ADHD and ASD: two manifestations of the same disorder?

Jan Buitelaar
Radboud University Medical Center
Donders Institute for Brain, Cognition and Behavior
Department of Cognitive Neuroscience, and
Karakter Child and Adolescent Psychiatry University Center
Nijmegen, The Netherlands

ESCAP, Madrid, June 20, 2015
<table>
<thead>
<tr>
<th></th>
<th>Speaker</th>
<th>Advisory Board</th>
<th>Research Support</th>
<th>Involved in clinical trials</th>
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</table>
Social-communication deficits

Fixated interests and repetitive behaviours
ADHD - Core Symptom Areas

- Inattention
- Impulsivity/Hyperactivity
ADHD and ASD: two manifestations of the same disorder?

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.
Outline of the talk

Clinical issues

Genetics

Cognitive measures

Brain function and structure

Implications – new concepts
ASD and ADHD are developmental disorders with early onset and strong persistence over time.

**ASD**
- Onset before age 3
- >90% persistence into adulthood

**ADHD**
- Onset before age 12
- About 50% have onset at 2-3 year
- 70% persistence into adolescence
- 30-50% persistence into adulthood
Clinical overlap between ASD and ADHD

25-50% of subjects with ASD have ADHD symptoms that merit clinical treatment (for review see Rommelse et al. Eur Child Adolesc Psychiatry 2010, 19:281-95.)
25-50% of children with ADHD are severe socially disabled and/or have at least mild ASD symptoms (Green et al., 1996; Luteijn et al., 2000; Goldstein and Schwebach, 2004; Mulligan et al., 2009; Nijmeijer et al., 2008; Santosh and Mijovic, 2004). This also applies to population samples (Reiersen et al., 2007) (for review see Rommelse et al., 2010).
Clinical overlap between ADHD and ASD - population-based sample

Reiersen et al., 2007
ADHD and developmental problems

Hartsough & Lambert, 1985
ADHD and ASD
ADHD and ASD
Theoretical models for overlap – co-occurrence

• One overarching disorder
• Common cause – shared risk factors
  – Genetic factors
  – Environment (e.g. obstetric adversity)
• Common neurobiological substrate
• Disorder A causes disorder B
• Disorder A is risk factor to disorder B
• Overlap in defining symptoms
One overarching disorder

ADHD - ASD

Phenotypic expression, Pleiotropy

ASD  ADHD  ASD+ADHD  other (ID, dyslexia, ..)
Are ASD and ADHD different manifestations of one overarching disorder?

Gradient model
Different disorders with common causes

Common causes

Specific causes ADHD

ADHD

ASD+ADHD

Specific causes ASD

ASD
Different disorders with common neural substrates

Common substrates, e.g. dysfunction of PFC

Specific causes ADHD
- ADHD
- ASD+ADHD

Specific causes ASD
- ASD
Outline of the talk

Clinical issues

Genetics

Cognitive measures

Brain function and structure

Implications – new concepts
Clinicians will rather often observe the following:

- Proband diagnosed with ASD
- Sibling later referred and diagnosed with ADHD (and ASD broad phenotype)
- Another sibling referred because of ADHD or dyslexia or social problems
Twin studies

- Genetic similarity
  - Monozygotic (MZ) twins (nearly) 100%
  - Dizygotic (DZ) twins ~ 50%
## Estimated heritabilities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Heritability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>90 (but lower in recent studies)</td>
</tr>
<tr>
<td>ADHD</td>
<td>80</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>80</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>80</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>70</td>
</tr>
</tbody>
</table>
Shared genetic influences on ADHD and ASD symptoms

• TEDS (community sample of 6,771 twins 8 year old)
• Ratings on the Childhood Asperger Syndrome Test
• Ratings on the Conners' DSM-IV subscales.
• ASD and ADHD traits were significantly correlated in the general population (.54 for parent data, .51 for teacher data).

