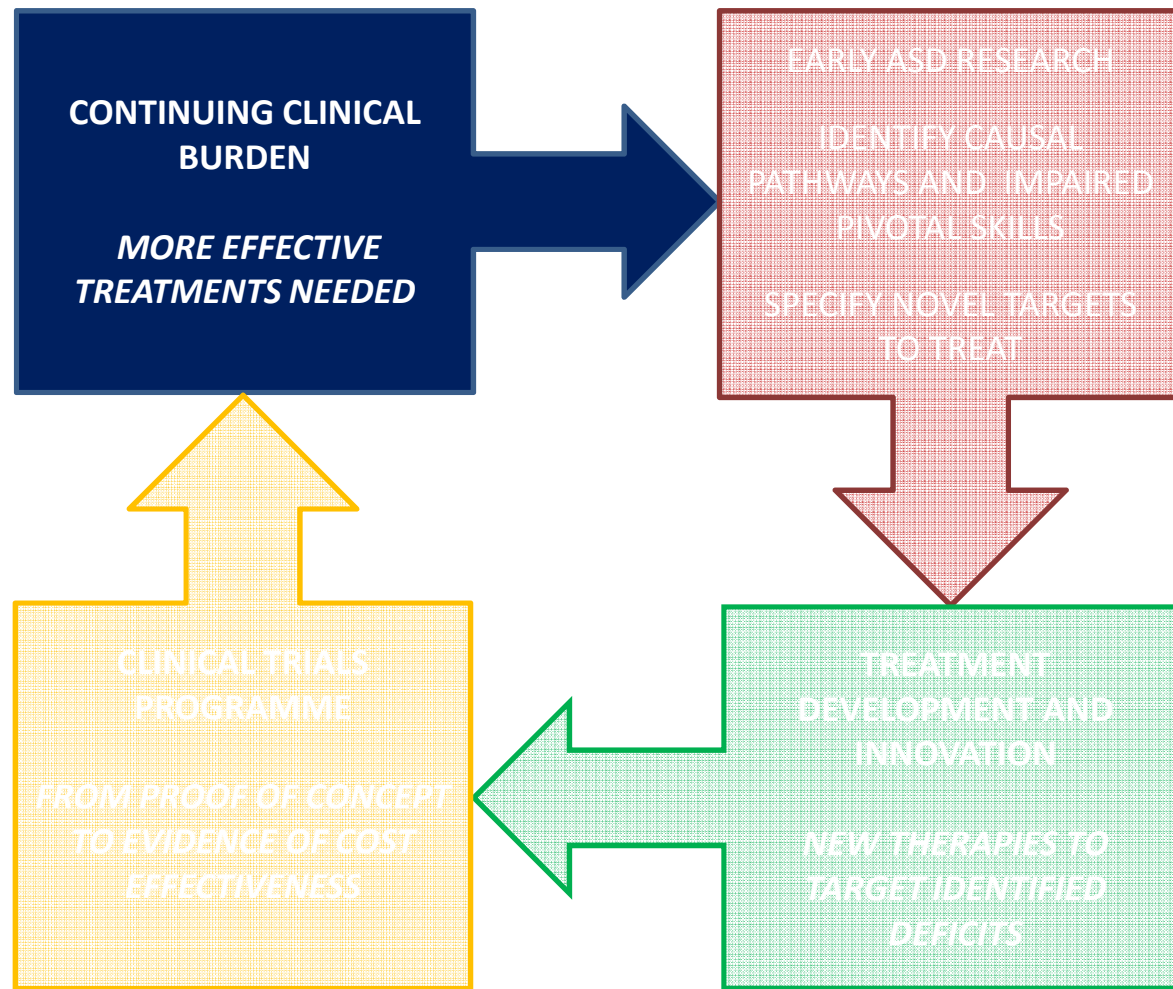


TRAJECTORIES OF INFANTS AT HIGH RISK OF ASD

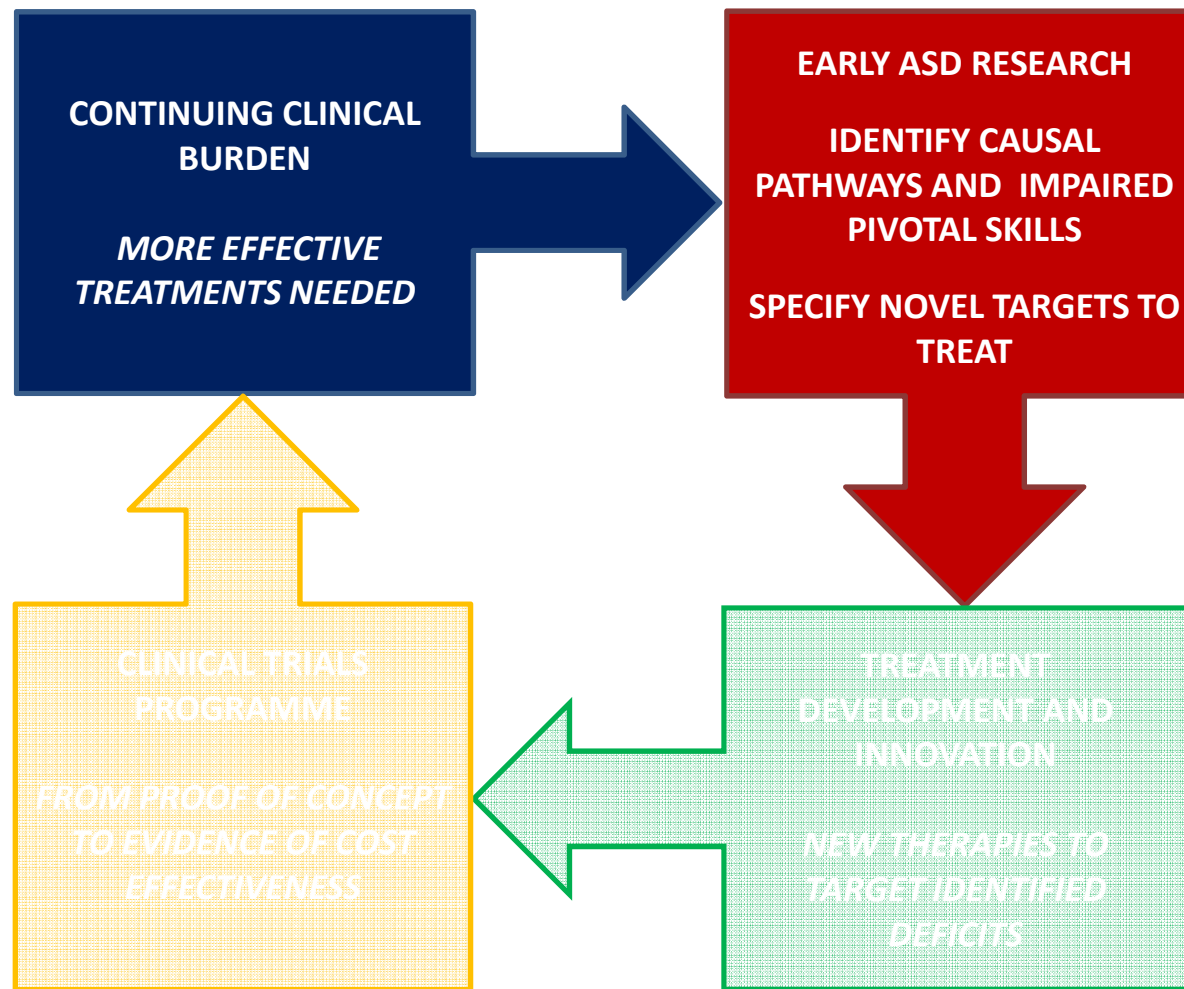
Herbert Roeyers

To help children and their families and reduce burden we need better treatments



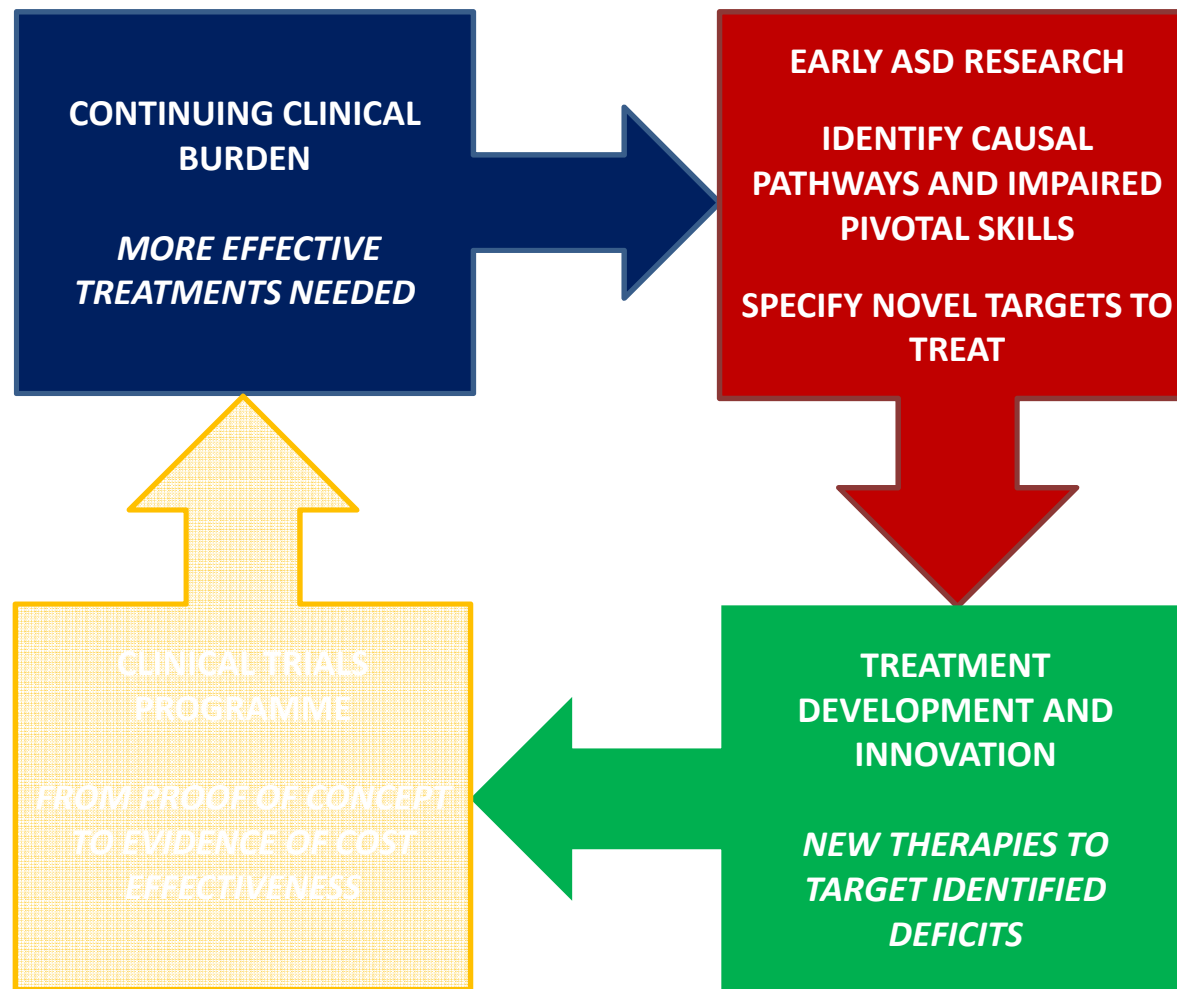
Treatments will improve as we understand ASD better

