THE NEUROLOGY OF ASD:

IMPLICATIONS FOR THE DIAGNOSIS AND TREATMENT OF EPILEPSY, INSOMNIA AND MOTOR IMPAIRMENT

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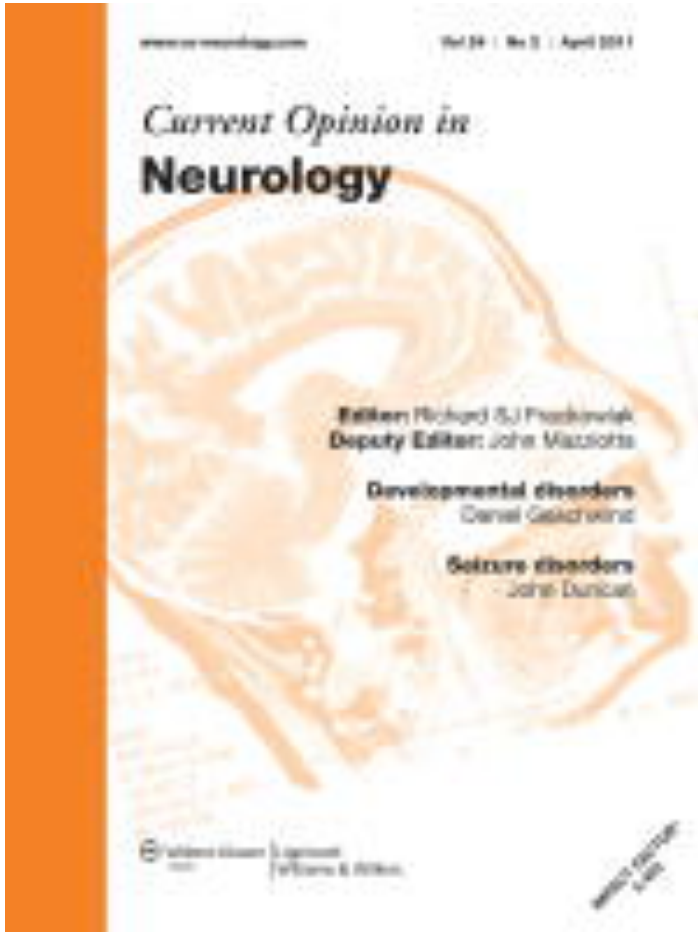
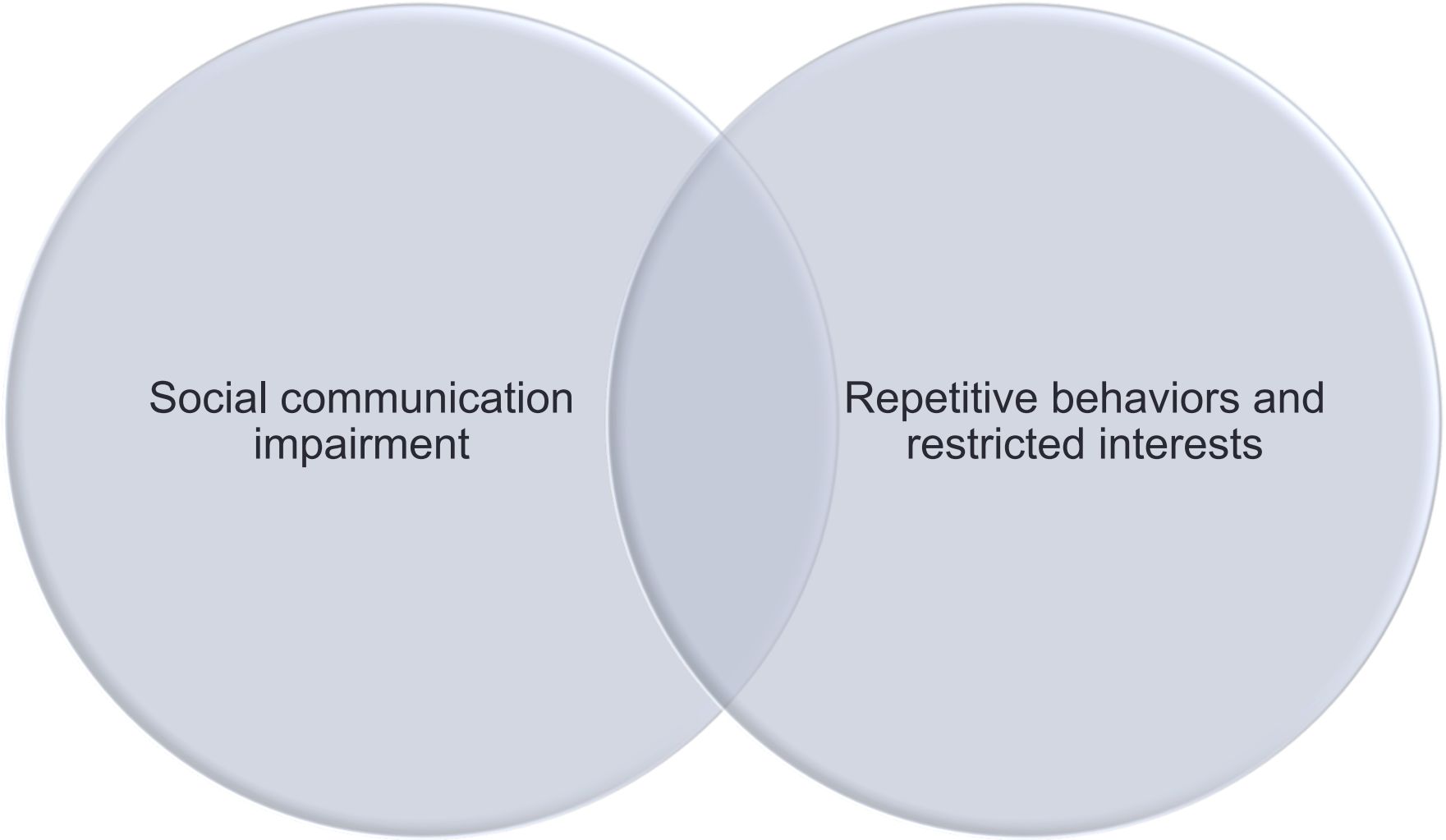
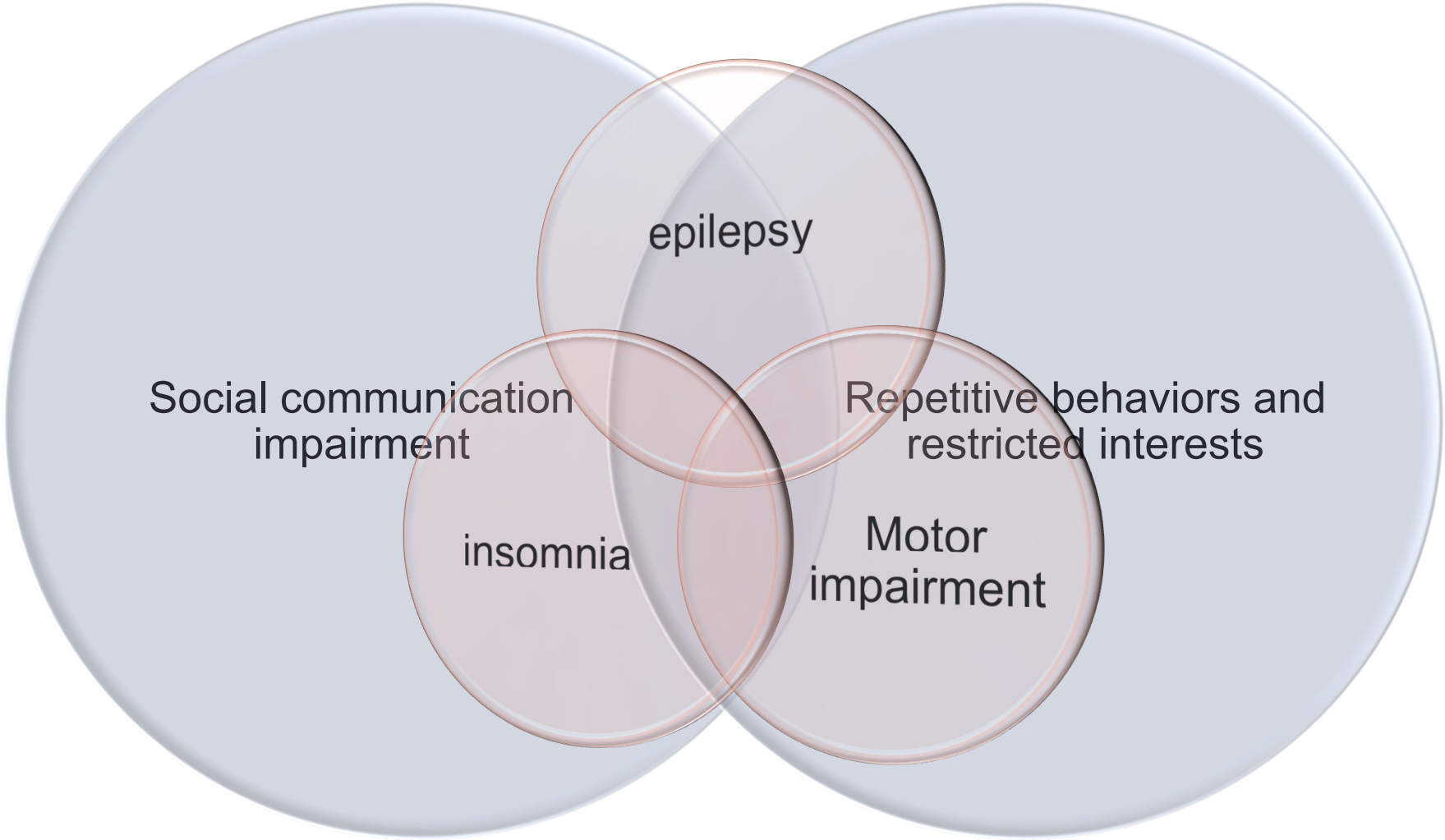
Outline

- Epilepsy
- Sleep impairment (insomnia)
- Motor impairment

- *Diagnosis and definitions*
- *Cause*
- *Clinical considerations*
- *Treatment*




