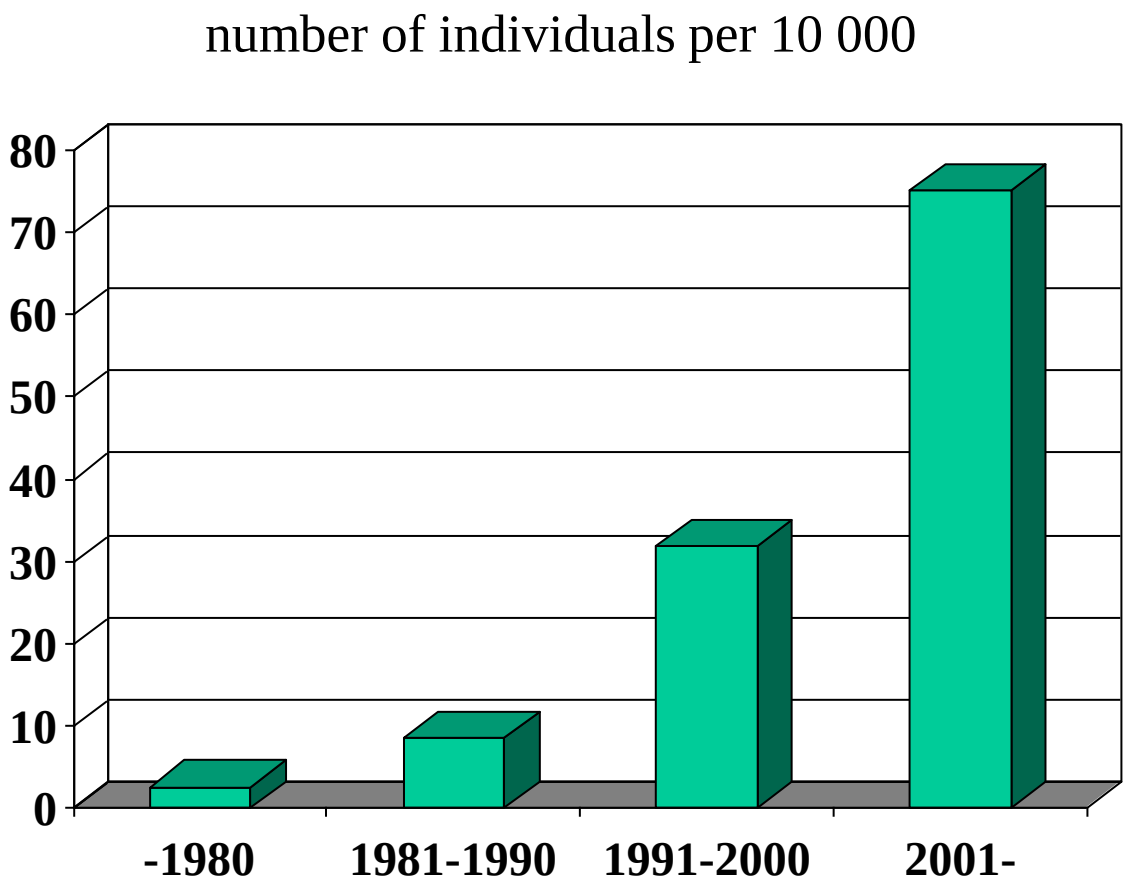
Autism Spectrum Disorders

- Autism: Leo Kanner 1943, Infantile autism, childhood psychosis.
- Asperger's syndrome: Hans Asperger 1944, Autistic psychopathies.
- High Functioning Autism
- DSM-IV: Pervasive Developmental Disorders: Autistic syndrome, Disintegrative syndrome (Heller's syndrome), Rett's syndrome, PDD-NOS (Pervasive Developmental Disorder-Not Otherwise Specified)
- DSM-5: Autism Spectrum Disorder

ASD

- 1-2% prevalence
- Autistic traits (symptoms): 3-7% prevalence

The autism epidemic



Criticism

- Risk of overdiagnosing? High functioning ASD has a very unclear limit against normality and som other diagnoses (ADHD personality disorder).

The triad of Lorna Wing

- Difficulties with social interaction
- Difficulties with social communication
- Difficulties with social imagination

Criteria for Autism Spectrum Disorder (DSM-5)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

- 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

- 2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

- 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to abscence of interest in peers.

Criteria continued

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:

- 1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

- 2. Insistence of samenes, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

- 3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

- 4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Criteria continued

- C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

- D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

- E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Severity concerning:

1.Social communication,
2. Restricted, repetitive patterns of behavior

- For 1 and 2 specify level.
- Level 1: Requiring support
- Level 2: Requiring substantial support
- Level 3: Requiring very substantial support

Specification according to DSM-5:

- 1. Intellectual function
- 2. Language development
- 3. Medical, genetic or environmental conditions
- 4. Other developmental functional deficit, other psychiatric condition or behavioural disorder
- 5. Catatonia

Factors important for the manifestation of the symptoms

- The severity of the autism spectrum disorder, the degree of autistic seclusion
- Language development
- Intellectual function

Positive sides of having ASD

- Skilled at observing details, systematic.
- Ability to concentrate at important interesting subjects.
- Stabile, trustworthy
- Unusual thoughts.
- Tells the truth, can not lie.

