22 q DS and autism spectrum disorder (ASD)

Research Autism/Lorna Wing series; The autisms: the significance of medical and other co-occurring conditions in autism

Implications for developments, diagnosis, assessment and intervention

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ASD

- Complex heterogeneous disorder
- Social, communication, restricted/repetitive
- Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, Le Couteur 1994)
- Brain imaging
- Genetics (Abrahams & Geschwind 2008)

How can genetics help us to understand ASD? Abrahams & Geschwind 2008)

- Growing list of genes in ASD
- Challenge: understand effect of genes on brain development and function
- single-gene syndromes (eg, 22q) - have ASD at much higher frequency than expected
- No single cause of ASD accounts for more than 1-2% of cases, so ASD-related syndromes important
- Study of known genetic syndromes/ASD may identify shared core features that are central to pathogenesis

ASD related syndromes (Abrahams & Geschwind 2008)

ASD-related syndromes

Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome
15q duplication — Angelman syndrome	*UBE3A* (and others)	>40%	1–2%
16p11 deletion	Unknown	High	~1%
22q deletion	*SHANK3*	High	~1%
Cortical dysplasia-focal epilepsy syndrome	*CNTNAP2*	~70%	Rare
Fragile X syndrome	*FMR1*	25% of males; 6% of females	1–2%
Joubert syndrome	Several loci	25%	Rare
Potocki–Lupski syndrome	Chromosome position 17p11	~90%	Unknown
Smith–Lemli–Optiz syndrome	*DHCR7*	50%	Rare
Rett syndrome	*MECP2*	All individuals have Rett syndrome	~0.5%
Timothy syndrome	*CACNA1C*	60–80%	Unknown
Tuberous sclerosis	*TSC1* and *TSC2*	20%	~1%

ASD related syndromes

- Comparative study of rare syndromes may help identify molecular features common to a variety of ASDs
- Within disorders, contrasting cases with and without ASD-like features may be informative (Abrahams & Geschwind 08)

Why is 22q important for ASD?

People with 22q DS -

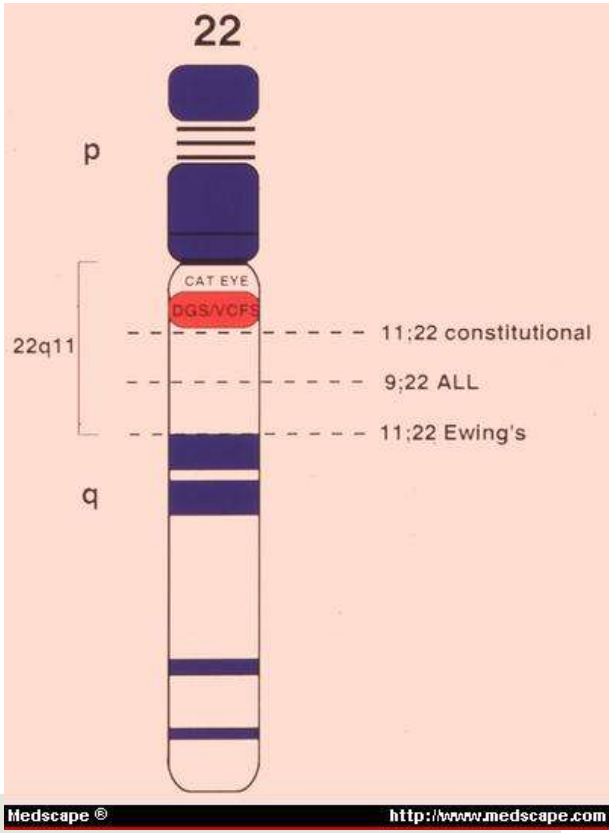
- Increased vulnerability to ASD (+ ADHD, affective disorders, psychosis) (Fine 2005, Gothelf 2007)
- These disorders are associated with differences in brain anatomy and function
- 22q DS - unique opportunity to understand the neurobiology of ASD

What's in a name?