To help children and their families and reduce burden we need better treatments



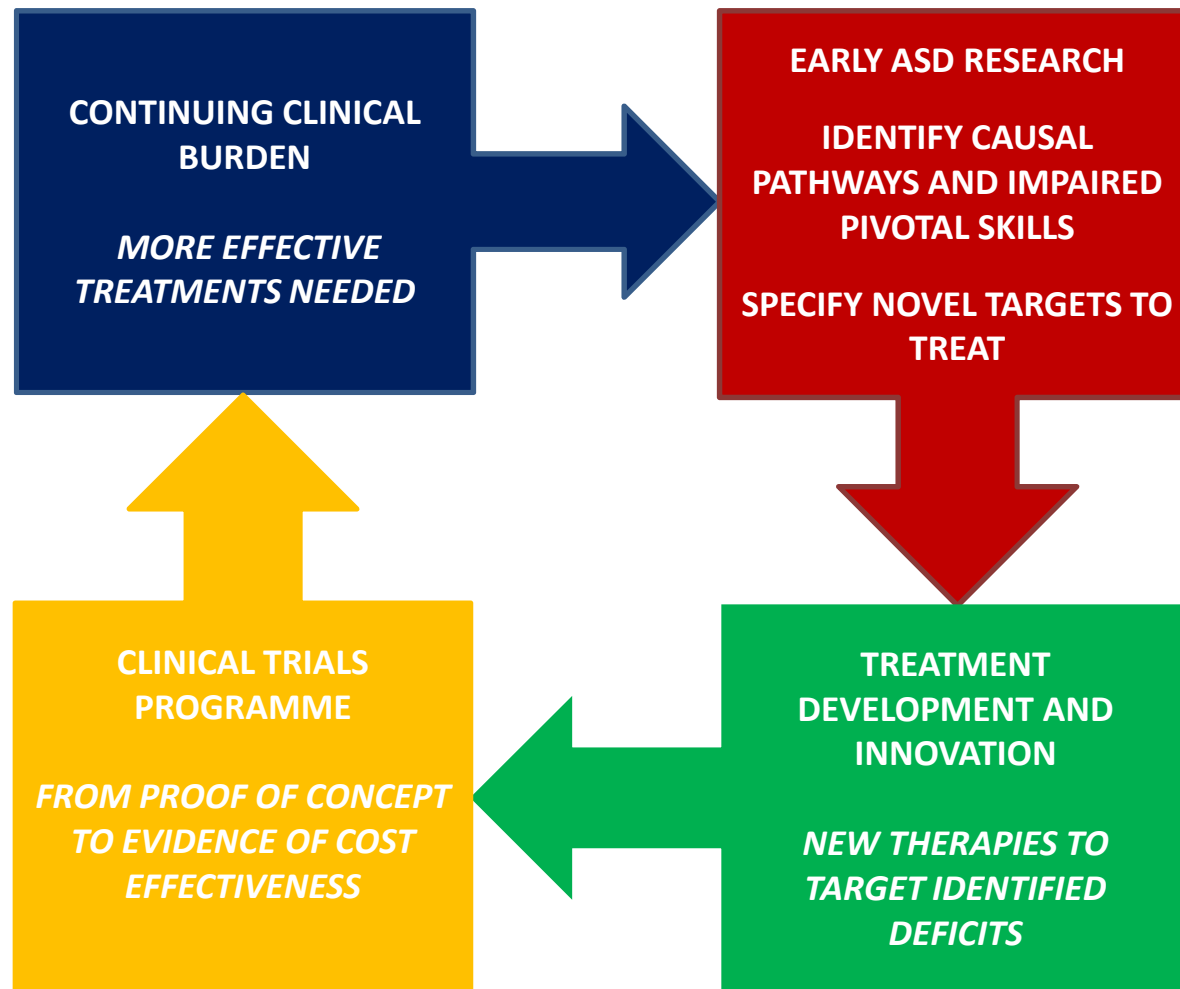
Treatments will improve as we understand ASD better

To help children and their families and reduce burden we need better treatments



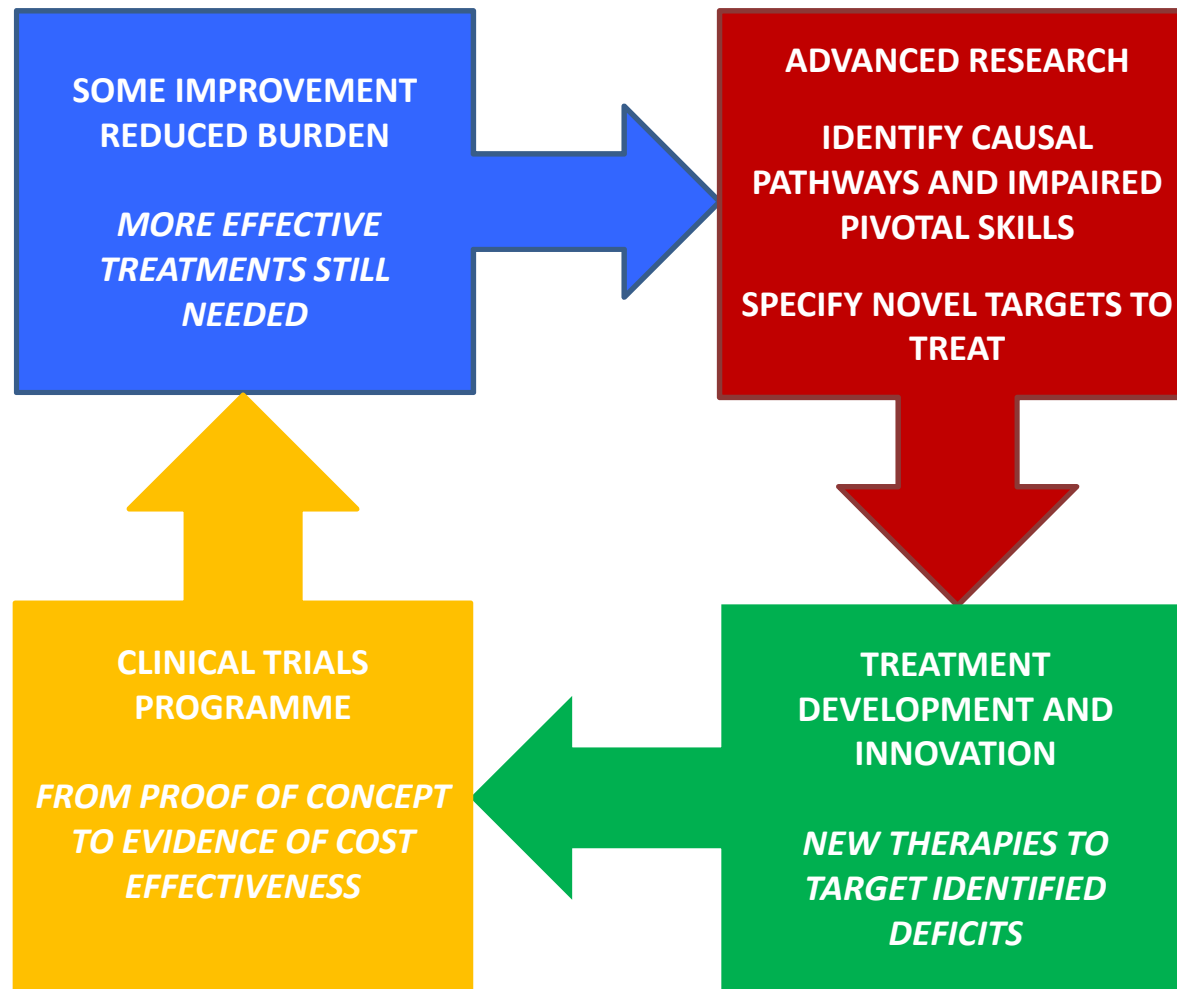
Treatments will improve as we understand ASD better

To help children and their families and reduce burden we need better treatments



Treatments will improve as we understand ASD better

To help children and their families and reduce burden we need better treatments



Treatments will improve as we understand ASD better

Knowledge about early emergence of ASD

- Initially retrospective studies
 - Interviews
 - Home-videos
 - Medical records
- Limitations
 - Recall bias
 - No description of developmental patterns
 - No neurophysiology, eye-tracking,.....

Knowledge about early emergence of ASD

- Initially retrospective studies
- Prospective population studies
- Limitations
 - Large sample sizes needed
 - Limited data collection
 - Drop out
 -

Screening for Autism Spectrum Disorders in Flemish Day-Care Centres with the Checklist for Early Signs of Developmental Disorders

Mieke Dereu · Petra Warreyn · Ruth Raymaekers ·
Mieke Meirsschaut · Griet Pattyn · Inge Schietecatte ·
Herbert Roeyers

Best differentiation between ASD and no ASD

<i>12 – 24 monts</i>
<ul style="list-style-type: none">• IJA pointing• doesn't like to be touched

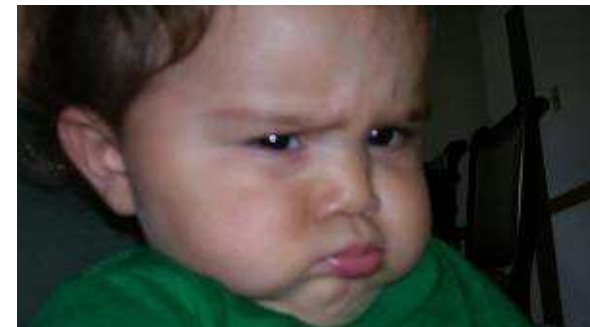
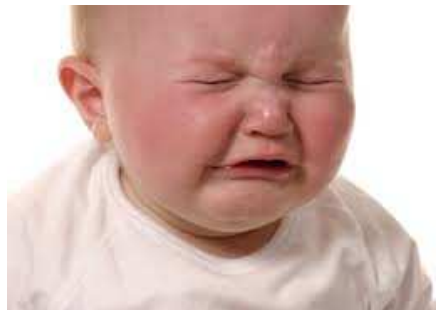
<i>24 – 36 months</i>
<ul style="list-style-type: none">• IJA pointing• RJA

Knowledge about early emergence of ASD

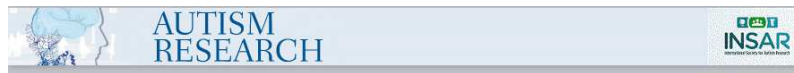
- Initially retrospective studies
- Prospective population studies
- Prospective studies with high risk groups
 - Early markers
 - Early detection
 - Developmental trajectories and mechanisms
 - Early intervention
 - Characterization of broader (milder) autism phenotype
 - Estimates of recurrence risk

Also limitations

- Expensive
- Difficult to fund
- Slow publication output
- Great effort for families and researchers
- Working with (very) young children is not always easy



Increasing number of prospective studies with high risk groups



RESEARCH ARTICLE

Infants At-Risk for Autism Spectrum Disorder: Patterns of Vocalizations at 14 Months

Dunia Garrido , Linda R. Watson, Gloria Carballo, Rocio Garcia-Retamero, and Elizabeth R. Crais

NEW RESEARCH

18-Month Predictors of Later Outcomes in Younger Siblings of Children With Autism Spectrum Disorder: A Baby Siblings Research Consortium Study

Katarzyna Chawarska, PhD, Frederick Shic, PhD, Suzanne Macari, PhD, Daniel J. Campbell, PhD, Jessica Brian, PhD, Rebecca Landa, PhD, Ted Hutman, PhD, Charles A. Nelson, PhD, Sally Ozonoff, PhD, Helen Tager-Flusberg, PhD, Gregory S. Young, PhD, Lonnie Zwaigenbaum, MD, Ira L. Cohen, PhD, Tony Charman, PhD, Daniel S. Messinger, PhD, Ami Klin, PhD, Scott Johnson, PhD, Susan Bryson, PhD

Developmental Science

Developmental Science 12:5 (2009), pp 798–814

DOI: 10.1111/j.1467-7687.2009.00833.x

PAPER

Gaze behavior and affect at 6 months: predicting clinical outcomes and language development in typically developing infants and infants at risk for autism

Gregory S. Young,¹ Noah Merin,² Sally J. Rogers¹ and Sally Ozonoff¹

1. MIND Institute, Department of Psychiatry and Behavioral Sciences, School of Medicine, University of California, Davis, USA
2. Neuroscience Graduate Group, University of California, Davis, USA

Research in Autism Spectrum Disorders 17 (2015) 95–105



Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: <http://ees.elsevier.com/RASD/default.asp>



Social information processing in infants at risk for ASD at 5 months of age: The influence of a familiar face and direct gaze on attention allocation



Dewaele Nele*, Demurie Ellen, Warreyn Petra, Roeyers Herbert

Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

ARCHIVAL REPORT

Disengagement of Visual Attention in Infancy is Associated with Emerging Autism in Toddlerhood

Mayada Elsabbagh, Janice Fernandes, Sara Jane Webb, Geraldine Dawson, Tony Charman, Mark H. Johnson, and The British Autism Study of Infant Siblings Team

CHILD DEVELOPMENT



Child Development, March/April 2013, Volume 84, Number 2, Pages 429–442

Developmental Trajectories in Children With and Without Autism Spectrum Disorders: The First 3 Years

Rebecca J. Landa
Kennedy Krieger Institute and The Johns Hopkins University School of Medicine

Alden L. Gross
The Johns Hopkins Bloomberg School of Public Health and Aging Brain Center, Institute for Aging Research Hebrew SeniorLife, Harvard Medical School

Elizabeth A. Stuart
The Johns Hopkins Bloomberg School of Public Health

Ashley Faherty
Kennedy Krieger Institute

Eur Child Adolesc Psychiatry (2013) 22:341–348

DOI 10.1007/s00787-012-0368-4

ORIGINAL CONTRIBUTION

Infants at risk for autism: a European perspective on current status, challenges and opportunities

Sven Bölte · Peter B. Marschik · Terje Falck-Ytter ·

Tony Charman · Herbert Roeyers ·

Mayada Elsabbagh



(Enhancing the Scientific Study of Early Autism)

COST Action BM1004



EUROSIBS

The European Babysibs Autism Research Network

Mission Statement

Partners

For Researchers

For Families

Links

Eurosibs is a consortium of researchers who are studying infants with risk factors for developmental disorders in Europe. The goal of the Consortium is to facilitate the implementation of a common protocol of standardized and experimental measures. Further, the consortium will work towards a common platform for sharing data from the common protocol within and outside the consortium.