- All genetic correlations were >.50
- Higher genetic correlations at more extreme levels of ADHD and ASD

Ronald et al., 2008, J Child Psychol Psychiatry 49:535-42
Shared genetic influences on ADHD and ASD symptoms

- Adult sample of 674 young Australian Twins
- Self-report data from 11 SRS items and 12 DSM-IV ADHD symptoms
- Phenotypic correlation between ASD and ADHD symptoms was moderate.
- ADHD and ASD traits were both moderately heritable.
- **The genetic correlation between SRS and ADHD was 0.72**

Reiersen et al., 2008, Twin Res Hum Genet 11:579-85
Shared genetic influences on ADHD and ASD symptoms


<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetic Effects</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorders</td>
<td>0.80</td>
<td>0.29–0.91</td>
</tr>
<tr>
<td>ADHD</td>
<td>0.79</td>
<td>0.61–0.88</td>
</tr>
<tr>
<td>Developmental coordination disorder</td>
<td>0.70</td>
<td>0.35–0.83</td>
</tr>
<tr>
<td>Tic disorder</td>
<td>0.56</td>
<td>0.37–0.68</td>
</tr>
</tbody>
</table>
Shared genetic influences on ADHD and ASD symptoms

Lichtenstein et al., 2010, Am J Psychiatry
Cell Nucleus Containing 23 Pairs of Chromosomes

Genes

Chromosomes

Bases

DNA Strand
Causes of genetic disease

- Monogenic Diseases
  - High Penetrance
  - Frequency of genetic defect
  - Very rare: 0.001
  - Rare: 0.01
  - Uncommon: 0.1
  - Common: 0.001

- Multi-factorial Diseases
  - Intermediate Penetrance
  - Low Penetrance

(Adapted from McCarthy et al., 2008)
Causes of genetic disease

(adapted from McCarthy et al., 2008)
Causes of genetic disease

(adapted from McCarthy et al., 2008)
Copy Number Variation

Chromosomal aberrations 1kb – 3Mb
Disease-Based Studies of Genetic Mutations

- Adult/late-onset diseases
  - Schizophrenia
  - Bipolar disorder
- Pediatric/developmental diseases
  - Epilepsy
  - Autism
  - Mental retardation
  - Birth defects

Discovery of rare CNV associated with disease

CNV-Based Studies of Expression in Families and General Population Samples

- Severe phenotypes (core)
- Observable if assessed adequately
- Mutation carrier (no observable phenotype)

Spectrum of variable expression

Core phenotypes differ for specific CNVs

- Schizophrenia
- Epilepsy
- Autism
- Mental retardation
- Birth defects

- 22q11.2 deletion
- 15q13.3 deletion
- 1q21.1 deletion
Rare and common variants converge into the same gene-protein networks.
300-1000 causal genes

20-40 gene networks

5-10 biological pathways
SNPs – Single Nucleotide Polymorphisms

13,000,000 SNPs in human genome
• used as landmark for chromosomal location
• may change function/regulation of a gene product
Polygenic risk scores were calculated in the ALSPAC population sample ($N = 8229$) based on a discovery case-control genome-wide association study of childhood ADHD.

Regression analyses were used to assess whether polygenic scores predicted ADHD traits and ASD-related measures (pragmatic language abilities and social cognition) in the ALSPAC sample.

Polygenic risk for ADHD showed a positive association with ADHD traits (hyperactive-impulsive, $p = .0039$; inattentive, $p = .037$)

Polygenic risk for ADHD was also negatively associated with pragmatic language abilities ($p = .037$) but not with social cognition ($p = .43$).

Martin et al. Biol Psychiatry 2014 Feb 25
Polygenic score predicting multiple correlated outcomes

Based on ADHD case-control contrast

Polygenic score predicting multiple correlated outcomes

Biological overlap of ADHD and ASD: evidence from copy number variants

### Table 1

Number of Pathways Achieving Given Levels of Enrichment Significance (*p* < .05, *p* < .01, *p* < .001) in the Autism Spectrum Disorder (ASD) Dataset That Were Also Significantly Enriched at the Same Significance Level in the Attention-Deficit/Hyperactivity Disorder (ADHD) Sample

<table>
<thead>
<tr>
<th>CNV Type (ASD)</th>
<th><em>p</em> &lt; .05</th>
<th><em>p</em> &lt; .01</th>
<th><em>p</em> &lt; .001</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pathways</td>
<td><em>p</em></td>
<td>No. of Pathways</td>
</tr>
<tr>
<td>De novo</td>
<td>58</td>
<td>.006</td>
<td>9</td>
</tr>
<tr>
<td>Inherited</td>
<td>72</td>
<td>.001</td>
<td>16</td>
</tr>
<tr>
<td>All</td>
<td>100</td>
<td>&lt;.001</td>
<td>20</td>
</tr>
</tbody>
</table>

Note: *p* Values are given for the test of whether the number of enriched pathways is greater than would be expected by chance. CNV = copy number variant; de novo = confirmed not to have been transmitted from either parent.

