Neurodevelopmental Disorders: concept and empirical models

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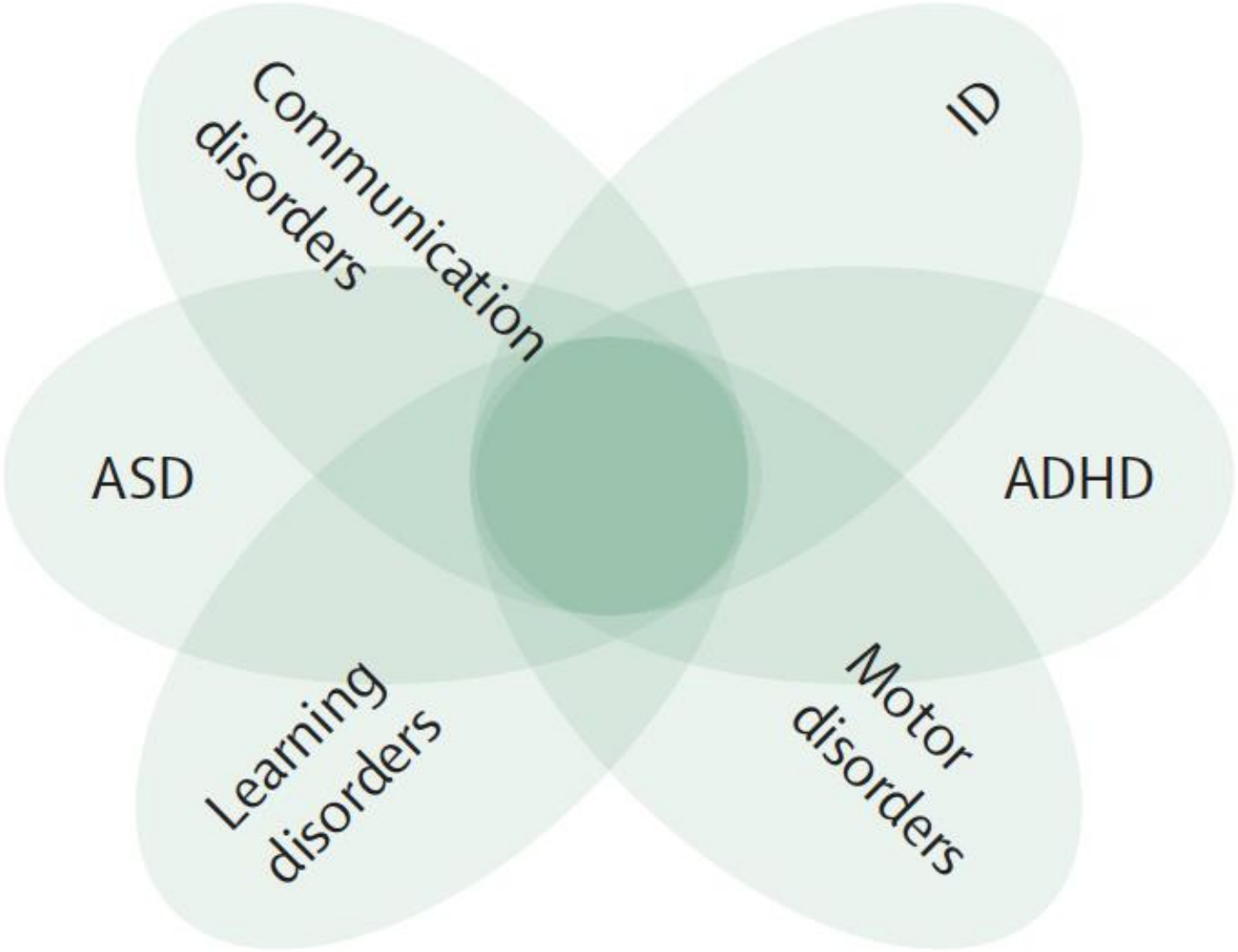
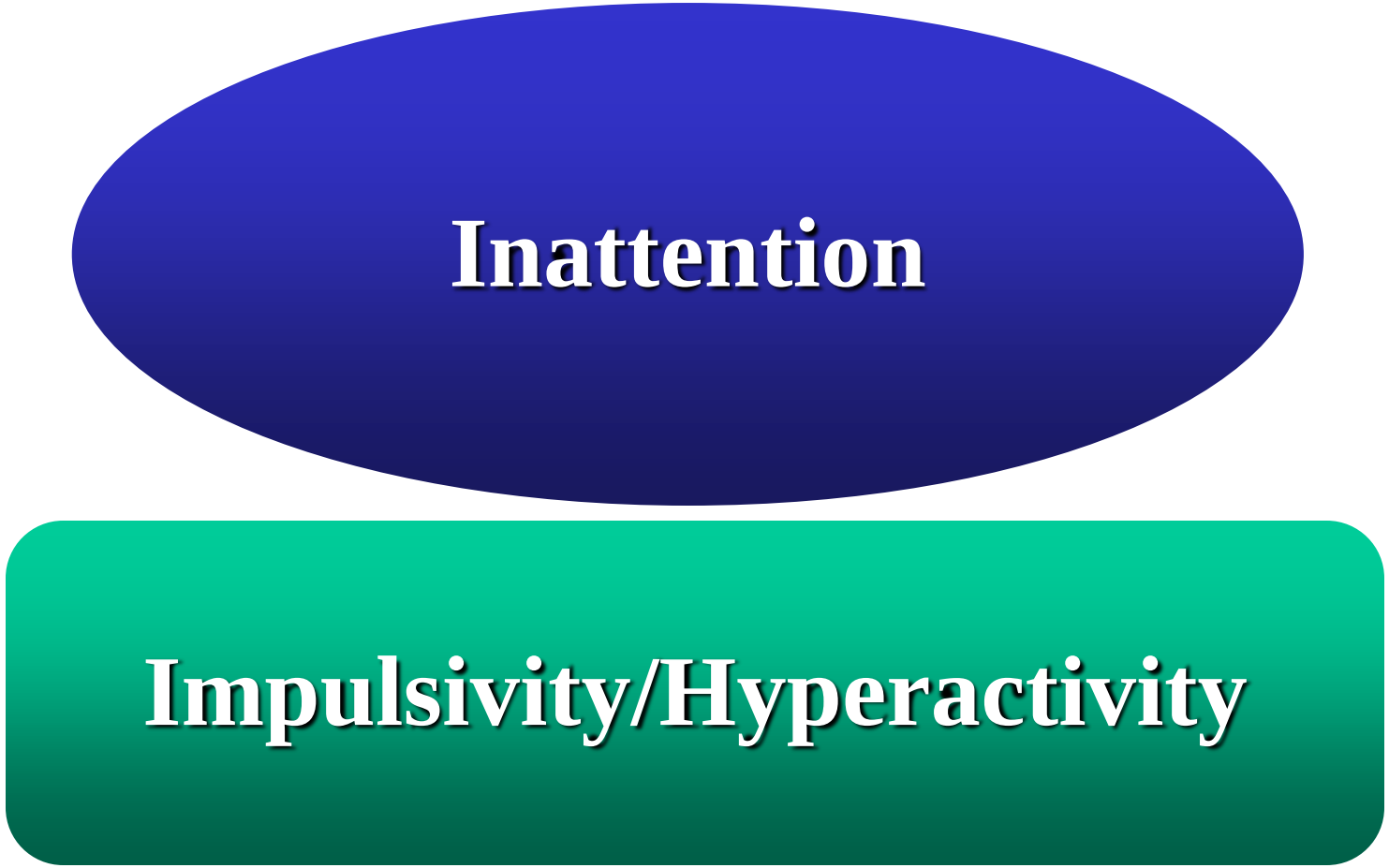
Broader spectrum of neurodevelopmental disorders