Ghent baby study: 5 cohorts



Siblings first wave + controls first wave



Siblings second wave + controls second wave



Preterms <30 weeks of gestation



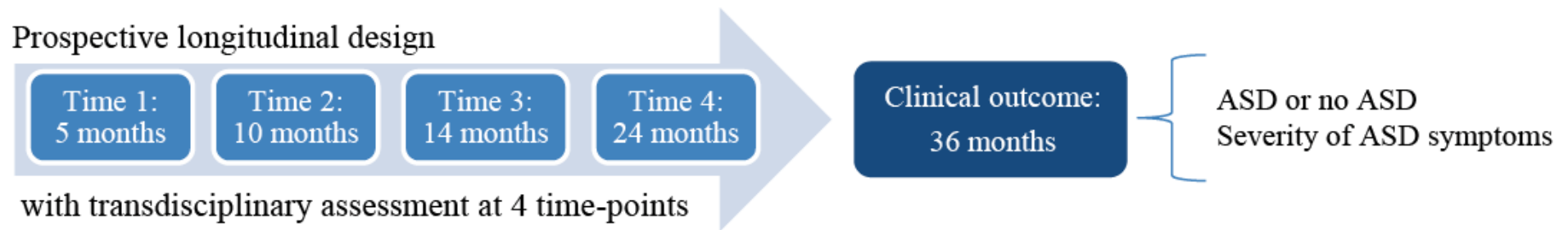
Flemish baby study

Ghent University and KULeuven

500 infants at high risk

- Siblings
- Preterms
- Children with feeding problems

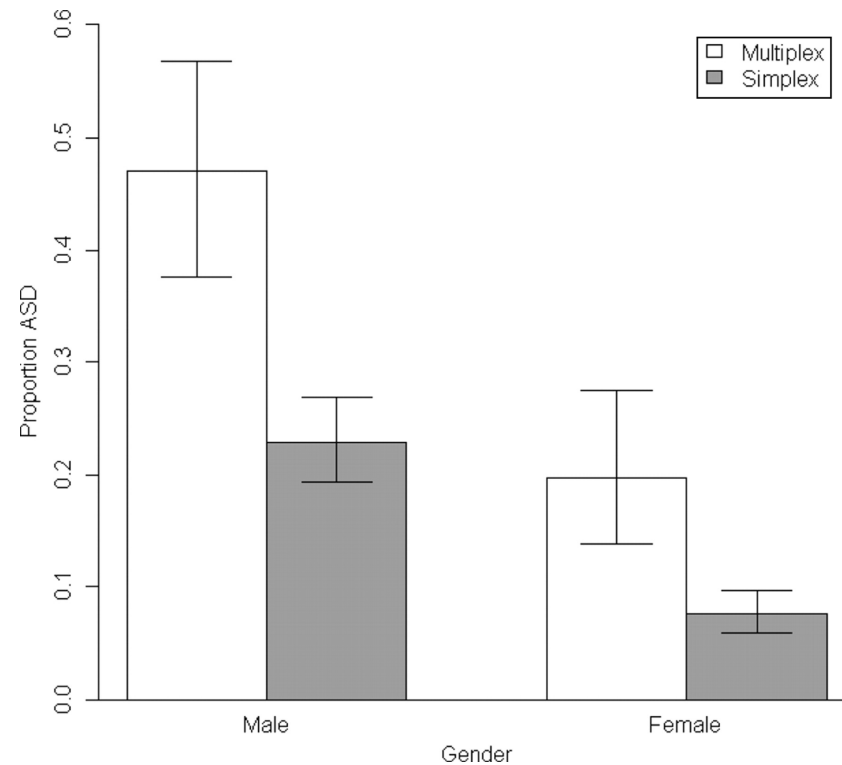
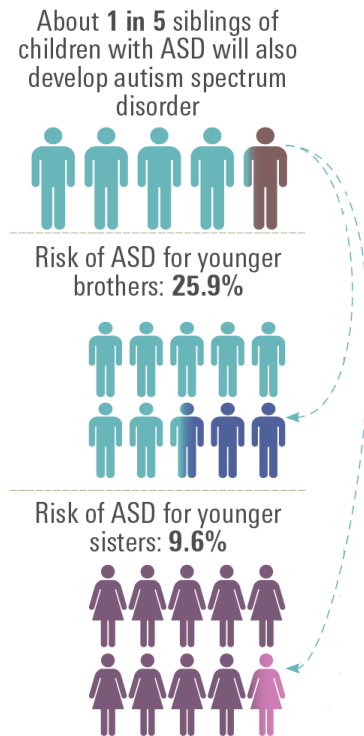
Start October 1st, 2017



Siblings

(Ozonoff et al., 2011)

- Recurrence rate: 18.7 %





15-20% ASD



$\pm 15\%$ BAI



$\pm 15\%$ 'other'



50-55% typical

Original Article

Child Psychiatry & Human Development

pp 1-11

First online: 06 November 2015

Extremely Preterm Born Children at Very High Risk for Developing Autism Spectrum Disorder

[Liedewij Verhaeghe](#) , [Mieke Dereu](#), [Petra Warreyn](#), [Isabel De Groote](#), [Piet Vanhaesebrouck](#), [Herbert Roeyers](#)

10.1007/s10578-015-0606-3

[Copyright information](#)

- < 27 weeks gestation
- 28% clinical diagnosis
- Additional 12% research diagnosis

Prematurity and ASD



- Positive Parent-reported screens

3% - 41% young children (Kuban et al., 2009; Limperopoulos et al., 2008; Moore et al., 2012; Dudova et al., 2014; Gray et al., 2015)
16% - 19% older children and youngsters (Johnson et al., 2010; Pinto-Martin et al., 2011)

- Diagnosis ASD:

1 - 13% around the age of 2 (Dudova et al., 2014; Gray et al., 2015)
4.5% - 8% in (late) childhood (Johnson et al., 2010, Treyvaud et al., 2013)



Contents lists available at ScienceDirect

Developmental Review

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



From early markers to neuro-developmental mechanisms of autism

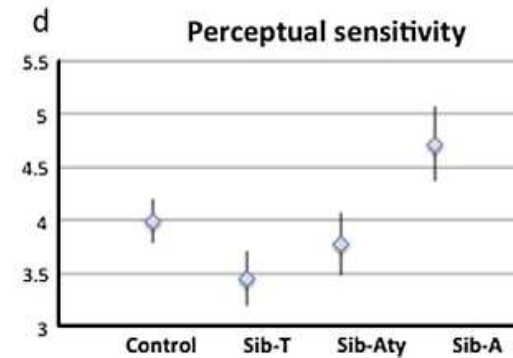
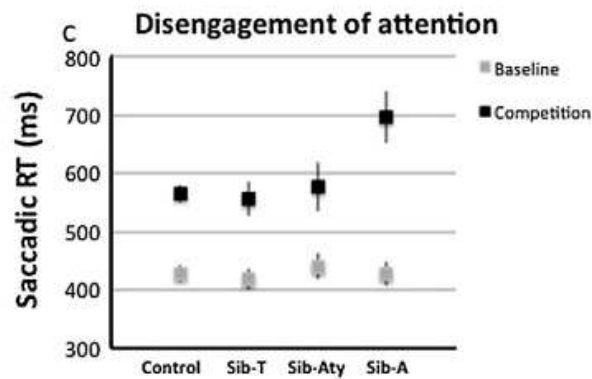
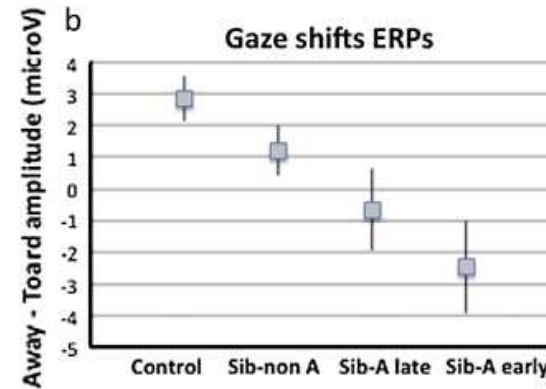
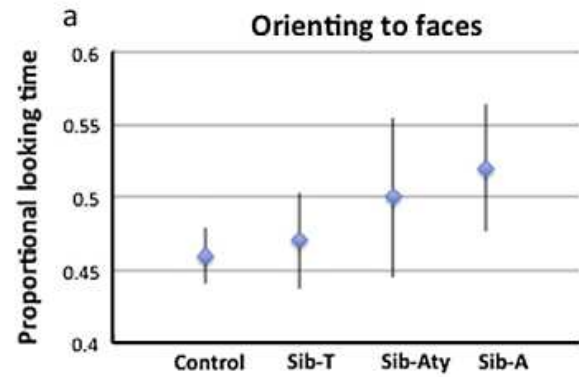


T. Gliga^{a,*}, E.J.H. Jones^a, R. Bedford^b, T. Charman^c, M.H. Johnson^a

^aCentre for Brain and Cognitive Development, Birkbeck College, University of London, United Kingdom

^bBiostatistics Department, Institute of Psychiatry, King's College London, United Kingdom

^cPsychology Department, Institute of Psychiatry, King's College London, United Kingdom





RESEARCH

Open Access



Behavioral, cognitive, and adaptive development in infants with autism spectrum disorder in the first 2 years of life

Annette Estes^{1,2*}, Lonnie Zwaigenbaum³, Hongbin Gu^{4,5}, Tanya St. John¹, Sarah Paterson⁶, Jed T. Elison⁷, Heather Hazlett^{5,9}, Kelly Botteron¹⁰, Stephen R. Dager⁸, Robert T. Schultz⁶, Penelope Kostopoulos¹¹, Alan Evans¹¹, Geraldine Dawson^{9,12}, Jordana Eliason³, Shanna Alvarez¹, Joseph Piven^{5,9} and IBIS network

Conclusions: These findings reveal atypical sensorimotor development at 6 months of age which is associated with ASD at 24 months in the most severely affected group of infants. Sensorimotor differences precede the unfolding of cognitive and adaptive deficits and behavioral features of autism across the 6- to 24-month interval. The less severely affected group demonstrates later symptom onset, in the second year of life, with initial differences in the social-communication domain.

Eur J Pediatr (2017) 176:1259–1262
DOI 10.1007/s00431-017-2951-7



SHORT COMMUNICATION

Early motor delays as diagnostic clues in autism spectrum disorder

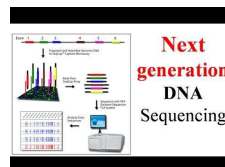
Susan R. Harris¹

Very early markers of ASD

- Brain structure and functioning
- (Sensory) motor problems
- Social and especially non-social attention and stimulus processing
- Typical autism features appear later
- Suggests involvement of the whole brain and not just the “social brain”
- Key question:
 - Unique mechanism (e.g. synaptic dysfunction)?
 - Or independent factors that work independently?