Social communication impairment
Repetitive behaviors and restricted interests


epilepsy
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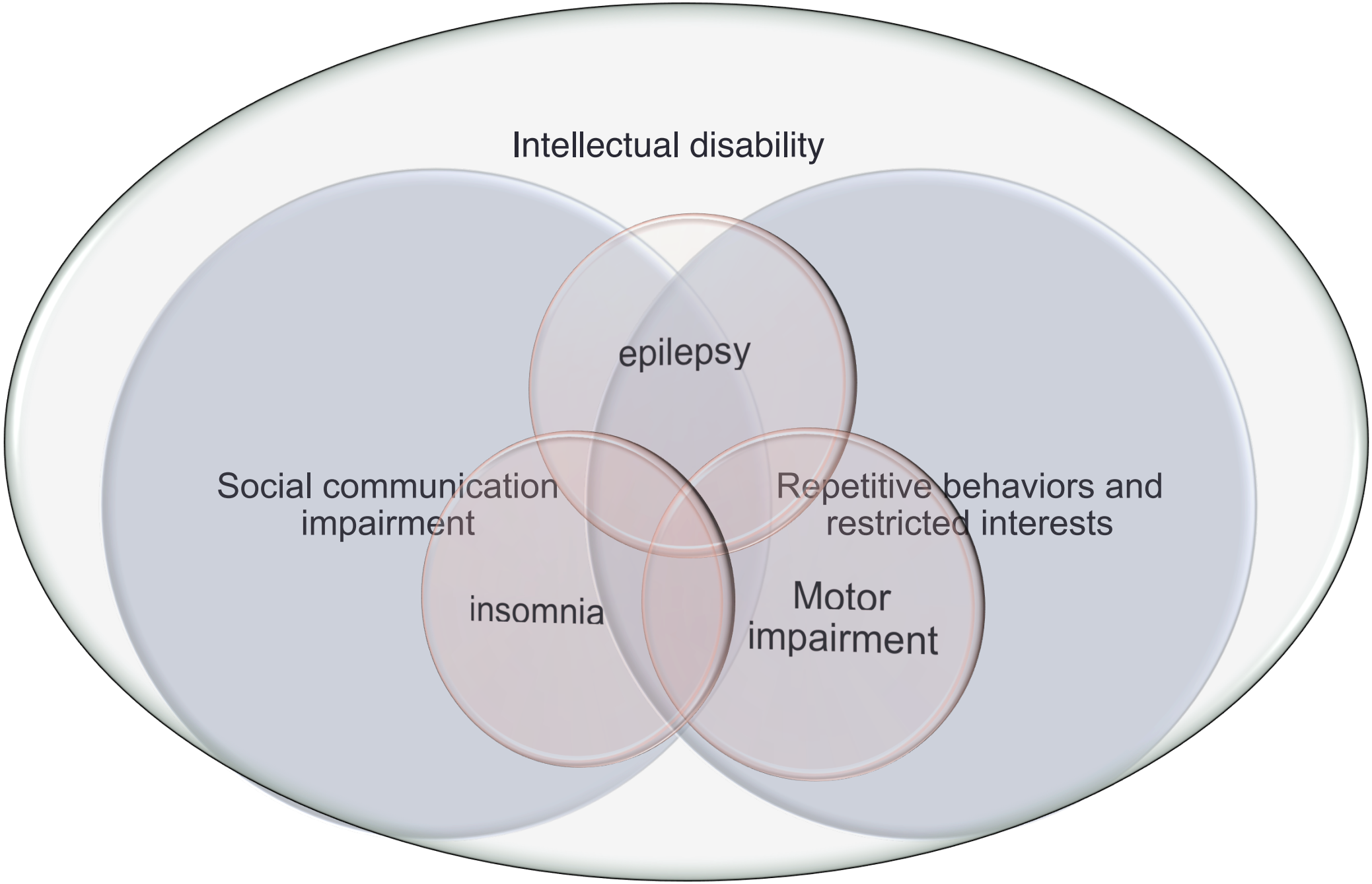
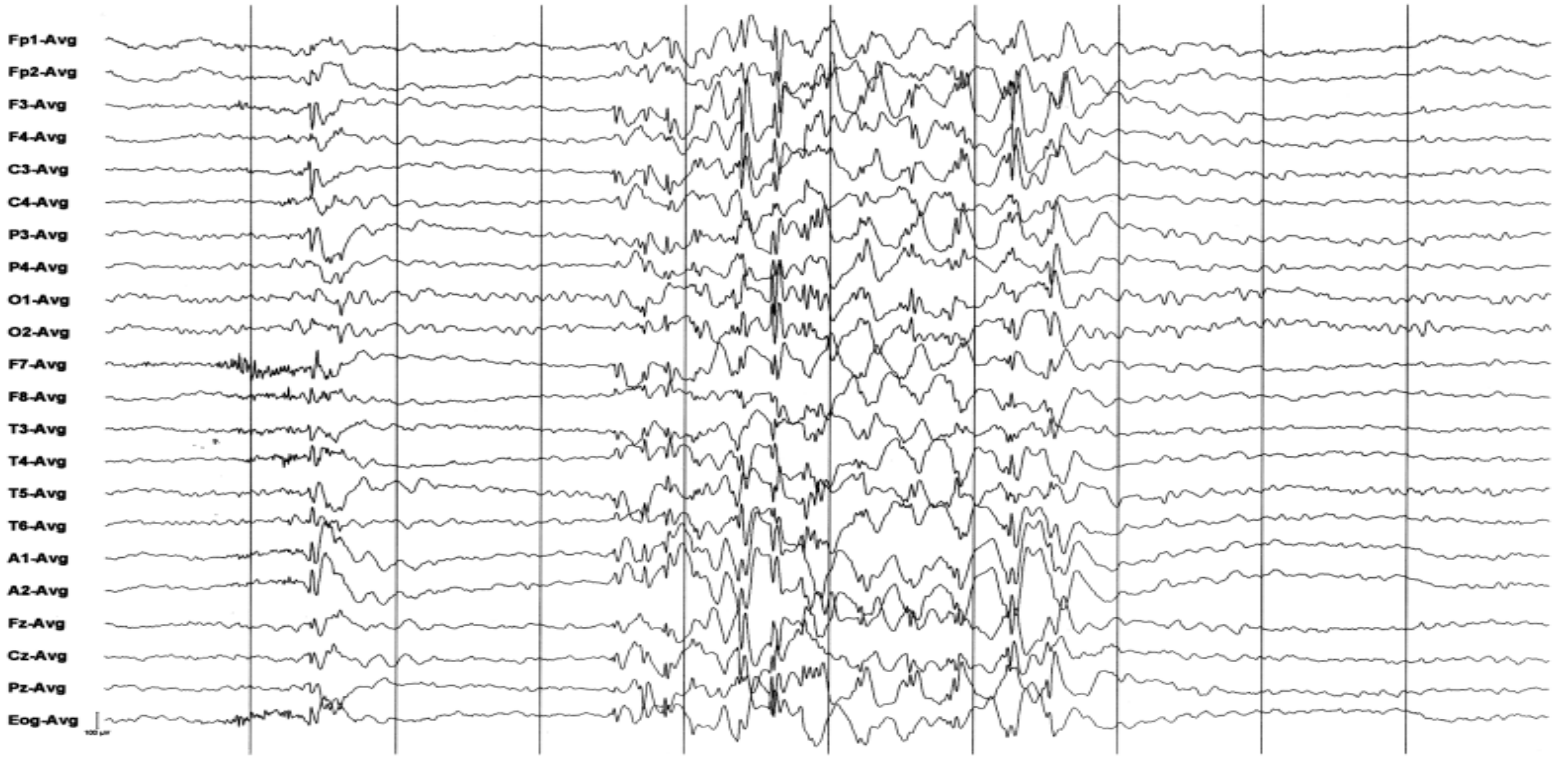
Motor impairment

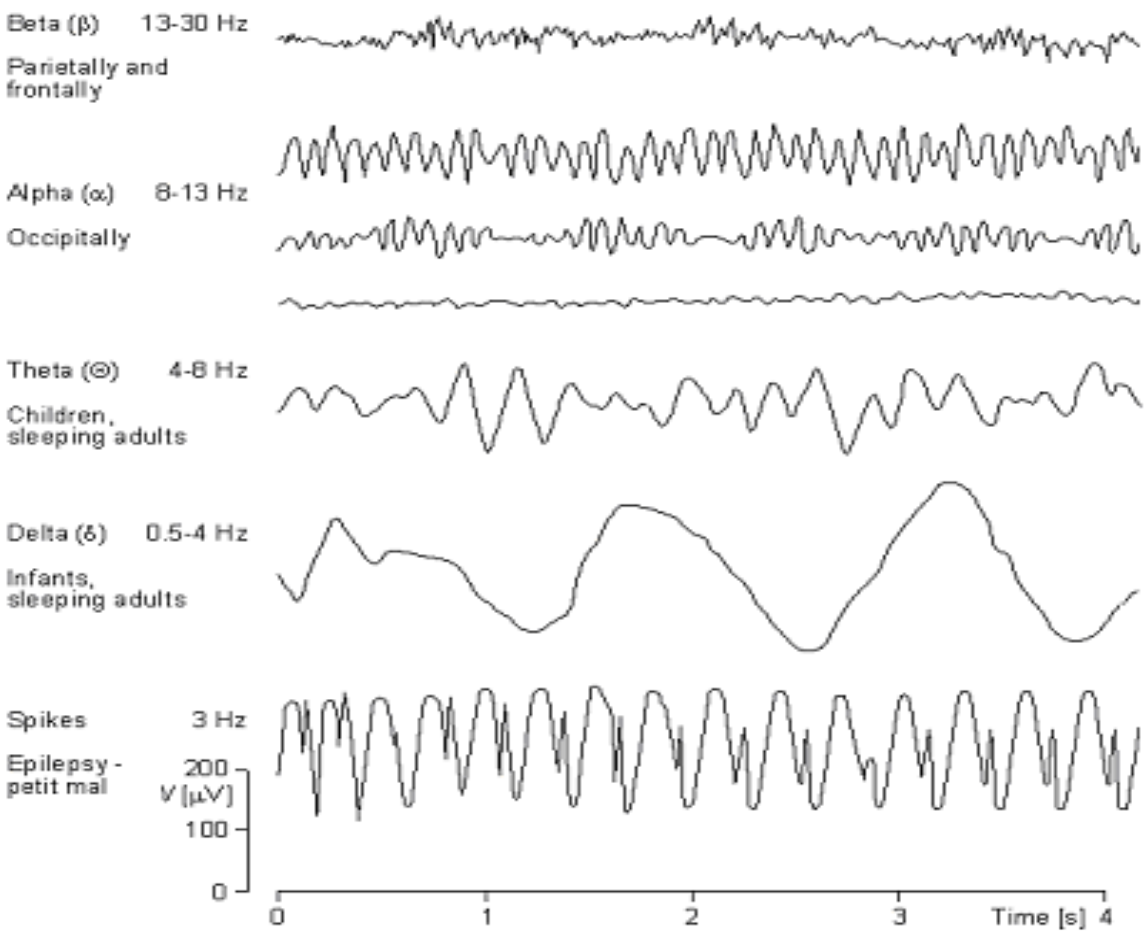

Intellectual disability
epilepsy
Social communication impairment
Repetitive behaviors and restricted interests
insomnia
Motor impairment

Epilepsy

- More than one unprovoked seizure in a lifetime
- Diagnosed by clinical events and also by EEG (electroencephalogram)
- EEG picks up brain activity (firing of neurons) at the surface of the scalp



Oscillations: Defined by frequency, morphology and location



Epilepsy

- Known since the first reported case of autism
- Abnormal EEG's reported in up to 50%
- Prevalence of epilepsy in ASD approximately 20%
- Prevalence of ASD in epilepsy is approximately 5%
- However, reported rates vary tremendously (5-46%) based on population studied
- No primary seizure type defined

What is the pathophysiology?