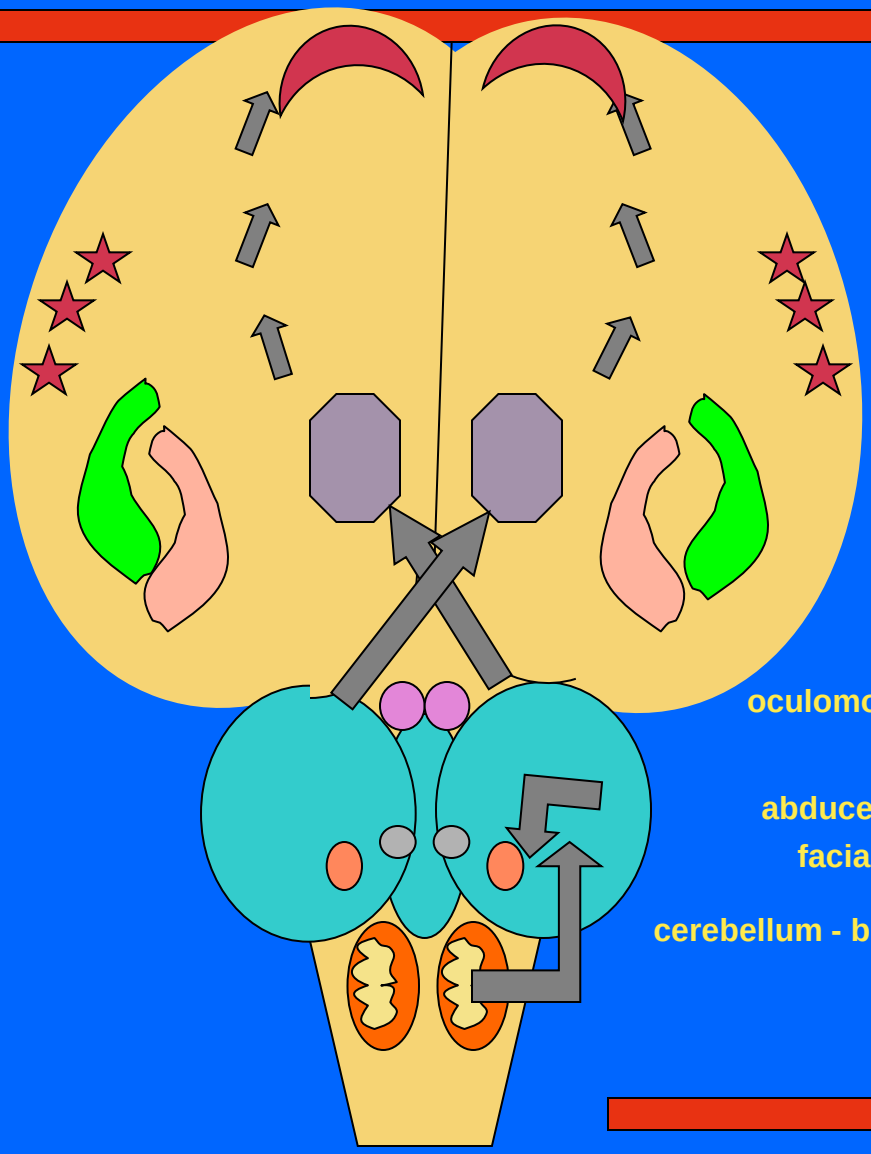
Is there a continuum or two or more kinds of ASD?

- Individuals with high functioning autism: higher heritability, fewer imigrants, lower frequency of other syndromes, epilepsy, pre- and perinatal complications or other somatic complications.
- The importance of perception and language. The Trigger-Treshold-Target Model. Enhanced synaptic plasticity-decreased pruning (Mottron et al., Neurosci Biobeha Rev 2014, Samson et al. J Psychiatr Res 2015)

Language and motor/perceptual function

- Early language development with sensory/motor problems
- Late language development with good motor and perceptual functions and echolalia

BRAIN REGIONS FUNCTIONALLY ALTERED in AUTISM?



frontal cortex
prefrontal cortex
parietal cortex

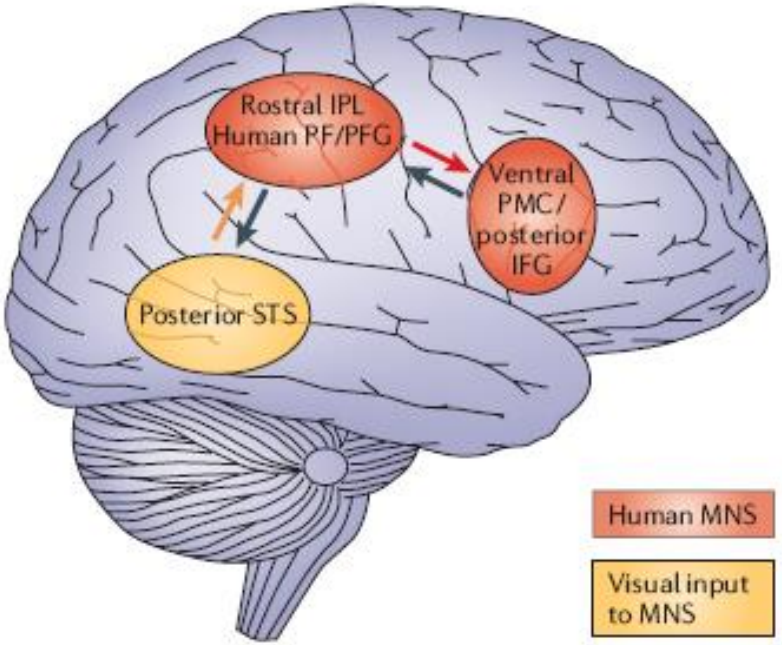
thalamus
fusiform gyrus
inferior temporal gyrus

