Cognitive neuroscience approaches to autism
Latest perspectives

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Autism

• Autism is defined in the DSM-IV-TR as exhibiting at least six symptoms total, including
  – at least two symptoms of qualitative impairment in social interaction
  – at least one symptom of qualitative impairment in communication
  – and at least one symptom of restricted and repetitive behavior
• Sample symptoms include
  – lack of social or emotional reciprocity
  – stereotyped and repetitive use of language or idiosyncratic language
  – and persistent preoccupation with parts of objects
• Onset must be prior to age three years, with delays or abnormal functioning in either social interaction, language as used in social communication, or symbolic or imaginative play
• The disturbance must not be better accounted for by Rett syndrome or childhood disintegrative disorder
• ICD-10 uses essentially the same definition
Outline

• Cognitive-level theories
• Brain-level theories
• Genetic theories
• The environment
• At risk sibling studies
• New hypotheses
• Diagnosis and prevalence
• Screening tests – behavioural / brain / genetic
• Intervention
• Outstanding questions

My research

• Basic research rather than clinical
• Recently published studies on autism: face recognition, motion processing, neurocomputation
• Current work: study of laterality in motor movements in naturalistic situations, as a marker of cerebral organisation (with G. Forrester, D. Mareschal)
Dense data coding for behaviour

Explanatory framework: multiple levels?

- Genes
- Brain
- Cognitive
- Behaviour
- Environment
- Epigenetics

- One cause or many?
- One disorder or many?

Figure 2. Basic causal model of autism as a mentalising deficit.

Cognitive-level theories (late 80s)

- Weak central coherence
- Theory of mind
- Executive Function deficits
Brain-level theories

- Brain size
- Brain morphology
- Brain connectivity
- Micro-brain structure
- Movement artifacts?

Brain size and autism

- Autistic brains are larger at some points in development

Redcay & Courchesne (2005)

Brain morphology
Brain connectivity

- **Structural** issue in wiring up the brain?
- **Functional** connectivity: disconnection between anterior and posterior?
- Over-reliance on some **forms** of connectivity?
  - Short-range over long-range connectivity
  - Thalamo-cortico over cortico-cortico connectivity

- Relation to **cognitive** phenotype
  - Weak central coherence
  - Executive function deficits

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Micro-brain structure

Neuron number and size in prefrontal cortex of children with autism.
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Abstract

CONTEXT: Autism often involves early brain overgrowth, including the prefrontal cortex (PFC). Although prefrontal abnormality has been theorized to underlie some autistic symptoms, the cellular defects that cause abnormal overgrowth remain unknown.

OBJECTIVE: To investigate whether early brain overgrowth in children with autism involves excess neuron numbers in the PFC, DESIZN, SETTING, AND CASES: Postmortem prefrontal tissue from 7 autistic and 6 control male children aged 2 to 16 years was examined by expert anatoists who were blinded to diagnostic status. Number and size of neurons were quantified using stereological methods within the dorsolateral (DLPFC) and medial (MPPC) subdivisions of the PFC. Cases were from the eastern and southeastern United States and died between 1990 and 2009.

MAIN OUTCOME MEASURES: Mean neuron number and size in the DLPFC and MPPC were compared between autistic and control postmortem cases. Correlations of neuron number with deviation in brain weight from normative values for age were also performed.

RESULTS: Children with autism had 63% more neurons in the PFC (mean, 1.94 billion, 95% CI, 1.57-2.31) compared with control children (1.16 billion, 95% CI, 0.90-1.42; P < .002), including 75% more in DLPFC (1.57 billion, 95% CI, 1.20-1.94 in autistic cases vs 0.88 billion, 95% CI, 0.66-1.10 in controls; P < .003) and 39% more in MPPC (0.36 billion, 95% CI, 0.30-0.40 in autistic cases vs 0.24 billion, 95% CI, 0.23-0.34 in controls; P < .001). Brain weight in the autistic cases differed from normative mean weight for age by a mean of -17.5% (95% CI, 10.2%-24.0%; P < .001), while brains in controls differed by a mean of 0.2% (95% CI, -0.9% to 9.9%; P = .96). Plots of counts by weight showed autistic children had both greater total prefrontal neuron counts and brain weight for age than control children.

CONCLUSION: In this small preliminary study, brain overgrowth in males with autism involved an abnormal excess number of neurons in the PFC.