Biological overlap of ADHD and ASD: evidence from copy number variants

• After correction for multiple testing, genes involved in 3 biological processes (*nicotinic acetylcholine receptor signalling pathway, cell division, and response to drug*) showed significant enrichment for case CNV hits in the combined ADHD and ASD sample.

• The results of this study indicate the presence of significant overlap of shared biological processes disrupted by large rare CNVs in children with these 2 neurodevelopmental conditions.

Conclusions sofar

• Evidence for genetic overlap between autism and ADHD
• Multifactorial and oligogenetic forms
• Both disorders of synaptic structure/efficiency, cell adhesion, neurite outgrowth, signalling pathways
Outline of the talk

- Clinical issues
- Genetics
- **Cognitive measures**
- Brain function and structure
- Implications – new concepts
Cognitive deficits

• Both ASD as ADHD are heterogenous at the cognitive level

• Data suggest multiple impairment models rather than one universal or primary cognitive deficit
Anoek Oerlemans

Jolanda van der Meer

Catharina Hartman

Nanda Rommelse
Are ASD and ADHD different manifestations of one overarching disorder?

- Latent class analysis (LCA) was performed on Social Communication Questionnaire (SCQ) and Conners’ Parent Rating Scale (CPRS-R:L) data of 644 children.
- Classes were compared for comorbid symptoms and their cognitive profiles of motor speed and variability, executive functioning, attention, emotion recognition and central coherence.

Are ASD and ADHD different manifestations of one overarching disorder?

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>ADHD</th>
<th>ADHD(+ASD)</th>
<th>ASD(+ADHD)</th>
<th>Contrasts based on p-values of .05</th>
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<tbody>
<tr>
<td>N</td>
<td>418</td>
<td>109</td>
<td>59</td>
<td>58</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
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<th>SD</th>
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<tbody>
<tr>
<td>Age</td>
<td>9.5</td>
<td>2.4</td>
<td>9.9</td>
<td>2.8</td>
<td>11.2</td>
<td>3.3</td>
<td>11.5</td>
<td>2.7</td>
</tr>
<tr>
<td>% male</td>
<td>45.7</td>
<td></td>
<td>66.1</td>
<td></td>
<td>81.4</td>
<td></td>
<td>86.2</td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>111.7</td>
<td>18.7</td>
<td>107.1</td>
<td>19.1</td>
<td>101</td>
<td>21.2</td>
<td>105.5</td>
<td>19.7</td>
</tr>
<tr>
<td>SCQ</td>
<td>4.1</td>
<td>4.4</td>
<td>6.9</td>
<td>4.7</td>
<td>16.3</td>
<td>7.2</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Inatt</td>
<td>47.3</td>
<td>6</td>
<td>64.7</td>
<td>8.3</td>
<td>73.3</td>
<td>8.8</td>
<td>62.6</td>
<td>8.2</td>
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<tr>
<td>Hyp/Imp</td>
<td>48.2</td>
<td>6.7</td>
<td>64.8</td>
<td>9.8</td>
<td>79.8</td>
<td>8.2</td>
<td>66.7</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Hypotheses

H1: overarching disorder hypothesis: If true, symptomatic expression can be regarded as ‘noise’ and classes will more similar than different in associated traits

⇒ LC1 = LC2 = LC3 = …

H2: ADHD is a less severe subtype within the ASD spectrum. LCA will then identify at least one ADHD class without ASD symptoms, but no ASD class without ADHD symptoms, and all classes will show rather similar associated traits

⇒ LC1 (ADHD) < LC2 (ASD) < LC3 (ADHD+ASD).

Hypotheses

Ho: Alternatively, ASD and ADHD do not constitute different expressions of one overarching disorder. In this case, the LCA will identify at least some classes with pure ADHD or ASD symptoms. Further, the classes will be more different than similar in terms of associated traits

⇒ LC1 ≠ LC2 ≠ LC3 …

Latent Class Analysis
Are ASD and ADHD different manifestations of one overarching disorder?

Cognitive tests

a. Baseline speed and variability

Fixation  Signal

b. Facial emotion recognition

Cognitive tests

c. Inhibition and cognitive flexibility: compatible and incompatible trials.

Left compatible  Right compatible  Left incompatible  Right incompatible

d. Visuo-spatial attention and working memory.

Are ASD and ADHD different manifestations of one overarching disorder?