Flemish baby study: Protocol overview

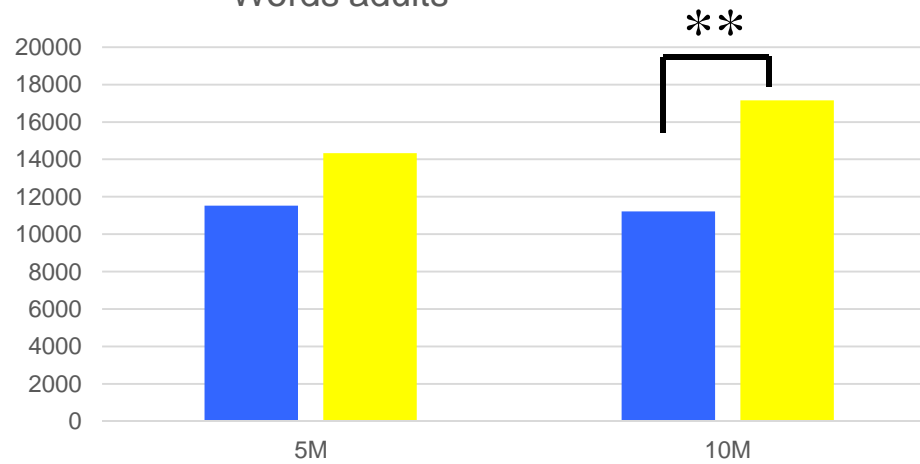
Genetics and metabolism	Neurophysiology	Facial dynamics	Behaviour	Environment
<ul style="list-style-type: none"> • Pedigree, medical history • Known CNV risk variants, monogenic causes of ASD • Neurometabolic abnormalities <p>Methods: SNP array, CNV analysis, sequencing, metabolic screening, questionnaire, clinical genetic workup in a subset of children</p>	<ul style="list-style-type: none"> • Assymetry, connectivity, mMSE, γ-band abnormalities • Responses to visual and auditory stimuli <p>Methods: fNIRS and EEG/ERP</p>	<ul style="list-style-type: none"> • Facial action coding: geometric and textural features, temporal profiles • Abnormal facial expressions <p>Methods: video recordings and analyses</p>	<ul style="list-style-type: none"> • Early signs of ASD: deficits in social communication and interaction, RRBI • Other: language, play, attention skills, motor skills, cognitive development, temperament, behaviour problems <p>Methods: individual tests, observations, eye tracking tasks, questionnaires</p>	<ul style="list-style-type: none"> • Pre-, peri-, neonatal factors • Demographics • Parent-child interaction • Parenting behaviour and stress • Parent characteristics <p>Methods: observations, questionnaires</p>
Child factors				Environmental factors



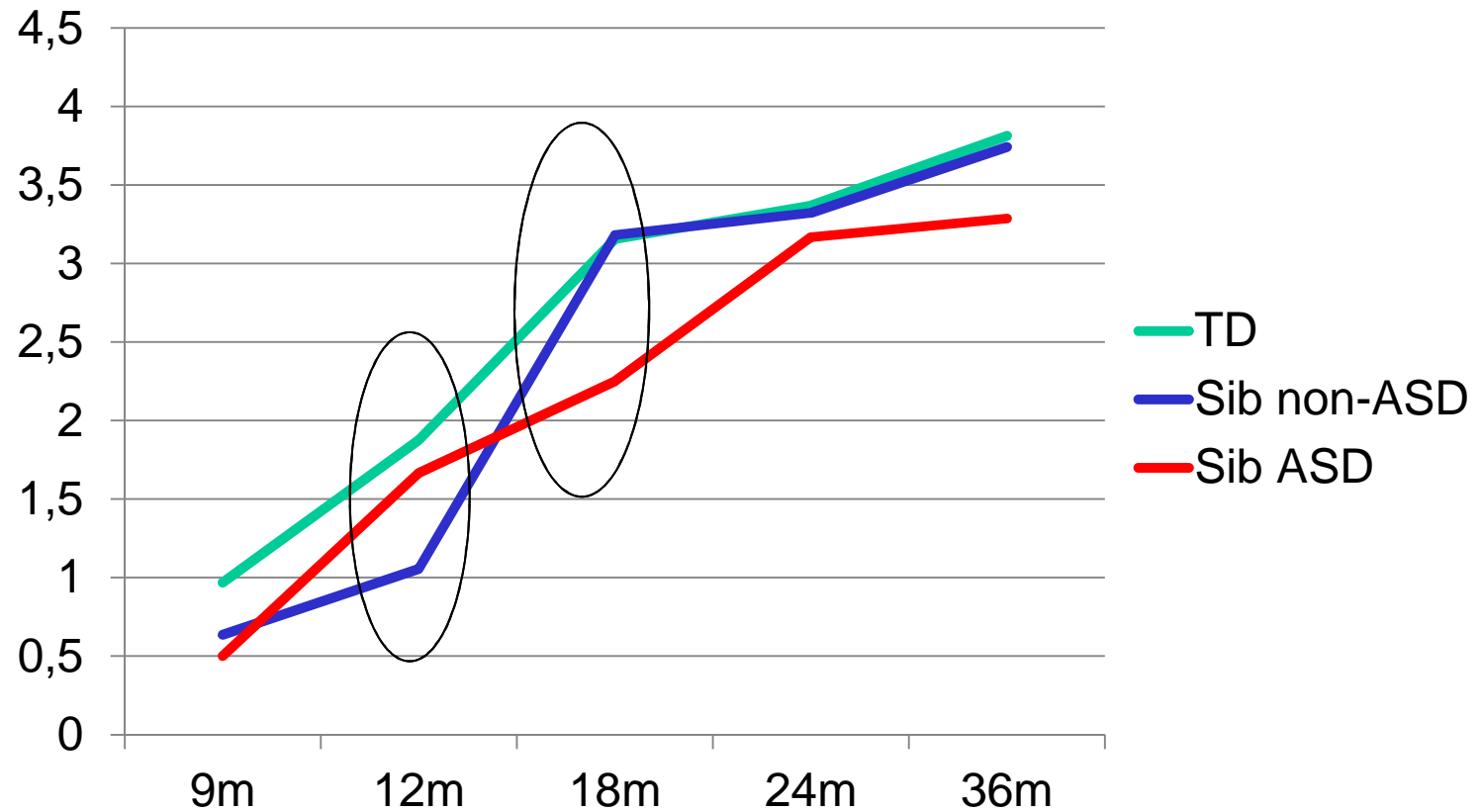
Language Environment Analysis (LENA)



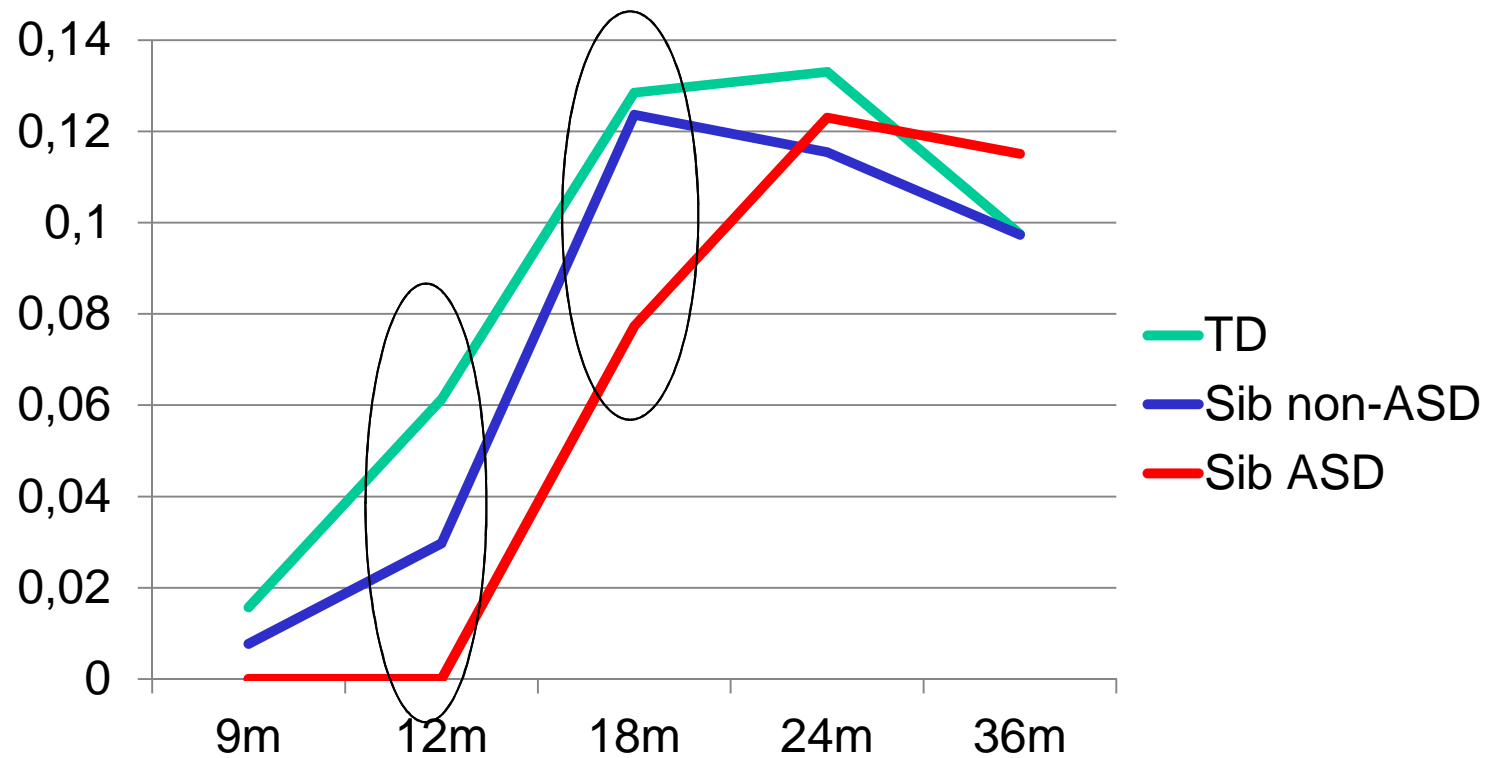
Words adults



Siblings: Response to joint attention



Siblings: Initiating joint attention (ratio)



Siblings: prosocial motivation

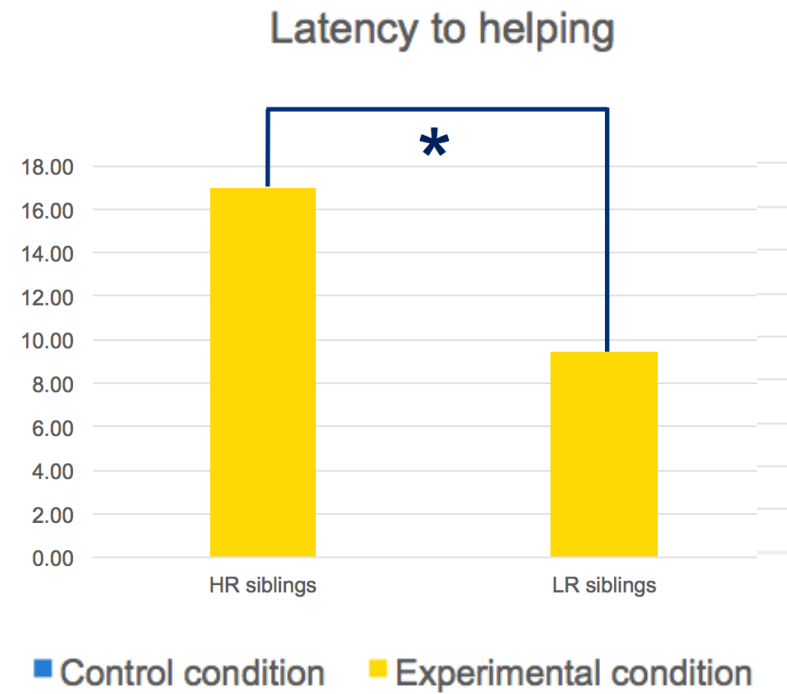
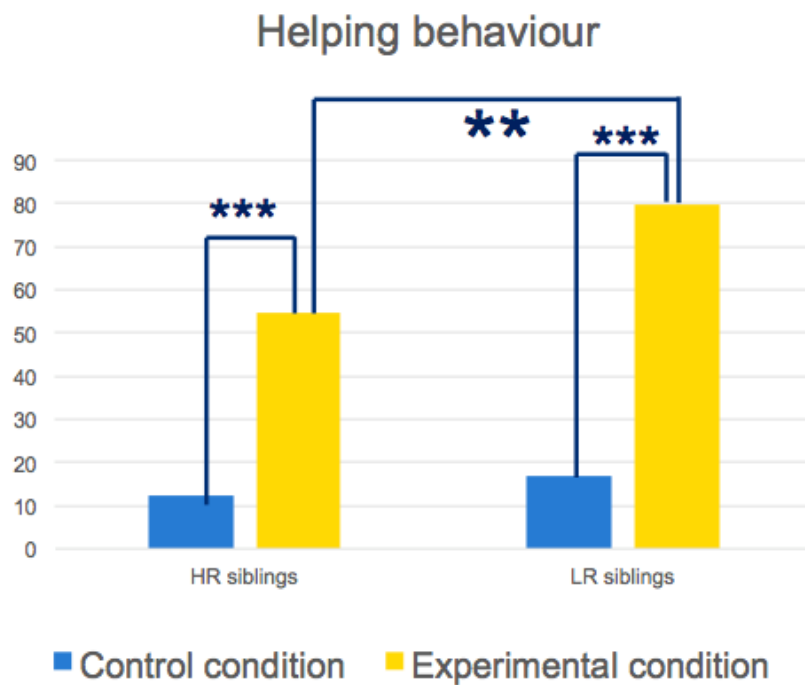