Genetic theories

- Genetic heterogeneity
- Syndromes displaying autistic symptoms may provide an opening to understanding genetic pathways
- The majority of cases involve common variants (not mutations)
- Genetic studies dependent on phenotyping – concerns this is not done carefully enough
- Twin studies of large populations suggest triad of autistic traits may have different genes underlying them
Genetics and autism

- High heritability (but not 100%)
  - Genetic cause must be probabilistic
  - Mediating factors unclear, some environmental? (pregnancy complications?)

- Some chromosomal sites implicated (5, 6, 7, 16, 20, X)

- Heterogeneity?
  - 10% cases of autism from known disorders (FraX, TS, DS)
    - Artefact of poor phenotyping?
  - 10% from spontaneous mutations? (copy number variations CNV)
  - 80% accumulation of common polymorphisms carrying risk for autism?

- Co-morbidity?
  - A common (30%) polymorphism of CNTNAP2 is found at above chance levels in both autism and SLI; a rare CNV is found in both autism and ADHD
  - Common cause of two separate disorders?

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Moss, Oliver et al. (2009)
Mean item level scores on the Repetitive Behaviour Questionnaire

Profiles of repetitive behaviour across syndromes
Moss, Oliver et al. (2009)
Mean item level scores on the Repetitive Behaviour Questionnaire

- Heterogeneous intellectual disability (56)
- Angelman (104)
- Lowe (56)
- Cornelia de Lange (101)
- Fragile X (191)
- Prader-Willi (189)
- Cri-du-Chat (58)
- Smith-Magenis (42)

Neurocomputational theories

- Variety of hypotheses about deficits at level of neurocomputation
- All need to explain how these deficits lead specifically to triad of deficits in high-level cognition
Computational models of autism

• Gustaffson (1997): self-organising maps
  – Autism = imbalance of short-range excitatory / long-range inhibitory connections on cortical maps. Too much inhibition => over-detailed features

  – Autism = a surfeit of internal resources causing over-fitting of the data (too much detail)

• McClelland (2000): neural codes
  – Autism = from too conjunctive / insufficiently componential neural codes

• Grossberg & Seidman (2006): adaptive resonance networks
  – Autism = oversensitive novelty parameter causing too many resources (over-fitting) + unstable dynamics between cortical and limbic systems

• Simmons et al. (2007): neural noise
  – Autism = increased levels of neural noise in sensory systems

• Lewis & Elman (2008): associator networks
  – Autism = brain over-growth impacting long-range (integrative) connections

The environment

• Autism is not caused by the environment
  – MMR hypothesis incorrect
  – Refrigerator parent hypothesis incorrect

• Genetic risk + environmental trigger

• Quasi-autism can be caused by (very severe) deprivation

• Early environment may be a protective factor (if genetic risk is known)
Quasi-autism following deprivation

- Romanian adoptees, 10% incidence of ‘quasi-autism’ (Rutter et al., 1999)
  - Disinhibited attachment disorder
  - Cognitive deficits (flexibility)
  - Idiosyncratic interests
  - Milder and better outcome than ASD
  - Associated with smaller head size

- Variable pattern across children: heterogeneity
Enrichment as a protective factor


**Enriched rearing improves behavioral responses of an animal model for CNV-based autistic-like traits.**

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**Abstract**

Patro-Cuapi syndrome (PTLS, MIM 604983), characterized by neurobehavioral abnormalities, intellectual disability and congenital anomalies, is caused by a 3.7-Mb duplication in 15q11.2. Neurobehavioral studies determined that 70-80% of PTLS subjects tested positive for autism or autism spectrum disorder (ASD). We previously chromosome engineered a mouse model for PTLS (Dig11) with a duplication of a 2 Mb genomic interval syntenic to the PTLS region and identified consistent behavioral abnormalities in this mouse model. We now report anterose posterior plasticity with behavioral assays established to evaluate core and associated autistic-like traits, including tests for social abnormalities, ultrasonic vocalizations, perseverative and stereotypic behaviors, anxiety, hearing and memory deficits and motor defects. Alterations were identified in both core and associated ASD-like traits. Rearing this animal model in an enriched environment mitigated some, and even rescued selected, neurobehavioral abnormalities, suggesting a role for gene-environment interactions in the determination of copy number variation-mediated autism severity.

