Autism Spectrum Disorders
Update and current research directions

Department of Psychiatry Grand Round

Eric Fombonne, OHSU
April 2d, 2013
Outline

• Brief history
• Diagnostic challenges for an heterogeneous phenotype
• Screening and early detection
• Epidemiology
• Neuropsychology and the brain
• Etiology: environment? Genetics? Both?
• Treatment progresses
• Outcome in adult life
Kanner’s infantile autism

• 11 cases described in 1943
• language abnormalities, insistance on sameness, social withdrawal, stereotypies,…
• no dysmorphic signs, thought to be normally intelligent
• unusual parental personality traits
• innate disturbance of affective contact
Autism: brief background

• Identified by Kanner in 1943, but existed in medical literature much before
• Kanner described a rather severe phenotype: since then, milder forms have been recognized
• Evidence accumulated in the 1970s and 1980s that;
  – It is a disorder of brain development
  – Parents are not responsible for it
  – Unrelated to schizophrenia or ‘childhood psychoses’
  – Despite a trend for improvement with age, it is a life long condition
  – Special education interventions emerged in the 1970s that transformed positively their outcome and life
• In many countries, these children are misdiagnosed and professional/public awareness is lagging
Current definition

Qualitative developmental abnormalities

– in language/communication

– in social interaction and reciprocity

– repetitive/rigid patterns of play, behaviors and interests

– evident before age 3
Language/communication abnormalities

- No babbling, language delay
- No compensation by alternate modes of communication
- No pointing (*protodeclarative vs protoimperative*)
- No gestures (*nodding, shaking, waving bye-bye, etc..*)
- Receptive language
- Pronominal reversal
- Neologisms, idiosyncratic sentences
- Conversation abnormalities
- Alteration of the pragmatic aspects
- Literal understanding
Social interaction abnormalities

- Poor eye gaze and social smiling
- No social orientation
- Greeting behaviors
- Affectionate behaviors
- Social play
- Offering/seeking comfort
- Sharing enjoyment
- Facial and affect expressions
- Emotional recognition
- Lack of friendships, loner
Repetitive behaviors/Unusual interests

- Hand and finger mannerisms
- Unusual sensory reactions
- Unusual attachment to objects (*metal objects,...*)
- Non functional use of objects/toys (*lining up,...*)
- Obsessive behaviors, rituals
- Resistance to change
- Insistance on sameness
- Rigid, inflexible routines
- Odd pursuits
- Circumscribed interests
Variable clinical presentations
Mitchell, 2 years 10 months: ADOS Birthday party

Show video clip
Autism

**COM**
- No language
- Little babble, self-directed
- No pointing or showing
- No gestures

**SOC**
- No orientation to name
- Abnormal eye contact
- Reduced facial expressions
- No affect sharing

**REP**
- Odd hand posturing
- No imaginative play

*Behaviors rated on ADOS module 1*
Current DSM-IV PDD subtyping

- Autistic disorder
  - severe impairments in the 3 domains

- PDD-NOS
  - less severe ( 2 domains out of 3)
  - and/or atypical age of “onset”

- Asperger disorder
  - no significant language delay
  - intellectual functioning in the normal range

- Childhood Disintegrative Disorder
  - period of normal development up to age 2
DSM-5: Changes... and resistance to change

• Inclusion into one single broad class of Neurodevelopmental disorders

• Eliminate ‘Onset of symptoms before age 3’:
  – Good as most often based on uncertain recall
  – Will help diagnosis in childhood and adult life

• 2 as opposed to 3 dimensions:
  – Appropriate as Social and Communication deficits are the same
  – Factor analyses do support a two-dimension spectrum

• Use of qualifyers
  – to index particular features, ie regressive pattern, mental retardation, etc...

• One single diagnosis: ASD
  – no more Asperger, PDD-NOS, or high- / low-functioning
Screening and Detecting ASD

Screening General Population

- ASQ
- M-CHAT, SCQ
- SRS

Early Detection

- Speech Therapist, Pediatrician, Neurologist, ....

- STAT PDDST- 2

Diagnostic Confirmation

Specialist Team in Tertiary Center

- ADI-R
- ADOS-G
The persisting issue of late diagnosis.....