Experimental condition: help required

Control condition: no help required

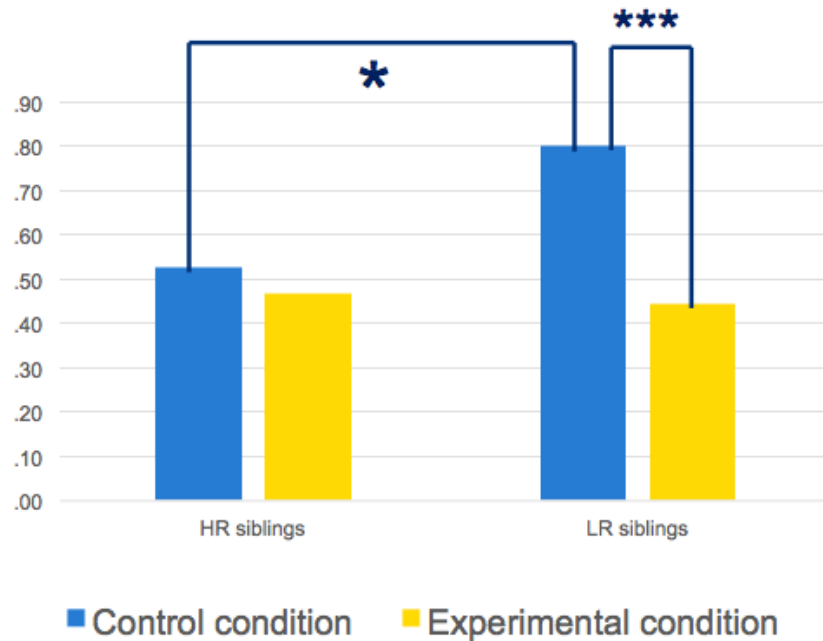
(cf. Warneken & Tomasello, 2007)

Siblings: prosocial motivation at 24 M

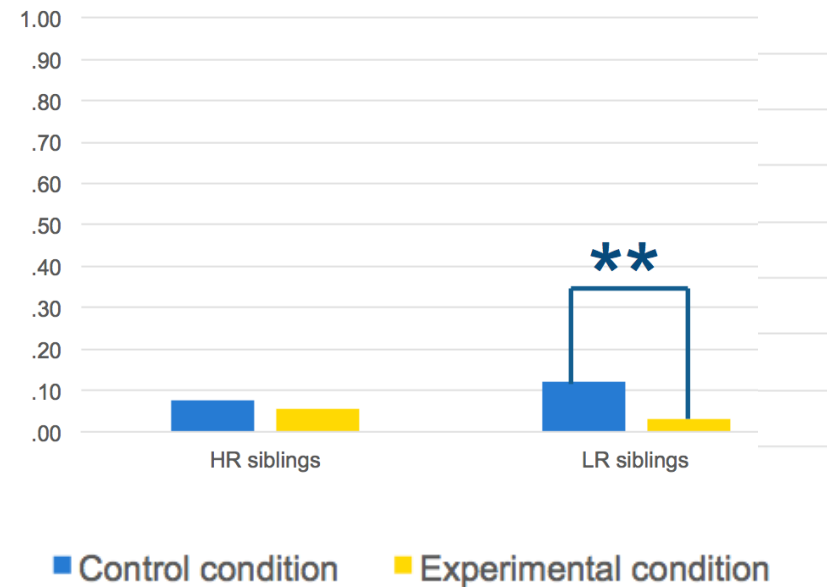


Siblings: prosocial motivation at 24 M

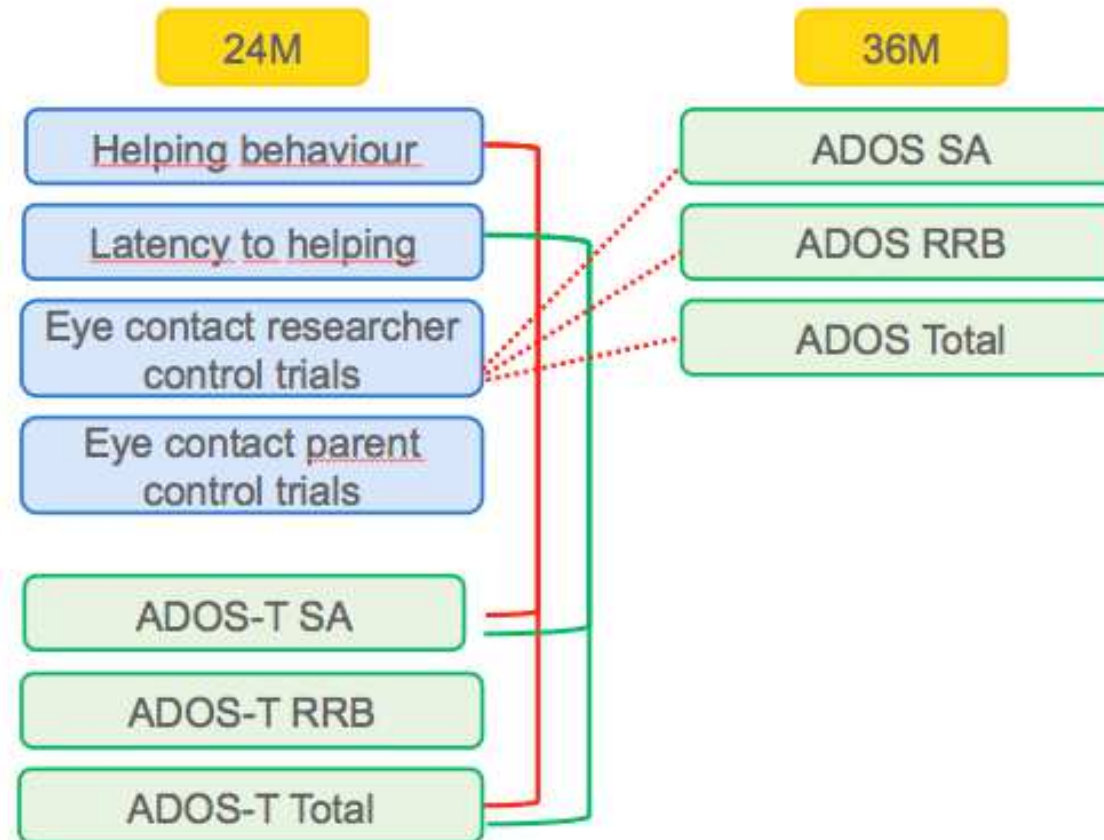
Eye contact to researcher



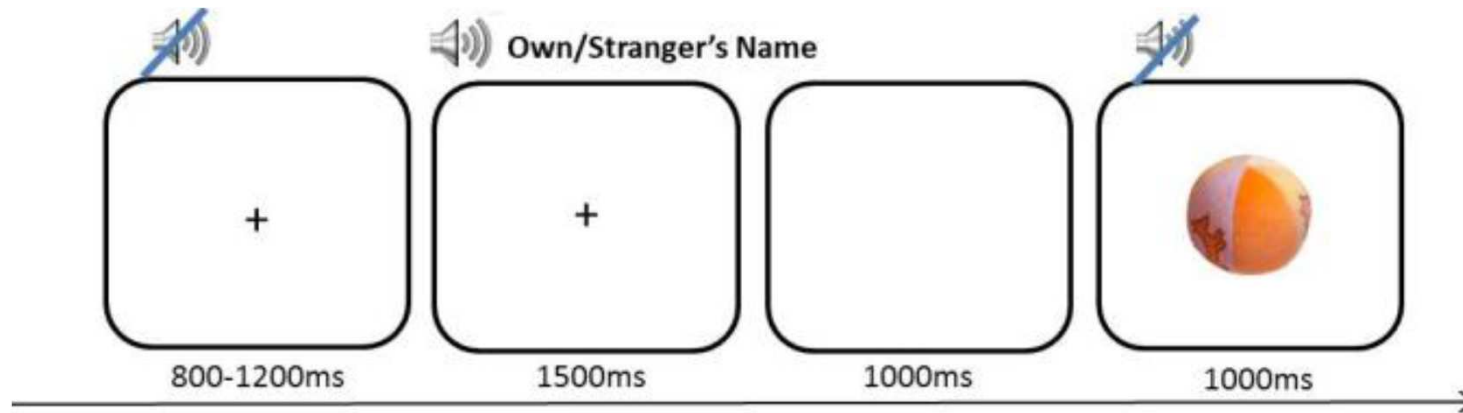
Eye contact to parent



Siblings: prosocial motivation at 24 M



Siblings: response to name

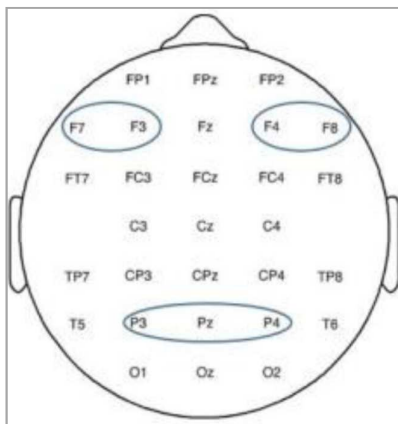


METHODS

Electrodes of ROIs:

left & right frontal areas, parietal area

Time-windows for ERP components:



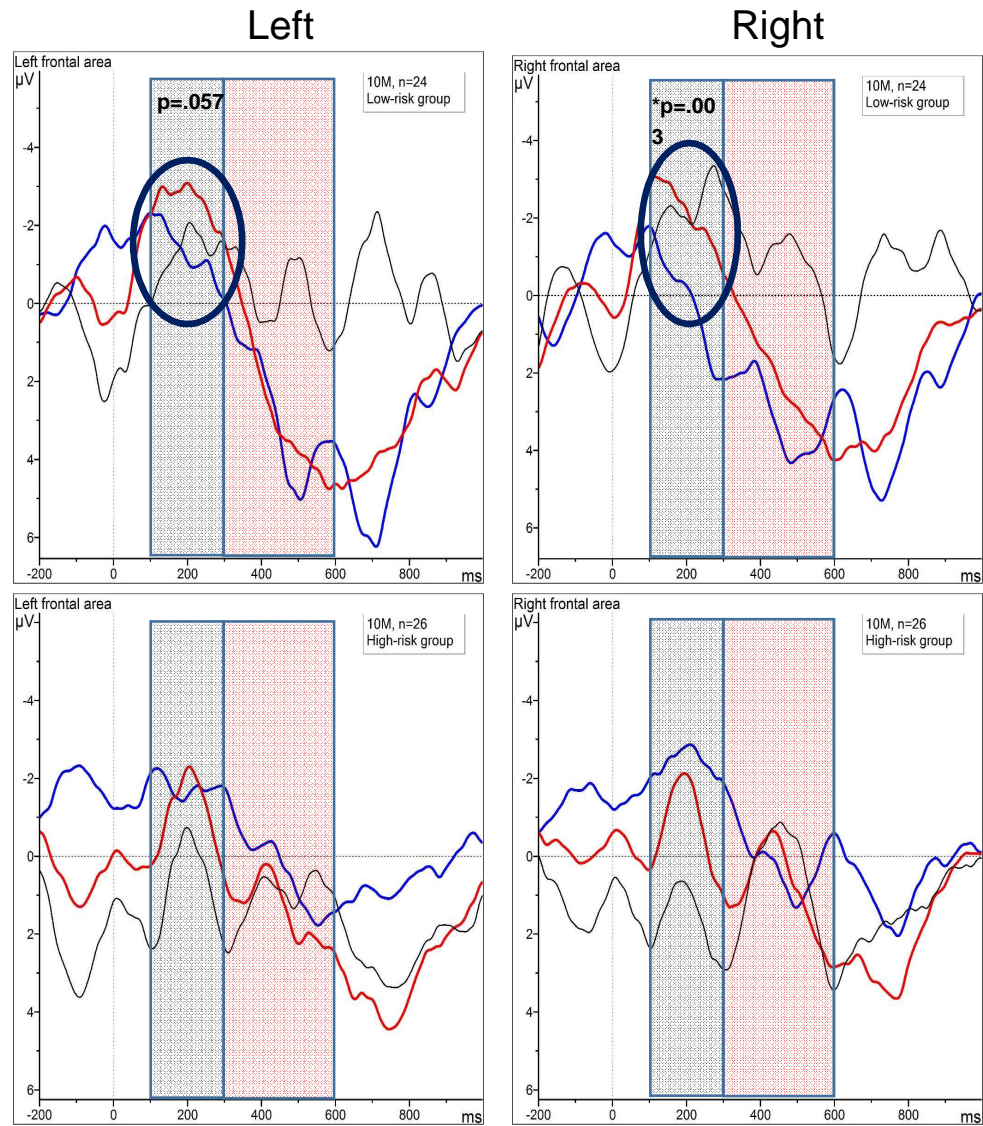
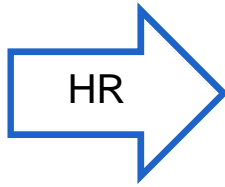
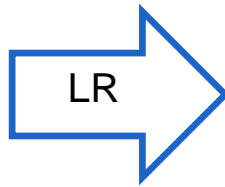
100-300ms
Involuntary
attention