oculomotor

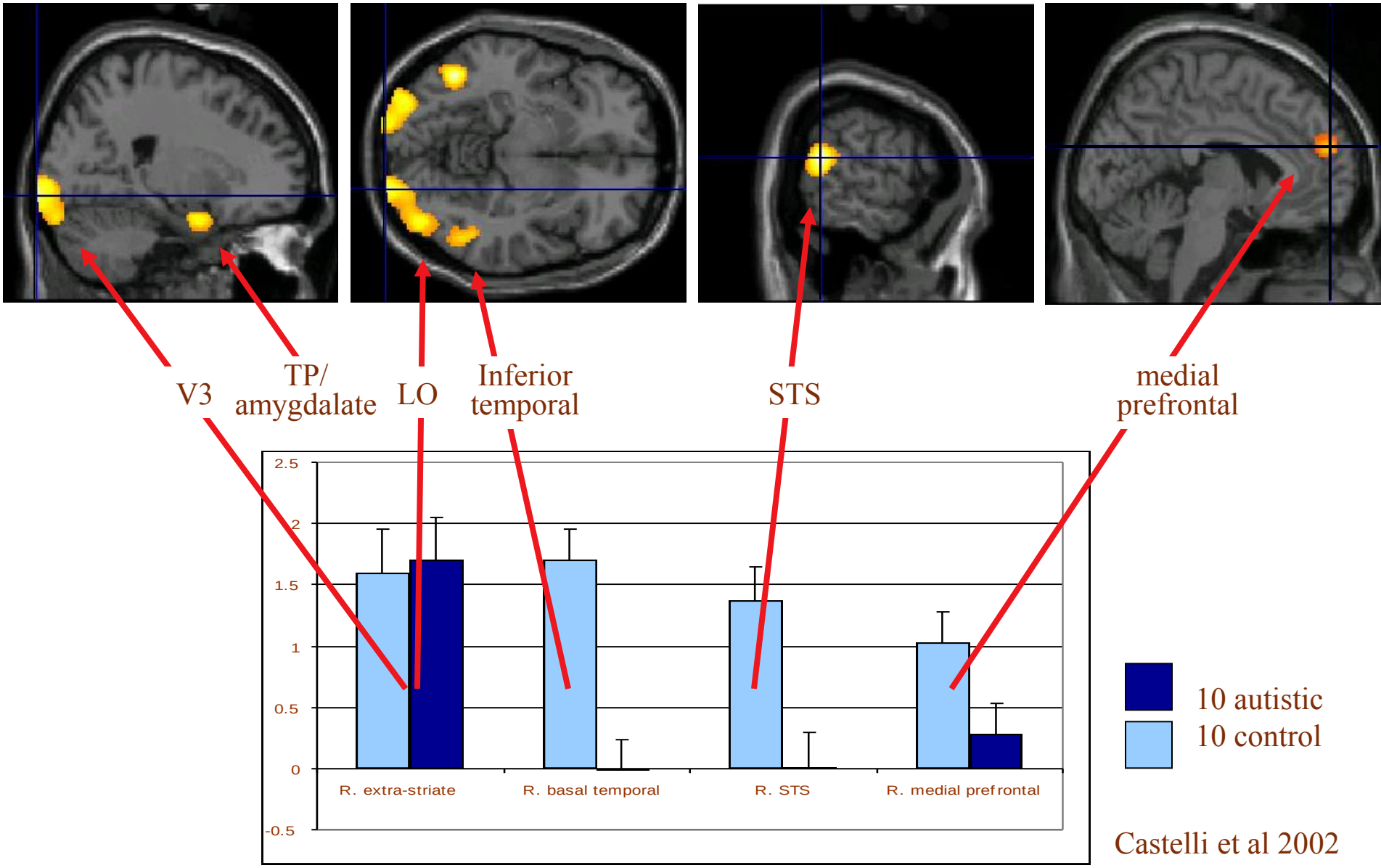
abducens
facial

cerebellum - brain stem loops

Mirror neurons



Brain activity associated with mentalising

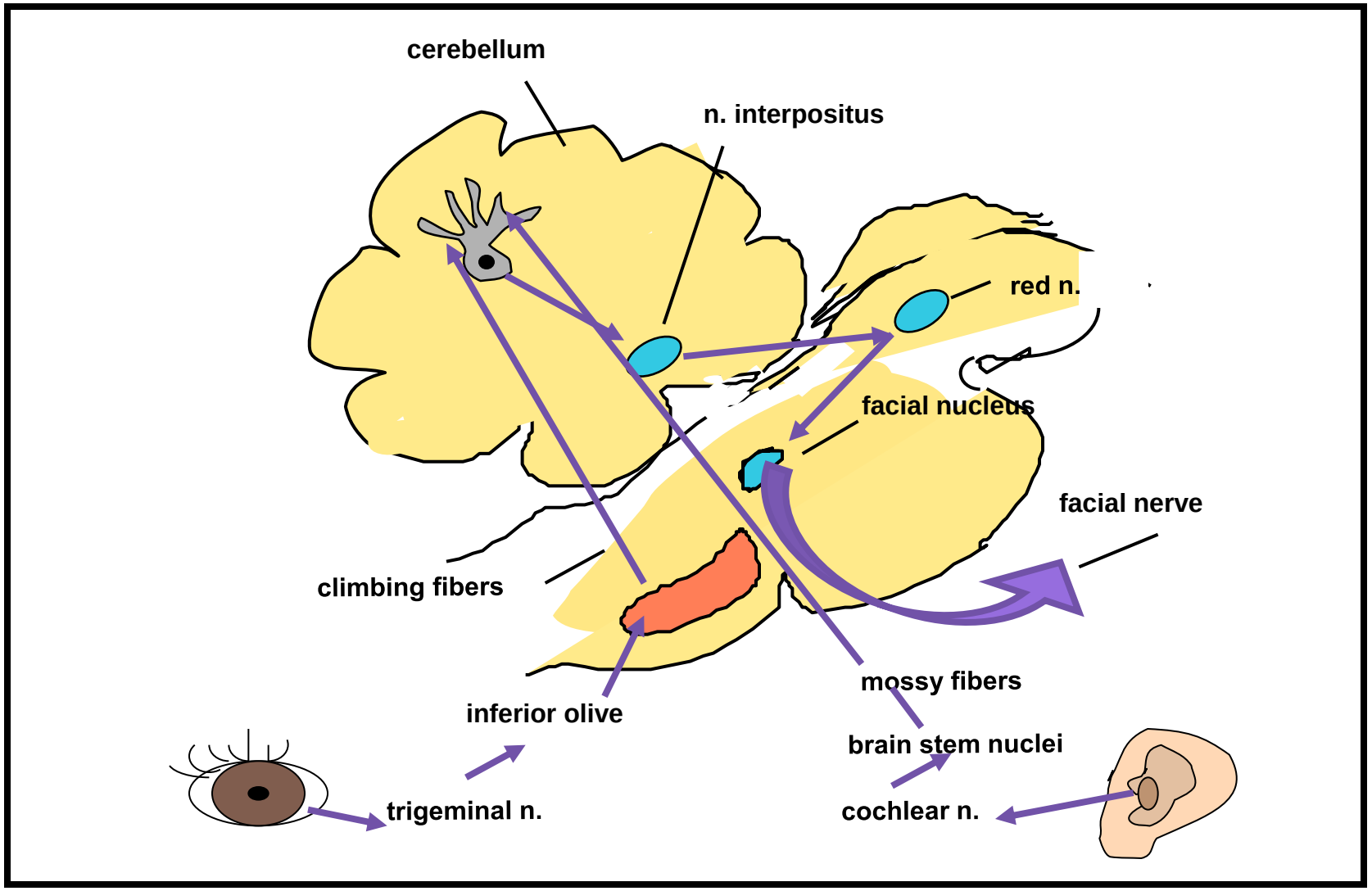


Castelli et al 2002

Cerebellum

- Several studie show less cerebellar volume and less activation assessed with fMRI in ASD.

