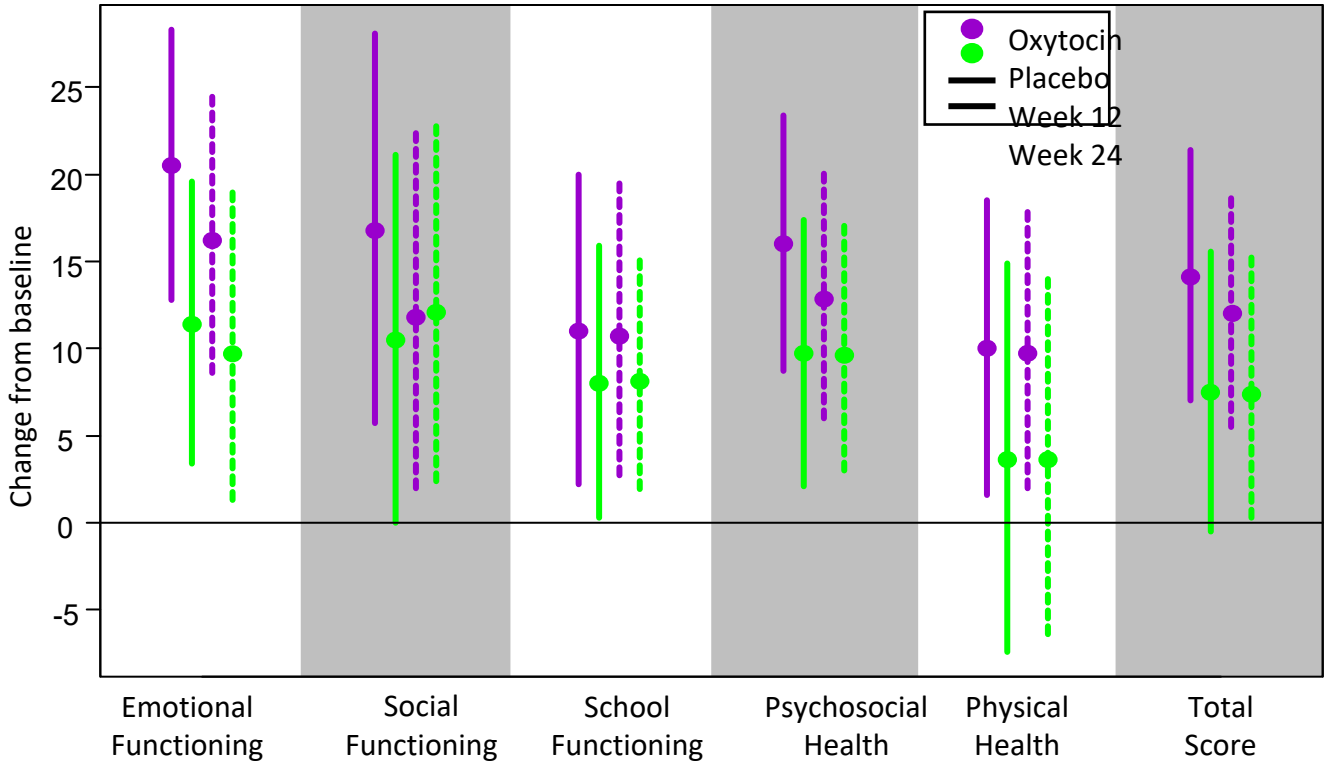
RCT of oxytocin vs placebo in youth with autism