300-600ms
Attention
engagement

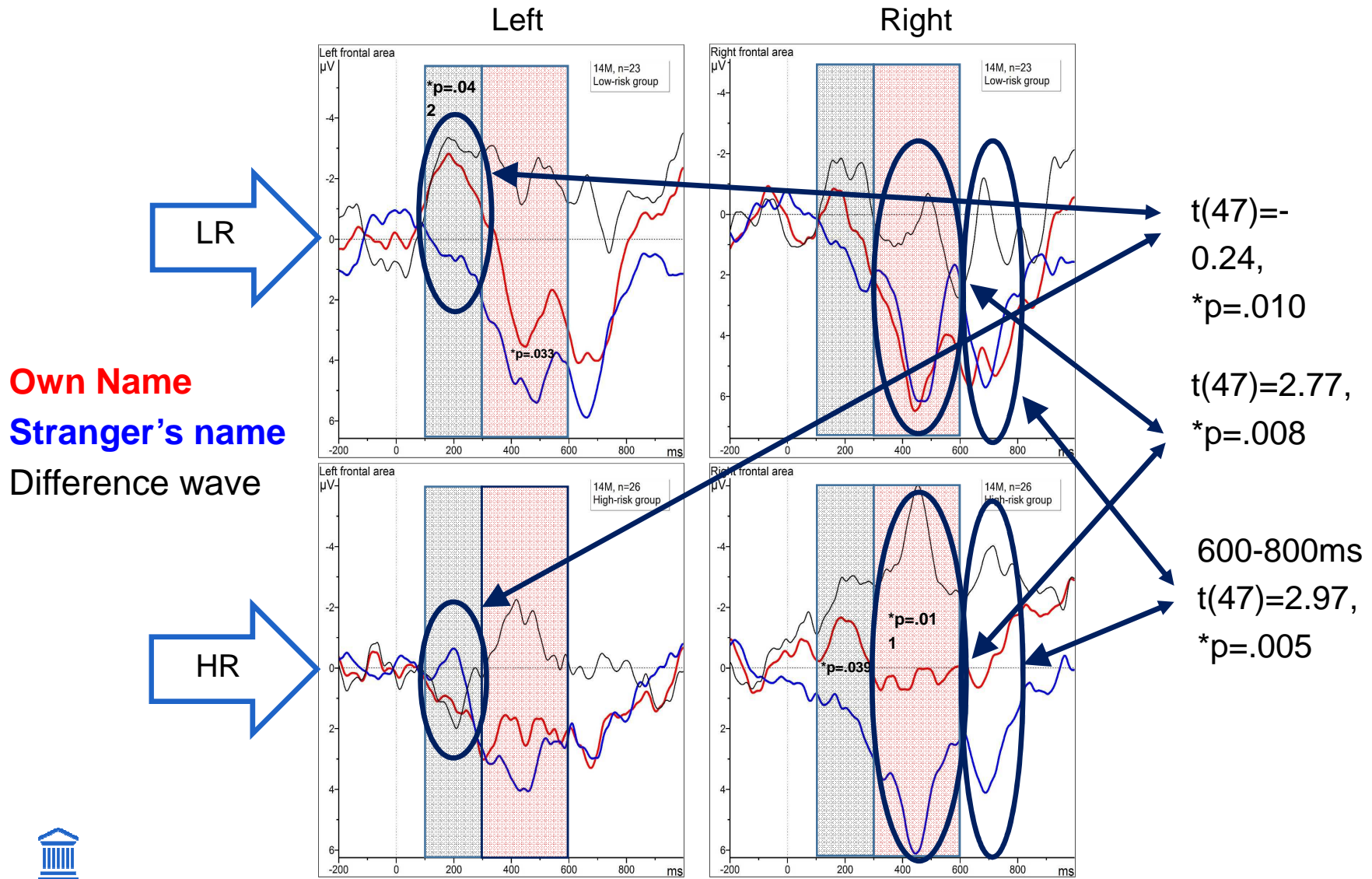
600-800ms
Sustention of
attention

10 MONTHS FRONTAL AREA

Own Name
Stranger's name
Difference wave



14 MONTHS FRONTAL AREA



LR

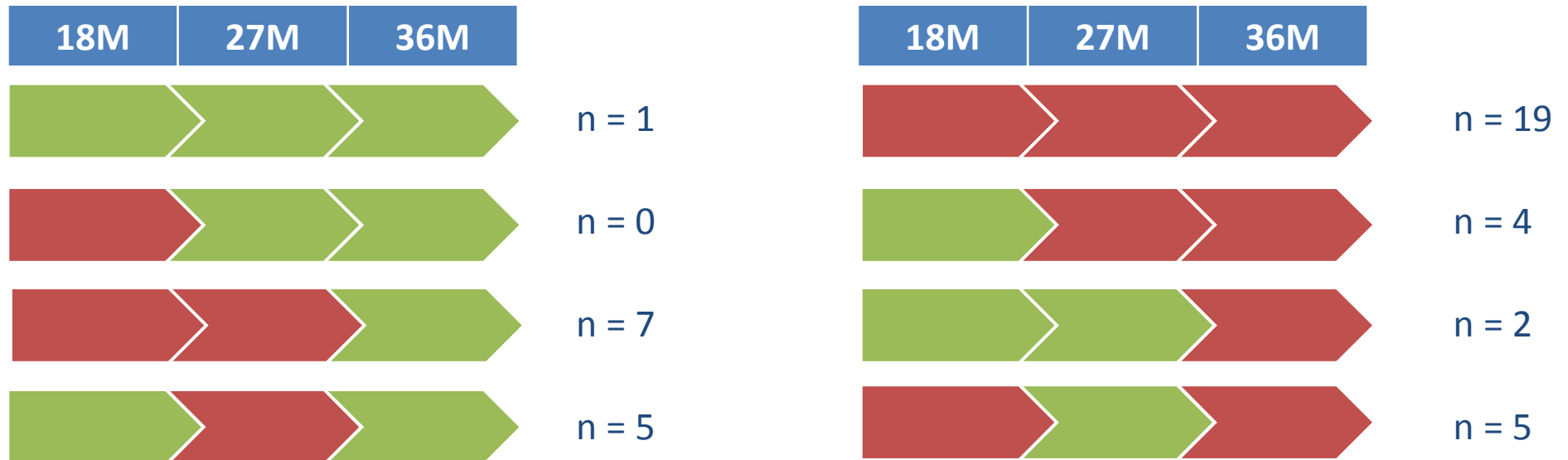
Own Name
Stranger's name
Difference wave

HR

Stability of ASD symptoms in preterms

- Stability between assessments at 18-, 27- and 36 months

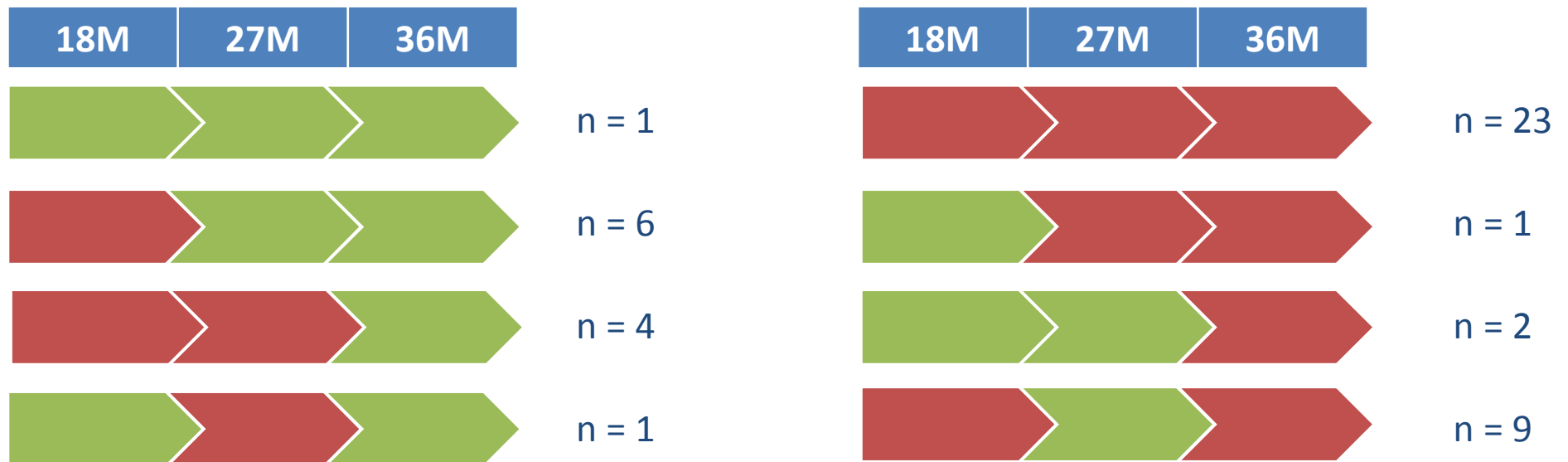
Stability of ASD parent-reported screening



Stability of ASD symptoms in preterms

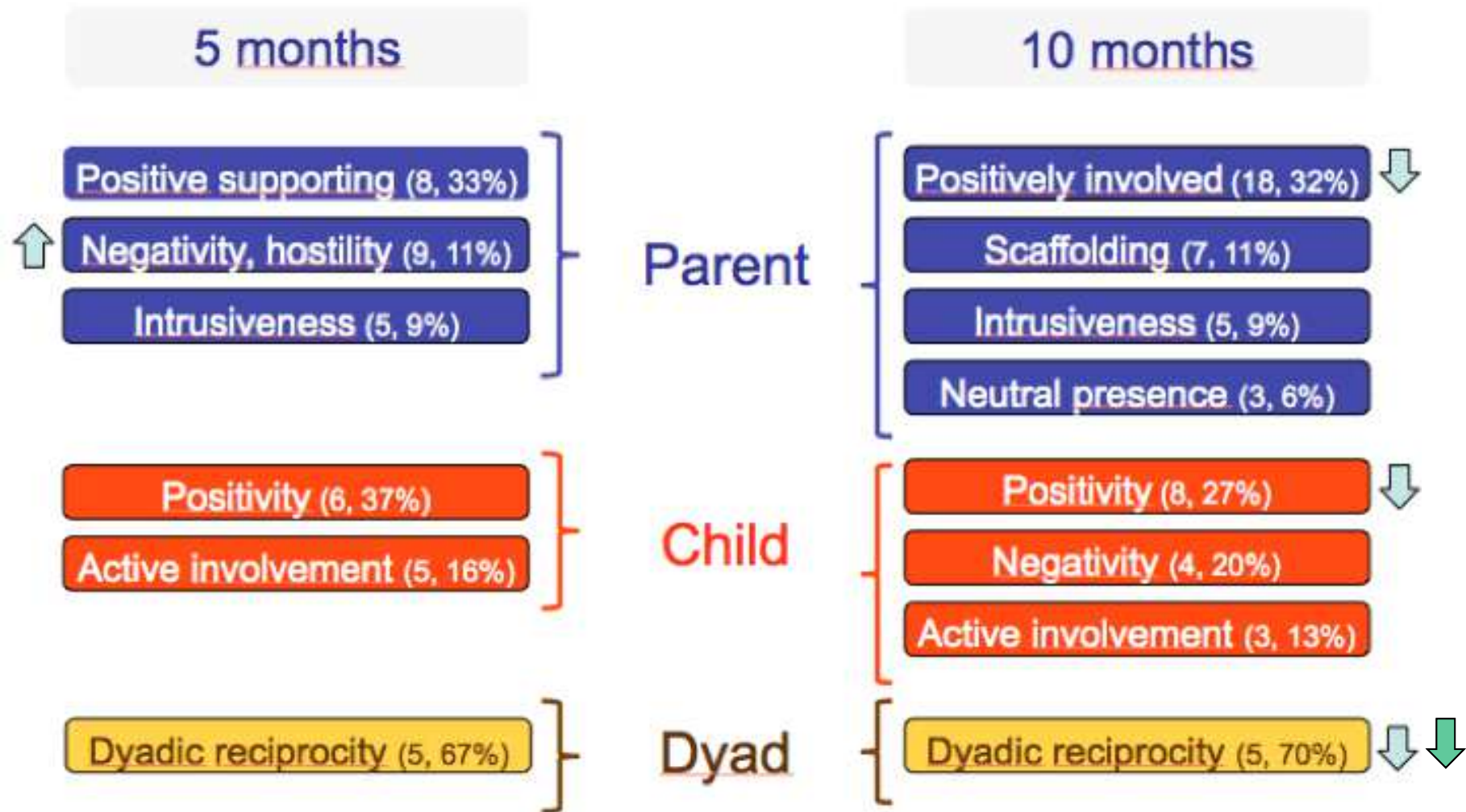
- Stability between assessments at 18-, 27- and 36 months