Thapar et al. Lancet Psychiatry, 2017 Apr;4(4):339-346

ADHD - Core Symptom Areas

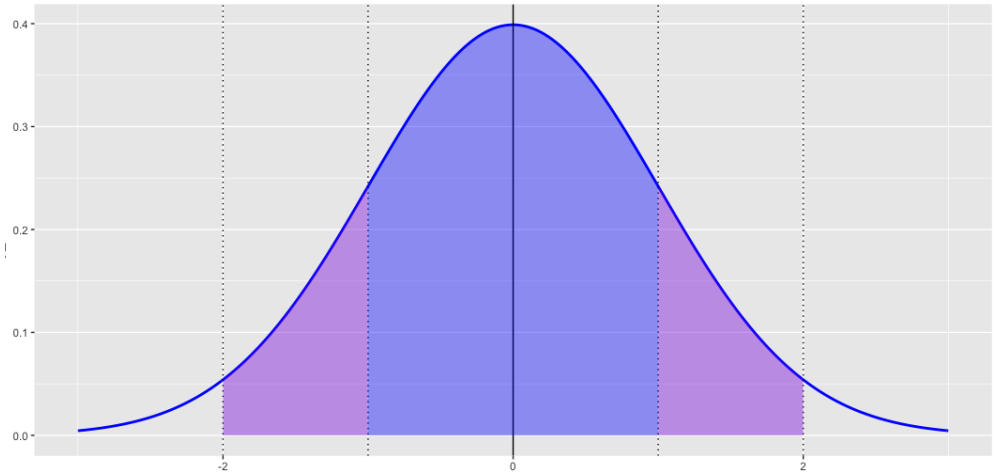


Autism Spectrum Disorder

Social-communication deficits

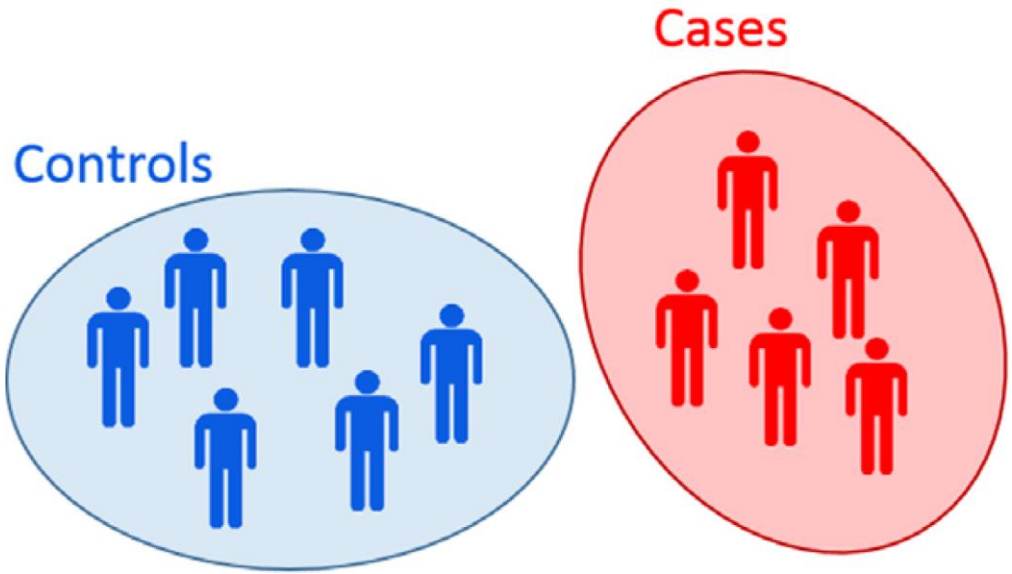
Fixated interests, repetitive behaviours, and abnormal sensory processing

Neurodevelopmental Disorders



- Extreme of normal variation
- Quantitative variation
- Neurodiversity
- Dimensional modal

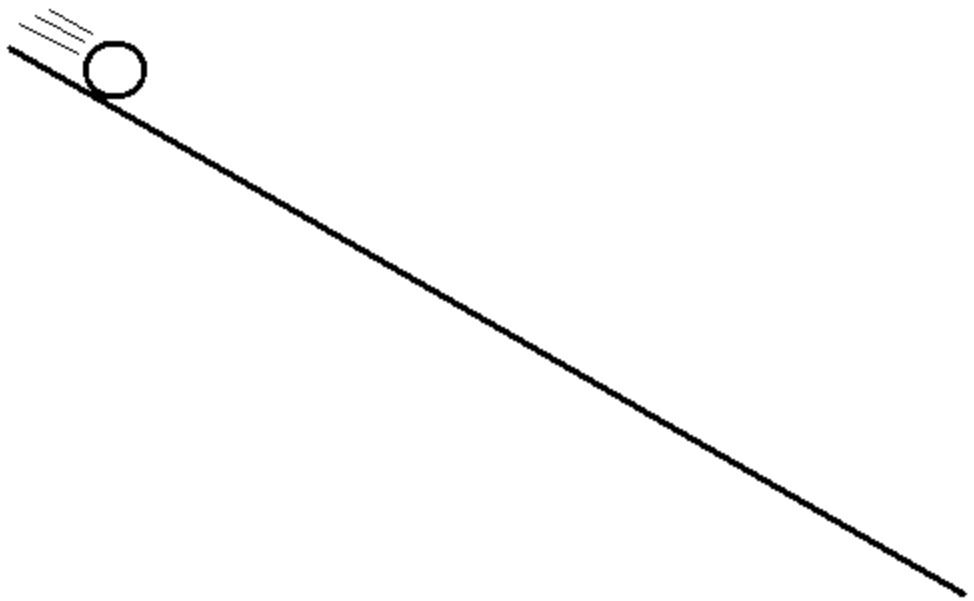
4 D's
•Disease,
•Disorder
•Disability
•Difference

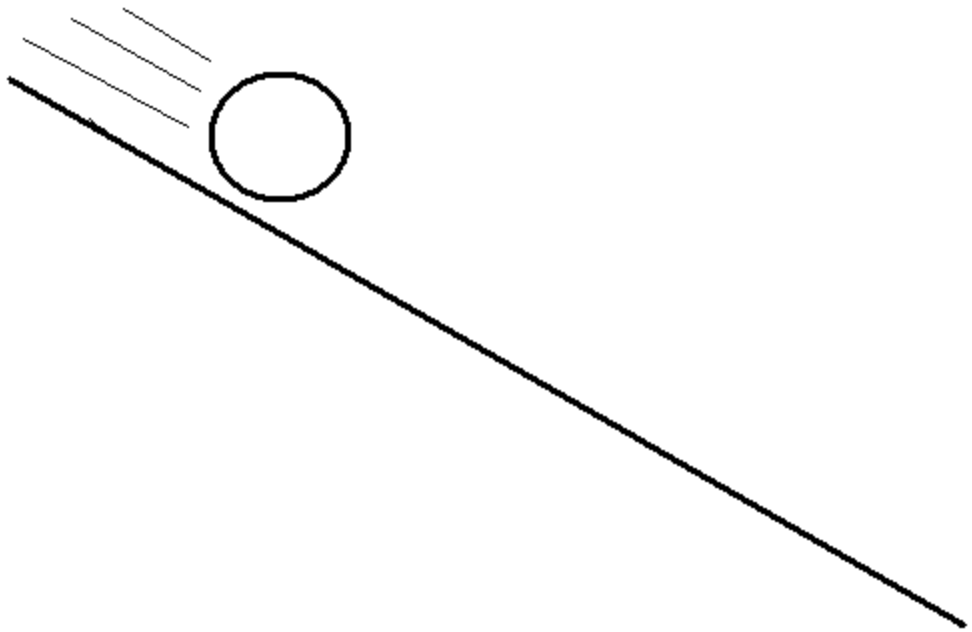


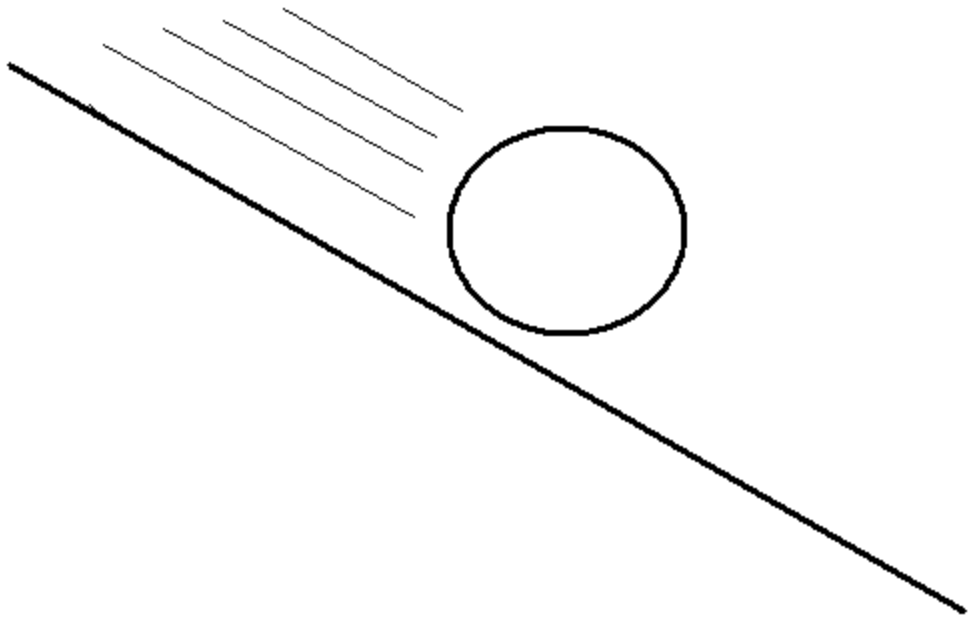
- Disease
- Abnormality
- Qualitative differences
- Psychopathology
- Categories