p=0.02

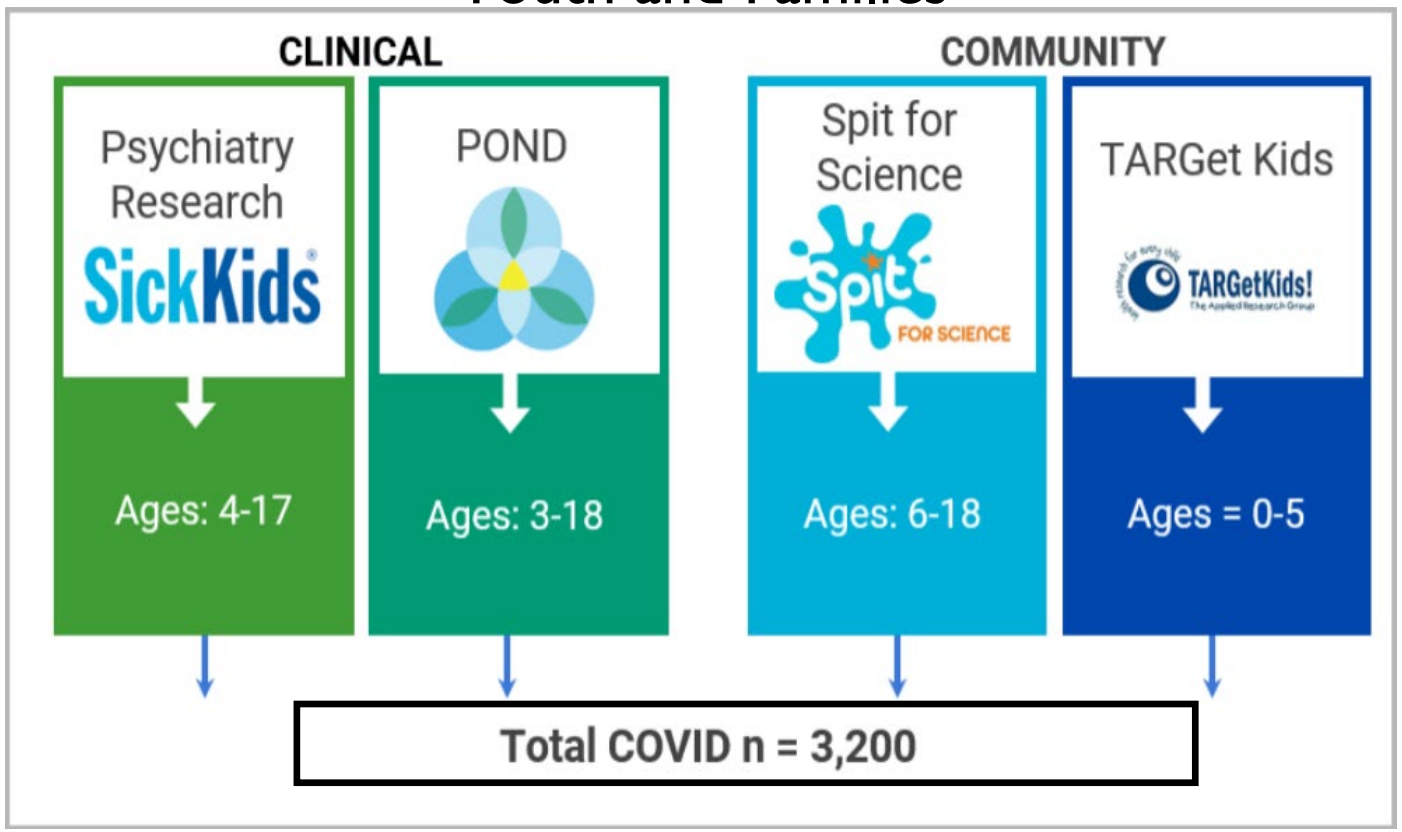


p=0.3



autism RESEARCH CENTRE

Real-Time Monitoring of Mental Health Impact of COVID-19 on Canadian Children, Youth and Families



CRISIS AFAR: An International Collaborative Study of the Impact of the COVID-19 on youth with NDDs (Lead: A. DiMartino)

Daphne Korczak, MD (PI)

Psychiatry UNIVERSITY OF TORONTO

SickKids | Centre for Brain & Mental Health

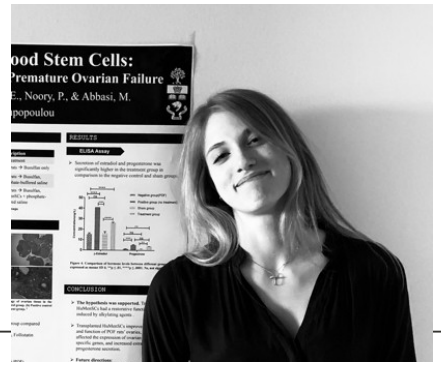
CIHR IRSC

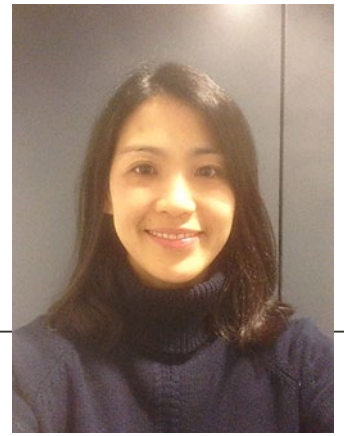
Ontario Ministry of Health

The Edwin S. H. Leong Centre for Healthy Children UNIVERSITY OF TORONTO

Heterogeneity on response to the pandemic

Paediatrics & Child Health, 2022, XX, 1–7
DOI: https://doi.org/10.1093/pch/pxab111
Advance access publication 5 May 2022
Original Article





OXFORD

Original Article

Mental health profiles of autistic children and youth during the COVID-19 pandemic

Marina Charalampopoulou BSc[1,*], Eun Jung Choi PhD[1,*], Daphne J. Korczak MD[2,3], Katherine T. Cost PhD[2], Jennifer Crosbie PhD[2,3], Catherine S. Birken MD MSc FRCPC[4,5], Alice Charach MD[2,3,5,6], Suneeta Monga MD[2,3], Elizabeth Kelley PhD[7,8], Rob Nicolson MD[9], Stelios Georgiades PhD[10], Muhammad Ayub MD[8], Russell J. Schachar MD[2,3], Alana Iaboni PhD[1], Evdokia Anagnostou MD[1,4]

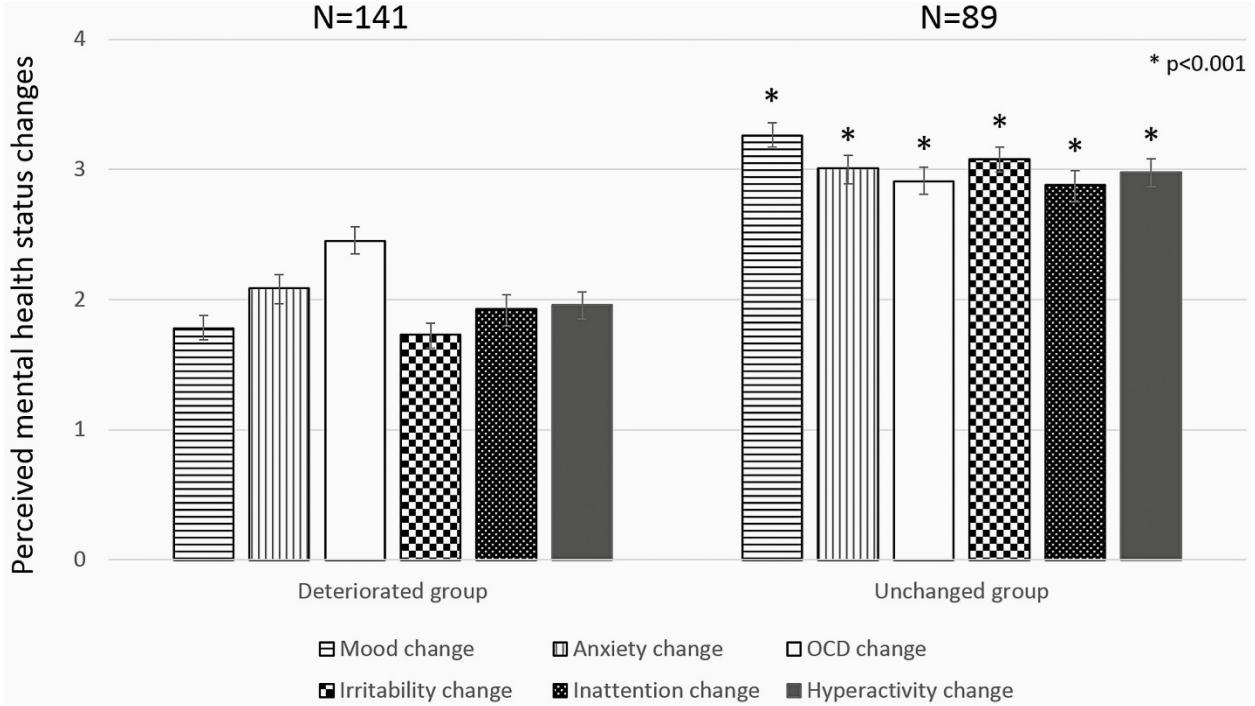
Figure 2. MH changes were examined in six measures (Mood, Anxiety, OCD symptom, Irritability, Inattention, ...