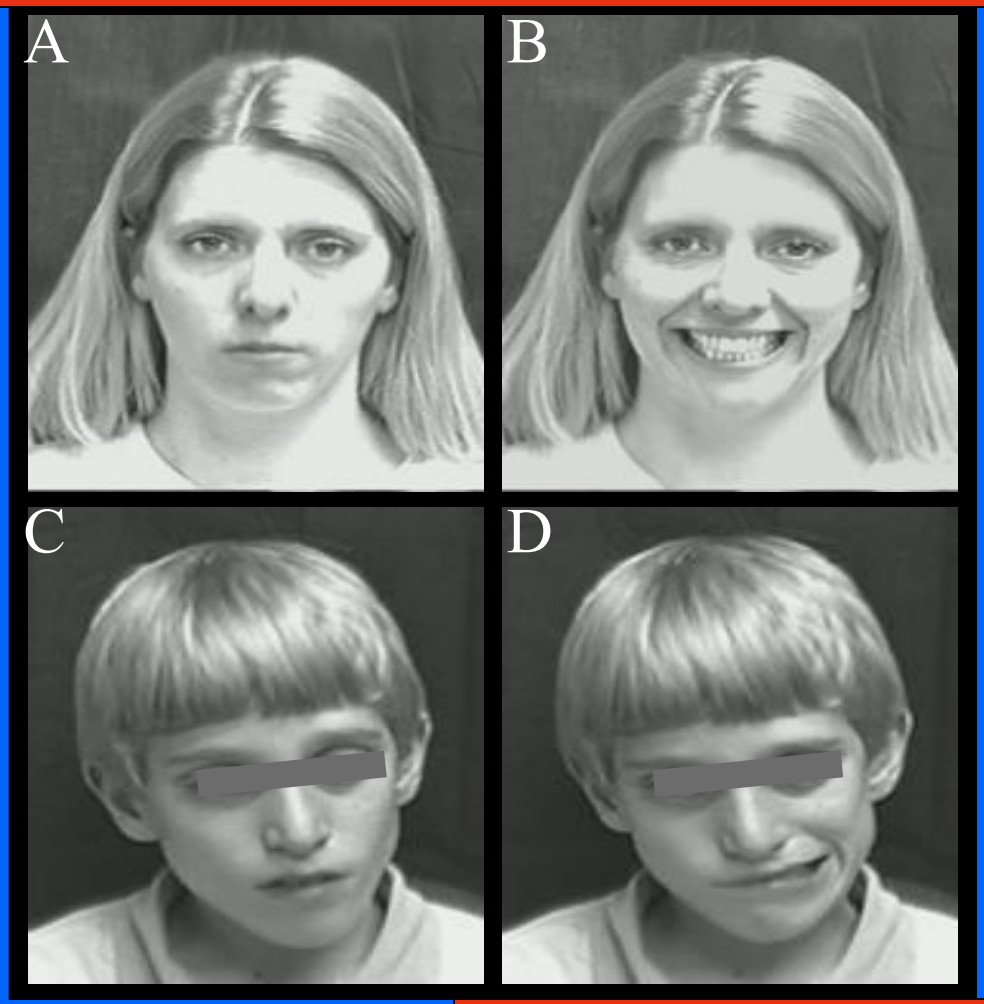
NEURONAL PATHWAYS of the CONDITIONED EYEBLINK



IMITATION of FACIAL EXPRESSION in AUTISM (Bennetto, 2001)