These neurodevelopmental disorders are thought to result from the disruption of normal brain development and related neurobiological mechanisms during the prenatal and early postnatal period

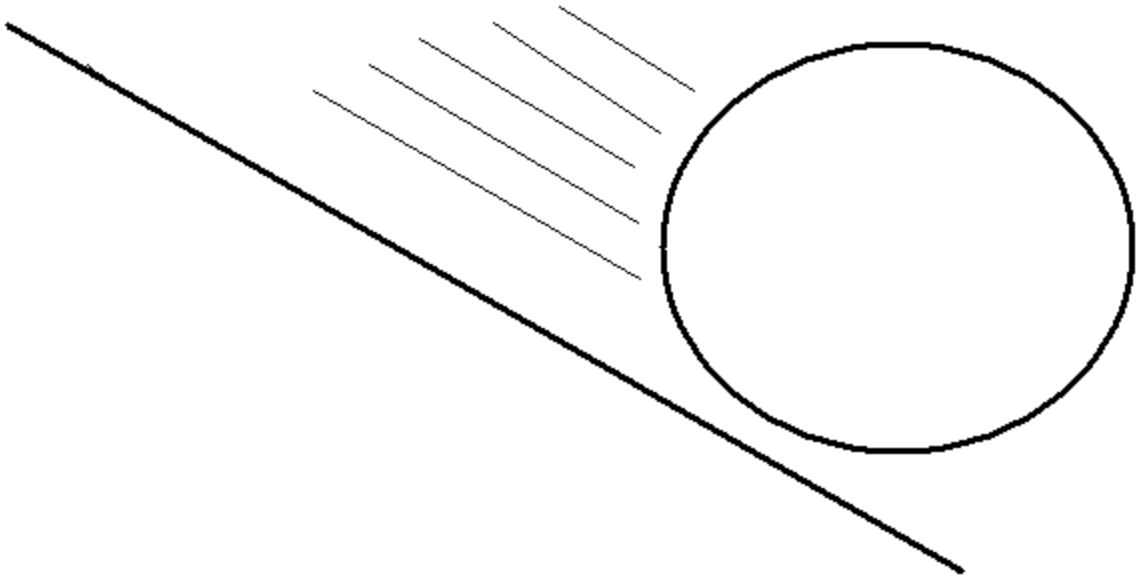
The developmental “snowball” rolls downhill over time……





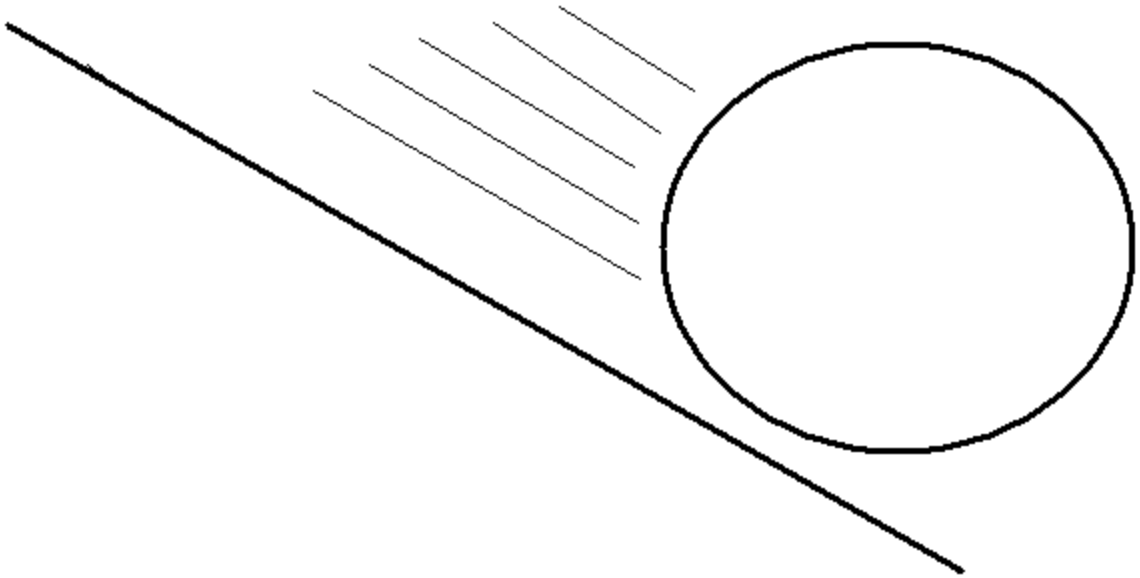


…….gathering speed and mass (loadings for psychopathology and atypicality).

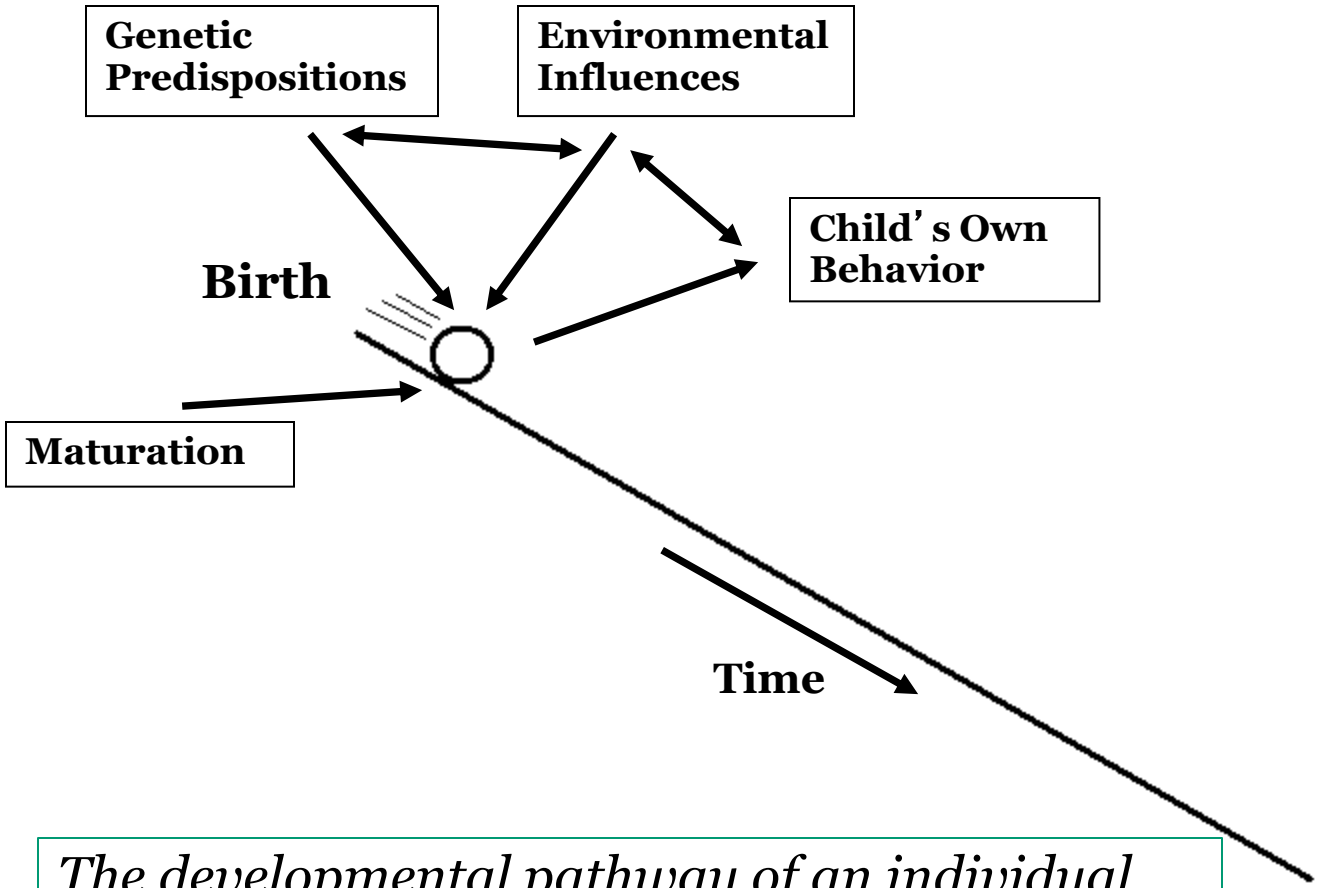


“Outcome”?