COVID stress / material deprivation

Pre-existing internalizing symptoms

Parental mental health

Loss of School / medical services



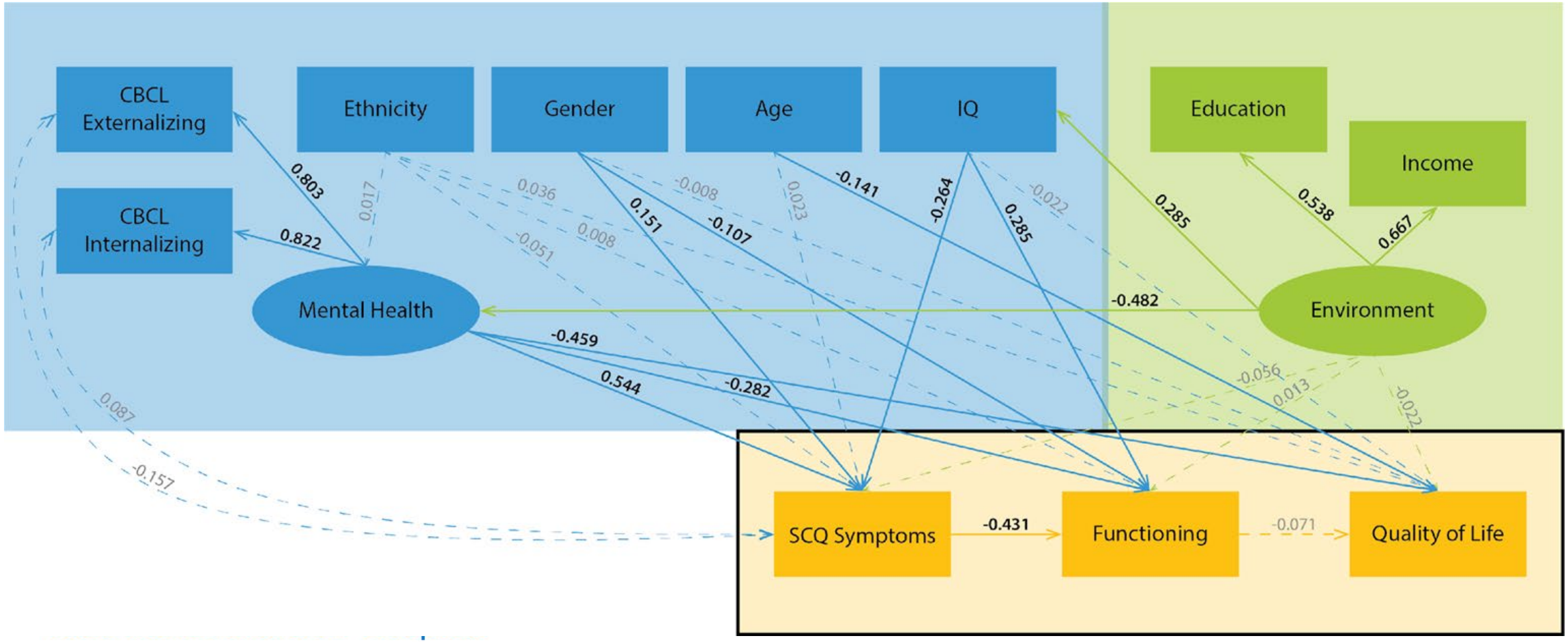
?third cluster, better?

Good parental mental health / Financial security

Paediatr Child Health, pxab111, https://doi.org/10.1093/pch/pxab111

Quality of life in Canadian autistic children and youth

Maryam Mahjoob



Facing Your Fears:

Virtual Implementation trial for anxiety in children with autism

Brian & Anagnostou et al, in review

THE PROGRAM

The research team used the FYF curriculum, adapted for virtual delivery

The Program covered:

- Identifying signs and symptoms of anxiety
- Increasing awareness of anxiety provoking situations
- Srategies to reduce anxiety over time
- Facing fears and coping in anxiety provoking situations

The Program has a critical parent component, which includes:

- Psycho-education of anxiety disorders and basic CBT principles
- Identifying and managing children's anxious behaviours
- Discussion around parental anxiety and its impact on children's anxiety
- Teaching parents to support their children through hands-on practice
- Opportunities to learn from and support other parents