PMID: 23423060 (PubMed: in process). PMCID: PMC3934575 (Available on 2013/7/19)

**Fathers bequeath more mutations as they age**

Genome study may explain link between paternal age and conditions such as autism.
At-risk sibling studies

- Autism is heritable
- Early markers allow early intervention
- Study development of autism in infancy
- Longitudinal studies of babies whose older sibling(s) have autism
  - Some proportion will turn out to have autism diagnosed at age 3
  - Compare to at-risk but no autism, and to controls
- Example
  - British Autism Study of Infant Siblings (BASIS)

BASIS: [www.basisnetwork.org](http://www.basisnetwork.org)

- Led by Mark Johnson (CBCD BabyLab Birkbeck)
- Collaborators
  - Tony Charman (IOE), Patrick Bolton (IOP), Simon Baron-Cohen (Cambridge), Jonathan Green (Manchester), Declan Murphy (IOP)
  - CBCD Team: Mayada Elsabbagh, Teea Gliga, Leslie Tucker, Janice Ferinand, Kim Davis, Helena Riberio
  - IOE Team: Greg Pasco, Susie Chandler, Kristelle Hudry
- Funding
  - MRC, Autistica, Autism Speaks (USA)
Example of design

What picture is emerging?

- Early behavioural indicators identified
  - Most commonly early (non-verbal) social communication behaviours
- Some surprising findings
  - Differences have not emerged before 12m
  - Early ‘engagement’ at 6m not atypical
  - Neural responses might be more sensitive than behavioural manifestations
- Different clinical vs. scientific approaches
  - Identifying risk markers for caseness/outcome
  - Understanding the ordering and interactive influences on perturbations and trajectories
New hypotheses

• Extreme male brain: empathising versus systematising

• Developmental compounding: Early social attentional deficits have knock-on effect across development

• Bayesian hypothesis: explanation of atypical perception is insufficient top-data cognition – too data driven

• Pruning hypothesis: originating in study of regressive sub-type – autism caused by over-pruning of connectivity early in development

The extreme male brain theory of autism

Simon Baron-Cohen

The key mental domains in which sex differences have traditionally been studied are verbal and spatial abilities. In this article I argue that the neglected domain for understanding human sex differences are ‘verbalising’ and ‘systemising’. The male brain is a defined prefrontal region that systematising is significantly better than empathising, and the female brain is defined as the opposite cognitive profile. Using these definitions, autism can be considered as an extreme of the central nervous system. There is increasing psychological evidence for the extreme male brain theory of autism.
Intervene early to train attention to social stimuli?
Pruning hypothesis

- Neurocomputational-level hypothesis of cause of autism
- Originates in a study of regressive sub-type

- **Pruning** is a normal phase of brain development
- **Hypothesis**
  - This is phase is *over-aggressive in autism*, damaging functional circuits to produce regression
  - Link to broader autistic phenotype - non-regressive sub-type is due to individual differences: slower development or earlier pruning
Different rates of synaptogenesis across different regions of human cerebral cortex (data from Huttenlocher & Dabholkar, 1997)
Those children with autism showing language loss were showing faster early development.

Regression might be more widespread but hidden by delay?

Figure 4 Rate of language loss by age of speech acquisition and group (as Table 2 Rule a: Autism N = 134 except for 2 with missing age at first words, SLI N = 70)

Individual differences in onset of pruning?

Relevant longitudinal empirical data on synaptic density are missing for humans.
Linking pruning to connectivity accounts?

Initial over-connectivity → Normal pruning → Aggressive pruning biased against long-range connections

Predictions of the pruning hypothesis

• Emergence of symptoms should follow the differential onset of pruning in different brain areas
  – First symptoms should be sensory and motor
• There will be genetic risk factors that are separately heritable
  – Sibling may inherit risk factor but not aggressive pruning
  – Brain size predicted to be a risk factor, not a direct cause
  – Delay predicted to be a risk factor, not a direct cause
  – In sibling studies, predicts more differences between
    • (autism + at-risk) vs. (controls) than
    • (autism) vs. (at-risk + controls)
Predictions of the pruning hypothesis

• Earliest phases of development will be typical, or reflect risk factors (delay)
• Early environment will be a protective/risk factor
  – Deprivation increases risk
  – Early intense stimulation reduces risk
• Late environment / intervention will not be able to normalise the system
  – Lost connectivity cannot be restored
  – Intervention must make the best of residual connectivity

Test hypothesis with prospective sibling studies

• Findings beginning to emerge
• Rogers (2009) reviewed initial findings on early development of children who then showed autism
  – Surprising lack of overt behavioural identifiers at 6 months
    • Normal-looking social behaviours
  – Deficits in sensory responsivity and gross motor development often appear before social problems
  – Extreme range of severity in each of the symptoms in affected toddlers
What picture is emerging?