(1) SAME CAUSE:

Same pathophysiological mechanisms that lead to abnormal synaptic plasticity (connectivity) and excitatory/inhibitory imbalance

Commonly seen in syndromes such as Fragile X, Rett syndrome, Tuberous Sclerosis Complex

Commonly seen in rare copy number variants and other mutations associated with ASD

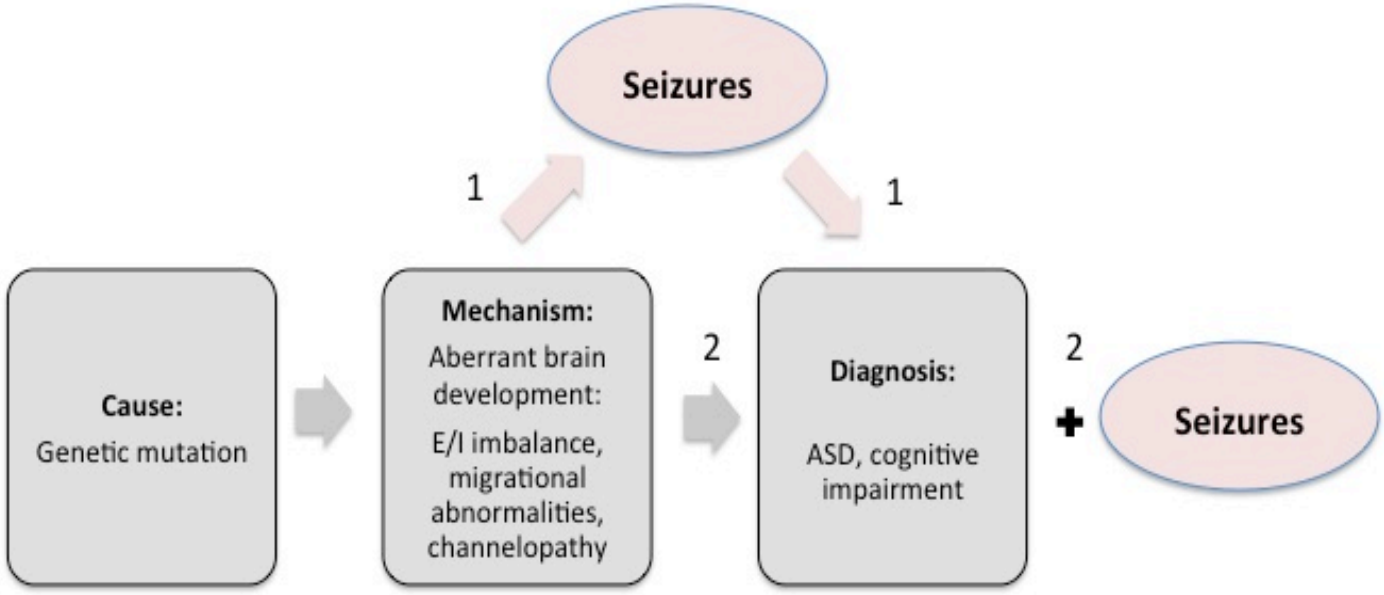
- 15q13.3, 16p13.11, 5q14.3, 17q12

All genetic etiologies overlap with Intellectual Disability (ID)

(2) SEIZURES BEGET FURTHER BRAIN INJURY THAT LEADS TO ASD

Epilepsy: Cause or effect?

Pathway 1: Genetic variant/mutation causes aberrant brain development or function, leading to seizures which, in turn, impair early cognitive and social development



Pathway 2: ASD and epilepsy are sequelae of a common process, starting from genetic variant/ mutation to aberrant brain development etc.

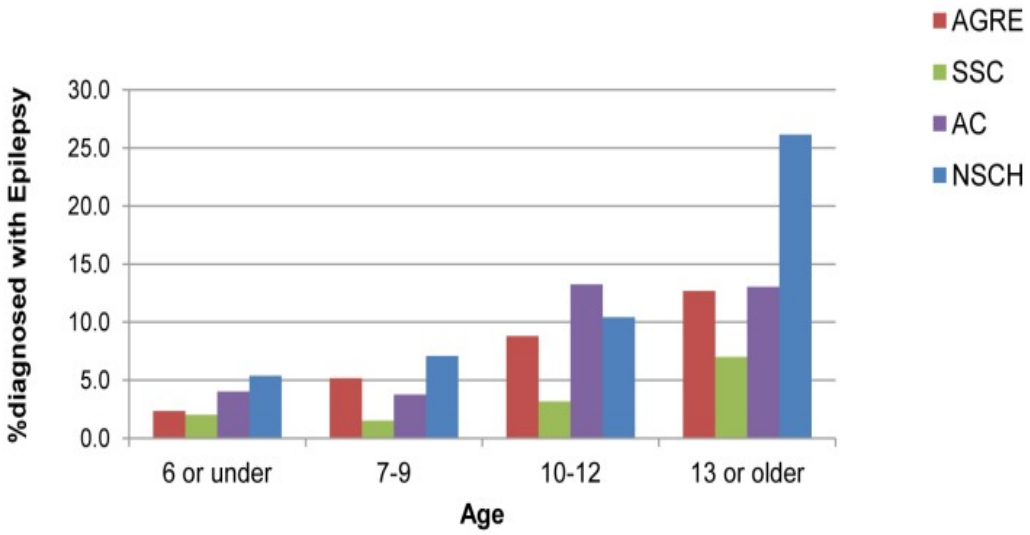
Jeste SS and Geschwind DH, 2013

Epilepsy: clinical considerations overview

- Clear link to intellectual disability (ASD + ID = more likely to have epilepsy than ASD alone)
  - Double the rate of epilepsy in children with ASD/ID
- Possible link to developmental regression
- More common in girls with ASD
- Often have more motor and behavioral impairments

Viscidi et al, 2013

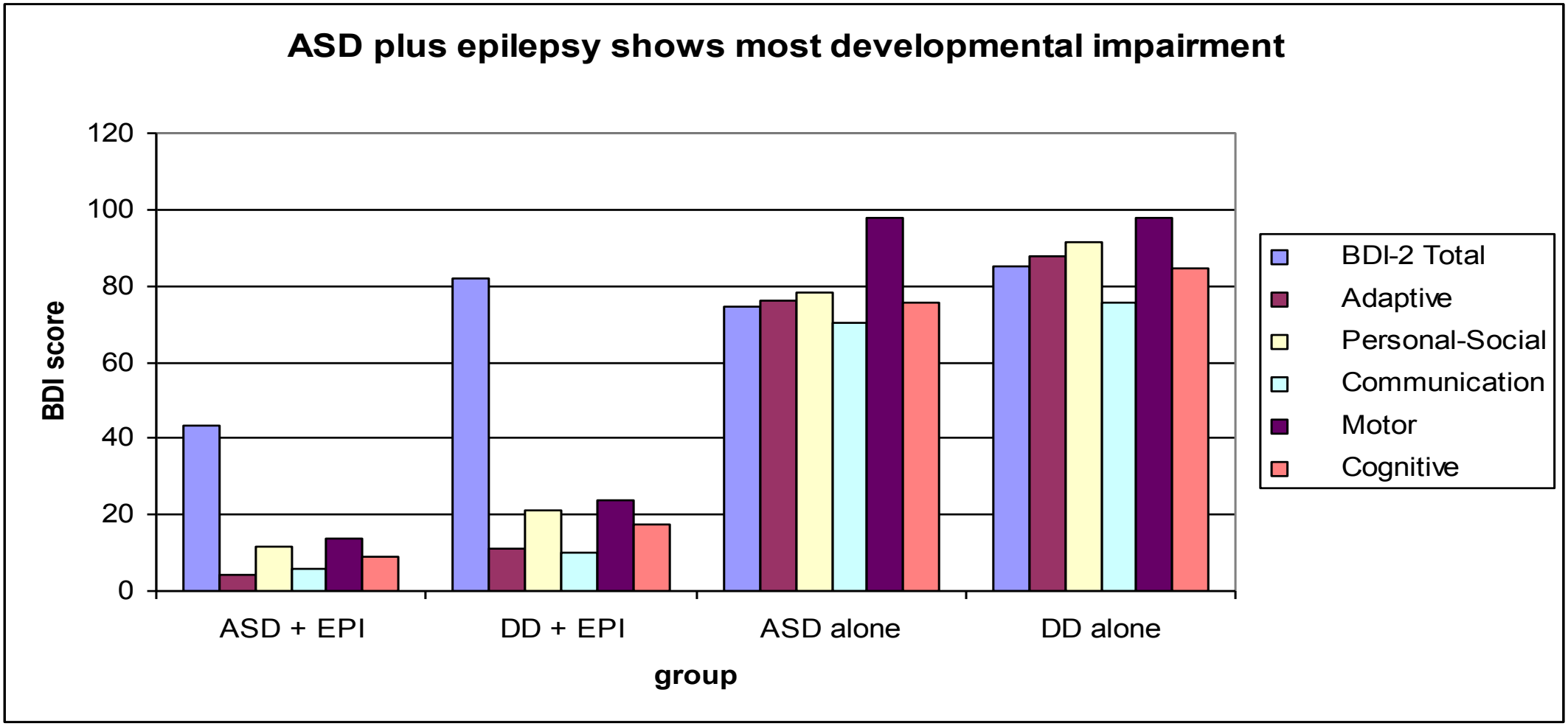
- 5,815 children with ASD (largest study of ASD and epilepsy
- Compared clinical characteristics of children with and without epilepsy
- Average prevalence 12.5%
- Children > 13, prevlalence 26%
- Epilepsy associated with lower IQ, poorer adaptive and language function, developmental regression and more severe ASD sx



Clinical characteristics

- *Hara, 2007*
  - Retrospective study of 130 children followed in developmental disabilities clinic in Japan
  - 25% of sample had epilepsy
    - Intellectual disability more common
    - Lower “social maturity” scores
    - Higher frequency of use of psychoactive medications
- *Turk et al, 2009*
  - Two groups of sixty 7-17 yr olds, w/ and w/out epilepsy
  - Case control with age and verbal IQ matched
    - Percentage of females was higher in epilepsy group
    - Increased motor deficits
    - Increased adaptive behavior deficits
    - One item in nonverbal communication: “stares too long and too hard”
    - Several items on social interaction scale: difficulties with peers, psychological barriers, and socially shocking behaviors.

Clinical characteristics



Adapted from Smith and Matson, 2011

Long term follow up

- *Bolton et al, 2011*
  - 150 individuals with ASD followed up into adulthood
  - Epilepsy developed in 22%, with majority developing it after age 10
  - 88% had GTC, majority well controlled with 1-2 AED's
  - Epilepsy associated with: gender, ID, poor verbal abilities, family BAP

Epilepsy may confer increased mortality

- *Pickett et al, 2011*
  - Mortality data in ASD from California Department of Developmental Disabilities Services
    - Mortality 5-6x higher in those with ASD plus epilepsy than ASD alone (but still much less than epilepsy alone which was 15x higher)
  - 39% of brains donated to Autism Tissue Program came from individuals with autism and epilepsy

Abnormal EEG's

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *10: 132–134 (2004)*

Epileptic Encephalopathies and Their Relationship to Developmental Disorders: Do Spikes Cause Autism?