Data from the longitudinal “Pathways” study of 400 Canadian preschoolers with ASD

Mean age at parental recognition of first symptoms = 18 months

→ delay of 18 months
Home videos

• 1st birthday familial videos

• rating by experienced clinicians, blind to later diagnostic status

• set of predictors:
  • gaze monitoring, showing, pointing, responding to name differentiate autism from normal and non-autistic retarded controls
  • down to 8 months
M-CHAT

Please fill out the following about how your child usually is. Please try to answer every question. If the behavior is rare (e.g., you've seen it once or twice), please answer as if the child does not do it.

1. Does your child enjoy being swung, bounced on your knee, etc.?  
2. Does your child take an interest in other children?  
3. Does your child like climbing on things, such as up stairs?  
4. Does your child enjoy playing peek-a-boo/hide-and-seek?  
5. Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?  
6. Does your child ever use his/her index finger to point, to ask for something?  
7. Does your child ever use his/her index finger to point, to indicate interest in something?  
8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?  
9. Does your child ever bring objects over to you (parent) to show you something?  
10. Does your child look you in the eye for more than a second or two?
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)  
12. Does your child smile in response to your face or your smile?  
13. Does your child imitate you? (e.g., you make a face—will your child imitate it?)  
14. Does your child respond to his/her name when you call?  
15. If you point at a toy across the room, does your child look at it?  
16. Does your child walk?  
17. Does your child look at things you are looking at?  
18. Does your child make unusual finger movements near his/her face?  
19. Does your child try to attract your attention to his/her own activity?  
20. Have you ever wondered if your child is deaf?  
21. Does your child understand what people say?  
22. Does your child sometimes stare at nothing or wander with no purpose?  
23. Does your child look at your face to check your reaction when faced with something unfamiliar?

© 1999 Diana Robins, Deborah Fein, & Marianne Barton
Epidemiology
Pervasive Developmental Disorders in Preschool Children: Confirmation of High Prevalence

Suniti Chakrabarti, M.D., F.R.C.P.C.H., M.R.C.P.
Eric Fombonne, M.D., F.R.C.Psych.

Objective: The rate of reported pervasive developmental disorders has increased, and the authors found a rate of 62.6 per 10,000 in a previous study of preschoolers in Stafford, U.K. They conducted another survey in 2002 to estimate the prevalence in children in a later birth cohort and to compare it to previous findings from the same area.

per 10,000, with a 95% confidence interval (CI) of 45.2–74.9, for all pervasive developmental disorders, 22.0 per 10,000 (95% CI= 14.1–32.7) for autistic disorder, and 36.7 per 10,000 (95% CI=26.2–49.9) for other variants. These rates were not significantly different from the previous rates. The mean age at diagnosis was 37.8 months, and 53.1% of the children were originally re-
Prevalence of ASDs, USA 2008 (CDC, 2012)

4 fold variation

Health records only
Health and education records
USA

Prevalence per 1000

Alabama, Colorado, Florida, Wisconsin, Missouri, Pennsylvania, Arkansas, South Carolina, Colorado, Georgia, Maryland, North Carolina, Arizona, New Jersey, Utah, USA

1.13%
It happened in the 1990’s...
Trends in Minnesota

Individual with Disabilities Educational Act (IDEA)

DSM-III-R

ICD-10

DSM-IV

Gurney et al., 2003
Prevalence and access to services

Population

Services

Same prevalence

Low access to services

High access to services
The graph shows the incidence of ASD cases per 10,000 children across different age groups and birth cohorts from 1981 to 2002. The 1991-92 birth cohort is noted to exhibit an "age effect" as it ages, indicating a peak in incidence at around 11 years of age.
# Oregonian youth with ASDs