…….gathering speed and mass (loadings for psychopathology and atypicality).

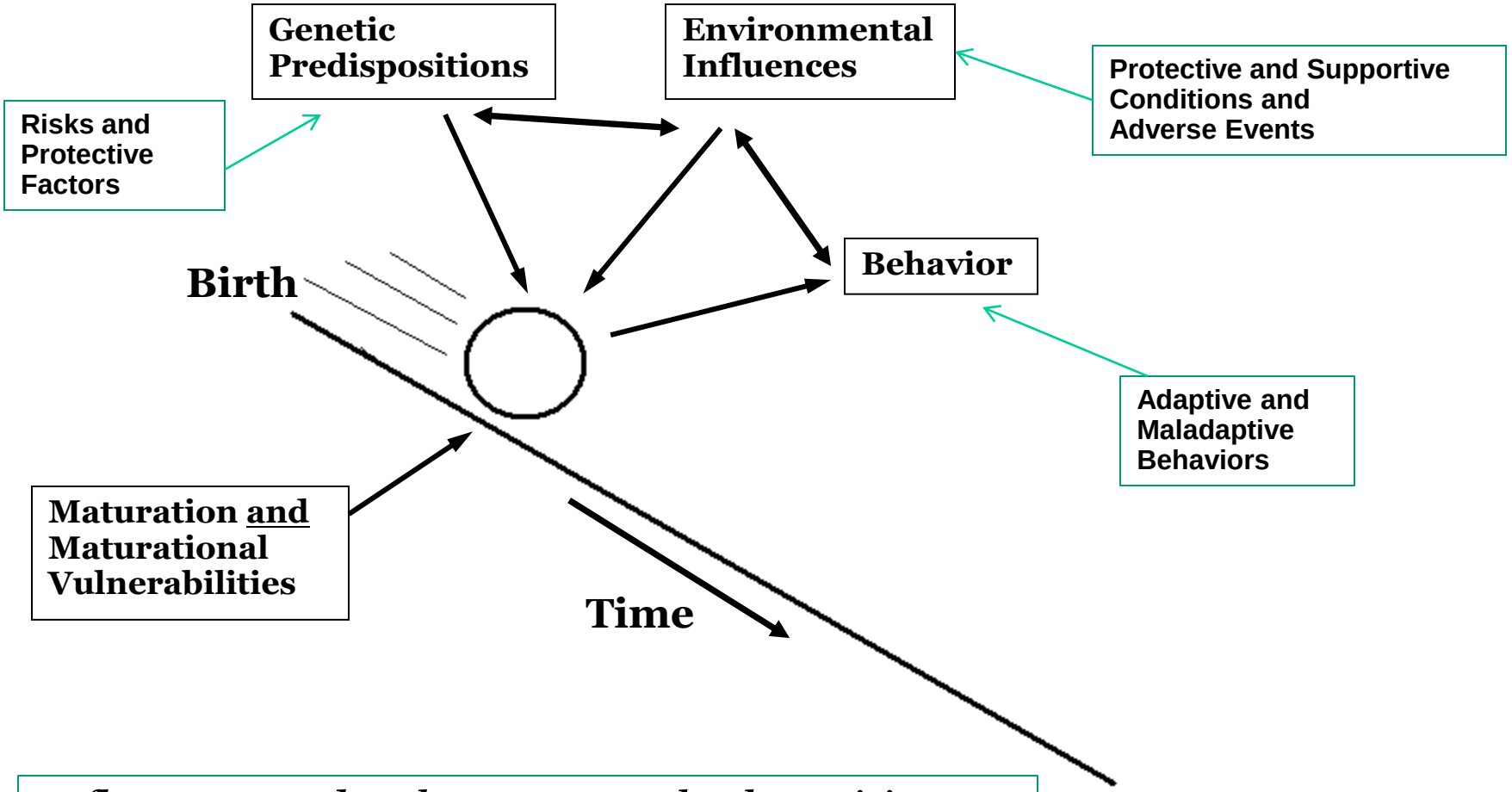


“Outcome”?

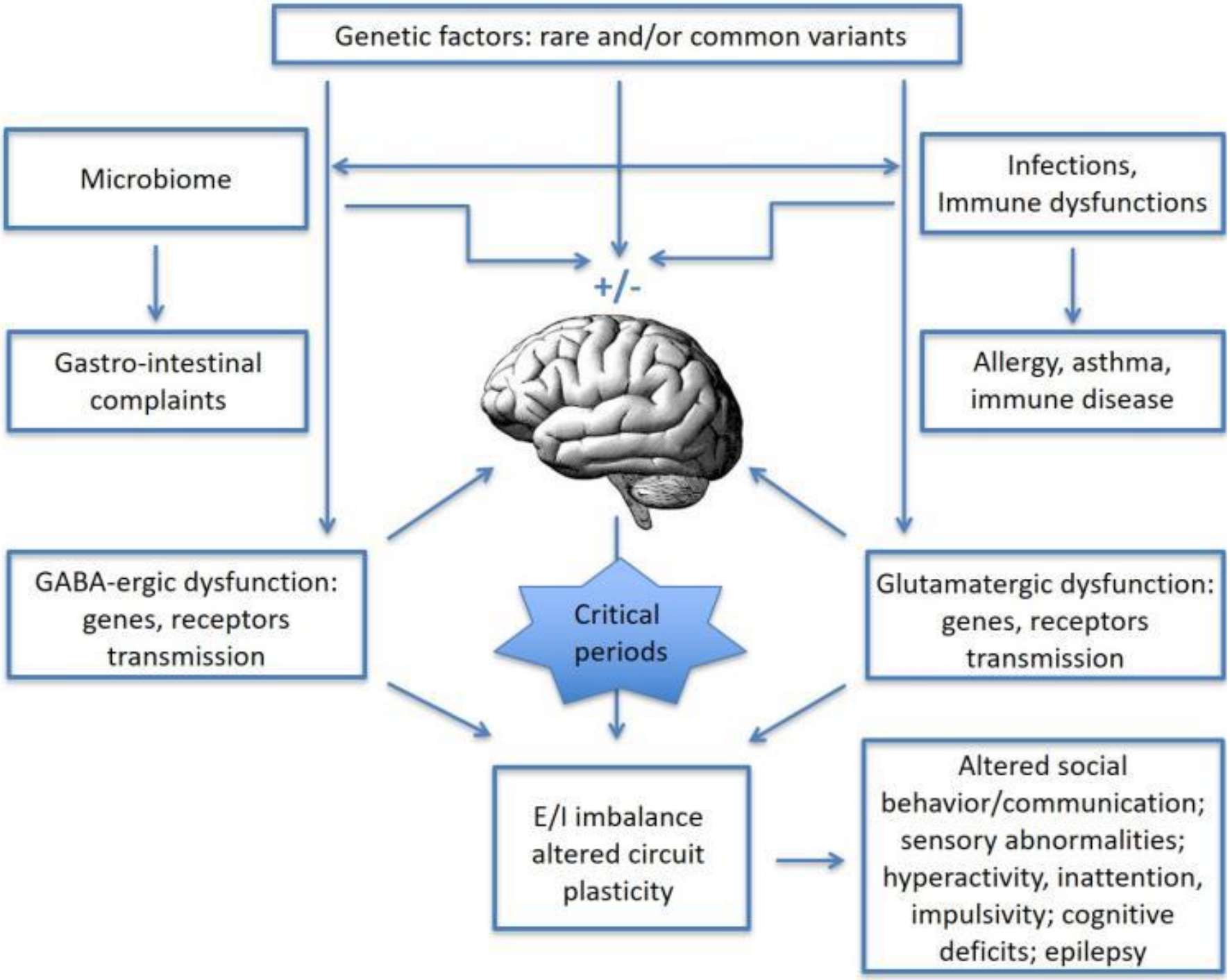


The developmental pathway of an individual child reflects not only genetic endowment and environmental effects, but also the interactions among these and the child's own activity over time.

"Outcome"



Influences on development are both positive and adverse. Likewise, the individual's behaviors over time are both adaptive and maladaptive.

