The Foetal Testosterone Theory of Autism

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Collaborators

• Psychology and Brain Scanning
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• Hormones and Genetics
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Autism Spectrum Conditions

- Social and communication difficulties
- Narrow interests/obsessions/routines
- Classic autism: 4:1 (male:female)
- Asperger Syndrome: 9:1
- 1% of the population
Why single out foetal testosterone?

• Male foetuses produce twice as much testosterone

• Individual differences are 20-fold

• Testosterone has organizational effects on brain development
Sex differences in the brain

Males > Females
- INAH (interstitial nuclei of the anterior hypothalamus)
- Amygdala
- Planum parietale
- Planum temporale

Females > Males
- BST (bed nucleus of the stria terminalis, hypothalamus)
- Corpus callosum
- Anterior commissure

From Hines 2003
Spontaneous Toy Choice

**Vehicles, constructional**

**Dolls, emotional stories**

Hines 2003
Spontaneous toy choice: monkeys

Alexander and Hines 2002
Occupations and Sex Ratios

math, computing, physics, engineering, tool-making

Primary school teaching, counseling

SAT-Maths 1972-97
Empathy and Systemizing

• **Empathy (E)**
  – Identifying another person’s thoughts and feelings
  – responding with an appropriate emotion

• **Systemizing (S)**
  – Analysing or building a system
  – Mechanical, abstract, natural, collectible
sarcastic  stern

suspicious  dispirited

Females  Males  AS

x  22.1  19.5  16.6
sd  (2.0)  (2.6)  (2.9)

JCPP  1997
The Empathy Quotient (EQ)

- People often tell me I went too far in driving my point home in a discussion

- I often find it difficult to judge if something is rude or polite

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>AS</td>
<td>20.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Males</td>
<td>41.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Females</td>
<td>47.2</td>
<td>10.2</td>
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JADD 2004
## Systemizing Mechanics

<table>
<thead>
<tr>
<th></th>
<th>AS</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Males</td>
<td>16.3</td>
<td>10.3</td>
</tr>
<tr>
<td>Females</td>
<td>(3.1)</td>
<td>(2.8)</td>
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**Diagram:**

If the wheel rotates as shown, P will
(a) move to the right and stop
(b) move to the left and stop
(c) move to and fro
(d) none of these

**References:**
- JADD, 2004
- Int J. Learning Dis, 2001
The Systemizing Quotient (SQ)

- If I were buying a car, I would want to obtain specific information about its engine capacity.
- If there was a problem with the electrical wiring in my home, I'd be able to fix it myself.

<table>
<thead>
<tr>
<th>Group</th>
<th>SQ</th>
<th>SEM</th>
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<tbody>
<tr>
<td>AS</td>
<td>35.9</td>
<td>(15.2)</td>
</tr>
<tr>
<td>Males</td>
<td>30.3</td>
<td>(11.7)</td>
</tr>
<tr>
<td>Females</td>
<td>24.1</td>
<td>(9.5)</td>
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</tbody>
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Proc Royal Soc 2003
Attention to detail: Prerequisite for systemizing

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>AS</th>
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<tbody>
<tr>
<td></td>
<td>66.7</td>
<td>46.2</td>
<td>32.2</td>
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<tr>
<td></td>
<td>(36.7)</td>
<td>(20.5)</td>
<td>(27.0)</td>
</tr>
</tbody>
</table>

JCN, 1997
fMRI studies: females > males

Eyes Test

Embedded Figures Test

Brain and Cog (2006)
E-S Model

Empathizing

Systemizing

<table>
<thead>
<tr>
<th>Type B</th>
<th></th>
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<tbody>
<tr>
<td>Type E</td>
<td></td>
</tr>
<tr>
<td>Type S</td>
<td></td>
</tr>
<tr>
<td>Extreme E</td>
<td></td>
</tr>
<tr>
<td>Extreme S</td>
<td></td>
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</table>
Plotting individuals by EQ and SQ
### % showing each profile

<table>
<thead>
<tr>
<th>Diff</th>
<th>Case</th>
<th>Men</th>
<th>Women</th>
<th>AS</th>
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</thead>
<tbody>
<tr>
<td>E &gt; S</td>
<td>female brain</td>
<td>17</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>S &gt; E</td>
<td>male brain</td>
<td>54</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>S &gt;&gt; E</td>
<td>extreme male</td>
<td>6</td>
<td>0</td>
<td>65</td>
</tr>
</tbody>
</table>
Innate sex differences?