## Age groups

<table>
<thead>
<tr>
<th></th>
<th>0-2</th>
<th>3-5</th>
<th>6-8</th>
<th>9-11</th>
<th>12-14</th>
<th>15-17</th>
<th>Total under 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portland-Beaverton Pop. size</td>
<td>91,586</td>
<td>90,704</td>
<td>88,937</td>
<td>88,214</td>
<td>87,851</td>
<td>84,877</td>
<td>532,169</td>
</tr>
<tr>
<td>Vancouver N ASD estim.</td>
<td>916</td>
<td>907</td>
<td>889</td>
<td>882</td>
<td>879</td>
<td>849</td>
<td>5,322</td>
</tr>
<tr>
<td>Oregon Pop. size</td>
<td>136,223</td>
<td>147,471</td>
<td>145,820</td>
<td>140,616</td>
<td>145,310</td>
<td>142,639</td>
<td>858,079</td>
</tr>
<tr>
<td>Oregon N ASD estim</td>
<td>1,362</td>
<td>1,475</td>
<td>1,458</td>
<td>1,406</td>
<td>1,453</td>
<td>1,426</td>
<td>8,581</td>
</tr>
</tbody>
</table>

Based on 2010 population census estimates and a (conservative) prevalence estimate of 1%
Current international studies of autism

- Mexico
- Brazil
- Qatar, Saudi Arabia
- Israel
- China
- South Korea

Legend:
- High Income
- Developing
School Visit and Screening: East District

Cultural differences:

Autism versus Reactive attachment disorder
TABLE 3. Prevalence Estimates of Autism Spectrum Disorders (ASDs) in a South Korean Community

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>2.64</td>
<td>1.91–3.37</td>
</tr>
<tr>
<td>General-population sample</td>
<td>1.89</td>
<td>1.43–2.36</td>
</tr>
<tr>
<td>High-probability group</td>
<td>0.75</td>
<td>0.58–0.93</td>
</tr>
<tr>
<td>ASD Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ASD</td>
<td>2.64</td>
<td>1.91–3.37</td>
</tr>
<tr>
<td>Autistic disorder</td>
<td>0.94</td>
<td>0.56–1.34</td>
</tr>
<tr>
<td>Other ASDs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.70</td>
<td>1.08–2.32</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.74</td>
<td>2.57–4.90</td>
</tr>
<tr>
<td>Female</td>
<td>1.47</td>
<td>0.60–2.37</td>
</tr>
</tbody>
</table>
Neuropsychology and the brain
Theory of Mind deficit: the Sally and Ann story

Sally and Ann are 2 friends

Sally puts her favourite marble in her basket

Sally goes out to do something else

Meanwhile, naughty Ann transfers the marble from Sally’s basket to her own box

Test question: when she returns, where does Sally look for her marble?

and the answer is.....?
Weak central coherence: local vs global processing
• Control subject:
  – “What happened was that the larger triangle – which was like a bigger kid or a bully, and he had isolated himself from everything else until two new kids come along and the little one was a bit more shy, scared, and the smaller triangle more like stood up for himself and protected the little one. The big triangle got jealous of them, came out, and started to pick on the smaller triangle. The little triangle got upset and said like “what’s up?”, “why are you doing this?”...

• Autism subject:
  – “Starts when a small equilateral triangle breaks out of a square. A small sphere or circle appears and slides down the broken triangle. The triangle were either equilateral or isosceles. Later, the small, I think, isosceles triangle and sphere bounce around each other, may be because of a magnetic field....”
Thinking about things and thinking about people
Eye-tracking studies
## Macrocephaly in idiopathic autism

<table>
<thead>
<tr>
<th>Study</th>
<th>N with autism</th>
<th>N with macrocephaly</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodhouse et al., 1996</td>
<td>82</td>
<td>28</td>
<td>34.1</td>
<td>23.9-44.4</td>
</tr>
<tr>
<td>Davidovitch et al., 1996</td>
<td>148</td>
<td>27</td>
<td>18.2</td>
<td>12.0-24.5</td>
</tr>
<tr>
<td>Lainhart et al., 1997</td>
<td>91</td>
<td>13</td>
<td>14.3</td>
<td>7.1-21.5</td>
</tr>
<tr>
<td>Stevenson et al., 1997</td>
<td>100</td>
<td>24</td>
<td>24.0</td>
<td>15.6-32.4</td>
</tr>
<tr>
<td>Fombonne et al., 1999</td>
<td>126</td>
<td>21</td>
<td>16.7</td>
<td>10.2-23.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>547</strong></td>
<td><strong>113</strong></td>
<td><strong>20.6</strong></td>
<td><strong>17.3-24.1</strong></td>
</tr>
</tbody>
</table>