Barry R. Tharp*

Departments of Neurology and Pediatrics, The M.I.N.D. Institute, University of California, Davis, Sacramento, California

Isolated EEG abnormalities

- RATES VARIABLE: 21-60% depending on type of EEG and sample studied

Authors	Rates	Notes
Tuchman & Rapin, 1997	21% (68% in epilepsy, 13% without)	Most well cited study: 392 kids
Tuchman et al, 1997	46%	24 hour EEG: No seizures but language regression
Kim et al, 2006	60%	24 hour EEG: Suspicion of seizures but found not to have them
Chez et al, 2006	60%	24 hour EEG: No history or suspicion of seizures

Studies of those with isolated EEG discharges

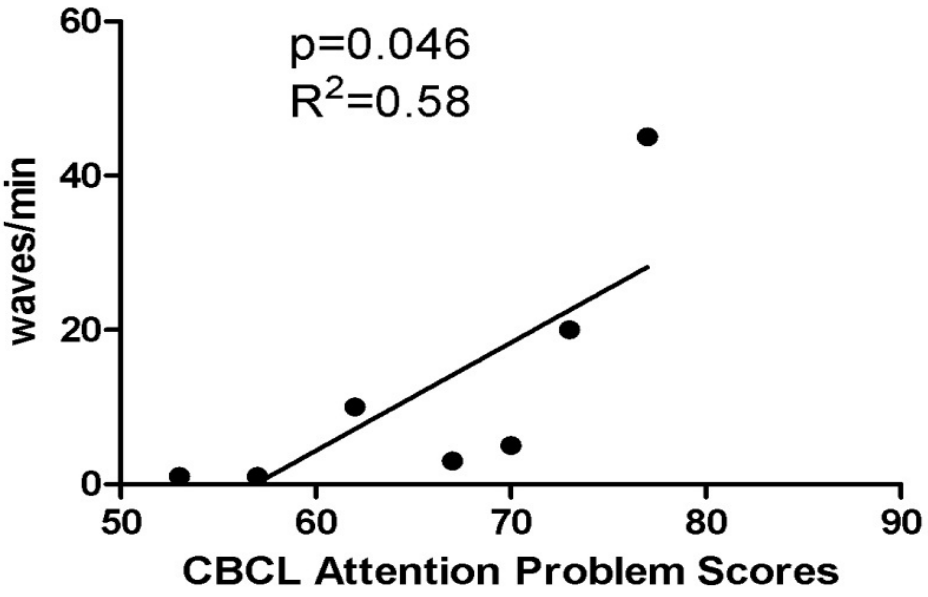
- Recent preliminary data from small sample at Vanderbilt *(Barnes et al., paper presented at IMFAR, 2011)*
- 3 groups
  - Typically Developing (TD, n=12)
  - ASD without epileptiform discharges (A NE, n=30)
  - ASD with epileptiform discharges (A E, n=10)
- Examined differences on behavioral measures – some specific to ASD
- Within ASD+ group they correlated frequency of discharges with behavior

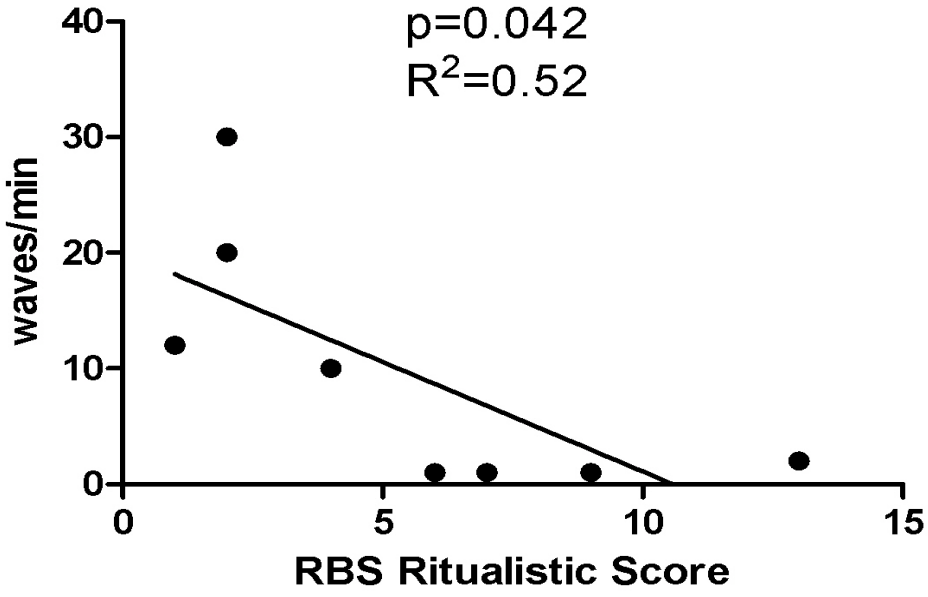
Courtesy of Sarah Spence

Correlation with discharge frequency

Higher frequency discharges are correlated with higher attention problems on CBCL

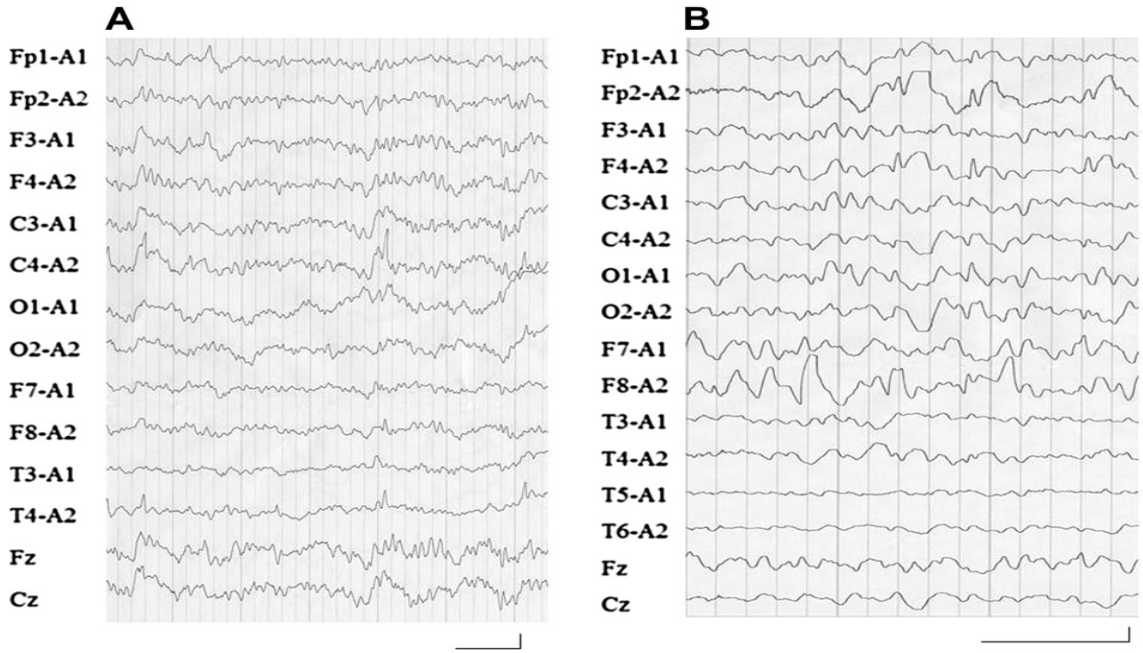
Conversely higher frequency discharges are correlated with LOWER repetitive behavior scores on RBS-R.





Can EEG predict epilepsy in ASD?

- *Kanemura et al, 2012*
  - 21 children with ASD studied prospectively between ages 3 and 6 years
  - Obtained EEGs every 6 months for at least 6 years
  - EEG abnormalities in 11/21 patients (52.4%)
  - Frontal paroxysms significantly associated with later development of epilepsy (partial with secondary generalization)



Epilepsy: Recommended Workup

- AAN and AAP guidelines do not recommend routine EEG for children with ASD (2000)
- Obtain prolonged sleep deprived EEG if:
  - Evidence of clinical seizures
  - History of developmental regression espeically in toddlers and preschoolers
  - Situations with high index of suspicion that epilepsy could be present

    (Known genetic syndrome that confers a high risk for epilepsy)

Epilepsy: Treatment

- Because of the tremendous heterogeneity in seizure type, there is not one gold standard treatment for epilepsy in ASD
- Early recognition and treatment important

- Anti-epileptics
  - **Leviteracitam: behavioral side effects**
  - Valproic acid: liver toxicity
  - Benzodiazepenes: drowsiness
  - Lamotrigine: Steven Johnson syndrome

VIEWS & REVIEWS

NINDS epilepsy and autism spectrum disorders workshop report

Tuchman et al, *Neurology* 2013

Short term goals:

1. Defining the clinical characteristics of ASD/epilepsy
2. Better characterizing the seizure patterns in ASD
3. Elucidating the role of ID in ASD/epilepsy
4. Creation of a large clinical database

Long term goals:

1. Search for genetic and environmental causes
2. Identification of novel drug targets and combinations of behavioral and drug treatments

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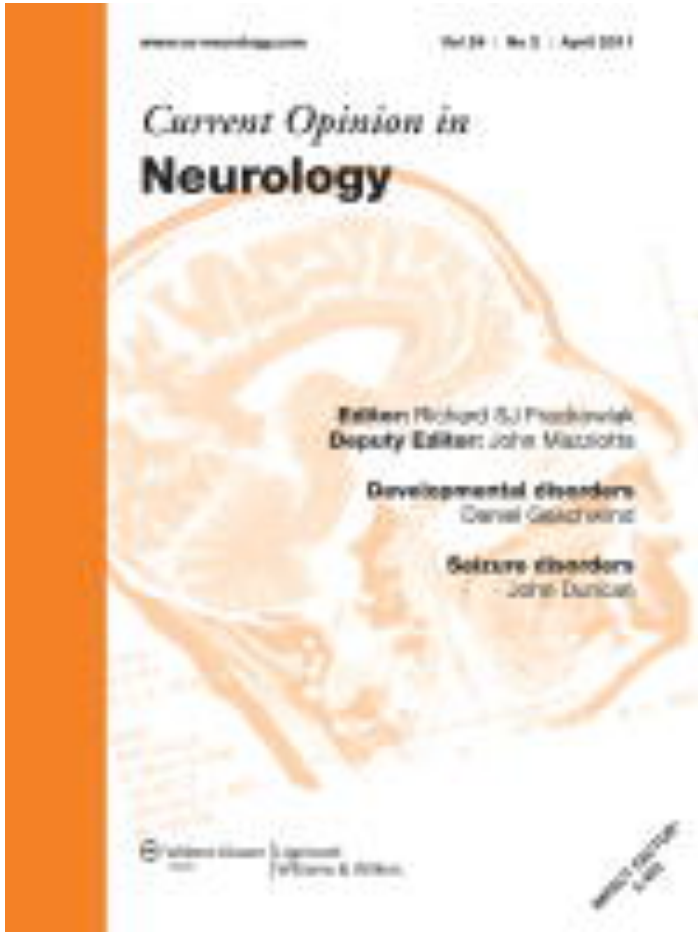