Model

Imitator with Autism

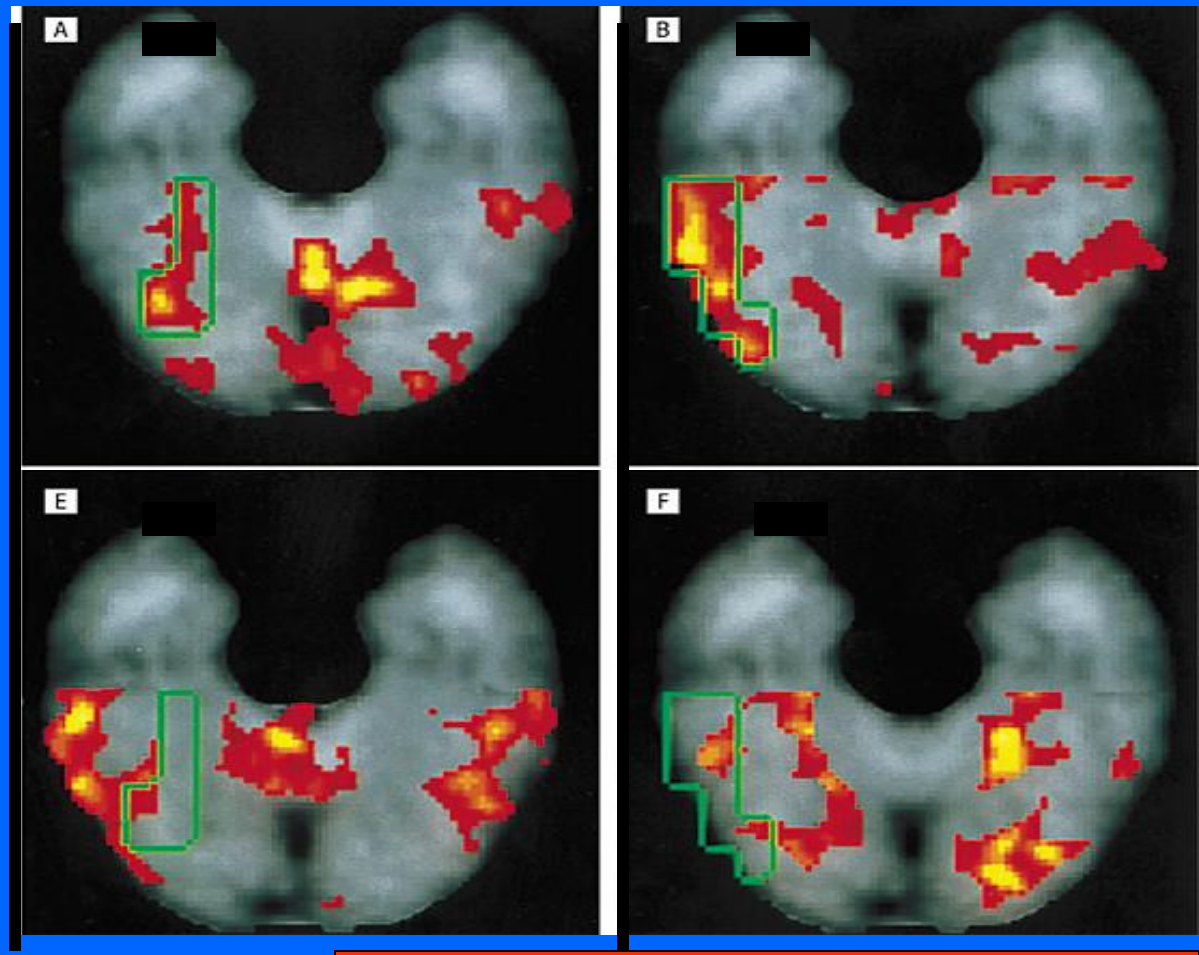


ACTIVITY in the VENTRAL TEMPORAL LOBE during FACIAL DISCRIMINATION (Schultz et al., 2000)

OBJECT **FACE**

CONTROL GROUP

AUTISM GROUP



The default mode network, interconnectivity

- A network from the brainstem to the cerebellum and medial parts of the temporal lobes and the frontal lobes in wakefullness without focusing or interacting with others. Low functioning in indiviuals with ASD and low activation in silence. Wandering thoughts, thoughts about future and earlier experiences. Thoughts about relations, mentalisation. Self referential mental activity.

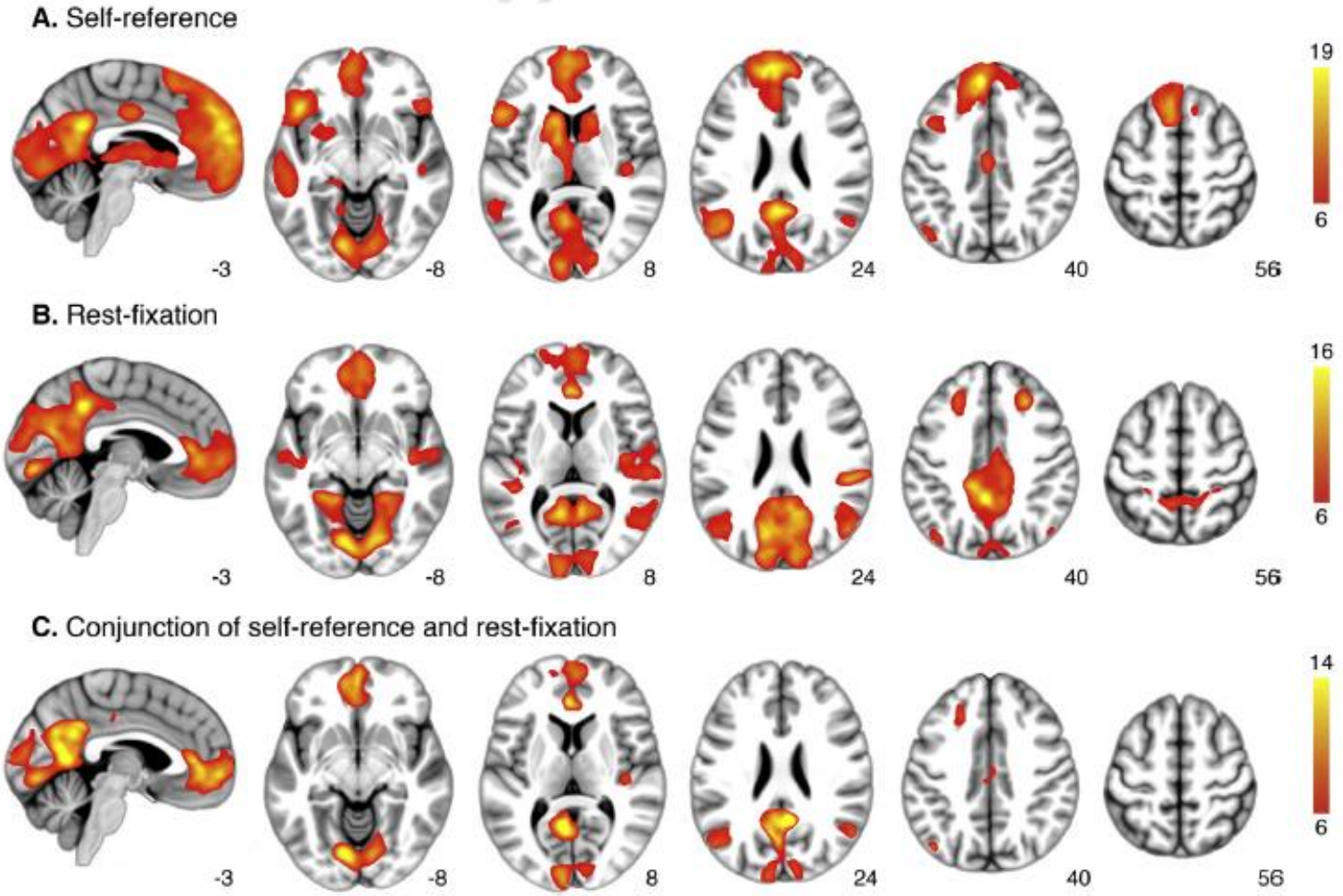


Fig. 1. Activation maps for the self-referential and rest-fixation tasks. Activations to self-reference (A) and rest-fixation (B), relative to external attention baseline, are illustrated, along with a conjunction map for self-reference and rest-fixation (C). All activations are thresholded at $P_{FWE} < 0.001$. Left = left.