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Are ASD and ADHD different manifestations of one overarching disorder?

Are ASD and ADHD different manifestations of one overarching disorder?

2 classes with high scores on ASD and ADHD symptoms, however with strongly different performance on visuo-spatial skills

Gradient overarching disorder hypothesis

• In support
  – an ADHD class without ASD symptoms
  – absence of an ASD class without ADHD symptoms
  – cognitive functioning of the simple ADHD-class is less impaired than that of both comorbid classes.

• In conflict
  – severity of ADHD, comorbid oppositional and anxiety symptoms and cognitive problems were not the highest in the ASD(+ADHD) class
  – some specificity of cognitive deficits across classes.
Homogeneous combinations of ASD-ADHD traits and their cognitive and behavioral correlates in a population-based sample

- Sofar, approaches to identify more homogeneous subgroups have studied variability only in the affected population.
- Here we aim to identify subgroups of children with distinct ASD -ADHD trait profiles in the general population, using measures sensitive across the ASD and ADHD trait continua, including the unaffected ends, and show how these subgroups differ in terms of cognitive functioning.

Van der Meer, Lappenschaar, Hartman, Greven, Buitelaar, Rommelse. J Attention Disorders 2014
Homogeneous combinations of ASD-ADHD traits and their cognitive and behavioral correlates in a population-based sample

- We examined continuously distributed ASD and ADHD traits in relation to other internalizing and externalizing problems and cognitive functions in **378 children (6-13 years) from a population sample**.
- Latent class analyses (LCA) were conducted on the Autism Quotient (AQ) and the Strengths and Weaknesses of ADHD symptoms and Normal behavior (SWAN) rating scale.

Van der Meer, Lappenschaar, Hartman, Greven, Buitelaar, Rommelse. J Attention Disorders 2014
Homogeneous combinations of ASD-ADHD traits and their cognitive and behavioral correlates in a population-based sample

• In addition to three concordant classes with low (10.1%), medium (54.2%) or high (13.2%) scores on both traits, LCA revealed two discordant classes with more ADHD than ASD characteristics (ADHD>ASD, 18.3%) and vice versa (ASD>ADHD, 4.2%).

• Classes were dissociated in visual-spatial functioning, with ASD>ADHD exhibiting superior, and ADHD>ASD and the class with high scores on both traits, inferior performances.

Van der Meer, Lappenschaar, Hartman, Greven, Buitelaar, Rommelse. J Attention Disorders 2014
Are ASD and ADHD different manifestations of one overarching disorder?

Homogeneous combinations of ASD-ADHD traits and their cognitive and behavioral correlates in a population-based sample

Conclusions

• A minority of children displays atypical discordant trait profiles characterized by differential visual-spatial functioning.
• This dissociation was previously also reported in clinical classes with ASD and ADHD, suggesting that heterogeneity in ASD and ADHD is rooted in heterogeneity present in the lower unaffected end of the distribution

Van der Meer, Lappenschaar, Hartman, Greven, Buitelaar, Rommelse. J Attention Disorders 2014
Cognitive subtyping

Behavior / symptoms

Cognition
### Using cognitive subtyping to examine the relationship between ASD and ADHD

<table>
<thead>
<tr>
<th>Task</th>
<th>Measurement potential</th>
<th>Dependent variable(s)</th>
</tr>
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<tbody>
<tr>
<td>Baseline Speed(^{a,b})</td>
<td>Speed and variability of motor output as response to external cue</td>
<td>Mean reaction time (ms) and variability (SD of reaction time in ms)</td>
</tr>
<tr>
<td>Digit Span (WISC-III)(^{a,c})</td>
<td>Verbal Attention</td>
<td>Number of correct reproduced digits in identical (forward) order</td>
</tr>
<tr>
<td></td>
<td>Verbal Working Memory</td>
<td>Number of correct reproduced digits in reversed (backward) order</td>
</tr>
<tr>
<td>Visuo-Spatial Sequencing(^{a,b})</td>
<td>Visuo-Spatial Attention</td>
<td>Number of correct reproduced sequences in identical (forward) order</td>
</tr>
<tr>
<td></td>
<td>Visuo-Spatial Working Memory</td>
<td>Number of correct reproduced sequences in reversed (backward) order</td>
</tr>
<tr>
<td>Block Patterns (WISC-III)(^{a,c})</td>
<td>Visual pattern recognition</td>
<td>Number of correct and timely completed geometric designs</td>
</tr>
<tr>
<td>Facial Emotion Recognition(^{a,b})</td>
<td>Capacity to identify the facial emotional expression of happiness, sadness, anger and anxiety.</td>
<td>Mean reaction time (ms) and accuracy on four emotions</td>
</tr>
</tbody>
</table>