Head circumference: age-related changes

Courchesne et al. 2004
Abnormal enlargement in frontal lobes

autistic children 2 - 4 yrs

White matter volumes

Gray matter volumes

Courchesne et al. 2004
Cerebral white matter volume

Courchesne et al. 2004
Thinner Corpus Callosum
Hypoactivation of fusiform gyrus to face

Schultz, 2005
Hypoactive “social” brain areas in ASD

IFG, Inferior frontal gyrus (hypoactive during facial expression imitation);
pSTS, posterior superior temporal sulcus (hypoactive during perception of facial expressions and eye gaze tasks);
SFG, superior frontal gyrus (hypoactive during theory of mind tasks, i.e., when taking another person’s perspective);
A, amygdala (hypoactive during a variety of social tasks);
FG, fusiform gyrus, also known as the fusiform face area (hypoactive during perception of personal identity)
Functional underconnectivity in ASD

fMRI studies involving language, working memory, problem solving, and social cognition
Whole-blood 5HT in autistic probands and relatives

Comparisons with controls: all significant at p<.001

Leboyer et al., 1999
Etiology

Environmental causes
Genetic risk factors
autism?
NAS epidemiological survey

Autism Disorder count per 100,000 births

Chen, Fombonne et al., 2004

monovalent measles vaccine
1988 mass introduction of MMR
Hypothesized effect
change mumps strain

Chen, Fombonne et al., 2004
Birth cohort prevalence rates and EthylHg exposure

Montréal Survey: 180 subjects

Mass vaccination campaign against meningitis

Fombonne et al., Pediatrics, 2006
Louder than Words
A Mother’s Journey in Healing Autism
Jenny McCarthy

Evidence of Harm
Mercury in Vaccines and the Autism Epidemic: A Medical Controversy
David Kirby
Measles vaccines efficacy and safety have been established.

Measles epidemics in USA (1990), Netherlands (1999), Ireland (2000)

IOM, MRC and other committees favoured the rejection of these two hypotheses.

“Falsehood flies and the truth comes limping after; so that when men come to be undeceived it is too late: the jest is over and the tale has had its effect.”

Jonathan Swift
The Examiner, Number 15 (November 9), 1710

400,000 deaths/year
Environmental risk factors

- **Not associated:**
  - MMR and other immunizations, mercury exposure, gluten and casein in diet, etc..
  - Family dysfunction, parental mental disorder (maternal depression), neglect and abuse, abnormal parenting

- **Reasonable evidence**
  - Early gestational exposures to specific drugs (*misoprostol, valproic acid, thalidomide*), congenital rubella
  - Increased parental age
  - Use of ART (*assisted reproductive technologies*)
  - Preterm birth, very low birth weight (<1,500 g)

- **Preliminary/need replication**
  - SSRI during pregnancy
  - Gestational exposure to pesticides
  - Pollutants (pre- and post(?)-birth)
  - ...
Rates of Disorder in Cotwins

- Stoffenburg et al., 1989
- Bailey et al., 1995

Broader autism phenotype

MZ
DZ
MZ
DZ

SOC ONLY
COG ONLY
SOC & COG
AUTISM

Steffenburg et al., 1989
Bailey et al., 1995
New recurrence risk estimates: baby sib consortium

- Old recurrence estimates: 3-10%
- Prospective study of 664 at risk infants followed up to age 3
- 18.7% of siblings had ASD at age 3
- If the family is multiplex, there is a 3-fold increase in males and a 2-fold increase in females
- Risk is not associated with gender or level of functioning of the older sibling
- Implications for genetic counselling

*Ozonoff et al. 2011*
Genetics of autism: a complex architecture

• CNVs (microdeletions and microduplications than usually encompass several genes) occur in about 10% of ASD probands
  – Multiple hits are a reported mechanism, with those affected with developmental delays are about 8 times more likely to have 2 CNVs than controls
  – CNVs in chromosome 15 in conjunction with mutations in specific genes (e.g., SHANK2) have been reported in subjects with autism