Infant Behavior and Dev (2000)

<table>
<thead>
<tr>
<th></th>
<th>Face</th>
<th>Mobile</th>
<th>Equal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>25</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>Girls</td>
<td>36</td>
<td>17</td>
<td>47</td>
</tr>
</tbody>
</table>
Amniotic testosterone

Injection of FT masculinizes female rat brain and behaviour

Produced by testes and adrenal glands, crosses blood brain barrier

Binds to androgen receptors in cytoplasm, modulates serotonin and GABA, and prevents apoptosis
Testosterone production

Produced by testes in boys and adrenal glands in girls

Hines (2003)
Follow-up study

12-19 weeks in pregnancy:
- amniocentesis

12-24 months:
- eye contact,
- vocab

8 yrs:
- empathy, systemizing, attention, MRI, autistic traits
Eye contact at 12m

Infant Behav. & Dev. 2002

Looking up at the face during a 10 minute play session
Vocabulary size at 24m

Which of these words does your child know and produce?
My child would worry about how another child would feel if they weren’t invited to a party.

My child gets upset at seeing others crying or in pain.

**Empathy (EQ) at 8 yrs**

Social Neurosci 2006
My child likes to collect things

My child is interested in different types of vehicles

Systemizing at 8 yrs

Euro J Endocrin 2006
Embedded Figures Test at 8 years old

Find the target shape as quickly as you can

Auyeung et al, submitted
FT and autistic traits (AQ)

JADD, 2001; Auyeung et al, 2009

My child prefers to do things with others rather than on his/her own.

My child prefers to do things the same way over and over again.
FT and the corpus callosum

Hofer method

(Chura et al 2009)
10 sex steroid genes show nominally significant association with AQ, EQ, or Asperger Syndrome

Chakrabarti et al, 2009  
*Autism Research*
3 sex steroid genes remain significant after permutation testing

(*= survived in both expts)
using UNPHASED and PLINK, 1000 permutations, taking the minimum p value
FWER-corrected p value

• *CYP11B1  8q21 mutated in CAH
  (CYTOCHROME P450, FAMILY 11, SUBFAMILY B, POLYPEPTIDE 1)

• ESR2  14q23.2 masculinizes brain
  (ESTROGEN RECEPTOR)

• CYP17A1  10q24.3 mutated in PCOS
  (CYTOCHROME P450, FAMILY 17, SUBFAMILY A, POLYPEPTIDE 1)
Other Evidence for the androgen theory

- **Timing of puberty**
  (Tordjeman et al, 1997; Knickmeyer et al, 2006; Ingudomnukul et al, 2007)

- **Testosterone related disorders** in women with AS and their mothers
  PCOS, breast and ovarian cancers, acne (Ingudomnukul et al, 2007)

- **Testosterone related characteristics** in women with AS and their mothers
  Hirsutism, tomboyism, bisexualism and asexualism (Ingudomnukul et al, 2007),
  and masculinized play (Knickmeyer et al, 2008)

- **Lower 2D:4D** ratio in autism, AS, and parents
  (Manning et al 2001; Swettenham et al, 2006)

- **SRD5A1, and AR genes** associated with autism
  (Henningsgson et al, 2009; Hu et al, 2009)

- **Congenital Adrenal Hyperplasia (CAH) females** have elevated AQ
  (Knickmeyer et al, 2006)
Conclusions

- There are average sex differences in the mind

- Foetal testosterone is associated with these psychological sex differences

- Testosterone, and the genes that control it, may be important in autism
For more information

www.autismresearchcentre.com

Thanks to:
The Nancy Lurie Marks Foundation
Medical Research Council UK
Target Autism Genome
SNP selection

- 216 SNPs
- Minor allele frequency of >0.2 in Caucasians
- SNPs chosen randomly across the gene
- Median SNP density was 1 SNP per 14.1kb
- Buccal smear DNA
- PCR based assays for genotyping
  - (Taqman, Applied Biosystems Inc)
Pathways in testosterone synthesis
The Eyes Test: brain activity

bilateral inferior frontal

Females > Males

Brain and Cog (2006)
Embedded Figures Test: brain activity

left fusiform & visual cortex

red: left
blue: right visual cortex

Females > Males

Brain and Cog (2006)
Analysis

• AQ and EQ:
  – Kruskal Wallis (non-parametric) ANOVA for each SNP because AQ-EQ were not normally distributed
  – A chi square was generated from this.

• Case-Control
  – Only included n = 155 controls with AQ < 25
  – Cochrane Armitage and then a Pearsons, for each SNP

• Correction for Multiple SNPs and Multiple phenotypes
  – Permutation Testing (using UNPHASED and PLINK)
  – 1000 permutations, taking the minimum p value
  – FWER-corrected p value
SNP in ESR2 associated with AQ

grey = ASC, black = controls