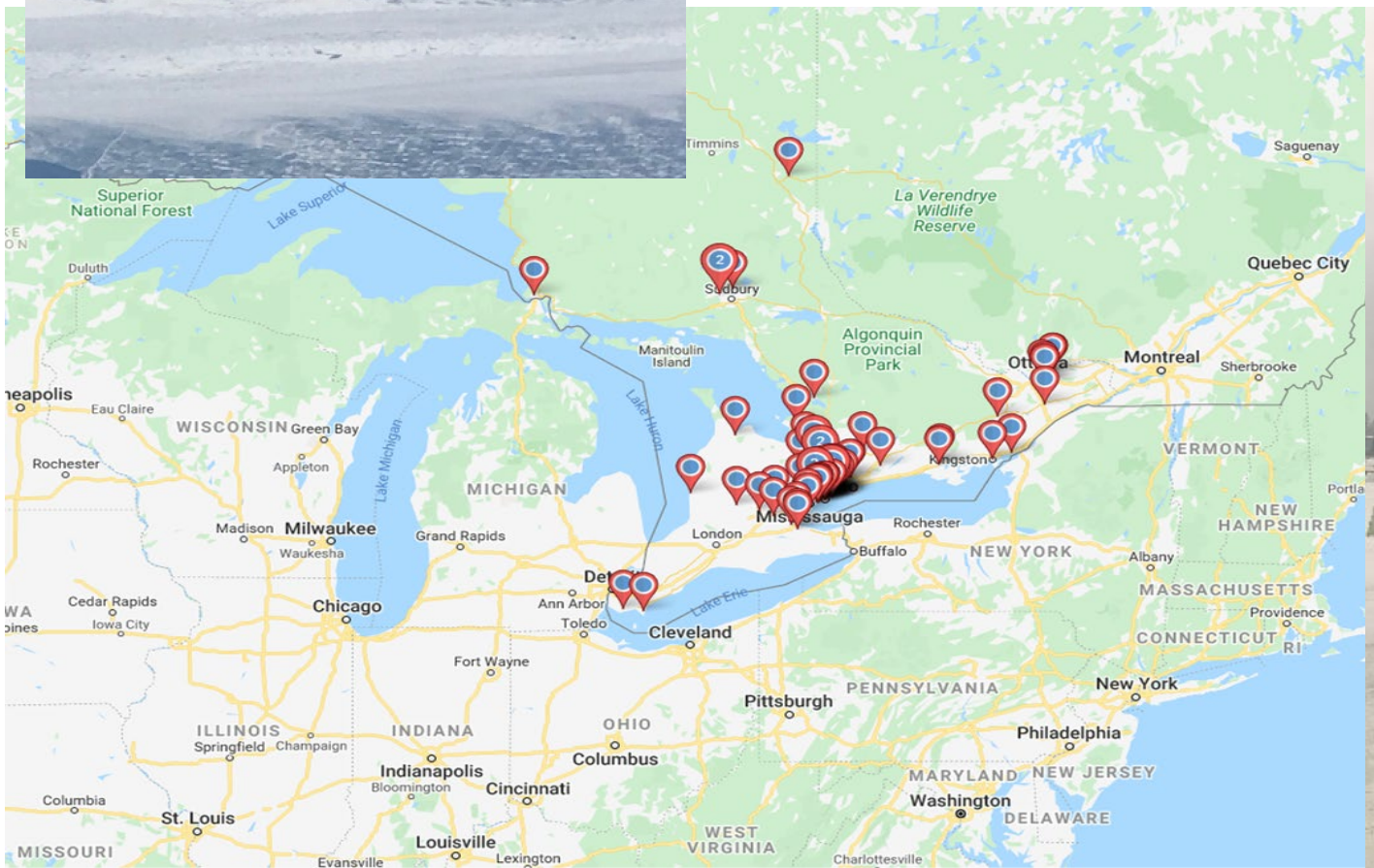
THE DELIVERY

- 100 families enrolled between January 2021 & December 2021 (4 enrollment rounds)
- Children were age 8-13
- 4-5 families per group session (20 groups total)

- 12 FYF group sessions delivered weekly via Zoom
- Sessions were approximately 90 minutes:
  - 45-60 minutes with parent and child
  - 30-45 minutes with parents alone
- Phone check-in calls were conducted with each parent individually at weeks 7 and 9

- 87 families completed the intervention program
- 80 families attended 10/12 sessions or more, suggesting high acceptility

Participant Distribution



The virtual adaptation of the FYF Program worked

Cut-off for clinical concern: 25

Mean parent reported anxiety (SCARED)

Pre-Intervention: 34.9

Post-Intervention: 27.9

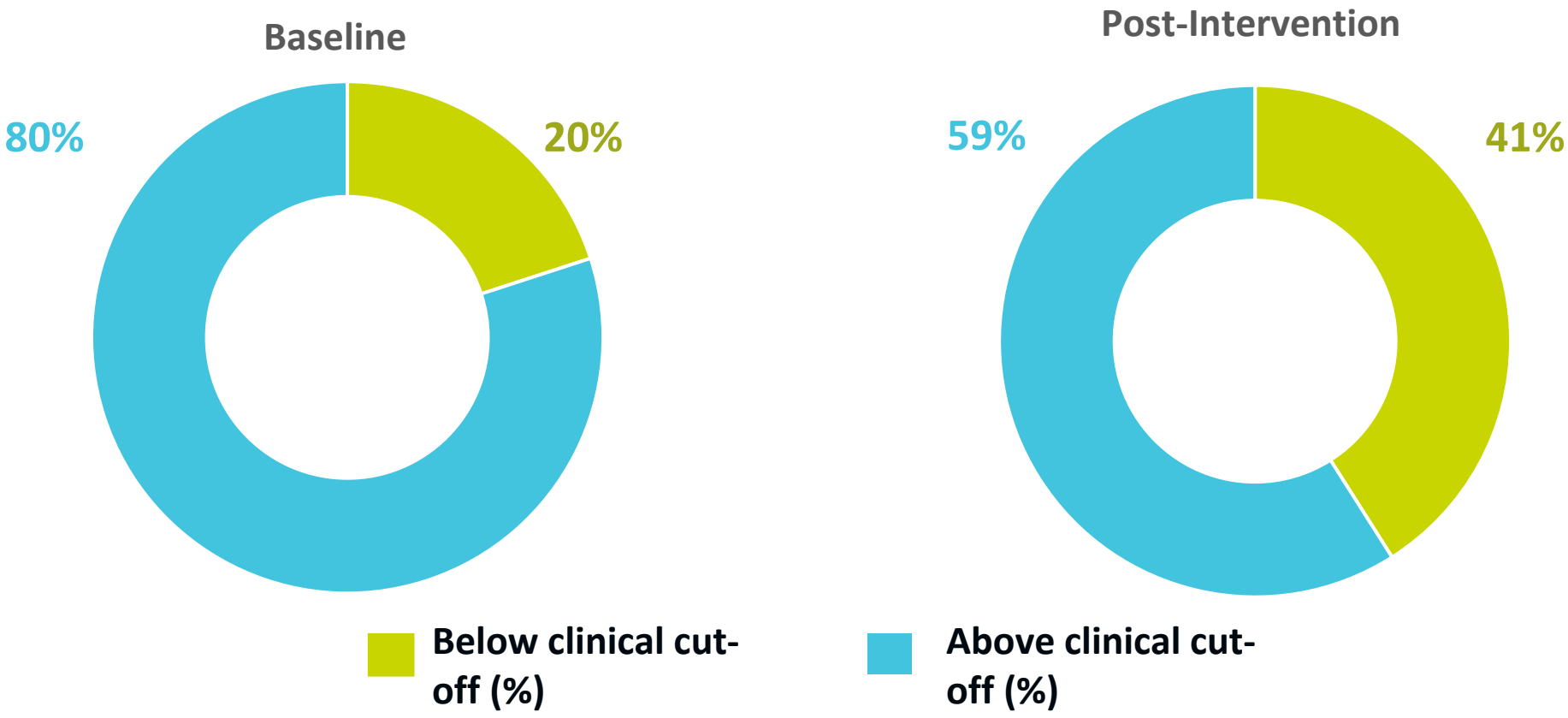
Mean child reported anxiety (SCARED)