Davey, C.G., et al., Mapping the self in the brain's default mode network, NeuroImage (2016)

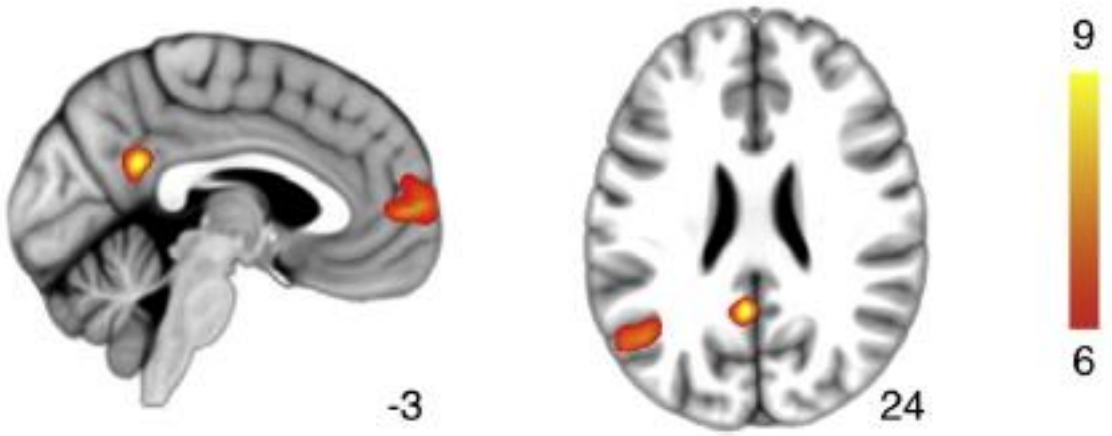


Fig. 3. Conjunction analysis of the rest-fixation and self-reference *minus* rest-fixation contrasts. The conjunction test identified regions that were not only active in rest-fixation (compared to the external attention task), but that also showed greater activation to self-reference relative to rest-fixation. Such activity was demonstrated in MPFC, ventral PCC, and left IPL. Activations are thresholded at $P_{FWE} < 0.001$. Left = left.

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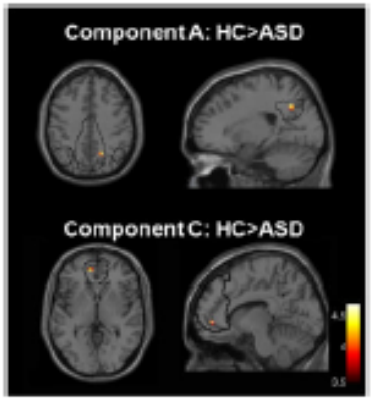

Fig. 2.

Group differences in the Default Mode sub-networks. Only the PrC in Component A and MPFC in component C showed significant group differences, such that patients had decreased strength of connectivity. Each map is masked with the corresponding component mask generated from all participants (black outline, see Fig. 1) and threshold at $p_{FDR} < 0.05$.

Michal Assaf[a,b,*], Kanchana Jagannathan[a], Vince D. Calhoun[a,b,c,d], Laura Miller[a], Michael C. Stevens[a,b], Robert Sahl[e], Jacqueline G. O'Boyle[a], Robert T. Schultz[f,g], and Godfrey D. Pearlson[a,b]

Neuroimage. 2010 October 15; 53(1): 247–256.

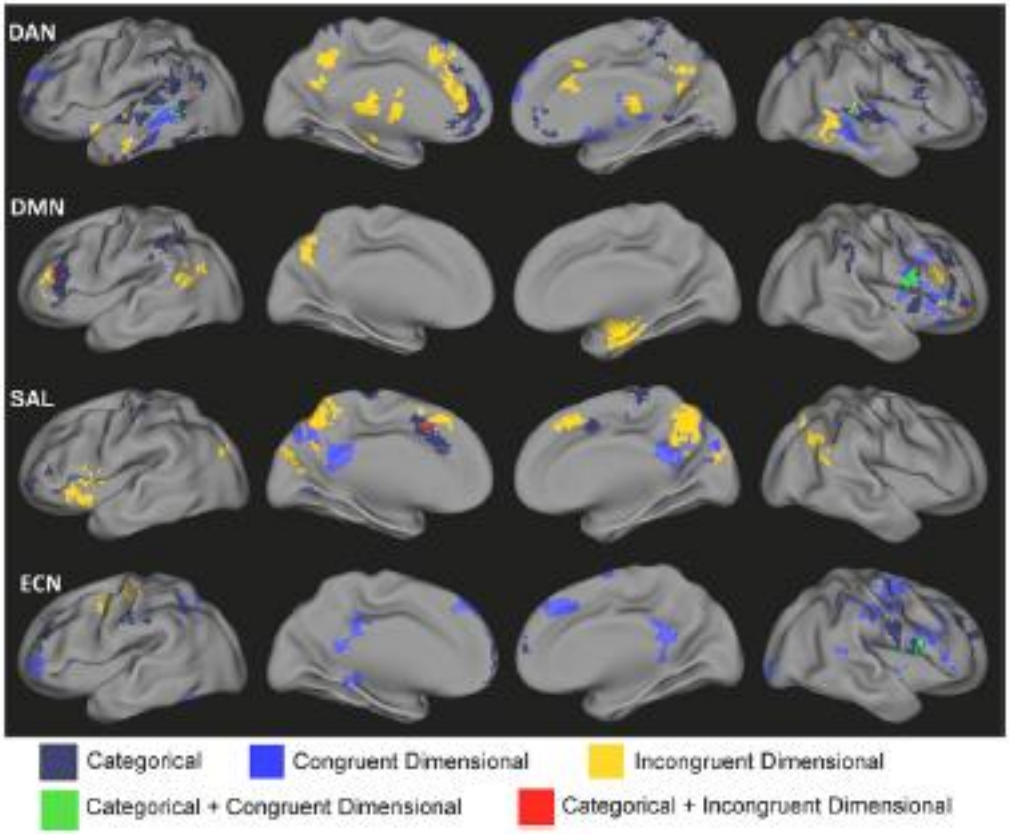

Figure 5. Composite maps of the dorsal attention network (DAN), default mode network (DMN), salience network (SAL), and executive control network (ECN) representing the regions demonstrating categorical effects of autism spectrum disorder on functional connectivity (white), consistent dimensional relationships for children with autism spectrum disorder and typically developing children (green), categorical differences in dimensional relationships between children with autism spectrum disorder and typically developing children (red), an overlap between categorical and congruent dimensional effects (blue), and an overlap between categorical and incongruent dimensional effects (yellow).