- mid 60's - Di George syndrome
- 1978 - Shprintzen syndrome
- Mid 80's - genetic testing: 90% of pts = deletion on 22q11
- Velocardiofacial syndrome (VCFS)
- if known chromosome 22q11.2 deletion = **chromosome 22q11.2 deletion syndrome (22 q DS)**
- If clinical presentation but no known cause = DiGeorge syndrome

22q DS: a genetically determined neurodevelopmental disorder

- Microdeletion of chromosome 22q11
- 1:2500-1:4000 births (Oscarsdottir et al, 04)
- most common microdeletion syndrome
- FISH test
- 90% de novo
- ~ 10 % - parental inheritance

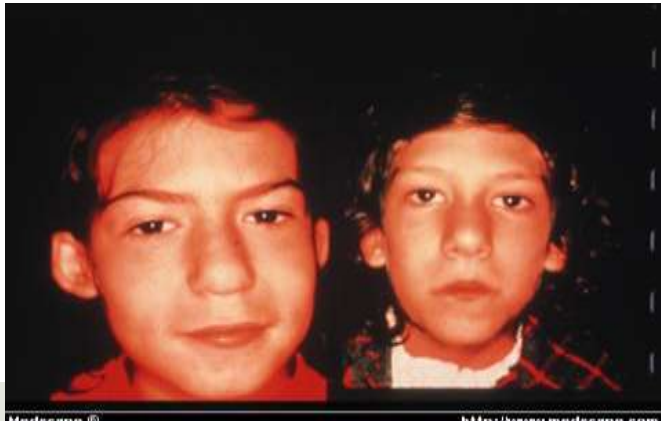


22q DS

Complex medical presentation (Gothelf 04)

- 75 % congenital cardiac anomalies
- 70% palate, dysmorphic facial features (Shprintzen 00)
- Renal, calcium & thyroid abnormalities
- leg pain/cramp, immunological

Neuropsychiatric/learning difficulties



22q DS and ASD

- Fine 2005: N = 98, 2-12 y old. (SCQ/ADI) 11% = autism, 14% = ASD
- Vorstmann 2006: N = 60, 9-18 y old. 50% ASD (N= 27 PDDNOS, N = 3 autism)
- Antshel 2007: N = 41, 6 – 16y old. 19% = autism, 21% = ASD (ADI)
- Murphy et al (preliminary data): n = 45, SRS 36% positive/DBC 30%. F > M
- ? difference to idiopathic ASD

Catechol-O-methyl transferase (COMT)

- COMT = enzyme critical in breakdown of dopamine, a key transmitter thought to influence cognition
- 22q - carry only 1 copy of COMT:

COMT 158 Met = low COMT activity

COMT 158 Val = higher COMT activity

- If Met - get more dopamine in PFC (Askoy 93)
- PFC: EF/sustained attention/verbal working memory
- COMT/22q: significant association: ADHD & OCD (Gothelf 07)
- COMT/22q: frontal and cerebellum (van Amelsvoort 07)

Case Study

- 19 y old male
- 22q DS diagnosed at 13y; seizures/low calcium
- Recurrent infections, low thyroid
- CAMHS refused care
- Residential College Hampshire
- ASD, ADHD (inattentive)
- Ix: cardiac, IQ, family genetics, genetic counselling
- liase w/ college, transition adult services - ?LD/CMHT, NAS

UK services

- Great Ormond Street 22q clinic - multidisciplinary: paeds, genetics, immuno, SALT, psychology, psychiatry. 5 yr reviews.
- Behaviour Genetics Clinic Maudsley: National Specialist Service: multidisciplinary psych assessment and management recommendations for adults with ASD, 22q DS
- Regional Cleft clinics
- Max Appeal
- Refer to paeds/CAMHS, planned transition to adult teams

What can 22q DS learn from ASD?