*Note: \(^{a}\) indicates a significant increase; \(^{b}\) indicates a significant decrease; \(^{c}\) indicates a significant difference.*
Using cognitive subtyping to examine the relationship between ASD and ADHD

- Latent class analyses (LCA) were performed on motor speed and variability, verbal and visual-spatial attention, verbal and visual-spatial working memory, visual pattern recognition and emotion recognition in 360 participants from a population based sample and 254 participants from a clinic based sample (5-17 years).
- Classes were compared on several behavioral symptom scales.

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

• LCAs in the population and clinic samples revealed a similar four class solution typified by qualitatively different speed-accuracy trade-offs:
  – high accuracy-medium speed (21.9% of the population sample and 16.5% of the clinic sample),
  – medium accuracy-high speed (24.2% and 24.4%),
  – low accuracy-medium speed (35.3% and 39.0%) and
  – low accuracy-low speed (18.6% and 20.0%).

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

- These classes were respectively associated with lowest en highest levels of ASD and ADHD symptoms in the clinical sample, with an overall strong predictive effect.
- Associations with clinical symptoms were much weaker in the population sample.
- Classes were not characterized by domain specific cognitive strengths or weaknesses.

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

Rommelse, Van der Meer, Hartman, Buitelaar (under review)

Clinic sample

Z-score (effect sizes)

more behavioral problems

high accuracy medium speed
medium accuracy high speed
low accuracy medium speed
low accuracy low speed

SCQ
AQ
CPRS
Hyperactivity
CPRS Inattention

Rommelse, Van der Meer, Hartman, Buitelaar (under review)

Donders Institute
for Brain, Cognition and Behaviour

Radboud University Nijmegen
Using cognitive subtyping to examine the relationship between ASD and ADHD

Population sample

more behavioral problems

Z-score (effect sizes)

-0.70
-0.50
-0.30
-0.10
0.10
0.30
0.50
0.70

- high accuracy medium speed
- medium accuracy high speed
- low accuracy medium speed
- low accuracy low speed

SCQ
AQ
CPRS Hyperactivity
CPRS Inattention
SWAN

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

Z-score (effect sizes)

Clinic sample

- Oppositional
- Cognitive problems
- Anxiety
- Perfectionism
- Psychosomatic
- Emotional lability

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Using cognitive subtyping to examine the relationship between ASD and ADHD

Rommelse, Van der Meer, Hartman, Buitelaar (under review)

- High accuracy medium speed
- Medium accuracy high speed
- Low accuracy medium speed
- Low accuracy low speed

Population sample

Z-score (effect sizes)

- Oppositional
- Cognitive problems
- Anxiety
- Perfectionism
- Psychosomatic
- Emotional lability

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Conclusions

- Cognitive subtyping appears a powerful strategy to uncover the mechanisms underlying ASD and ADHD.
- Do the cross-domain generic cognitive factors have a specific neural architecture: MRI studies needed.
- The weak associations between cognition and behavior in the population sample suggest that cognitive functioning may only predict behavior when other risk or protective factors are present.

Rommelse, Van der Meer, Hartman, Buitelaar (under review)
Conclusions

• There is clinical and genetic overlap between autism and ADHD

• Behaviour ➞ cognition and comorbidity: some evidence for autism and ADHD as part of an overarching disorder

• Cognition ➞ behavior: speed-accuracy trade-off; general principle of neural architecture
Outline of the talk

Clinical issues
Genetics
Cognitive measures
Brain function and structure
Implications – new concepts
Whole brain volume in 2-4 year olds (autism vs controls)

Courchesne et al., Neurology, 2001, 57, 245-254
Brain Volumes in ASD

Volume of cerebral white matter

Volume of cerebral gray matter

Couchesne et al., 2001
Brain volumes in ADHD

Castellanos et al., 2002
Total brain volume (= total gray + white matter)

Greven et al. JAMA Psychiatry 2015

- Main effects of ADHD diagnosis on total brain and total gray matter volumes
  - Total brain 32ml (2.5%), total gray matter 22ml (3%) smaller in subjects with ADHD
- No diagnosis x age effects
Principles of Organisation