Pre-Intervention: 34.5

Post-Intervention: 28.9

The virtual adaptation of the FYF Program worked

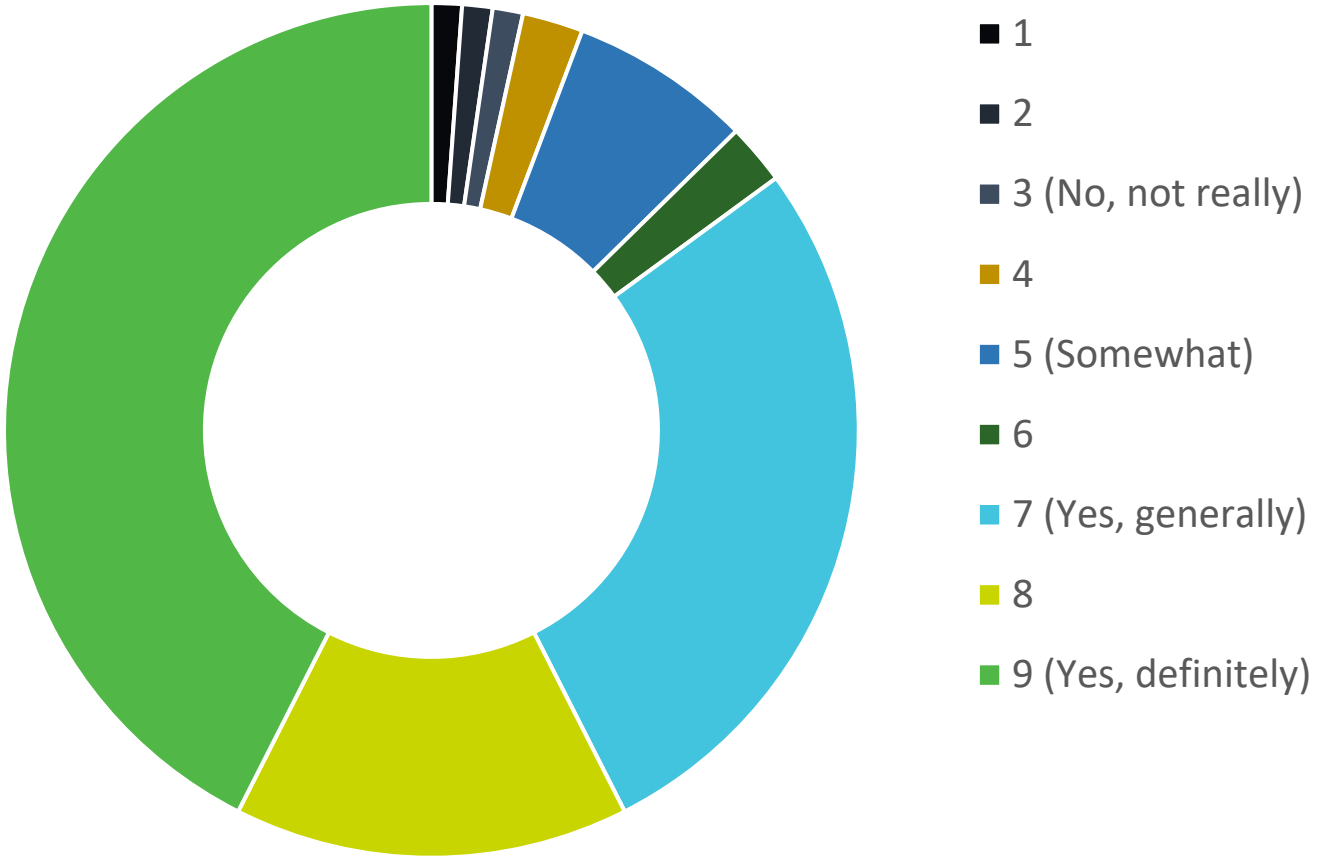
Intent to treat analysis



While material deprivation concerns were related to higher ratings of child anxiety at baseline, the higher deprivation did not impede children's ability to progress in the program

Parents reported high satisfaction with the virtual format

Were you satisfied receiving this intervention virtually (as opposed to an in-person program) ?



85% of parents reported they were "generally" to "definitely" satisfied with the virtual format

Holland Bloorview
Kids Rehabilitation Hospital

Principles of personalized interventions

The *Lancet* Commission on the future of care and clinical research in autism

Catherine Lord, Tony Charman*, Alexandra Havdahl, Paul Carbone, Evdokia Anagnostou, Brian Boyd, Themba Carr, Petrus J de Vries, Cheryl Dissanayake, Gauri Divan, Christine M Freitag, Marina M Gotelli, Connie Kasari, Martin Knapp, Peter Mundy, Alex Plank, Lawrence Scahill, Chiara Servili, Paul Shattuck, Emily Simonoff, Alison Tepper Singer, Vicky Slonims, Paul P Wang, Maria Celica Ysrraelit, Rachel Jellett, Andrew Pickles, James Cusack, Patricia Howlin, Peter Szatmari, Alison Holbrook, Christina Toolan, James B McCauley*