• Whole exome sequencing studies, focusing on rare single-letter mutations, have yielded significant and convergent findings in 4+ studies, adding 15% to the known genetic causal contributions to autism;
  – Over 600 family trios or quads have been sequenced, providing appropriate control data to estimate the mutation rate in the non-affected population
  – 400 at least killer nonsense de novo mutations are involved in autism, accounting for a large proportion of idiopathic cases
  – Mutations are 4 times more likely to come from paternally inherited genes
  – No gene stands out as an overwhelming cause of autism (reported in 2 or 3 cases)
  – Analysis of gene and protein networks point to structural proteins at excitatory and inhibitory connections between neurons, and also to the immune system and to chromatin structure
  – Nearly 40% of mutated genes in one study are part of an interconnected network of interacting proteins (Eichler)
  – There appears to be significant overlap between de novo mutations in genes for autism and a subset of the FMRP protein
Father’s age and number of de novo mutations

- Proband autistic
- Proband schizophrenic
- Proband parent of autistic case
- Other

Synaptic genes associated with ASD.

Synaptic vesicles (SV) and neurexins (NRXN) are present at the presynaptic side of a glutamatergic synapse. At the postsynaptic side, the NLGN and the glutamate receptors bind to scaffolding proteins of the postsynaptic density (PSD) such as SHANK3. FMRP controls the translation of several synaptic proteins. TSC1 and NF1 are regulating the actin dynamics and the morphology of the neuron. MECP2 (not shown here) regulates gene expression by modifying chromatin structure.
Treatments
When there is no cure...

there are thousands treatments
Pseudo-”treatments” for autism

- dolphin therapy
- auditory integration training
- scotopic sensitivity training
- holding therapy
- gentle teaching
- sensory integration
- cranial osteopathy
- hyperbaric oxygen chamber
- Vit B6/Mg2+

- communication facilitated
- pet therapies
- Doman-Delacato method
- Daily Life Therapy (Higashi)
- Option method
- music therapy
- brushing
- GFCF diet
- chelation
In the 1960s, psychoanalytical theories of autism culminate and lead to prolonged institutional treatment of children with autism who removed from their `refrigerator` mothers....
Double Blind Placebo Controlled trial of secretin

Owley et al., 1999
Educational and behavioral approaches

• TEACCH method (Schopler, 1970s)
  – Teacch classroom, one-on-one structured teaching sessions
  – Classroom environment structured to capitalize on strengths (visuo-spatial) and limit the effects of core deficits
  – Parental involvement to facilitate generalization

• Lovaas ABA studies (1987, 1989, 1993)
  – Claim of recovery in 50% of cases with intensive (40 hrs/week) of ABA home-based intervention. However:
    • Study did not use randomization
    • No actual count of hours in treatment
    • No fidelity measurement
    • Outcome measures non-standardized (recovery loosely defined)

• Later replication by Smith et al. (2000) in an RCT showed:
  – More modest effects
  – Tx intensity: 25 hrs/week
  – IQ gains smaller, and still in the impaired range
  – Most gains are seen in the PDDNOS group, not in the Autistic disorder group
• intervention should begin **as early as possible**
• at least 25 hours/week with year-round programming
• repeated and planned teaching opportunities (*with time intervals appropriate to developmental level*) should be implemented with one-on-one and small-group instruction to meet individual goals
• family involvement, parent education
• low student-teachers ratios in classrooms
• ongoing program evaluation and assessments with appropriate adjustments based on data
concombre
biscuits
pomme
pain
banane
parc
vidéo
télévision
terrain de jeux
livre
RCT of Early Intervention at age 18 months+

Promising results showing larger developmental gains and reduction in autistic symptoms if treatment is more intensive and younger age at initiation

Dawson et al., 2010; Pediatrics
## Systematic review of Early Intensive Behavioral Intervention