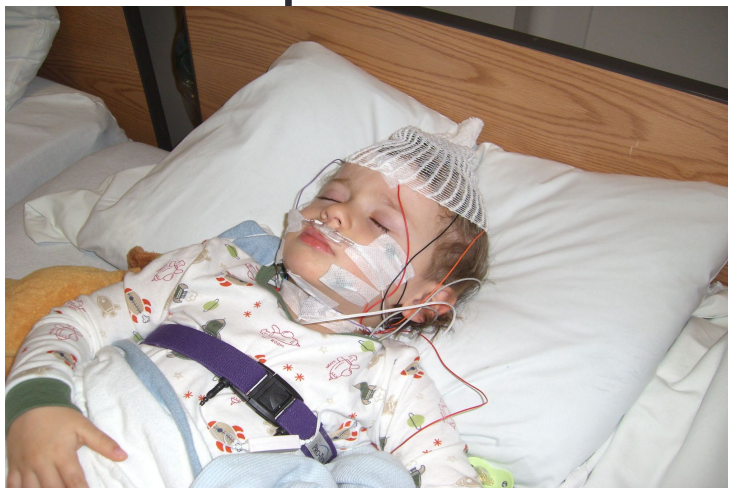
Sleep disturbance

- Clinically important
  - One of the most common complaints from parents
  - Prevalence ranges 53-78% (compared to 26-32% of TD kids)
- Scientifically neglected
  - Very few studies… although this is changing
- Conceptually intriguing
  - Sleep disturbance known to have profound effects on learning and memory, attention, behavior.
  - Unclear how much is specific to ASD phenotype as sleep disturbance also common in ID and other neuropsychiatric disorders.
  - Sleep known to be disturbed in epilepsy.
    - reciprocal relationship – sleep facilitates seizures and seizures disrupt sleep architecture (Malow 2004)


1
Interim between consciousness and sleep
Move to Stage 2 after 5-15 mins
2
Heart rate slows, brain does less complicated tasks
After another 15 mins, move into non-REM sleep, the Delta stage
3
Body makes repairs
4
Body temperature & BP decreases
Move into REM sleep approx 90 mins after first feeling sleepy
5 REM
Increase in eye movement, heart rate, breathing, BP & temperature
Sleep Cycle

Diagnosis of sleep impairment

- Gold standard for identifying sleep problems is overnight sleep study (actigraphy)
- Polysomnogram (PSG): records EEG, eye movements, heart rate, blood pressure, blood oxygenation, respirations
- Can be challenging to obtain in children with ASD
- Thus, studies often rely on questionnaires and reports



Questionnaire	Description	Format
Children's Sleep Habits Questionnaire (CSHQ) **CSHQ in toddlers and preschoolers**	Ages 4-10 Ages 2-5.5	45 items in 8 subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night awakenings, parasomnias, sleep disordered breathing, daytime sleepiness
Sleep Disturbance Scale for Children	Behavior over past 6 months in ages 5-15	26 items in 6 subscales: sleep initiation and maintenance, daytime sleepiness, sleep arousal, sleep-disordered breathing
Family Inventory of Sleep Habits	Ages 3-10	12 items including daytime and pre-bedtime habits, bedtime routine, sleep environment
Behavioral Evaluation of Disorders of Sleep Scale	Ages 5-12	5 types of sleep problems: expressive sleep disturbances, sensitivity to the environment, disoriented awakening, sleep facilitators, apnea/bruxism
BAERS	Ages 5-18	28 items into 5 subscales: going to bed, falling asleep, awakening, reinitiating sleep, wakefulness

Sleep impairment = insomnia

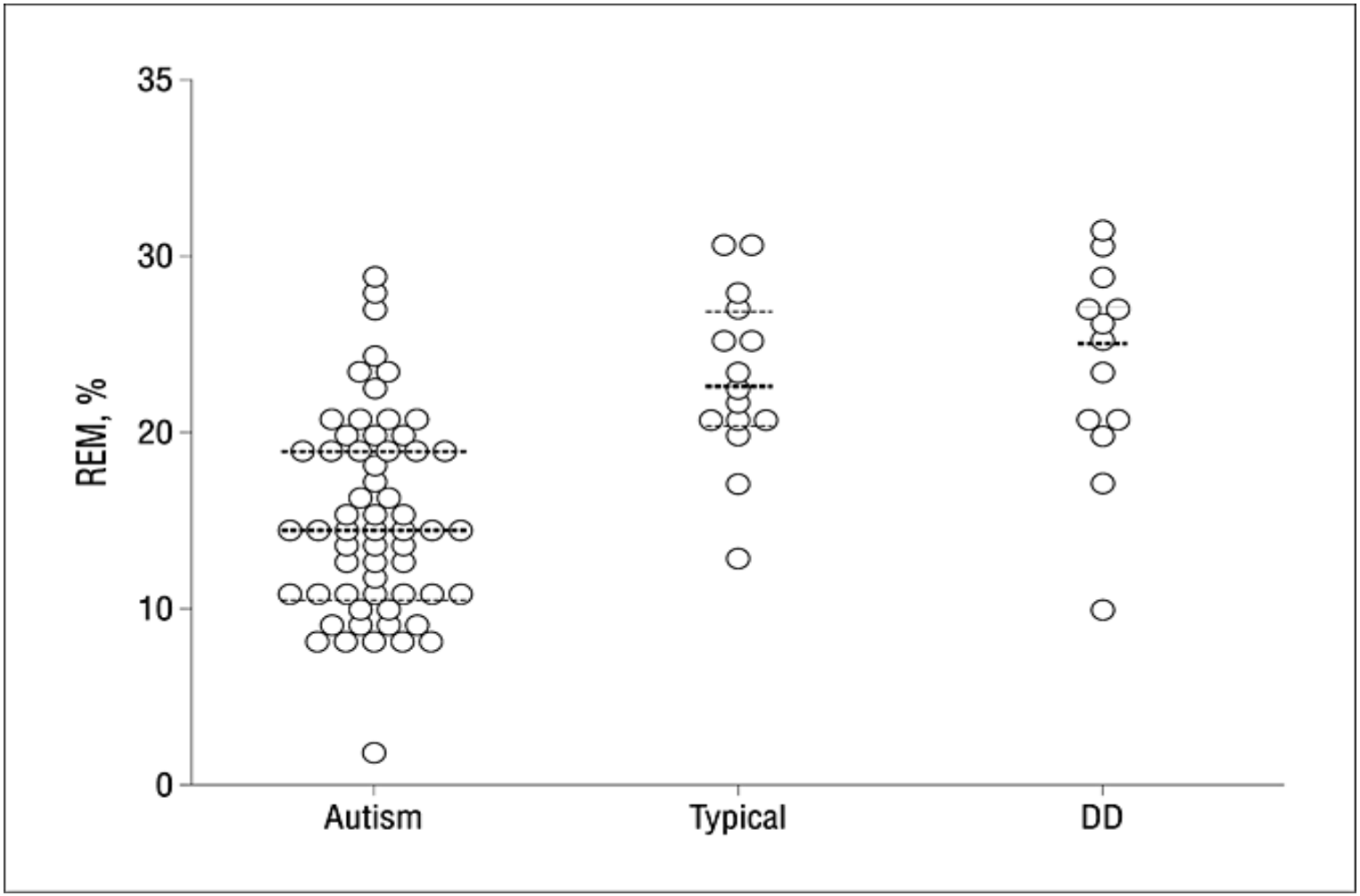
Behavioral assessment

- Repeated episodes of difficulty initiating or maintaining sleep
- Night awakenings
- Early morning awakenings
- Decreased need for sleep
- Challenges with limit setting around bedtimes

Actigraphy

- Prolonged sleep onset time (go to bed later)
- Longer sleep latency (take longer to fall asleep)
- Early awakening
- Frequent arousals and sleep fragmentation
- Increased duration of stage 1 sleep
- Decreased and abnormal non-REM sleep (stages 2-4)

Rapid eye movement (REM) sleep percentage significantly decreased in ASD compared to TYP and DD



Buckley, A. W. et al. Arch Pediatr Adolesc Med 2010;164:1032-1037.

ARCHIVES OF PEDIATRICS & ADOLESCENT MEDICINE

Clinical characteristics

- Children with ASD and sleep impairment have more comorbid behavioral and cognitive disturbances
- Other associated features: younger age, hypersensitivity, co-sleeping, epilepsy, ADHD, asthma, family history of sleep problems
- “Good sleepers” show **less:** affective problems, inattention/ hyperactivity, restricted/repetitve behaviors and **better** social interaction than “bad sleepers”.

Etiology of sleep impairment

- Ignore environmental cues that help entrain the sleep/wake circadian system
- Perseverate on activities or thoughts that interfere with sleep onset
- Communication limitations in understanding parents' expectations for bedtime
- Hypersensitivities may make settling down harder
- Neurobiological mechanisms: abnormal melatonin production (Rossignol, 2011)

Sleep committee of ATN: Practice parameters

(1) All children with ASD should be screened for insomnia

(2) Screening should be done for potential contributing factors, including other medical problems

(3) The need for therapeutic intervention should be determined

(4) Therapeutic interventions should begin with parent education in the use of behavioral approaches as *first line* approach