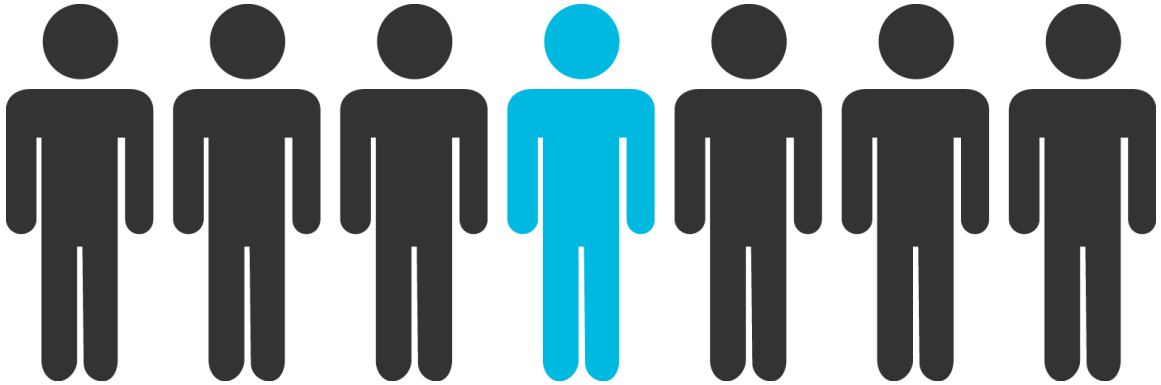

Genetic factors: rare and/or common variants
Microbiome
Infections, Immune dysfunctions
+/-
Gastro-intestinal complaints
Allergy, asthma, immune disease
GABA-ergic dysfunction: genes, receptors transmission
Critical periods
Glutamatergic dysfunction: genes, receptors transmission
E/I imbalance altered circuit plasticity
Altered social behavior/communication; sensory abnormalities; hyperactivity, inattention, impulsivity; cognitive deficits; epilepsy

Key words

Stratification / subtyping

Biomarkers

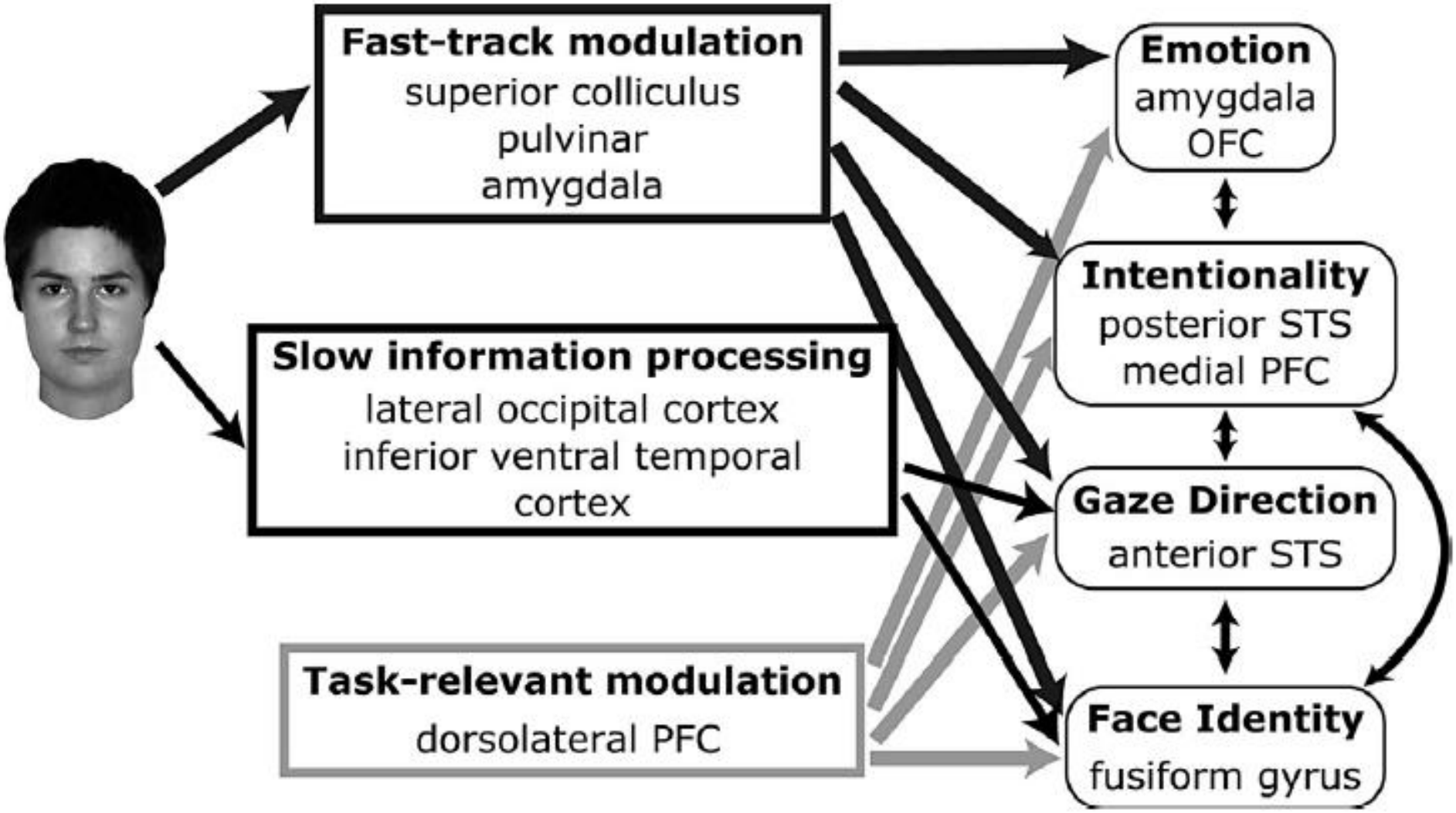
A biomarker is always about predictions that can be made for a particular individual.