- 22q – markedly limited mental health input
- Young organisation (Maxappeal.org.uk)/NAS
- International guidelines (Bassett et al 2011)
- UK guidelines due 2011

Future

Clinical services

Education of professionals

Adequate sample size

Robust assessments (MRI, behavioural, genetic, IQ)

Longitudinal studies

Treatment trials – psychological & medication

Sum

- 22q DS: complex neurodevelopmental condition
- Physical and neuropsychiatric symptoms
- Childhood: ASD, ADHD
- Late adolescence: emerging psychosis
- Model for investigating path from genes to brain development for ASD

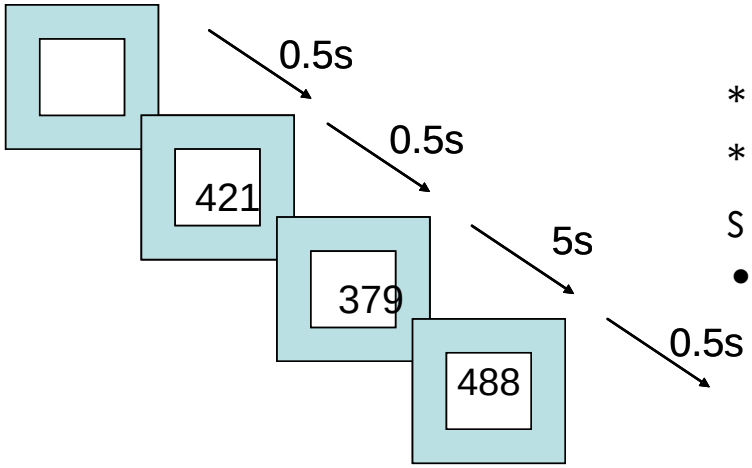
Sustained attention

Subjects 60 males, 11-18 years old, R handed, IQ > 70

- 20 ASD. ICD-10, ADI and ADOS. No ADHD (Conners,SDQ). Meds naive
- 20 ADHD. DSM-IV, Conners, SDQ. No ASD (SCQ). 50% stimulants; meds free 36 hrs pre scan.
- 20 typically developing controls
- No differences in age, IQ or motion
- Exclusion criteria: head injury, abnormality on MRI brain, genetic disorder associated with ASD (FRAX, TS, 22q), drug/alcohol dependency