(5) Pharmacologic therapy may be indicated in certain situations

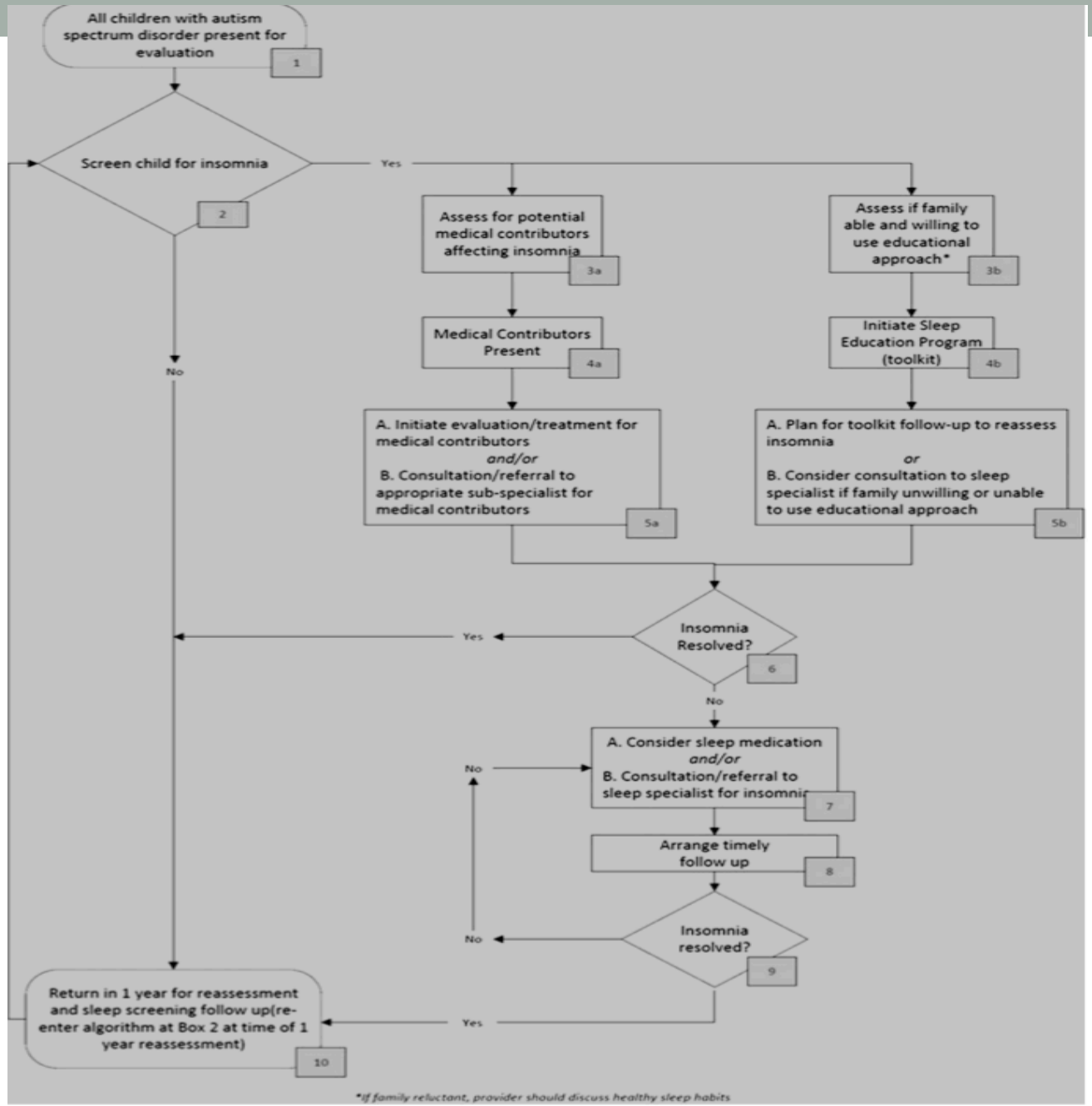
(6) There should be follow up after any intervention to evaluate effectiveness and tolerance of the therapy

Pediatrics, 2012

Screening questions:

1. Falls asleep within 20 min
2. Falls asleep in parents' bed
3. Sleeps too little
4. Awakens once during night

Medical Screening:
Reflux, constipation, seizures disordered breathing, pain/discomfort, nutrition
Exam: tonsils, tone, nasal congestion, dentition wheezing, eczema



Malow et al, 2012

Behavioral/Educational interventions

Educational intervention with parents: improves some aspects of sleep disturbance, varies by study—bedtime resistance, latency, duration, sleep anxiety, parasomnias, daytime sleepiness (Reed, 2009; Weiskop, 2005;)

Alternative treatments: Massage can be effective (Piravej, 2009; Escalona, 2001), aroma therapy ineffective (Williams, 2006)

- Sample educational targets: Goal setting, learning theory, partner support strategies, extinction techniques, cosleeping

Pharmacologic interventions

Melatonin: 2-10 mg, improves sleep latency and total sleep time, + nighttime awakenings (Wright, 2011; Garstand, 2006; Wirojanan, 2009; Paavonen, 2003, Biannotti, 2006; Malow, 2011; Andersen, 2008)

Mirtazapine: 7.5 – 45 mg, can improve sleep quality (Posey, 2001)

Clonidine: 0.1 mg, improved sleep latency and wakings (Ming, 2008)

Risperidone: improves sleep latency but not sleep duration, high rates of adverse outcomes (Aman, 2005 RUPP study)

Iron supplementation: 6 mg/kg x 8 weeks, improves restless sleep (Dosman, 2007)

Secretin: does not improve CSHQ scores (Honomichl, 2002)

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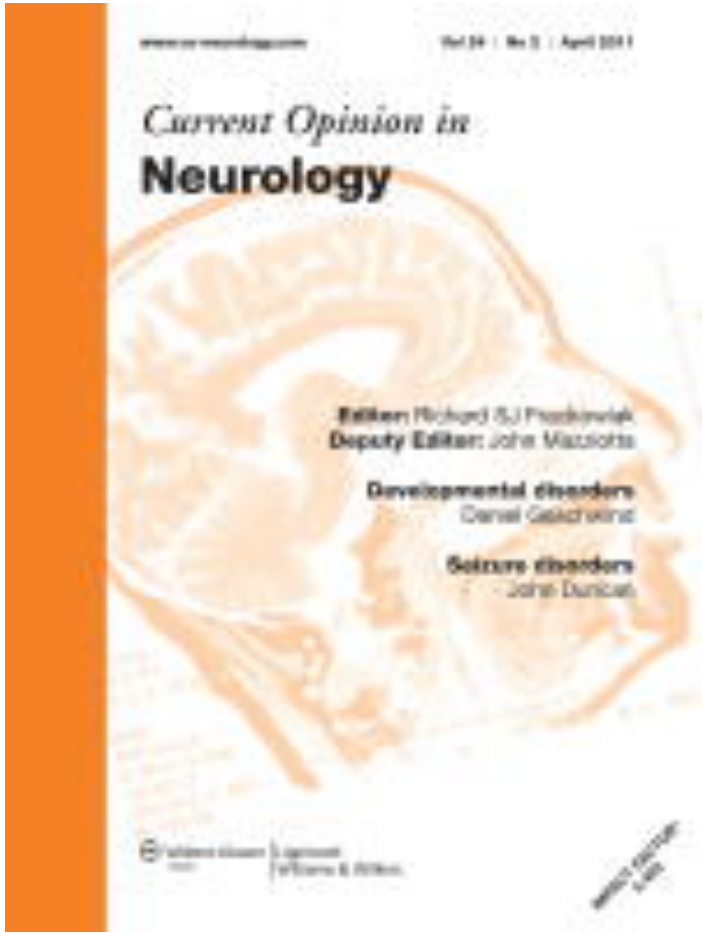


Motor definitions

- Strength: force a muscle can produce with effort
- Tone: muscle's resistance to passive stretch during rest
- Motor skills: Learned sequence of movements
  - Fine motor: small muscles
  - Gross motor: large muscles

Travel broadens the mind *Campos 2000*

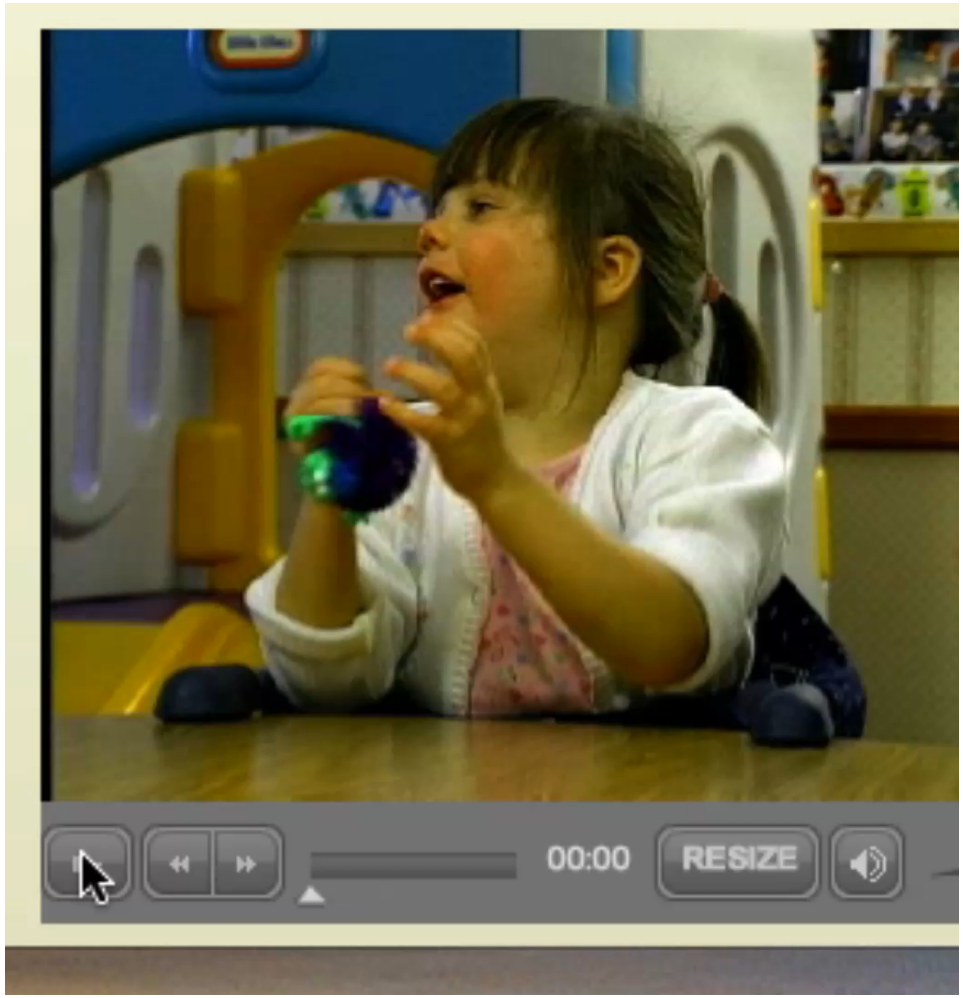
- “The onset of locomotion heralds one of the major life transitions in eary development and involves a pervasive set of changes in perception, spatial cognition, and social and emotional development”