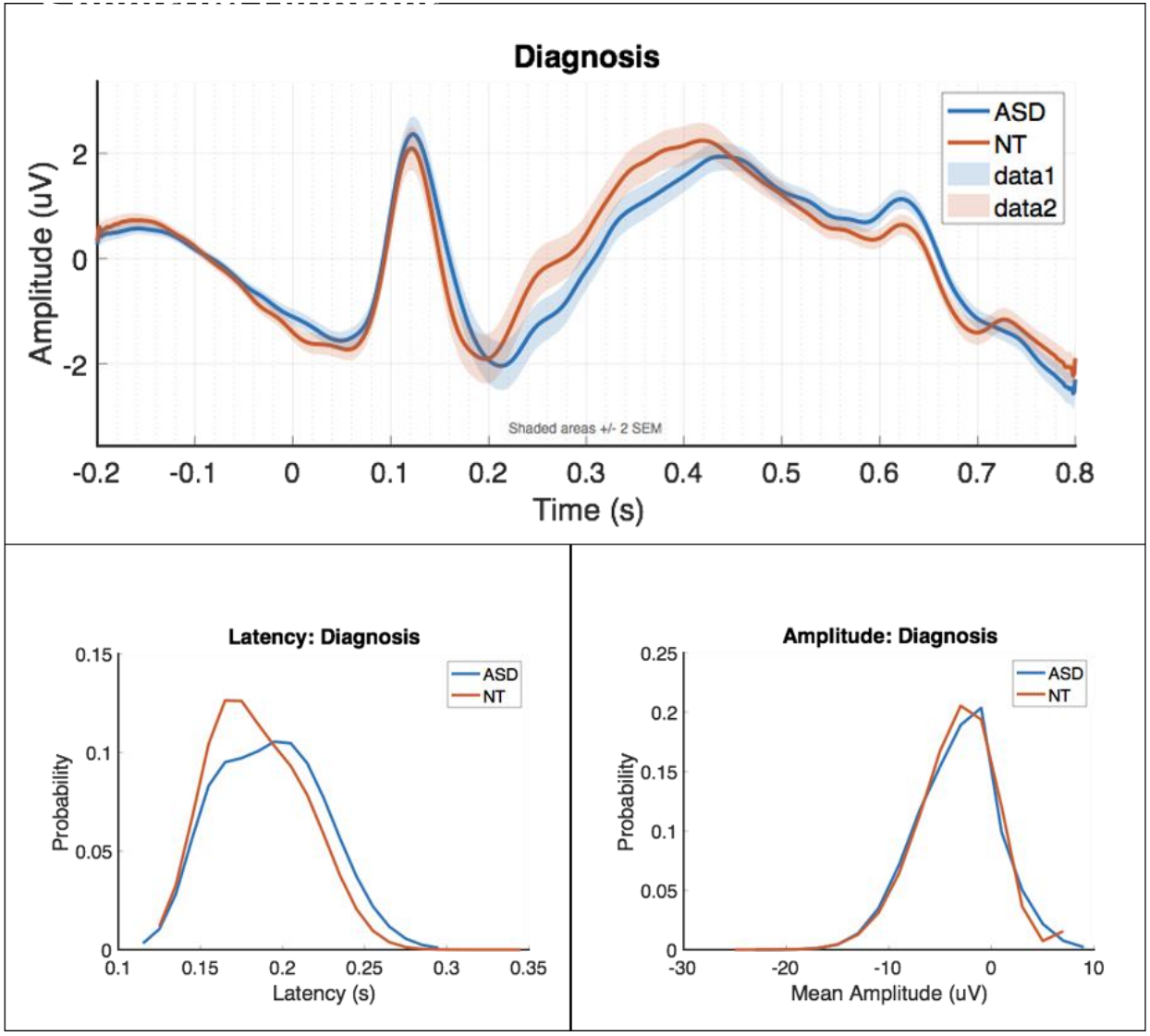
Types of biomarkers

Type of biomarker	Purpose	Setting / samples
Diagnostic marker	Predict ADHD classification (DSM-5 / ICD-11)	Clinical and research setting; Decision support tool
Risk marker	Detect ADHD earlier Can be used to stratify early risk groups / paths	High-risk infants, high-risk preschoolers
Prognostic marker	Predict symptom progression / remission Predict psychiatric and somatic comorbidity	From preschool to childhood; from adolescence to adulthood
Predictive marker	Predict treatment response	RCTs and observational clinical settings
Stratification marker	Detect homogeneous subgroups	Preschoolers, children, adolescents, adults

Face processing – face perception

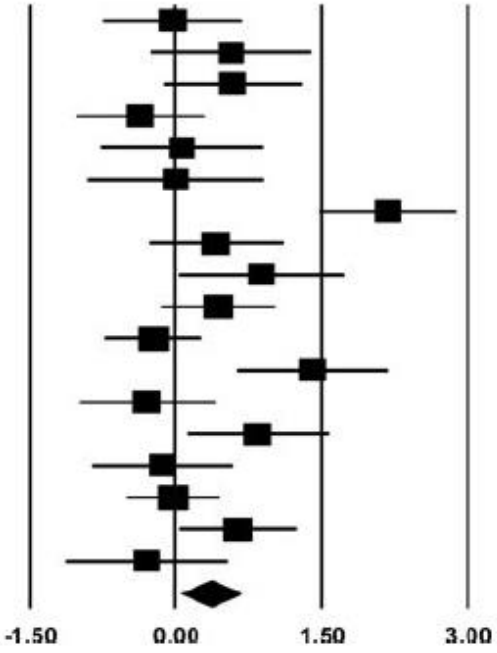


Biomarker proposal to EMA



Meta-analysis of N170 latency

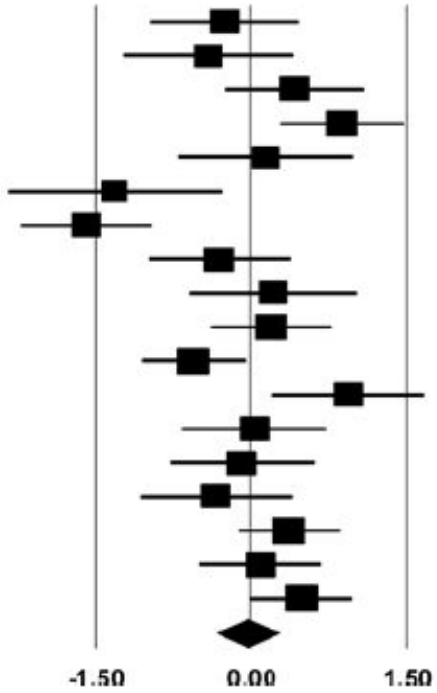
Study ID	Subgroup within study	Stimuli	Hedges's g	Lower limit	Upper limit	p-Value
Akechi et al., 2010 (20)	Child	Combined	-0.027	-0.746	0.693	0.942
Apicella et al., 2013 (21)	Child	Combined	0.575	-0.251	1.403	0.172
Batty et al., 2011 (22)	Child	Faces	0.589	-0.123	1.301	0.105
Churches et al., 2010; 2012a; 2012b (25,63,64)	Adult	Faces	-0.361	-1.023	0.301	0.286
Grice et al., 2005 (31)	Child	Faces	0.062	-0.778	0.902	0.885
Gunji et al., 2009 (32)	Child	Combined	0.002	-0.904	0.908	0.996
Hileman et al., 2011 (23)	Child	Combined	2.184	1.477	2.890	0.000
Khorrami et al., 2013 (53)	Child	Combined	0.416	-0.274	1.105	0.237
McPartland et al., 2004 (2)	Adult	Combined	0.885	0.035	1.735	0.041
McPartland et al., 2011 (18)	Child	Combined	0.440	-0.146	1.026	0.141
Neuhaus et al., 2016 (33)	Child	Combined	-0.227	-0.722	0.268	0.369
O'Connor et al., 2005 (27)	Adult	Combined	1.405	0.623	2.187	0.000
O'Connor et al., 2005 (27)	Child	Combined	-0.294	-0.995	0.406	0.410
O'Connor et al., 2007 (28)	Adult	Faces	0.847	0.118	1.575	0.023
Senju et al., 2005 (34)	Child	Combined	-0.135	-0.858	0.587	0.713
Tye et al., 2013; 2014 (65,66)	Child	Combined	-0.023	-0.505	0.459	0.926
Webb et al., 2006 (24)	Child	Combined	0.644	0.040	1.247	0.037
Wong et al., 2008 (35)	Child	Combined	-0.293	-1.125	0.540	0.491
			0.362	0.058	0.667	0.020



Kang et al. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 Aug;3(8):657-666.

Meta-analysis of N170 amplitude

Study ID	Subgroup within study	Stimuli	Hedges's g	Lower limit	Upper limit	p-Value
Akechi et al., 2010 (20)	Child	Combined	-0.252	-0.974	0.471	0.495
Apicella et al., 2013 (21)	Child	Combined	-0.417	-1.236	0.401	0.317
Churches et al., 2010; 2012a; 2012b (25,63,64)	Adult	Faces	0.422	-0.242	1.086	0.213
Cygan et al., 2014 (26)	Adult	Faces	0.880	0.285	1.476	0.004
Grice et al., 2005 (31)	Child	Combined	0.147	-0.694	0.988	0.732
Gunji et al., 2009 (32)	Child	Combined	-1.307	-2.334	-0.281	0.013
Hileman et al., 2011 (23)	Child	Combined	-1.585	-2.223	-0.948	0.000
Khorrami et al., 2013 (53)	Child	Combined	-0.305	-0.991	0.381	0.383
McPartland et al., 2004 (2)	Adult	Combined	0.214	-0.596	1.024	0.605
McPartland et al., 2011 (18)	Child	Combined	0.196	-0.368	0.779	0.511
Neuhaus et al., 2016 (33)	Child	Combined	-0.550	-1.053	-0.048	0.032
O'Connor et al., 2005 (27)	Adult	Combined	0.939	0.202	1.676	0.013
O'Connor et al., 2005 (27)	Child	Combined	0.034	-0.663	0.730	0.924
O'Connor et al., 2007 (28)	Adult	Faces	-0.085	-0.782	0.611	0.810
Senju et al., 2005 (34)	Child	Combined	-0.335	-1.065	0.395	0.369
Tye et al., 2013; 2014 (65,66)	Child	Combined	0.369	-0.120	0.859	0.139
Webb et al., 2006 (24)	Adult	Combined	0.097	-0.492	0.686	0.748
Webb et al., 2012 (29)	Adult	Combined	0.487	-0.004	0.978	0.052
			-0.034	-0.328	0.260	0.820