Functional specialization
- Localisation

Functional integration
- Connectivity
Neuronal network analysis
Distinct and shared intrinsic functional network centrality in ASD and ADHD

Di Martino et al. Biol Psychiatry 2013
Distinct and shared intrinsic functional network centrality in ASD and ADHD

ADHD: striatum and pallidum

One-way ANCOVA

A

B

C

D

E

Di Martino et al. Biol Psychiatry 2013
Distinct and shared intrinsic functional network centrality in ASD and ADHD

Di Martino et al. Biol Psychiatry 2013
Distinct and shared intrinsic functional network centrality in ASD and ADHD

Di Martino et al. Biol Psychiatry 2013
Conclusion

• ASD and ADHD are disorders of brain development and brain connectivity
• Sofar, stronger evidence for distinct than for shared neural correlates
• However, studies with small samples and DSM-based
Outline of the talk

Clinical issues

Genetics

Cognitive measures

Brain function and structure

Implications – new concepts
null
Implications

- Integrate/combine research on ASD and ADHD
- Apply theories on ASD to ADHD and vice versa
- Apply research approach used in ASD to ADHD and vice versa

Theories

1. Predictive coding – brain as a prediction machine
2. Failure of modularisation
3. Connectivity account
4. Different factors involved in etiology/genesis versus remission/recovery
5. Symptoms = secondary brain response to primary synaptic dysfunction
6. Secondary brain disease due to primary systemic disease (inflammation, microbiome, mitochondrial disease)
7. Etiology/onset due to failing/weak EF
ADHD and ASD: two manifestations of the same disorder?

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.
Synaptic Dysfunction
Autism and ADHD: developmental disorders

Humans

Children

Adults

Autism

Normal development

Functional brain maturation curve

Age

Abnormal development in NDD?

Characterization of functional connectivity with rs-fcMRI

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Radboud University Nijmegen
Theories about autism

Inattention
Hyperactivity
Impulsivity

ADHD
Neurodevelopmental disorder

This is different from a cerebral lesion in a mature brain

Wide spread ramifications of neural dysfunction towards a variety of clinical symptoms
Clinical symptoms

Compensatory processes may mask primary deficits

Abnormal neural processes

Brain

Genes

Environment
What is the problem?

Clinical symptoms

Abnormal neural processes

Noisy, less efficient information processing

Noise can be productive: leads to finetuning and optimisation

Too much noise is harmful
Brain Adaptation

Clinical symptoms due to brain adaptation

Not due to primary molecular / neural problems

Abnormal neural processes

Brain

Genes

Environment
Brain Adaptation and Alternative Developmental Trajectories

1. Redundancy
2. Reorganization
3. Niche Construction
4. Adjustment of Developmental rate

Implications – critical need of

• Studies of brain adaptation (genes and environmental factors)

• New interventions that not necessarily try to remediate the primary problems

• Studies in high-risk individuals (prior to developing symptoms, less confounded by later brain adaptation)
Onset versus Persistence vs Remission

Onset

Genes, E GxE

Remission

Genes, E GxE

Persistence

Genes, E GxE
Dynamics of Genetic and Environmental Risk Factors

Chang et al. JAMA Psychiatry 2013
Onset versus Persistence vs Remission

Different factors that influence onset and that influence remission

Onset

Genes, E
GxE

Remission

Genes, E
GxE

Persistence

Genes, E
GxE
Dynamics of Genetic and Environmental Risk Factors
The high-risk infant study design

- Participants are younger siblings of children with autism
- 20% of this group will develop autism (cf. 1% of the general population)

**High-risk**
- (1) 20% develop ASD
- (2) 80% do not develop ASD

**Controls**
- (3) 99% do not develop ASD

- Data of a European multi-site longitudinal study will be used
- Infants tested at 4, 10, 14, 24, and 36 months of age
The high-risk infant study design

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Controls
- Extend to high-risk for ADHD
Developmental Hypotheses

A. Risk factors

1. Pre/perinatal environmental risk factors
2. Genes (common, rare variants)
3. Neuroinflammation
4. Critical period, timing

Autism – early
ADHD - later
Getting answers from babies
More on the overlap between ASD and ADHD in the next symposium S6-03 17.00 – 18.30 in the Paris room
Getting answers from babies about autism

Mayada Elsabbagh and Mark H. Johnson

Centre for Brain and Cognitive Development, Birkbeck, University of London, Henry Wellcome Building, London, WC1E 7HX, UK
Questions?