Holland Bloorview
Kids Rehabilitation Hospital

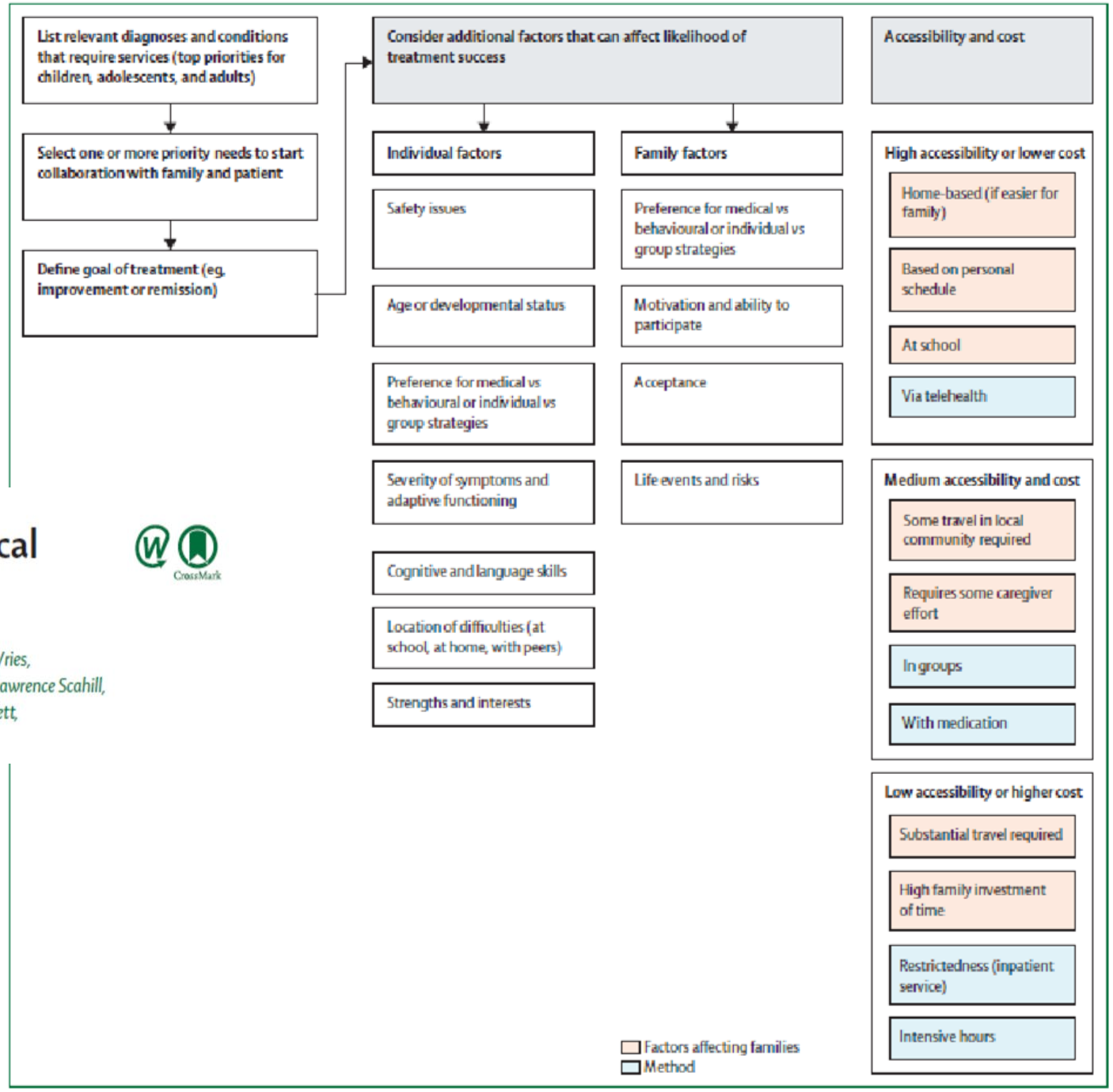


Figure 5: Stepped care and personalised health interventions

Summary

- Diversity is prominent also in
  - In response to intervention
  - In response to changes in environment and context
  - Stakeholder perspectives
- Predictors can be found as much in underlying biology differences, pre-existing or co occurring conditions, as in modifiable environmental factors such as parental supports, financial stress, and stability of services.
- Partner / Stakeholder priorities may not be stable, influenced by context, cultural values, and may have local specificity

Holland Bloorview
Kids Rehabilitation Hospital

Next Steps

autism RESEARCH CENTRE

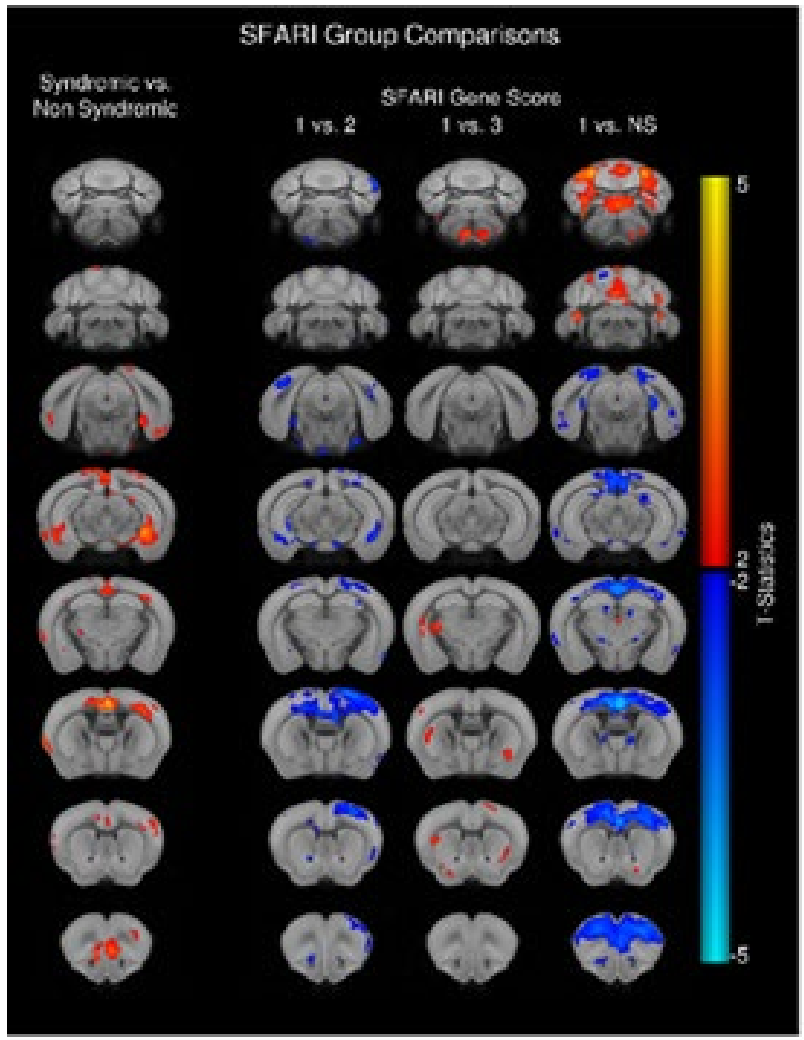
The *Lancet* Commission on the future of care and clinical research in autism