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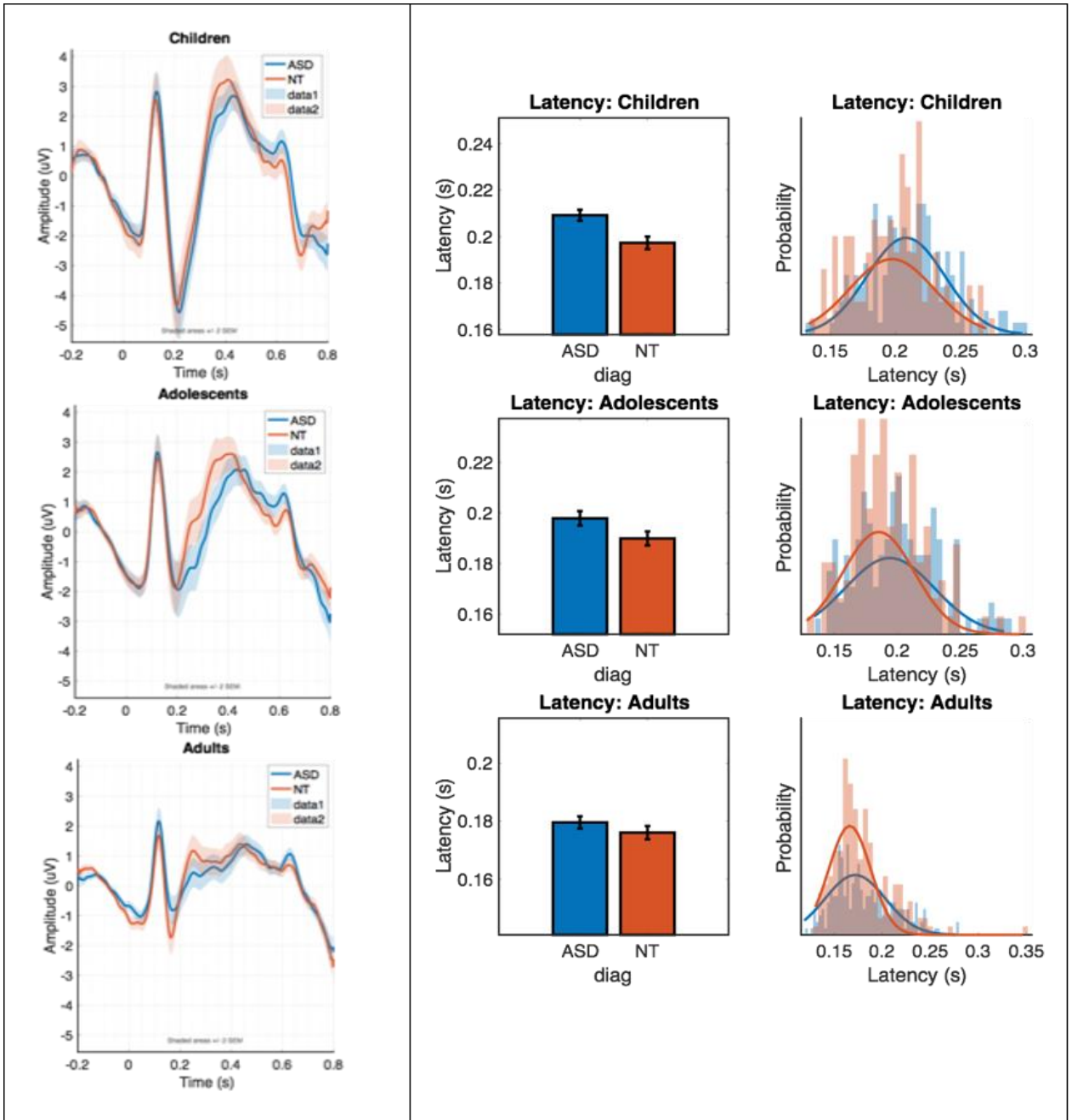
Biomarker proposal to EMA



Confounder ?

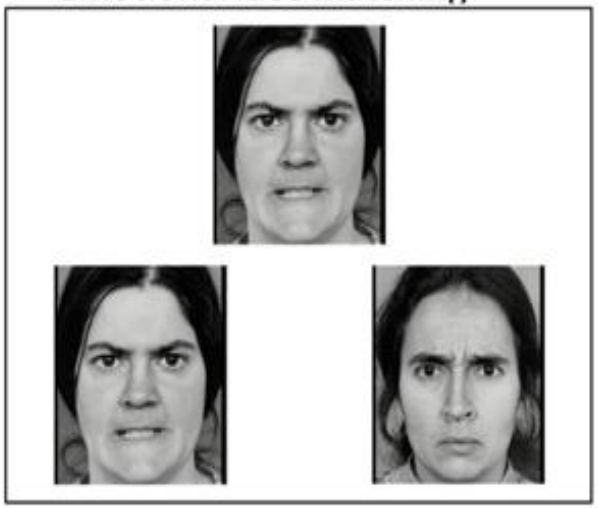
Partial Correlations for Association between N170 latency at P7/P8 to Upright Faces and Associated Symptoms, Controlled for Age

N170 latency P7/P8	ASD group
Verbal IQ	r(239) = -0.049, p = 0.448
Performance IQ	r(240) = -0.096, p = 0.137
DAWBA ADHD	r(160) = 0.011, p = 0.888
DAWBA internalising	r(211) = 0.049, p = 0.476
DAWBA externalising	r(211) = 0.045, p = 0.513