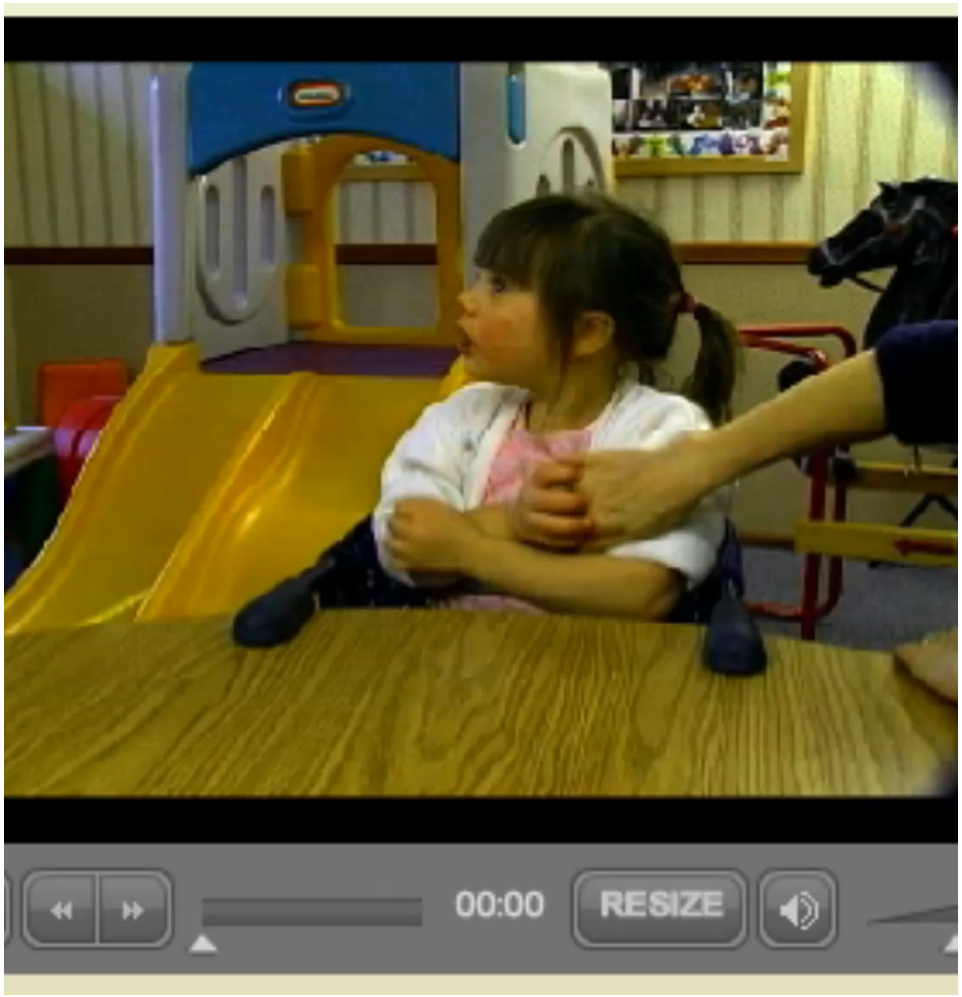
- From early infancy, motor skills are used to explore the environment, engage in physical play, initiate social interactions, and develop basic academic skills
- Advances in motor skills, such as gestures and object manipulation, lead to develoment of early language milestones

Motor impairment

- Repetitive behaviors part of diagnostic criteria
- Two pieces to this domain: insistence on sameness and repetitive behaviors (aka stereotypies)
- Often become more severe over development
- More predominant in children with severe language impairment

Repetitive behaviors





Courtesy of Autism Speaks

Repetitive behaviors

Courtesy of Autism Speaks

Motor impairment

- Remaining impairments not part of diagnosis, but prevalent
  - Motor delay
  - Hypotonia: improves over time
  - Incoordination
  - Gait impairment: toe walking common
  - Apraxia
  - Motor planning
  - Postural control

Motor delays

- Very relevant to potential early diagnosis, as oral motor skills and motor imitation predict language acquisition in infants with ASD (Gernsbacher, 2008; McDuffie, 2005; Stone, 2001)

- Home videos of children with ASD: delayed development of lying supine, sitting and walking (Ozonoff, 2008)

- Prospective infant-sibling studies: delayed onset of independent sitting and walking at 12 months (Iverson, 2007), head lag at 6 months (Flanagan, 2012), fine motor impairments at 6 months (Bolton, 2012), lower fine and gross motor scores on MSEL at 18 months (Landa, 2006), postural instability at 18 months (Iverson, 2007)

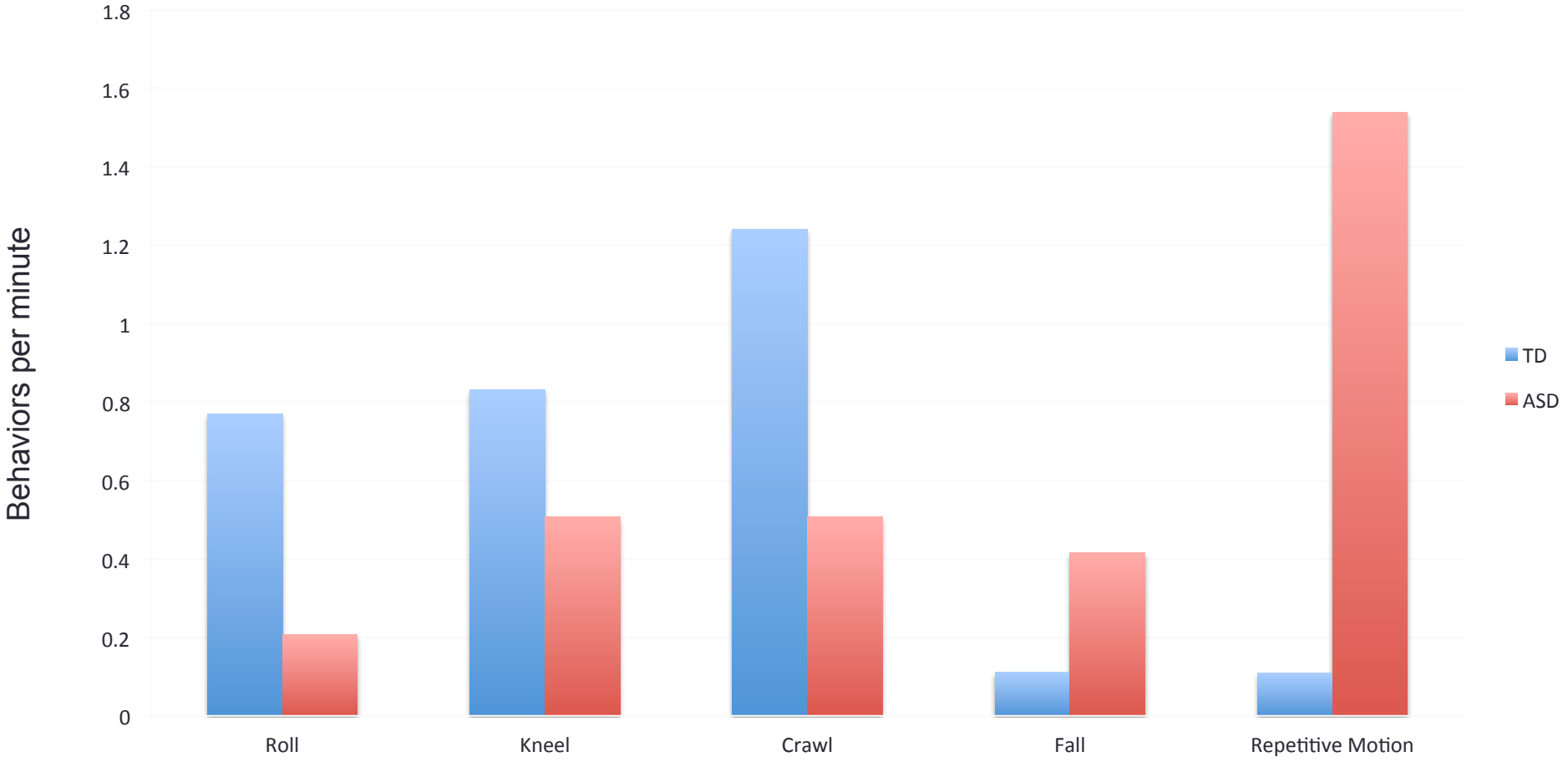
Infant motor data

- 65 infants in the infant-sibling study (11 developed ASD)
- Mullen Scales of Early Learning
- At age 6 months, wide range in achievement of gross motor milestones (MSEL scores ranging from 6 to 12).
- Gross motor function at age 6 months was significantly correlated with:
  - visual reception at 12 months ($p<0.05$),
  - receptive language at 12 months ($p<0.05$)
  - requesting at 12 months ($p<0.05$)

Hutman and Jeste, in preparation

Motor Behavior at 12 months

Motor Behavior at 12 months



Gait abnormalities

- Toe-walking
- Ataxia (unsteady gait)
- Variable stride length and duration
- Incoordination
- Postural abnormalities in head and trunk
- Reduced plantarflexion (pointing toes)
- Increased dorsiflexion (walking on heels)
- Stiffer gait with lack of “smoothness”

(Calhoun, 2011; Rinehart, 2006; Vilensky, 1981; Weber, 1978; Nobile, 2011)

Toe-walking

Courtesy of Autism Speaks

Incoordination

Fournier et al, 2010

- Meta-analysis of 41 studies investigating movement in ASD found significantly more motor incoordination and postural instability than controls
- Found improvement in coordination over time

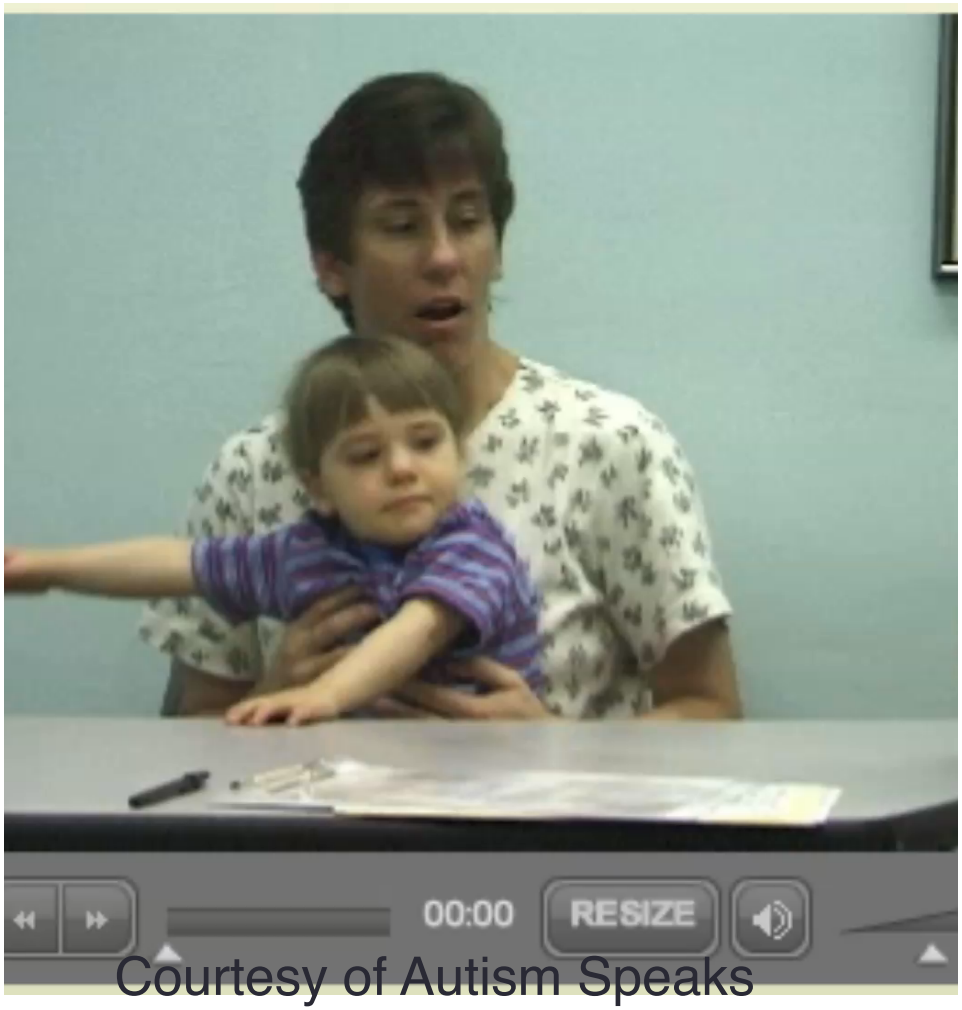
Incoordination

Courtesy of Autism Speaks

Dyspraxia

- Praxis: Performance of skilled movements
- Mostofsky and colleagues:
  - Impairment in gestures to command, imitation, tool-use
  - Poor handwriting
  - These impairments correlate with social, communication and behavioral deficits