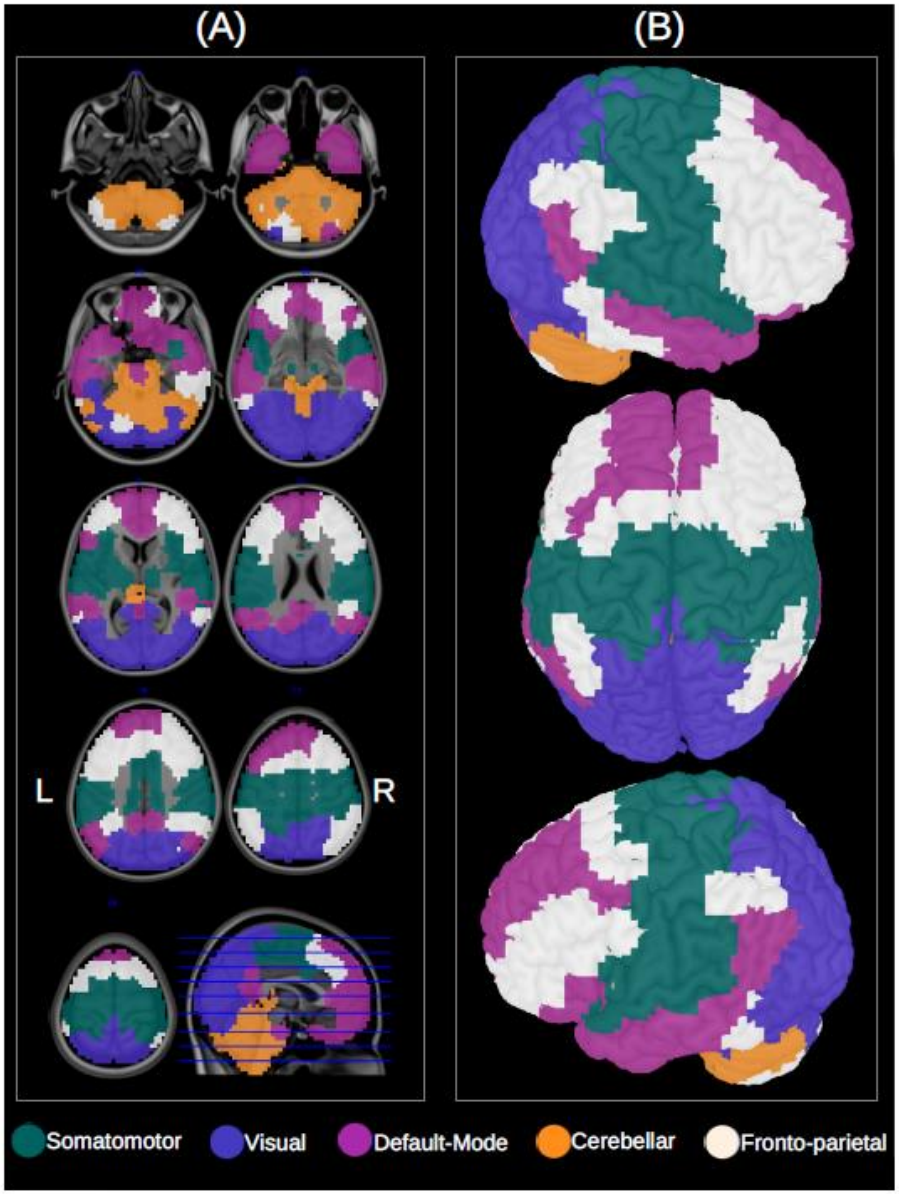

Figure 2. ROIs clustered into five modules. Each color represents one module. (A) The axial slices. (B) The 3D view of the whole brain.

Other findings concerning brain functioning

- Large brain volume before 5 years of age with thicker cortex which becomes thinner with age.
- Increased thurnover of synapses.
- Brain stem lesions in classic autism
- Low oxytocine-levels
- Increased levels of pre- and perinatal testosterone (Baron Cohen)
- Altered balance between excitation/inhibition and in mirrorneurons (altered mu-activity in EEG)
- Altered glutamate/GABA balance in classical autism

Etiology

- Heritability estimates of ASD: 70-90%. Genetic heterogeneity.
- Chromosome abnormalities: 22 q 11deletion, Fragile-X, XYY, XXY, X0
- Syndromatic autism: In tuberous sclerosis, neurofibromatosis, Rett syndrome et cetera.
- De-Novo mutations: especially low functioning autism.
- Pleiotropism: the same gene can be associated with different phenotypes.
- Several comorbid conditions that also can consititue differential diagnoses creating difficulties concerning early diagnosis. ESSENCE: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations.

Etiology continued

- About 20 times increased risk of ASD for siblings of a child with diagnosis.
- Increased risk for imigrants. Unknown cause.
- Prematurity, pre- and perinatal complications
- Infections. Rubella, CMV and others
- Toxins: Thalidomide.
- Extreme deprivation, poor attachment. Pseudo-autism should be significantly improved after ½-1 year.
- High testosterone levels pre- and perinatally.

The genetics of ASD

- Complicated situation with many genes involved and pleiotropism.
- Important common genes for different psychiatric conditions like ADHD schizophrenia and bipolar disorder and for language and learning disabilities.
- Epigenetics. Early conditions pre- and postnatally may change the expression of genes.

Autistic regression

- 10-50 % of children with ASD, 18-36 months of age.
- Usually during the second year of life.
- Loss of language and social skills. Typically after 3-5 words.
- Disintegrativ syndrome: After 2-3 years of normal development. Sometimes after an infection or moving to another country. Regression of language, communication, symbolic play but often not of the motor function.

Comorbidity

- Most comorbid conditions can also constitute differential diagnoses.
- Language disorders
- Intellectual disabilities
- ADHD
- Developmental Coordination Disorder (DCD)
- Extreme psycho-social understimulation/attachement disorder
- Deafness
- Blindness/visual impairment
- Landau-Kleffner's syndrome (aphasia, EEG- abnormalities with paroxysmal activity with left-sided dominance, epilepsia)
- Epilepsy
- Selective mutism
- Disintegrative disorder (Heller's Syndrome)
- Obsessive compulsive disorder.
- Schizophrenia: up to 40% have ASD before psychosis occur.
- Eating disorders
- Extreme Demand Avoidance (EDA): 1/5-1/10 of individuals with ASD.