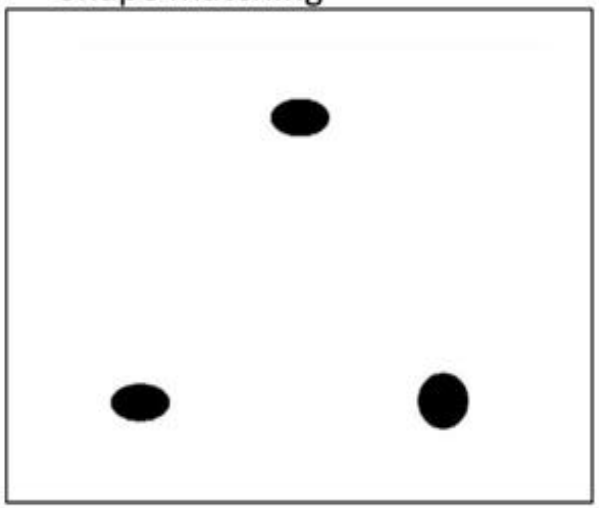
➔**No influence of comorbidities**

Biological plausibility - convergentie

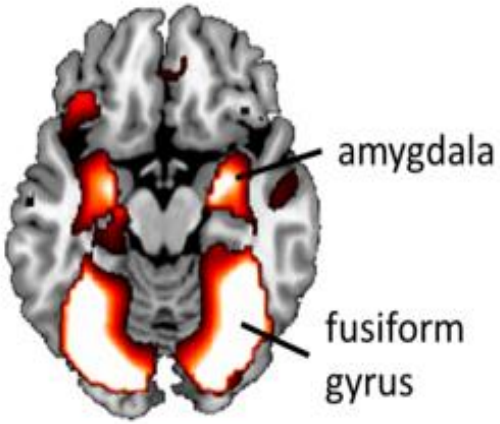
A) Condition 1:
Emotional face matching



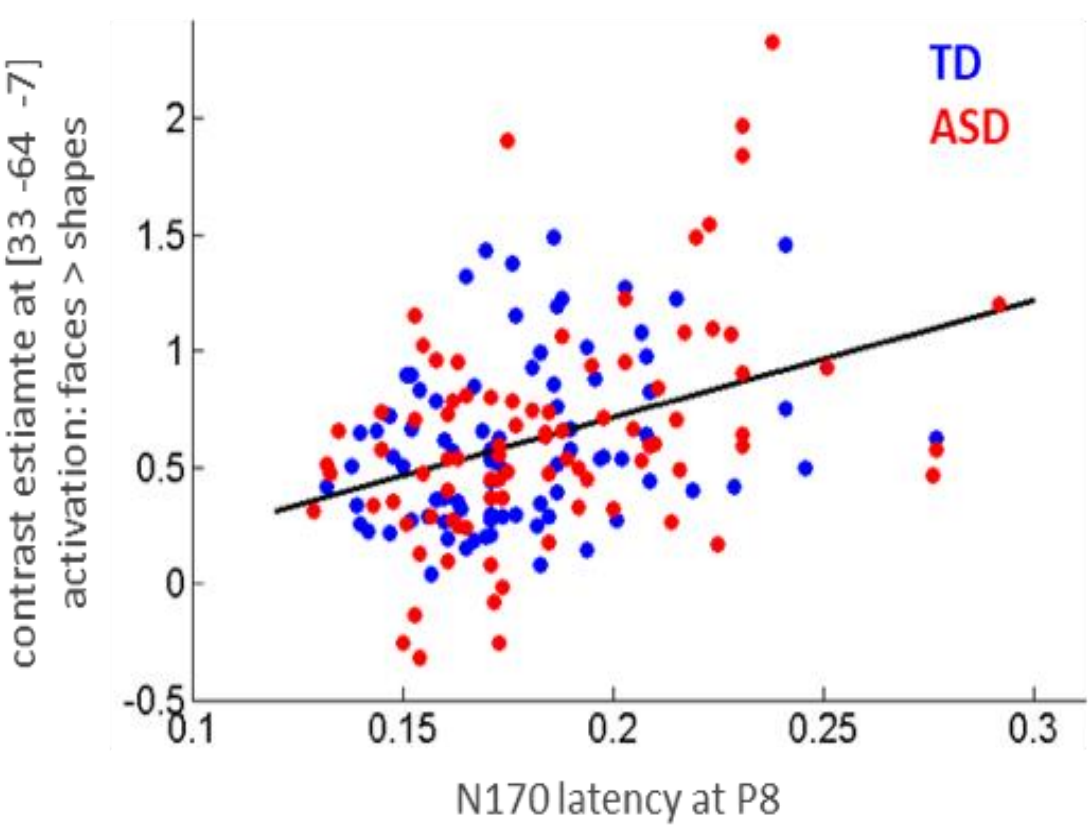
B) Condition 2:
Shape matching

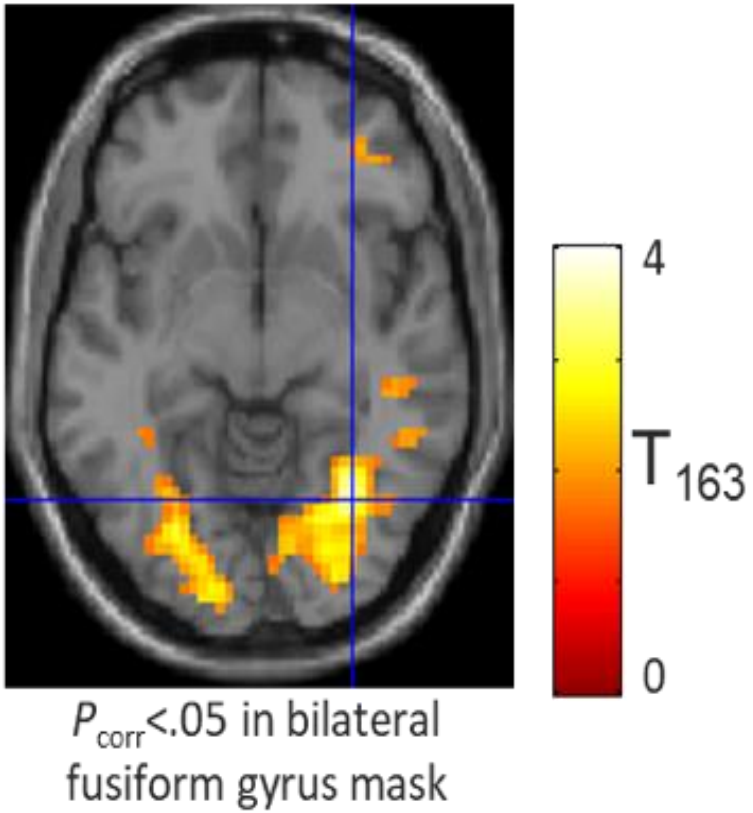


C) Functional activation in
contrast „faces > shapes“



Biological plausibility - convergentie





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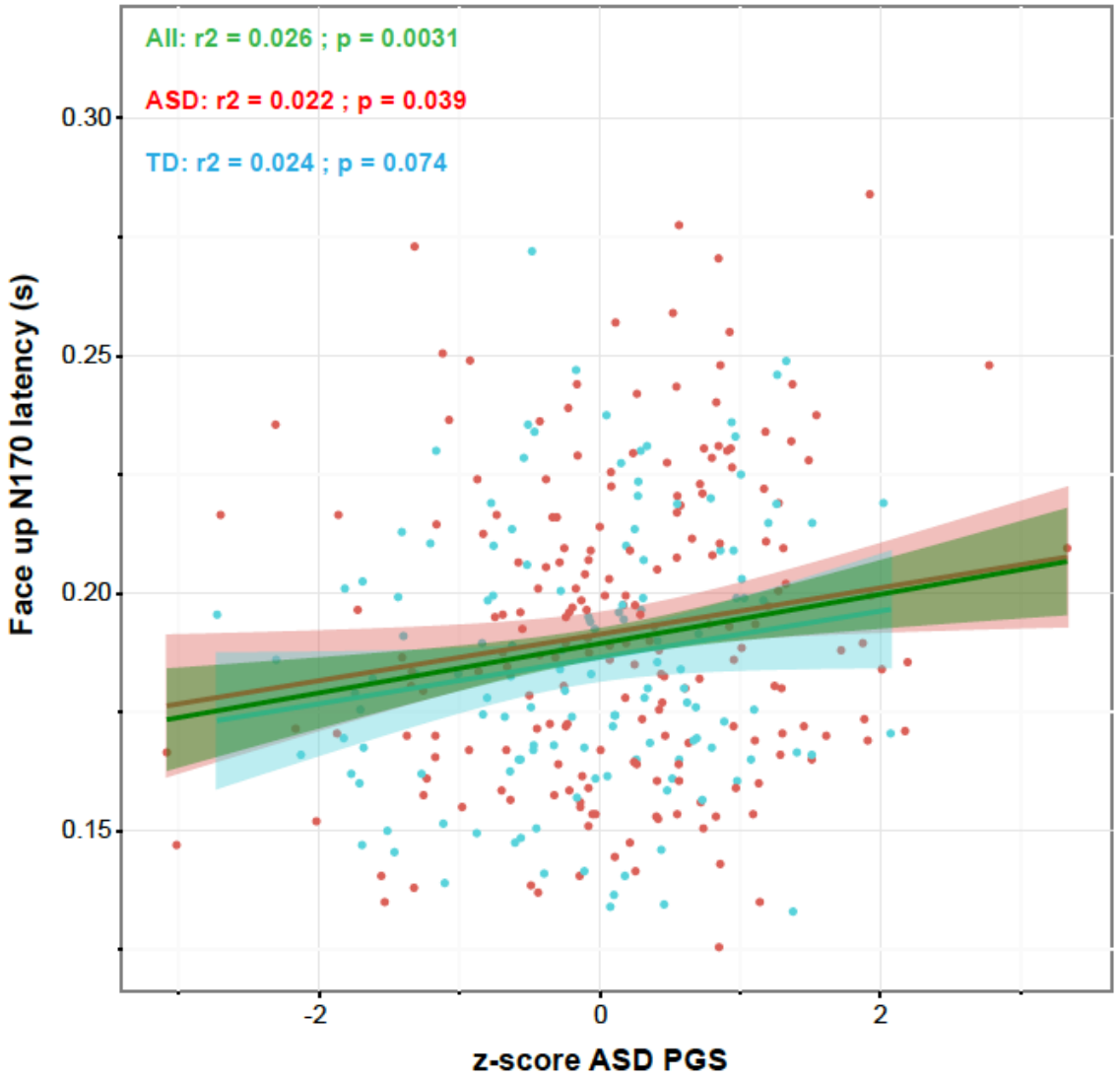

N170 and prediction of outcome

Association of the N170 Latency to Upright Faces at P7/P8 at Baseline with the Vineland Socialisation Subscale Scores at Baseline and at a Longitudinal Follow-Up Visit within the ASD Group

Subdomain	Baseline Assessment [a]	Follow-Up Assessment [b]
	N=213 with EEG and Vineland at baseline	N=145 with baseline EEG +Vineland at follow-up
Coping	r(208) = 0.010, p = 0.880	r(141) = -0.05, p = 0.538
Interpersonal Relationships	r(209) =-0.063, p = 0.366	r(137) =0.022, p = 0.796
Play and Leisure Time	r(209) = 0.014, p = 0.838	r(141) = -0.235, p = 0.005 [c]

N170 and prediction of outcome

Een nieuwe kijk op ADHD en autisme

Old concept	Modernised concept
Risk factors	Protective and risk factors; resilience
Symptoms	Symptoms plus functioning, wellbeing, QoL
Deficits	Strengths and weaknesses
Behavioural descriptions	Biological, genetic, cognitive and behavioural measures as input for precision medicine
Categoric / binary view	Dimensional view
Service and clinician-based care	Shared decision making, Self-management
Face-2-Face consultations	F-2-F and digital interventions / guidance