• Early behavioural indicators identified
  – Most commonly early (non-verbal) social communication behaviours

• Some surprising findings
  – Differences have not emerged before 12m
  – Early ‘engagement’ at 6m not atypical
  – Neural responses might be more sensitive than behavioural manifestations

• Different clinical vs. scientific approaches
  – Identifying risk markers for caseness/outcome
  – Understanding the ordering and interactive influences on perturbations and trajectories

“Similar White Matter Aberrations in Children With Autism and Their Unaffected Siblings: A Diffusion Tensor Imaging Study Using Tract-Based Spatial Statistics”

Naama Barnea-Goraly; Linda J. Lotspeich; Allan L. Reiss
Arch Gen Psychiatry. 2010;67(10):1052-1060

“both the autism and sibling groups had widespread, significantly reduced white matter fractional anisotropy values . . . white matter structure may represent a marker of genetic risk for autism or vulnerability to development of this disorder”
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Diagnosis

• Criteria for autism being changed in new DSM5
  – Types subsumed into a spectrum (autism, Aspergers, PDD-NOS, Childhood Disintegrative Disorder)
  – Two dimensions instead of triad: social and communication domains combined
  – Some concern that certain individuals would miss out on a diagnosis (mild, no learning disability)
  – Parents are worried
Incidence

• Has the incidence of autism increased?
• Or is there a shift in diagnosis type?
• Bishop blog (4.6.12):
  – Modern environment increases risk? [what factors?]
  – Assortative mating or older parents increases genetic risk [too slow]
  – Diagnostic substitution (from SLI, semantic-pragmatic, learning disability) [probably]
  – Diagnostic sensitivity [possibly some mild cases]

Comorbidity

• Gillberg (2010): diagnosis of ‘learning disability’ is dropping as ‘autism’ is rising
  – Comorbidity of ASD provides basis for diagnostic substitution:
    ASD is almost never an isolated phenomenon. Co-existing problems and disorders are the rule. These include learning disability (including non-verbal learning disability), epilepsy, motor control problems, ADHD, depression, and anxiety, gastrointestinal problems, and sleep disorders.
Screening tests
Behavioural / brain / genetic

• Is there a more reliable diagnostic marker for autism than behaviour? (Brain? Genes?)
• Finding reliable differences between disorder group and controls is different from designing a screening test
  – Screening tests need to be sensitive (pick up all cases) and specific (not pick up non-cases or other disorders)
• Recent claims:
  – Brain structure to detect Asperger’s syndrome
  – Genetic markers to predict autism
Screening tests: Bishop blog 3.7.10

- Four key considerations for a screening programme: take-up, costs, accuracy, and intervention
- Importance of base rate of disorder in population
  - Example: Oller et al. (2010): using vocal analysis to diagnose autism - sensitivity of 0.75 and specificity of 0.98

![Participant group size in study](image)

![Base rate corrected: autism 1%](image)

Diagnosis on brain structure: Ecker et al.

- Five ADULT brain structure measures (extension to children remains to be tested)
  1. The average convexity or concavity of large-scale features of the brain surface. This measures sulcal depth and gyral height
  2. Mean (radial) curvature. This assesses number of smaller convolutions on the surface of the brain.
  3. A measure of the degree of cortical folding in terms of metric distortion relative to an average template.
  4. Cortical thickness
  5. Pial area, a measure of the grey matter surface.
- Only classifier based on left hemisphere measures was effective
- Same classifier applied to ADHD group: 4 of 19 cases were classified as autistic, rest non-autistic

![Participant group size in study](image)
Intervention

- Recent systematic reviews of interventions
  - Behavioural, pharmacological
- Interventions do not normalise the cognitive system
- Training must be intense and prolonged, and generalisation of effects is unclear
- Evidence supports
  - Early intensive behavioral and developmental intervention for improving cognitive performance, language skills, and adaptive behavior in some groups of children
  - Promising for early intensive intervention under 2 years (data preliminary)
- Interventions focusing on providing parent training and cognitive behavioral therapy (CBT) for bolstering social skills and managing challenging behaviors useful for children with ASDs to improve social communication, language use, and symptom severity
- Challenging behaviours can be reduced by anti-psychotic drugs but there are side-effects; medication ineffective for social / communication symptoms
- A lot of treatments out there (health therapies, complementary, behavioural, educational) but not rigorously evaluated
Outstanding questions

• One disorder or many? (Sub-types?) One cause or many?
• Link between typical personality dimension and disorder?
• Relation of intellectual ability to autism dimension?
• What predicts whether an intervention will work on a given child?
• Intervene by altering behaviour versus controlling environment?
• Main stream or special education?

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