Dyspraxia



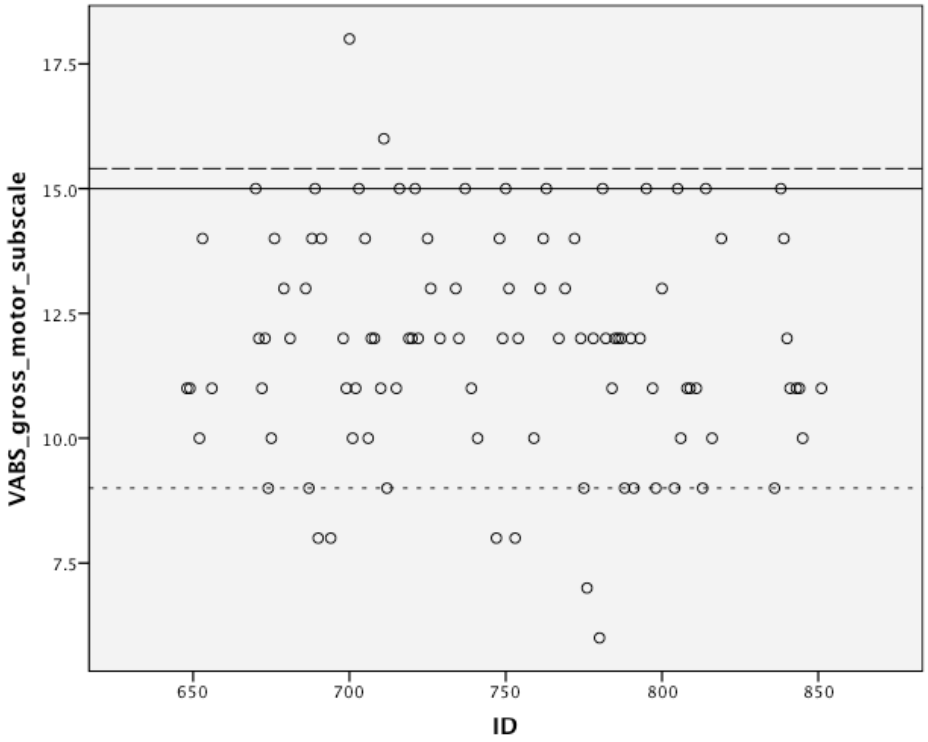
Courtesy of Autism Speaks

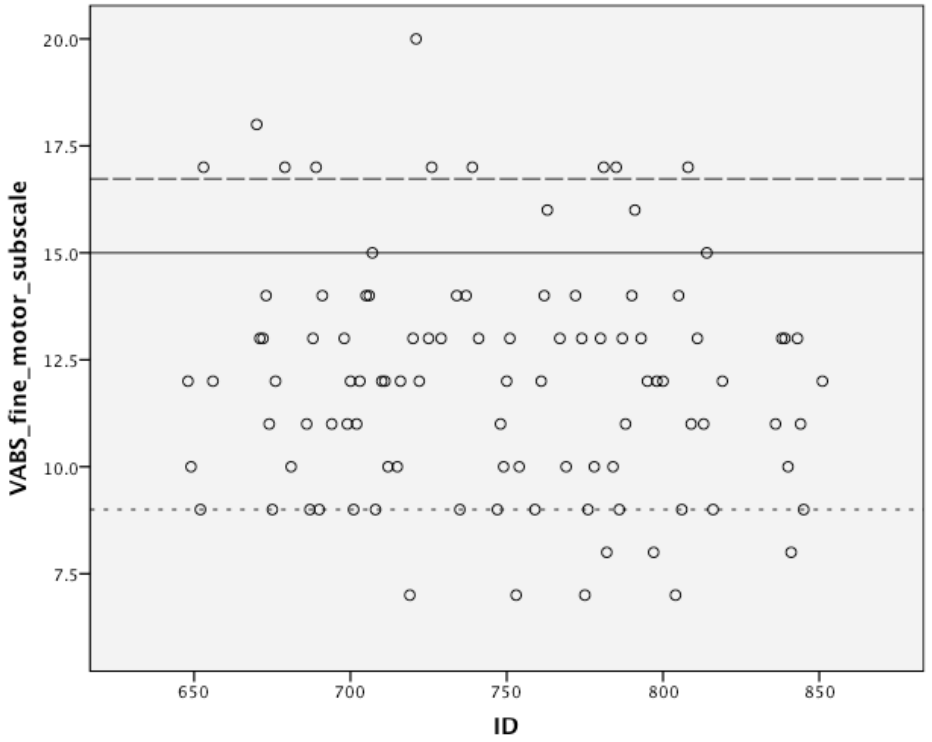
Adaptive motor impairment

- Functional motor skills (ie brushing teeth, turning a doorknob, catching a ball)
- Measured by the Vineland Adaptive Behavior Scales (VABS)
- Study of 100 children with ASD ages 2-5
- Children with ASD significantly delayed in both fine (mean 12) and gross (mean 11.9) adaptive motor skills
- 19% could not jump with both feet off the floor, 39% could not walk downstairs using alternate feet, 52% could not catch ball from 2-3 feet
- 19% could not turn a doorknob, 35% could not unwrap object, 84% could not use eraser without tearing paper

Jalnapurkar I and Jeste SS, 2013

Adaptive motor impairment





Jalnapurkar I and Jeste SS, 2013

Motor assessments

- Standardized scales: Mullen Scales of Early Learning
- Standardized neurological examination
- Questionnaires: Vineland Adaptive Behaviors motor skills subdomain: all ages
- PANESS (Denckla, 1977): Physical and neurological examination for soft signs (ages 6 and up)
- Movement ABC (Assessment Battery for Children): Ages 3-16

AMERICAN ACADEMY OF NEUROLOGY

Special Article

CME

Practice parameter: Evaluation of the child with global developmental delay

Report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society

M. Shevell, MD; S. Ashwal, MD; D. Donley, MD; J. Flint, MD; M. Gingold, MD; D. Hirtz, MD; A. Majnemer, PhD; M. Noetzel, MD; and R.D. Sheth, MD

Genetic testing AND neuroimaging (MRI is preferred) if additional history of gross motor delay

Neurology, 2003

Treatment

- Need standardized, controlled studies!
- May have important implications for outcome
- The only medication studied for motor deficits in ASD is Risperidone for repetitive behaviors

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: Risperidone for the Core Symptom Domains of Autism: Results From the Study by the Autism Network of the Research Units on Pediatric Psychopharmacology

Am J Psychiatry. 2005;162(6):1142-1148. doi:10.1176/appi.ajp.162.6.1142

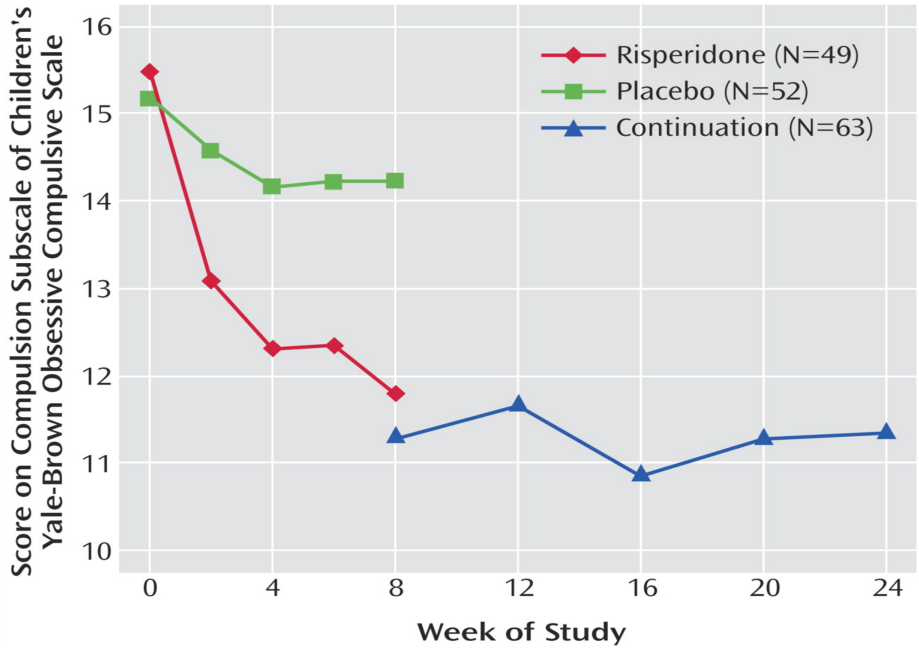


Figure Legend:

Scores for Compulsions on the Children's Yale-Brown Obsessive Compulsive Scale of Children and Adolescents in a Placebo-Controlled Risperidone Trial and Open-Label Continuation Study

Genetics of neurological comorbidities

Epilepsy	Motor impairment	Sleep disturbance
•TSC (TSC1 and TSC2)	•Rett syndrome •Hypotonia •Severe stereotypies	•Rett syndrome
•Rett syndrome (MECP2)	•AUTS2 •Motor delay	•1q21.1 deletion
•CNTNAP2	•Fox1 (A2BP1) •Motor asymmetry	•15q11.1q13.3 duplication
•SYN1	•NRXN1 deletion •Hypotonia	•18q12.1 deletion
•Fragile X	•2q23.1 deletion and duplication •Hypotonia •Motor delay	•SHANK3 (22q13.3 deletion)
•1q21.1 deletion	•15q11.1q13.3 duplication •Hypotonia	
•7q11.23 duplication	•SHANK3 (22q13.3 deletion) •Hypotonia	
•15q11.1q13.3 duplication		
•16p11.2 deletion		
•18q12.1duplication		
•22q11.2 deletion		
•SHANK3 (22q13.3 deletion)		
•UBE3A		

The Interstitial Duplication 15q11.2-q13 Syndrome Includes Autism, Mild Facial Anomalies and a Characteristic EEG Signature

Nora Urraca, Julie Cleary,[1] Victoria Brewer, Eniko K. Pivnick, Kathryn McVicar, Ronald L. Thibert, N. Carolyn Schanen, Carmen Esmer, Dustin Lamport, and Lawrence T. Reiter

Impaired social interactions and motor learning skills in tuberous sclerosis complex model mice expressing a dominant/negative form of tuberin

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Absence of CNTNAP2 Leads to Epilepsy, Neuronal Migration Abnormalities, and Core Autism-Related Deficits

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Summary

- ASD is a heterogeneous clinical disorder
- These co-morbidities include: epilepsy, sleep dysfunction and motor impairment
- Neurological co-morbidities are common and tightly associated with overall impairment
- Earlier screening and diagnosis of these areas may help improve developmental outcomes
- More research is needed on treatment of comorbidities specific to ASD, particularly treatment before the onset of impairment

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