ASD with other functional impairments

- Intellectual disability 15% (80% among indivuals with classic autism)
- Language disorder 30%
- Epilepsy 30% (among young adults)
- Impaired hearing 20%
- Impaired vision 10%
- Strabismus 30%
- CP < 5%
- ADHD 40%
- Tics and Tourette syndrome 80%

Classic autism and associated syndromes and disorders

- Fragile X 3%. FMR1 gene. Trinucleotide repeates (50- 200 premutation, >200 full mutation).
- Tuberous sclerosis 1%
- Wests syndrome (without tuberous sclerosis) 1%
- Neurofibromatosis 1-2%
- Rubella embryopathy 1-3% (globally but not in countries with high rate of vaccination against rubella)
- CMV <1%
- Herpes encephalitis <1%
- Moebius syndrome <1%
- Rett's Syndrome 5% of girls < 2-3 years of age with severe autism
- PKU <1% (especially among older individuals)
- Hypothyreosis <1%

Disorders continued

- More somatic disease, especially in low functioning autism, gastro- intestinal problems.
- Landau-Kleffners syndrome
- 22 q 11: 1/4000. ASD, ADHD, low IQ, sometimes inttectual disability, schizophrenia.
- Smith-Mageni's syndrome: 17 p 11.2 deletion: 1/20 000. Intellectual impairment, self injury, sleep disturbance, ASD, ADHD.
- Potocki-Lupskis syndrome: 17 p 11.2. duplication
- Angelman's syndrome: 15 q 11.2 – q 13. Maternal chromosome. Severe intellectual impairment, no language, ASD, epilepsy, ataxia, stereotypies, laughter attacs.
- Prader-Willi's syndrome: 15 q 11.2 – q 13. Paternal chromosome: Moderate intellectual impairment, muscular hypotonia, growth retardation, hyperphagia, ASD.
- 16 p 11.2: deletion or duplication: Slow language development, intellectual impairment, ASD.

Rett’s syndrome

- Described by Andreas Rett and Bengt Hagberg 1960
- 1/8000 girls, rare among boys, mutation in the MECP2 gene on the X- chromosome. Usually not familial.
- 6-18 months of normal development.
- Midline movements of hands: ”washing”.
- Head stops growing.
- Epilepsy, ataxia, scoliosis, neuropathy, hyperventilation.
- 90% in wheel-chair in adulthood.
- Severe intellectual disability, only occasionally development of speech.

Asperger's Syndrome

- In DSM-IV. Now considered as high functioning ASD. Unclear delineation from normality.
- Many develop personality disorders as adults.
- Clinically significant functional impairment.

Asperger's syndrome according to C. Gillberg and I.C. Gillberg

- Difficulties concerning social communication: inability to contact children of same age, not motivated to contact children of same age, inability to recognise social signals, socially inappropriate behaviour.
- Narrow interests: hinders other occupations, stereotyped repetitions, facts without deeper meaning.
- Strong need to introduce routines and interests: affecting all aspects of functioning, forced on other people.
- Language problems: late speech development, correct expressive language, formal and pedantic language, deviant melody of speech, difficulties understanding metaphores, taking everything litterally.
- Problems with non-verbal communication: limited use of gestures, inappropriate body-language, lack of facial expressions, aquard eye contact.
- Motor dysfunction

Psychological theories

- Mentalisation problems. Poorly developed Theory of Mind (ToM).
- Weak Central Coherence: focusing on details. Savant abilities.
- Executive function deficits
- Difficulties with memory for events, autobiographical memory.
- Difficulties with imitation and cognitive empathy (but often better affective empathy, at least in high functioning ASD)
- Dangerous combination: difficulties with both affective and cognitive empathy – resembles psychopathy.

Development

- 1/3 develop more symptoms in puberty. Some develop epilepsia and cognitive deteriorisation. 1/7 develop catatonia.

Assessment

- Rating scales. M-CHAT, ASSQ
- Developmental history from parents and teachers. ADI-R: Autism Diagnostic Interview. DISCO: Diagnostic Interview for Social and Communication Disorders.
- Observation at preschool or school.
- Observation at the clinic. ADOS: Autism Diagnostic Observation Schedule.
- Cognitive assessment. WPPSI, WISC, WAIS.
- Language assessment.
- Psychoeducational Profile

After diagnosis (primarily concerning low functioning ASD)

- Ophtalmologic and auditory examination
- EEG (especially during sleep)
- MRI (tuberous sclerosis, hydrocephalus and other conditions)
- CNV microarray, chromosome analysis, DNA-analysis concerning Angelmans syndrome, Rett syndrome, 22 q 11, 22 q 13 and Fragile-X.
- Brainstem audiometri
- TORCH-serology

Treatment

- Comorbid conditions: ADHD, depression, Epilepsy
- Behaviour symptoms: neuroleptics (e.g. olanzapine).
- Affective symptoms: SSRI, mood-stabilisers (Lithium or antiepileptics like valproate, lamotrigine, karbamazepine)
- Sleep problems: melatonine.
- Highly structured environment. Predictability. Low affective interactions.
- Intensive behavioural treatment of preschool children.
- Psycho- educative approaches. Social training. Social stories.
- Coaching.
- Adaptation of home and school. Support from child habilitation unit, special school.
- Psychotherapy: sometimes with individuals with high functioning ASD

None- evidence based ASD-treatment

- Specific pharmacological treatment of ASD.
- Omega-3 or other fatty acids. Some effect on ADHD and learning disabilites.
- Specific diet. Case descriptions.
- Swimming with dolphins et cetera.
- Psychotherapy: Might be beneficial for individuals with high functioning ASD but does not seem to ”cure” ASD. Can encourage better life-strategies.

Behaviour problems

- Self-injury
- Aggression
- Affective symptoms: depression, psychotic symptoms (hallucinations, delusions)
- Catatonia
- OCD: difficulties with Cognitive Behavioural Treatment. Diffuse border against stereotypic behaviour and tics.
- Conduct disorder: motor impairment if ADHD and/or ASD.
- Most important: right psychological approach. Structure, predictability concreteness in communication.
- Sometimes medication: Neuroleptics, SSRI, affect stabilisers

High functioning autism/ Asperger's syndrome in adulthood

- Some develop strategies and do not have a clinically significant impairment.
- Some develop depressions: risk of suicide.
- Some develop an ability of social imitation, especially women (often underdiagnosed).
- Many develop personality disorders, like narcissism or borderline personality disorder.
- Increased risk of developing schizophrenia.

Low functioning autism. prognosis

- Most will need much support and may not manage to live by themeselves or getting a paid work.

Girls with ASD

- Underdiagnosed.
- Shy or showing too little distance.
- Demand avoidance.
- Difficulties identifying danger.
- Difficulties understanding general context.
- More empathy than boys with ASD.
- Obsessiveness
- Rigidity
- Difficulties making choises.
- Difficulties planning.
- Anorexia.
- Borderline
- Interests: animals, relations.