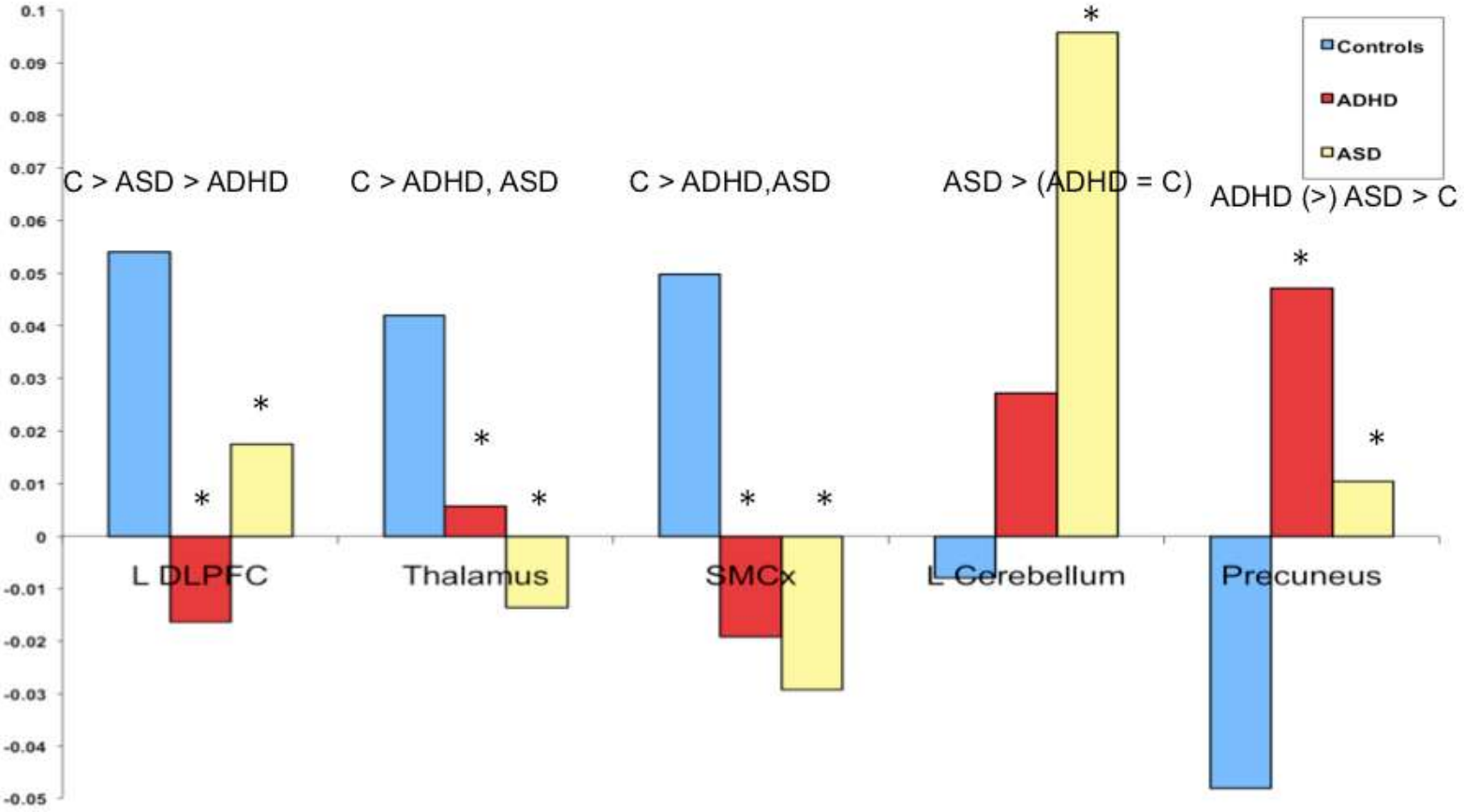
Sustained Attention Task

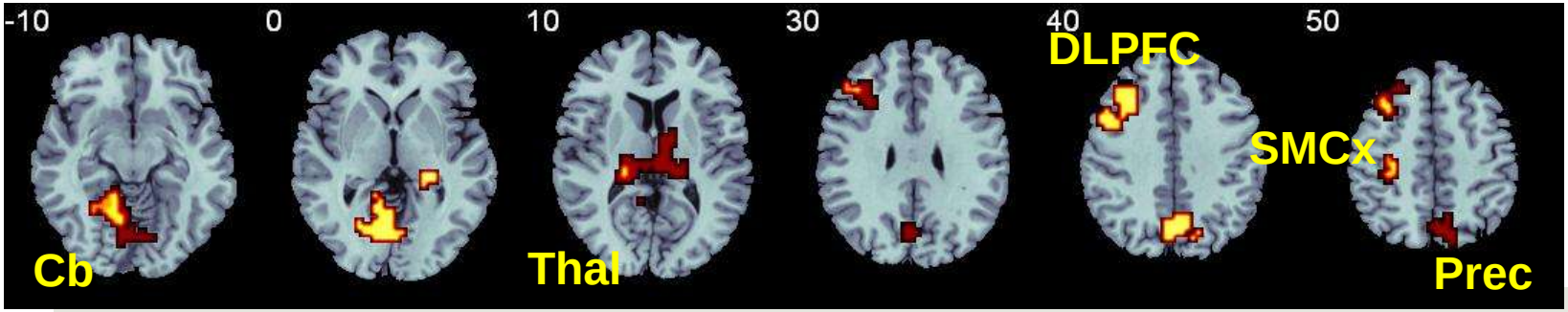
- 3T, XBAM non-parametric data analysis (Brammer 1997)
- 12 minute randomised event related



* 1 short predictable delay: 0.5 s
* 3 long, unpredictable delays: 2 s, 5s, & 8 s
- 300 trials: 240 short delays and 20 of each long delay