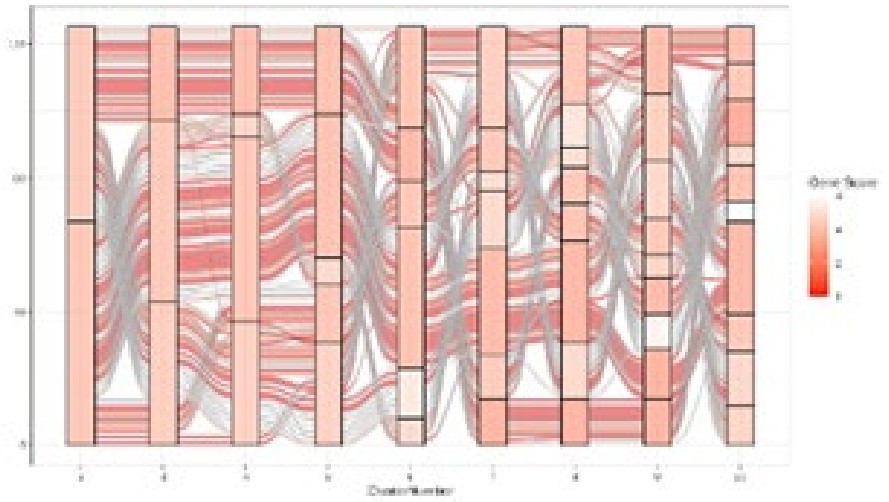
Catherine Lord, Tony Charman*, Alexandra Havdahl, Paul Carbone, Evdokia Anagnostou, Brian Boyd, Themba Carr, Petrus J de Vries, Cheryl Dissanayake, Gauri Divan, Christine M Freitag, Marina M Gotelli, Connie Kasari, Martin Knapp, Peter Mundy, Alex Plank, Lawrence Scahill, Chiara Servili, Paul Shattuck, Emily Simonoff, Alison Tepper Singer, Vicky Slonims, Paul P Wang, Maria Celica Ysrraelit, Rachel Jellett, Andrew Pickles, James Cusack, Patricia Howlin, Peter Szatmari, Alison Holbrook, Christina Toolan, James B McCauley*

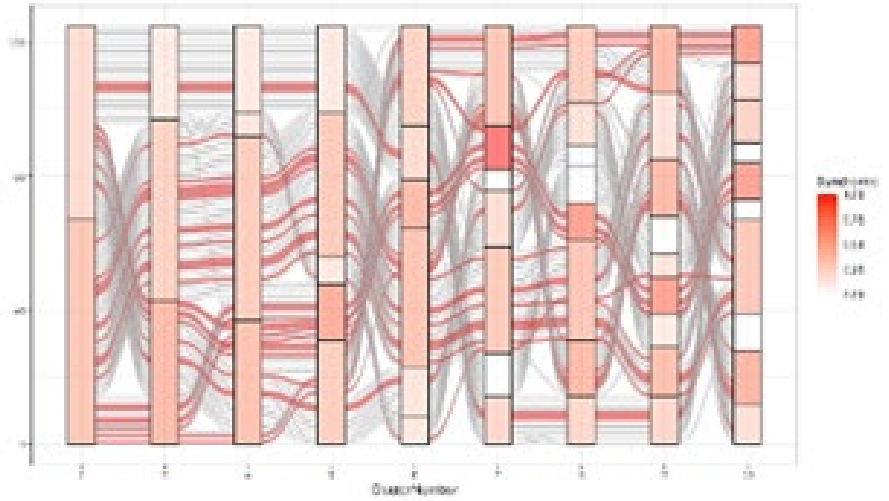
Key messages: actionable recommendations

- Although autism affects at least 78 million people worldwide, formal documentation of their existence is limited to a subset of countries. Formal documentation through governmental health-care, education, and social care systems for people with autism would be a first step in determining the needs and addressing the potential inequalities faced by these individuals.
- Autism is a complex but common neurodevelopmental disorder that requires personalised assessments and intervention strategies. A stepped care and personalised health model to assess and direct interventions can increase the effectiveness of approaches. Governments and health-care systems must recognise the need for integration across systems to support the needs of autistic individuals and their families across development.
- Autism is a neurodevelopmental disorder that changes with and affects development; a single assessment or a single treatment is never sufficient. Follow-up assessments and personalised treatment plans that focus on individual strengths, difficulties, and changes in contexts and expectations across the life span are needed.
- Interventions for autism and for co-occurring conditions should begin as soon as signs are noticed and then monitored with more comprehensive assessment once begun. No one should wait for months or years to start treatment because they are unable to find an appropriate assessment. However, within a reasonable period of time (depending on age and context), assessments do need to be supported and undertaken to identify personalised needs.
- Focused research strategies at the government or institutional level should be prioritised with an emphasis on clinical practice that can increase the understanding of what interventions work, for whom, when, how, with what general outcomes, and at what cost. National and international infrastructures should be developed to help such projects to move beyond single investigator-led (albeit multisite) studies to more integrated attempts that take into account individual differences within autism. Infrastructures should also support studies that build on each other and provide evidence for broader community implementation and effectiveness, rather than simply showing that an intervention is better than a waiting list or treatment as usual.
- Governments and services should monitor access to provision to ensure that underserved groups, including those who are minimally verbal, girls and women, minority ethnic groups, from socially disadvantaged backgrounds, or with severe co-occurring conditions, have equitable access to appropriate services.