Stability of diagnostic observation measure (ADOS-2)



Intermediate results on parent-child interaction

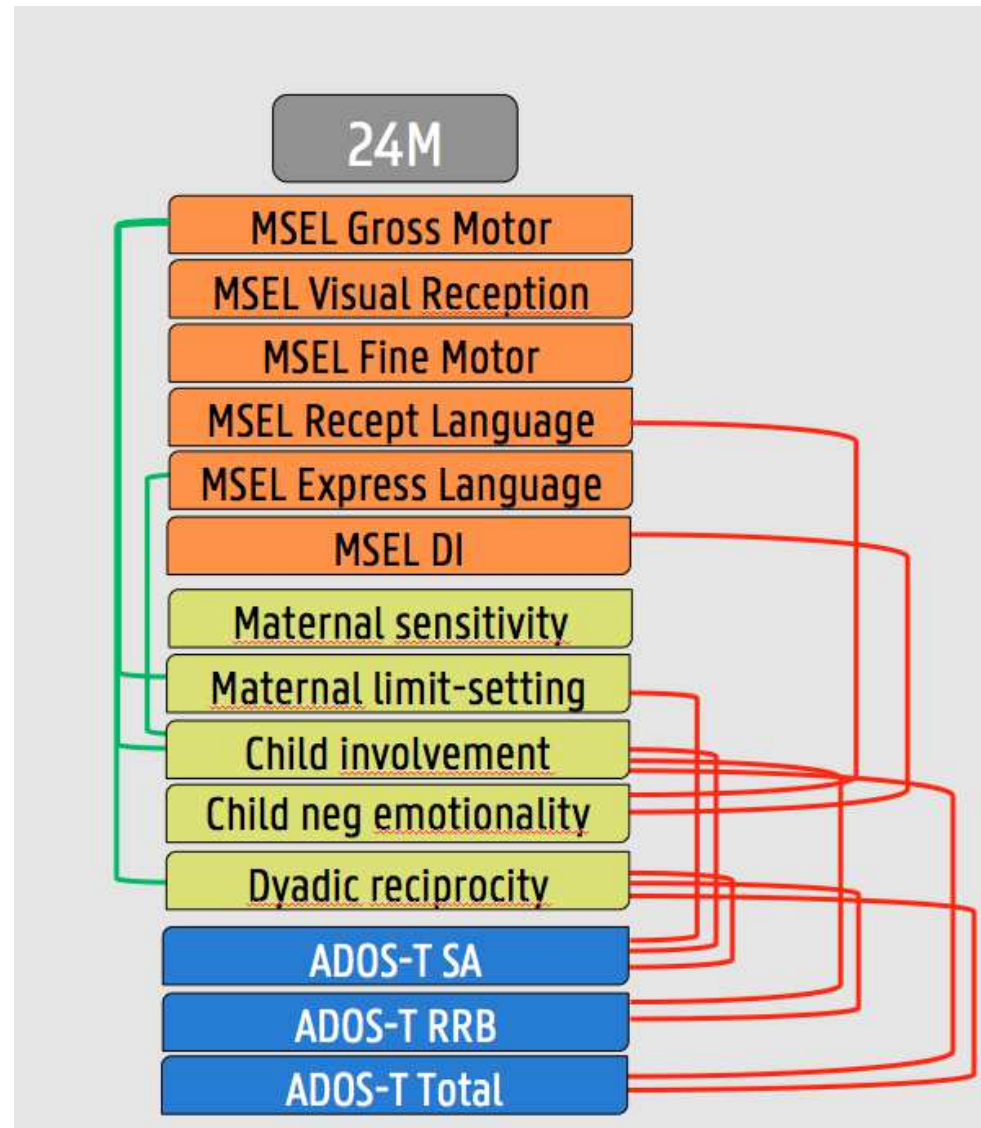
- 134 participants
 - 32 siblings of children with ASD
 - 35 siblings of children with a typical development (controls)
 - 67 preterm born children
- PCI coded with Feldman Coding Interactive Behaviour system
- Due to lack of consistency of original scales, factor analysis with oblimin rotation was conducted





Only significant associations are shown

24 months associations in siblings





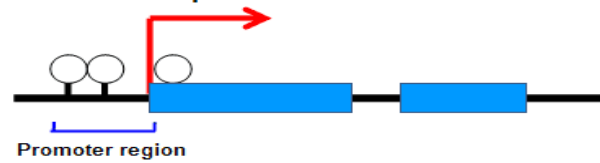
Epigenetic programming by maternal behavior

Ian C G Weaver^{1,2}, Nadia Cervoni³, Frances A Champagne^{1,2}, Ana C D'Alessio³, Shakti Sharma¹,
Jonathan R Seckl⁴, Sergiy Dymov³, Moshe Szyf^{2,3} & Michael J Meaney^{1,2}

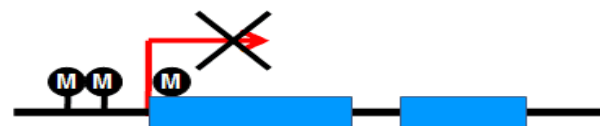
Here we report that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus. Offspring of mothers that showed high levels of LG and ABN were found to have differences in DNA methylation, as compared to offspring of 'low-LG-ABN' mothers. These differences emerged over the first week of life, were reversed with cross-fostering, persisted into adulthood and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter. Central infusion of a histone deacetylase inhibitor removed the group differences in histone acetylation, DNA methylation, NGFI-A binding, GR expression and hypothalamic-pituitary-adrenal (HPA) responses to stress, suggesting a causal relation among epigenomic state, GR expression and the maternal effect on stress responses in the offspring. Thus we show that an epigenomic state of a gene can be established through behavioral programming, and it is potentially reversible.

methylation

Genes that can be expressed



Genes inactivated by DNA methylation



-  Methylated
-  Unmethylated



ORIGINAL ARTICLE

Common DNA methylation alterations in multiple brain regions in autism

C Ladd-Acosta^{1,2}, KD Hansen^{2,3}, E Briem^{2,4}, MD Fallin^{1,2}, WE Kaufmann^{5,6} and AP Feinberg^{2,4}

Autism spectrum disorders (ASD) are increasingly common neurodevelopmental disorders defined clinically by a triad of features including impairment in social interaction, impairment in communication in social situations and restricted and repetitive patterns of behavior and interests, with considerable phenotypic heterogeneity among individuals. Although heritability estimates for ASD are high, conventional genetic-based efforts to identify genes involved in ASD have yielded only few reproducible candidate genes that account for only a small proportion of ASDs. There is mounting evidence to suggest environmental and epigenetic factors play a stronger role in the etiology of ASD than previously thought. To begin to understand the contribution of epigenetics to ASD, we have examined DNA methylation (DNAm) in a pilot study of postmortem brain tissue from 19 autism cases and 21 unrelated controls, among three brain regions including dorsolateral prefrontal cortex, temporal cortex and cerebellum. We measured over 485 000 CpG loci across a diverse set of functionally relevant genomic regions using the Infinium HumanMethylation450 BeadChip and identified four genome-wide significant differentially methylated regions (DMRs) using a bump hunting approach and a permutation-based multiple testing correction method. We replicated 3/4 DMRs identified in our genome-wide screen in a different set of samples and across different brain regions. The DMRs identified in this study represent suggestive evidence for commonly altered methylation sites in ASD and provide several promising new candidate genes.

Molecular Psychiatry (2014) 19, 862–871; doi:10.1038/mp.2013.114; published online 3 September 2013

Keywords: autism; brain; DNA methylation; epigenome; 450 k



Review

Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring

Avijit Banik¹, Deepika Kandilya¹, Seshadri Ramya¹, Walter Stünkel², Yap Seng Chong³ and S. Thameem Dheen^{1,*}

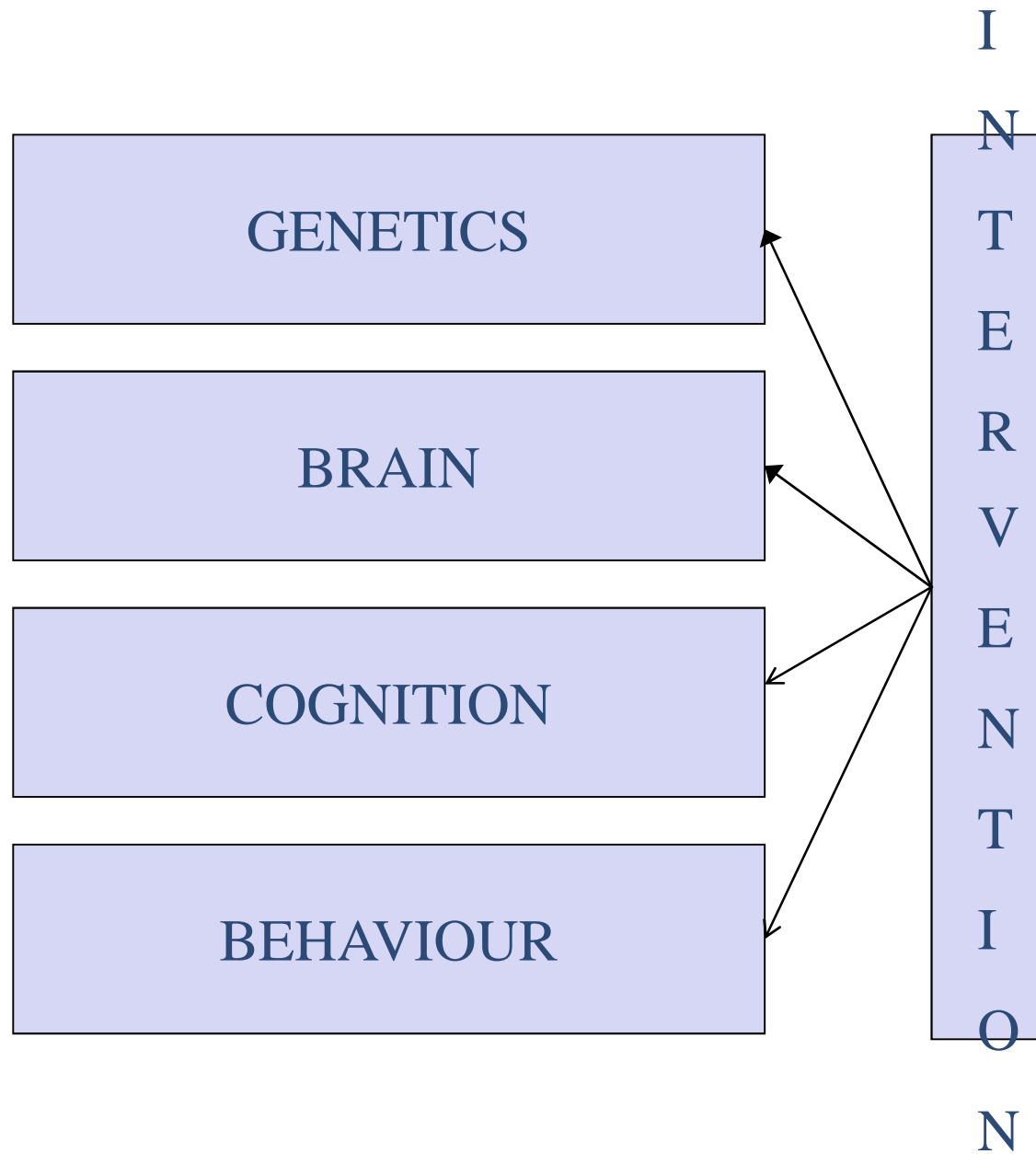
- ¹ Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117594, Singapore; antab@nus.edu.sg (A.B.); e0001953@u.nus.edu (D.K.); a0123640@u.nus.edu (S.R.)
 - ² Singapore Institute of Clinical Sciences, A*STAR, Singapore 117609, Singapore; walter_stunkel@sics.a-star.edu.sg
 - ³ Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore; yap_seng_chong@nuhs.edu.sg
- * Correspondence: antstd@nus.edu.sg