Results 2: Group Effect

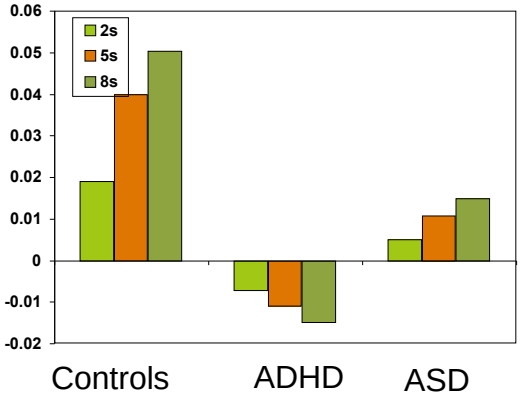




Results 3: ANOVA Group by Delay Interaction

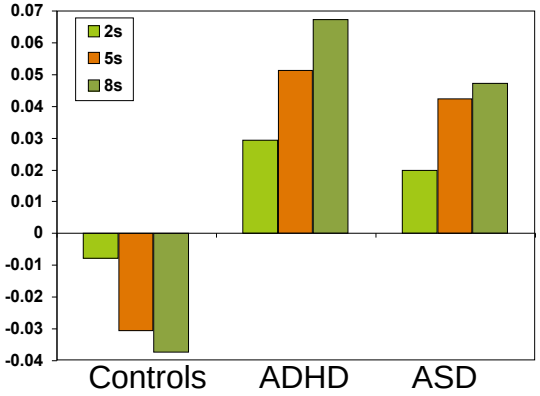
C > ASD > ADHD

L DLPFC



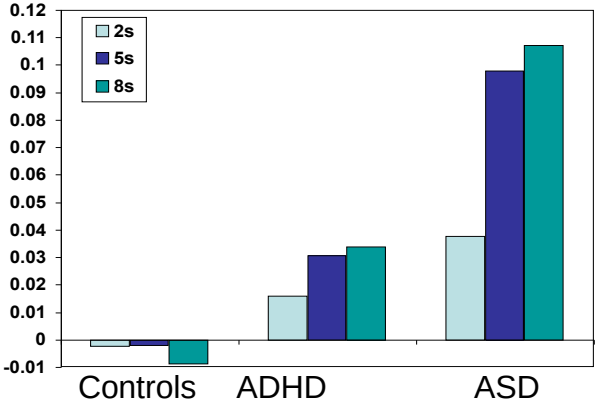
ADHD (>) ASD > C

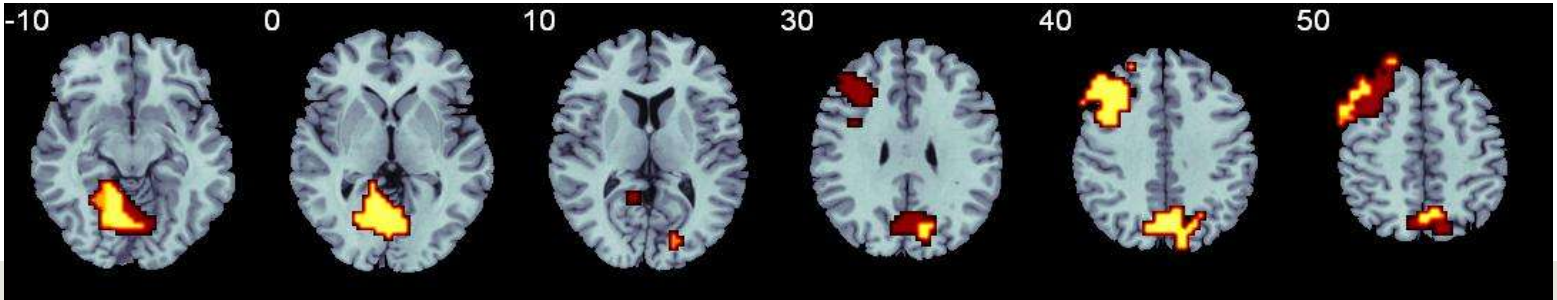
Precuneus



ASD > (ADHD + C)

L cerebellum





Summary: Fronto-thalamic Cerebellar Dysregulation

- Frontostriatal-thalamic cb loops: typical sustained attention (Lawrence 03)

Underactivation of left fronto-thalamic and over-activation of posterior areas

Common abnormalities to ASD and ADHD

- deficits in left fronto-thalamic networks and sensorymotor cortex
- compensation in posterior areas

Disorder specific differences

- ADHD: L DLPFC more impaired
- ADHD: increased precuneus (trend)
- ASD: L Cb significantly increased

Thank you

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