Next steps:







- Integrating across human and animal model data to identify clusters of patients based on imaging, omics etc. that a biological pathway can be targeted

Holland Bloorview
Kids Rehabilitation Hospital

Jason Lerch et al, in progress

Collaborations to get definitive answers to biological interventions: what, for whom, when, and for how long

A randomized placebo-controlled trial of ARBaclofen vs. placebo in the treatment of children and adolescents with ASD

"The ARBA" Study

Protocol #: ARB-05-2018

- **Canada-European collaboration**

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

AIMS•2•TRIALS

- ARBA study
  - Arbaclophen vs Placebo for social function

- Canada: 4 sites
  - Biological markers:
    - EEG (Sarah Lippe, Emily Jones)
    - Sensory discrimination task (GABRB3) (Nick Puts)

Sara Lippe

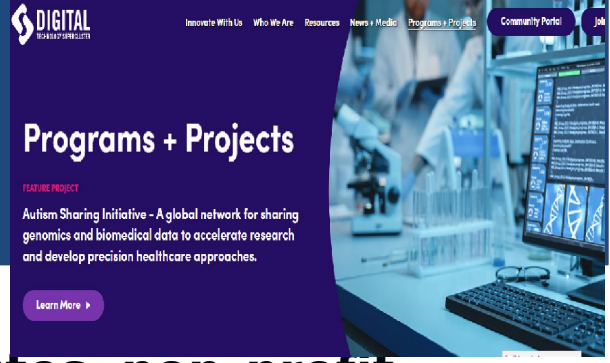
Emily Jones

Nick Puts

Celso Arango

- Continuous engagement with various stakeholder groups to understand
  - Principles of helping neurodivergent children and youth envision a “good life”
  - Predictors and opportunities for interventions to get to these personalized goals
  - Advocacy to address systemic predictors/ barriers to good life: not limited to health
  - Continue to evolve with evolving ideas of neurodiversity

The Autism Sharing Initiative (ASI)



A collaborative, global project bringing together research institutes, non-profit organisations and industry to build a secured network for sharing genomics and biomedical data gathered from consented autistic individuals who have participated in research.

12 partners

- Autism Speaks (US, CAN)
- DNAstack
- Excelar Technologies
- Holland Bloorview Kids Rehabilitation Hospital
- The Hospital for Sick Children
- King's College London
- Institute Pasteur
- McGill University
- Molecular You
- Ontario Brain Institute
- Pacific Autism Family Network
- Roche
- University of British Columbia

6 datasets

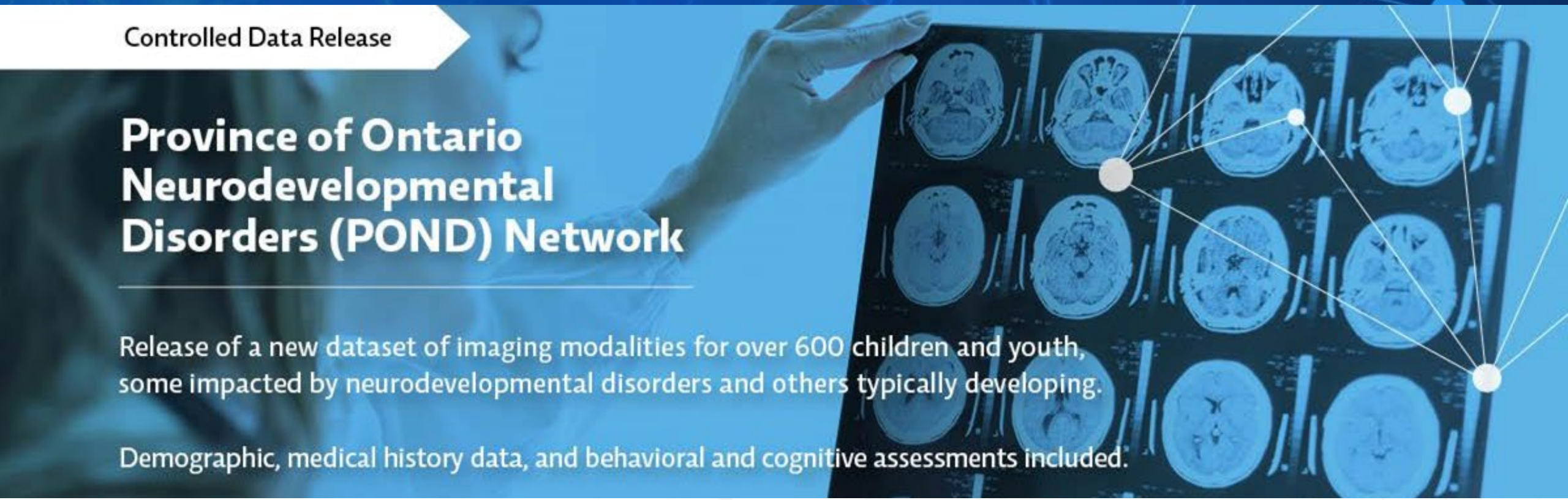
- AIMS-2-TRIALS (EU)
- iTARGET Autism Initiative (CAN)
- MSSNG (US, CAN)
- POND Network (CAN)
- In-house data:
  - Molecular You (CAN)
  - Roche (Global)

4 work streams

- Technology: building novel software to share, explore and analyse data
- Data: connecting consented data for secure sharing
- Policy: ensuring data is shared, accessed, and used in an ethical and legal manner
- Community: enabling autistic individuals to contribute new data through co-designed technology

This project is funded in part by the Digital Technology Supercluster
https://www.digitalsupercluster.ca/projects/autism-sharing-initiative/

Ontario Brain Institute



Explore these data at braincode.ca

ONTARIO BRAIN INSTITUTE | INSTITUT ONTARIEN DU CERVEAU

Brain-CODE

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

Thank you to families and individuals
who have participated in research

ONTARIO BRAIN INSTITUTE

SickKids

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Brain Canada Foundation

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

POND NETWORK
Province of Ontario Neurodevelopmental Disorders

AUTISM SPEAKS
It's time to listen.

The Azrieli Foundation

SFARI
SIMONS FOUNDATION
AUTISM RESEARCH INITIATIVE

HRSA

Thank you to all collaborators, co leads, especially the trainees, it's a privilege

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