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study Design/Quality</th>
<th>Study Results and Overall Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLA/Lovaas–based interventions and EIBI variants</td>
<td>1 RCT/fair quality(^5); 3 nRCTs/fair quality(^12),(^19),(^34); 5 prospective cohorts/3 of fair quality(^4),(^53),(^57); 2 retrospective cohorts/poor quality(^14),(^58); 6 prospective case series(^5),(^11),(^13),(^16),(^21),(^26); 6 retrospective case series(^20),(^22),(^25),(^29),(^35),(^38)</td>
<td>Young children who received high-intensity interventions (&gt;30 h/wk for 1–3 y by well-trained therapists) displayed improvements in areas of cognitive, language, and adaptive functioning; subgroups of children displayed a positive response to this intervention, although this subgroup has not yet been clearly described; there have been few randomized studies; few have used approaches as outlined in treatment manuals; there have been variations in interventions delivered and participant characteristics within studies; strength of evidence for UCLA/Lovaas–based intervention and EIBI variants in affecting language, cognitive, educational, and adaptive outcomes and ASD symptom severity is low</td>
</tr>
<tr>
<td>Comprehensive approaches for children &lt;2 y old</td>
<td>1 RCT/good quality(^2); 1 nRCT/fair quality(^15); 2 prospective case series(^32),(^38)</td>
<td>Improvements in cognitive, language, and adaptive behavior skills have been seen over 2 y of ESDM intervention; ESDM findings have not yet been replicated, and it is unclear how core ASD symptoms change in response to treatment; strength of evidence for comprehensive interventions for children &lt;2 y of age is currently insufficient</td>
</tr>
<tr>
<td>Parent training</td>
<td>3 RCTs/fair quality(^17),(^18),(^45); 1 nRCT/fair quality(^15); 3 prospective case series(^23),(^24),(^38)</td>
<td>There is some indication of short-term improvements in language, social, and adaptive skills for children whose parents receive training in these areas; there has been a lack of standardized measures and baseline differences among participants in some studies; data have not yet demonstrated long-term functional improvements across domains for any specific form of training; strength of evidence for changing core ASD deficit areas is insufficient</td>
</tr>
</tbody>
</table>

\(^nRCT\) indicates non-randomized controlled trial.
Brain normalization in children benefiting from EIBI

Greater brain activation during viewing people faces than objects

Greater brain activation correlates with improved social functioning

Dawson et al., 2012
## Progresses towards targeted drug treatment in ASD

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approved</th>
</tr>
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<tbody>
<tr>
<td>Amino acids</td>
<td>Arbaclofen</td>
<td>Arbaclofen</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Donepezil</td>
<td>Atomoxetine</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Cysteamine</td>
<td>IGF-1</td>
<td>Melatonin</td>
<td></td>
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<tr>
<td>Gaboxadol</td>
<td>Melatonin</td>
<td>Minocycline</td>
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<tr>
<td>Ketamine</td>
<td>Memantine</td>
<td>Acamprosate</td>
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<tr>
<td>Lithium</td>
<td>N-acetyl-cysteine</td>
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<tr>
<td>Topotecan</td>
<td>Oxytocin</td>
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<td></td>
<td>Rapamycin</td>
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</table>
Rescue of autistic-like behavior in Scn1a+/- mice by enhanced GABA-mediated neurotransmission

1. Haploinsufficiency of the SCN1A gene encoding voltage-gated sodium channel NaV1.1 causes Dravet`s syndrome (severe epilepsy, cognitive deficits, autistic behaviors)

2. Rare mutations in the SCN1A gene have been identified in individuals with autism (O'Roak et al., 2011)

3. In mutant mice, low-dose clonazepam completely rescued...

   impaired social behavior

   and

   impaired context-dependent fear-conditioning

Han et al., 2012
Placebo-controlled RCT of Arbaclofen in 63 subjects with FraX

Flexible titration, 4-week period, cross-over design, multisite - well tolerated
Arbaclofen reverses the phenotype in Fmr1-KO mice

No difference on main outcome measure (ABC-Irr)

Post-hoc differences in favour of active compound in those with more severe social impairments and on a new outcome measure (ABC-SA)

Berry-Kravis et al., 2012
Outcome of autism in adult life
Howlin & Moss, 2012

23 studies reviewed:

- 9 published between 1967 and 1999
- 14 since 2000

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>n</th>
<th>Age, years Mean (range)</th>
<th>IQ Mean (range)</th>
<th>Outcome, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poor-very poor</td>
</tr>
<tr>
<td>Lockyer and Rutter, Rutter and Lockyer, Rutter et al</td>
<td>Infantile autism</td>
<td>63</td>
<td>16</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Lotter</td>
<td>Autism</td>
<td>29</td>
<td>ns (16–18)</td>
<td>71 (55–90)</td>
<td>62</td>
</tr>
<tr>
<td>Rumsey et al</td>
<td>Infantile autism</td>
<td>14</td>
<td>28 (18–39)</td>
<td>9 had VIQ &gt;80</td>
<td>29</td>
</tr>
<tr>
<td>Tantam</td>
<td>Asperger syndrome</td>
<td>85</td>
<td>24 (ns)</td>
<td>ns</td>
<td>—</td>
</tr>
<tr>
<td>Gillberg and Steffenburg</td>
<td>Infantile autism</td>
<td>23</td>
<td>20 (16–23)</td>
<td>mixed</td>
<td>48</td>
</tr>
<tr>
<td>Szatmari et al</td>
<td>Autism, childhood schizophrenia-psychosis</td>
<td>16</td>
<td>26 (17–34)</td>
<td>92</td>
<td>25</td>
</tr>
<tr>
<td>Kobayashi et al</td>
<td>Autism</td>
<td>197</td>
<td>22 (18–33)</td>
<td>mixed</td>
<td>46</td>
</tr>
<tr>
<td>Ballaban-Gil et al</td>
<td>Autistic disorder</td>
<td>99</td>
<td>18 (12–30)</td>
<td>mixed</td>
<td>—</td>
</tr>
<tr>
<td>Larsen and Mouridsen</td>
<td>Autism and Asperger syndrome</td>
<td>18</td>
<td>36 (ns)</td>
<td>mixed</td>
<td>45</td>
</tr>
</tbody>
</table>

| Study                              | Diagnosis                              | n    | Age, years Mean (range) | IQ Mean (range) | Outcome, %a |
|                                    |                                        |      |                         |                 | Poor-very poor | Fair | Good-very good |
| Howlin et al                       | Autism                                 | 19   | 24 (21–27)             | ns (70–117)     | 74 | 11 | 16 |
| Engström et al                    | Asperger, high functioning autism      | 16   | 31                      | ns              | 12 | 75 | 12 |
| Howlin et al                       | Autism                                 | 67   | 29 (21–49)             | PIQ 75 (51–137) | 58 | 19 | 23 |
| Billstedt et al                    | Autistic disorder and atypical autism  | 108  | ns (17–40)             | ns              | 78 | 21 | 0  |
| Cederlund et al                    | Autism and Asperger syndrome           | 140  | 23 (16–36)             | ≥70             | 39 | 47 | 14 |
| Eaves and Ho                       | ASD                                    | 47   | 24 (ns)                 | mixed           | 47 | 32 | 21 |
| Hutton et al                       | Autism                                 | 135  | 35 (21–57)             | >30             | —  | —  | —  |
| Mazefsky et al                     | Autistic disorder                      | 17   | 21 (18–32)             | ≥70 in 29% of sample | — | —  | —  |
| Farley et al                       | Autism                                 | 41   | 33 (22–46)             | 89 (50–140)     | 17 | 34 | 48 |
| Hofvander et al                    | Autistic disorder, Asperger, PDD-NOS   | 122  | ns (16–60)             | ns (normal IQ)  | —  | —  | —  |
| Marriage et al                     | ASD                                    | 33   | 21 (19–37)             | ≥70             | ns | ns | 15 |
| Whitehouse et al                   | ASD                                    | 11   | 22 (16–28)             | ns              | —  | —  | —  |
| Gillespie-Lynch et al              | Autism                                 | 20 (from 70 at origin) | 26.6           | DQ 54 at first assessment | 50 | 20 | 30 |
| Taylor and Seltzer                 | ASD                                    | 241  | (20–35)                | ns              | —  | —  | —  |
### 2000-2011 follow-up studies: main findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having a good outcome</td>
<td>20%</td>
<td>4% - 50%</td>
</tr>
<tr>
<td>Living (semi-)independently</td>
<td>16%</td>
<td>4% - 56%</td>
</tr>
<tr>
<td>Lives with parents</td>
<td>41%</td>
<td>6% - 70%</td>
</tr>
<tr>
<td>In hospital care</td>
<td>5%</td>
<td>0% - 12%</td>
</tr>
<tr>
<td>Some form of employment</td>
<td>49%</td>
<td>6% - 94%</td>
</tr>
<tr>
<td>Some friendships</td>
<td>25%</td>
<td>10% - 36%</td>
</tr>
<tr>
<td>Long term intimate relationships/married</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