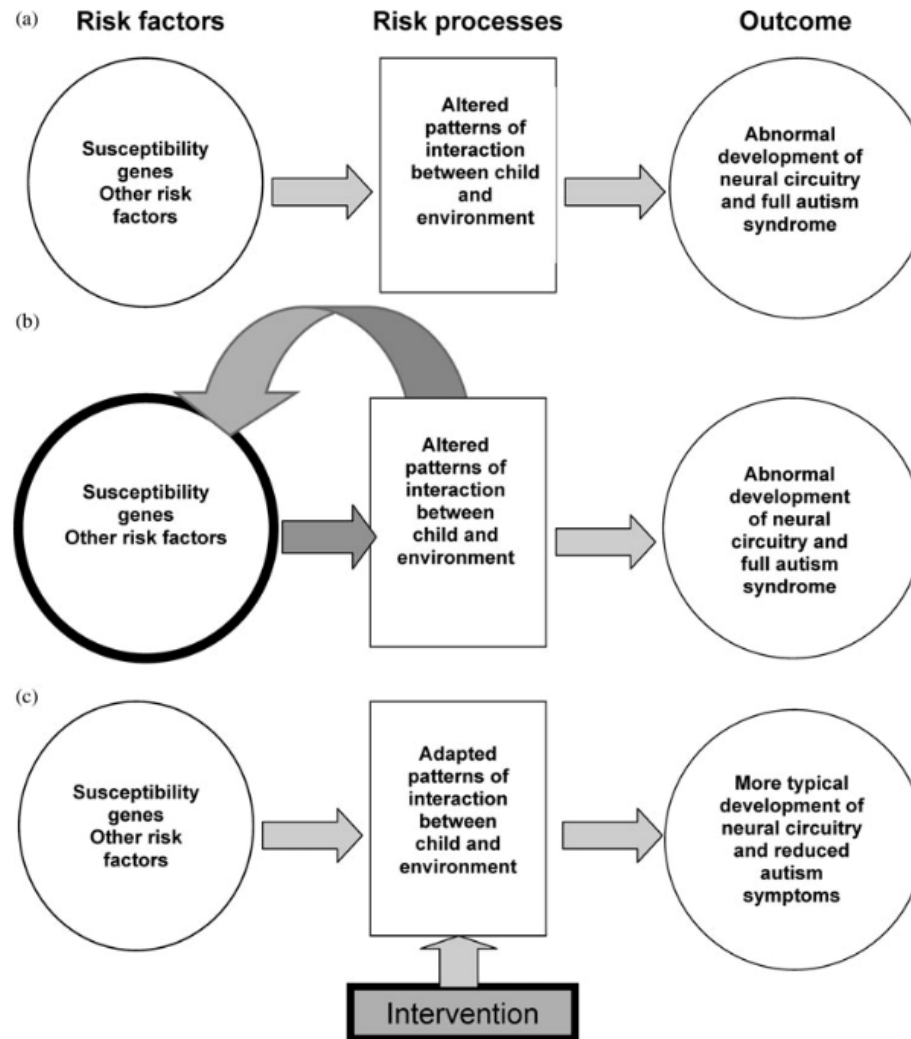
Academic Editor: Dennis R. Grayson

Received: 17 March 2017; Accepted: 19 May 2017; Published: 24 May 2017

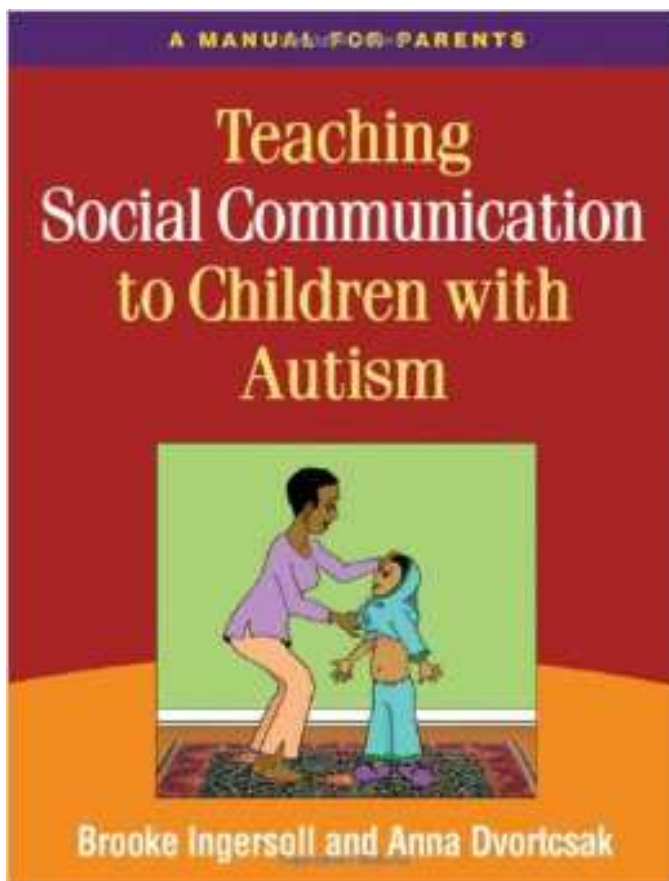
Early intervention

- National Research Council USA (2001): “Intervention should begin as soon as a child is suspected of having autism”
- Importance:
 - ▶ Prevent cumulative delay
 - ▶ ‘Sensitive periods’
 - ▶ Plasticity of the brain
 - ▶ Avoidance of secondary problems
 - ▶ Effect on parents and other family members
 - ▶ Lower cost and burden for society

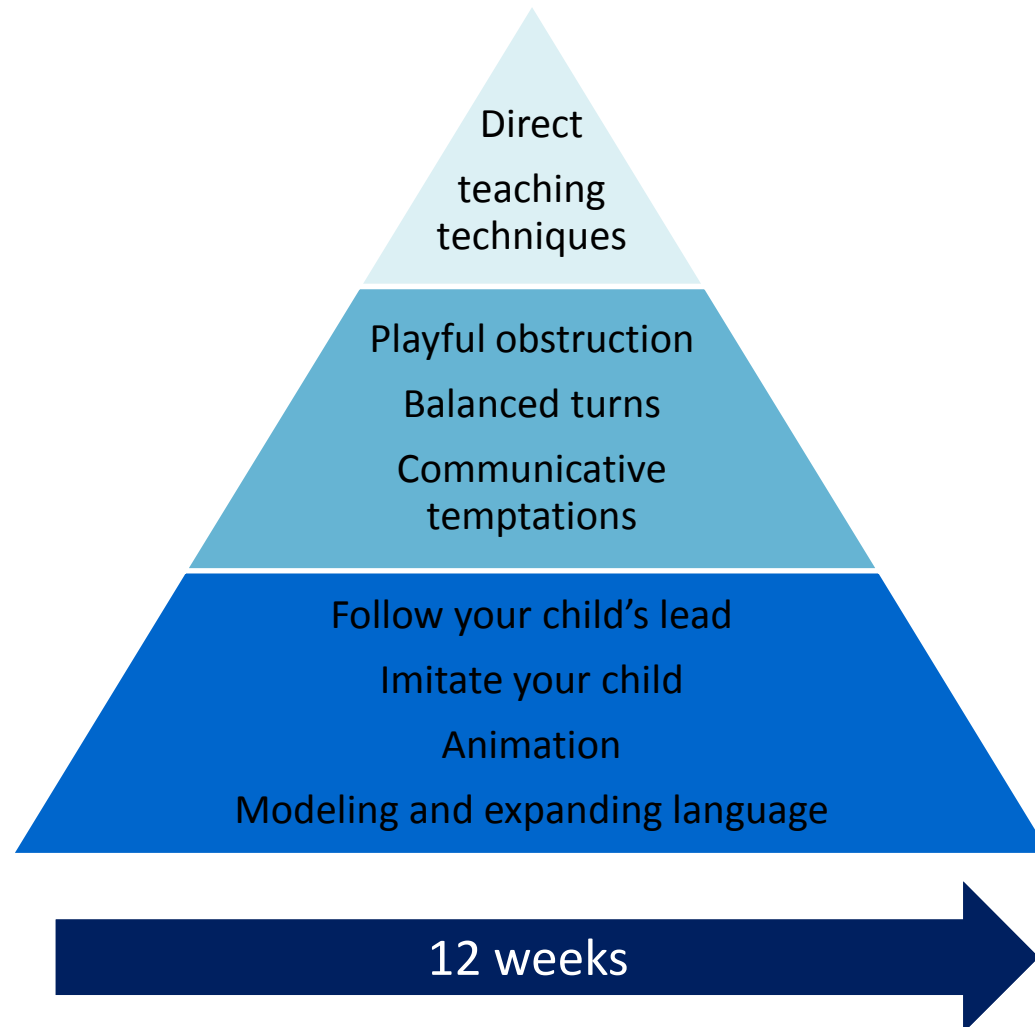




Dawson, 2008



Parent training



Parent training



Imitation



Social interaction

- Involvement of the child
- Synchronicity of the parent



Initiation joint attention

- Requesting
- Sharing interest



Play

- Duration
- Complexity

Parent training



Imitation ↑



Social interaction

- Involvement of the child ↑
- Synchronicity of the parent ↑



Initiation joint attention

- Requesting ↑
- Sharing interest =



Play

- Duration ↑
- Complexity =

J Autism Dev Disord (2015) 45:778–794
DOI 10.1007/s10803-014-2235-2

ORIGINAL PAPER

Feasibility and Effectiveness of Very Early Intervention for Infants At-Risk for Autism Spectrum Disorder: A Systematic Review

Jessica Bradshaw · Amanda Mossman Steiner ·
Grace Gengoux · Lynn Kern Koegel



The Lancet Psychiatry

Volume 2, Issue 2, February 2015, Pages 133–140



Parent-mediated intervention versus no intervention for infants at high risk of autism: a parallel, single-blind, randomised trial

Jonathan Green, Tony Charman, Andrew Pickles, Ming W Wan, Mayada Elsabbagh, Vicky Slonims, Carol Taylor, Janet McNally, Rhonda Booth, Teodora Gliga, Emily J H Jones, Clare Harrop, Rachael Bedford, Mark H Johnson, and the BASIS team*

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Randomised trial of a parent-mediated intervention for infants at high risk for autism: longitudinal outcomes to age 3 years

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Conclusions

- Prospective longitudinal studies with high-risk groups can teach us a lot about early ASD markers and pathways
- Unlikely that we will find a single marker
- Early markers are age-dependent
- A multimethod, multimodal and multicenter approach is needed
- Trajectories may be unpredictable, sometimes counterintuitive, but are more informative for mechanisms than cross-sectional markers
- Deviance vs delay? (but do we know the typical developmental patterns?)

Conclusions

- The insights may be very relevant for early intervention, even in the prodromal phase
- Intervention studies are necessary for the validation of causality
- Still unclear how representative high risk children with ASD are for the whole ASD population
- Are markers and patterns ASD specific?
 - Comorbidity
 - Prospective studies with TD and other disorders

Conclusions

- Inclusion of more than one at risk group in research is necessary
 - Siblings
 - Preterms
 - Children with early language problems
 - Dysmature children
 - Children with feeding problems
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- Current ASD screeners may not be valid or reliable for all these groups





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Thank you

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