No data on patterns of family life, or their children when applicable – Reduced fecundity- No data on quality of life – No data on parental life/concerns
Mortality in Utah follow-up study

305 ASD subjects (228 M/ 77F; 27% normal IQ)), followed-up to age 35.8 yr

29 deaths (20 M/ 9F) at mean age 25.5 yr

Table 2 Hazard rate ratios with population, cousin, and sibling control groups with and without covariates

<table>
<thead>
<tr>
<th>Control groups</th>
<th>Without covariates</th>
<th>With covariates&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRR (95% confidence interval)</td>
<td>Matched sets</td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>9.91 (5.70–17.22)</td>
<td>193</td>
</tr>
<tr>
<td>Female</td>
<td>20.71 (6.20–69.20)</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>7.92 (4.17–15.03)</td>
<td>150</td>
</tr>
<tr>
<td>Original DSM-III</td>
<td>10.50 (5.49–20.08)</td>
<td>193</td>
</tr>
<tr>
<td>Reclassified DSM-IV-TR</td>
<td>8.50 (2.94–24.57)</td>
<td></td>
</tr>
<tr>
<td>1st cousins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>8.08 (4.31–15.14)</td>
<td>166</td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>7.82 (2.78–21.98)</td>
<td>173</td>
</tr>
</tbody>
</table>

<sup>a</sup> Covariates included: maternal age, birth weight, gestational age, age at mother’s death, age at father’s death

* Bilder et al., JADD, 2012*
Factors influencing outcome

- IQ is a strong predictor:
  - Few subjects with an IQ<70 or 75 can live independently as adults
  - Among those with IQ>75, outcome is still variable, and can be poor despite a relatively high IQ

- Language development by age 5 or 6
  - Good outcomes are seen in subjects who develop useful speech by that age (with a few exceptions)

- Access to educational programs improves the prognosis

- Severity of autistic symptoms
  - In general, autistic symptom severity reduces from childhood to adulthood
  - Less clear effects; some studies show no relationship
  - Other studies document poorer outcomes in those children with more severe social impairments (i.e. Joint attention skills), and those with high repetitive/ritualistic behaviors

- Co-occurring medical and psychiatric problems impact negatively the outcome

- Social support in adulthood improves the outcome

- Behavioral interventions, supportive employment schemes are positive
Other issues to consider

• Raised lifetime risk of epilepsy
  – About 20-25%
  – Unusual peak of onset in teenage years
  – Association with female gender, lower IQ, more language deficits
  – Associated with mortality (drowning, choking,...)

• Legal issues:
  – no evidence for increased risk of criminality
  – usually crimes are curious and ‘naive’
  – may be caught more easily
  – SMASI risk: ??

• Need to support families: aging parents, impact on siblings
Optimal outcome: new study

- 44 HFA, 34 OO and 34 TD, mean age 13.2 yrs, mean NVIQ = 111

- All early childhood diagnostic history in the OO group blindly reviewed and confirmed

- Current assessments confirm the lack of difference on autistic diagnostic measures between OO and TD. Both OO and TD fare better than HFA

- No difference was found between OO and TD on:
  - Vineland scores
  - CELF 4 (language) scores
  - Benton test scores (facial recognition task)

- Conclusion: study adds evidence than the OO group truly exists. Further testing (fMRI, psychiatric assessments, attention capacity) are in progress to detect potential residual deficits in non-ASD domains

Fein et al., 2013