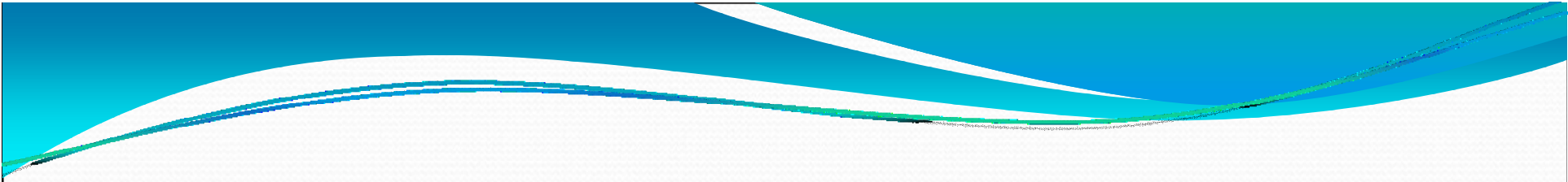


ADHD THROUGHOUT THE LIFE CYCLE:

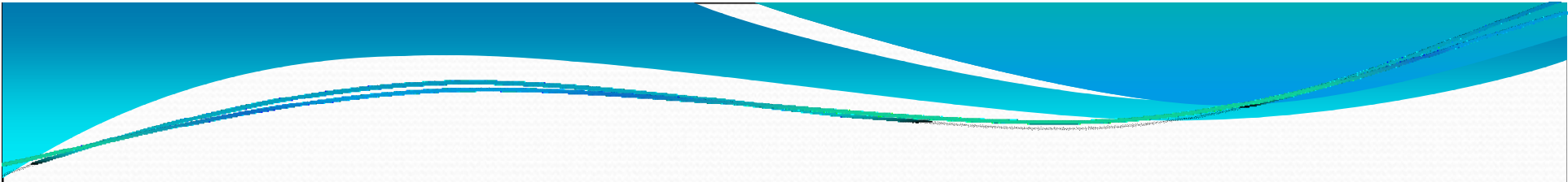
Epidemiology, Genetics, Neurobiology and
Developmental Course of Attention Deficit
Hyperactivity Disorder with a focus on Adult ADHD

Robin Moir



Conflict of Interest Disclosure

- Honorarium for this talk:
Janssen-Cilag
- Conference on Atomoxetine and ADHD:
Eli Lilly, Indianapolis, Indiana, 2002



Definition and Impact of ADHD

- Attention Deficit Hyperactivity Disorder is an early onset, clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity
- Its impact on society is enormous in terms of financial cost, stress to families, adverse academic and vocational outcomes, and negative effects on self-esteem

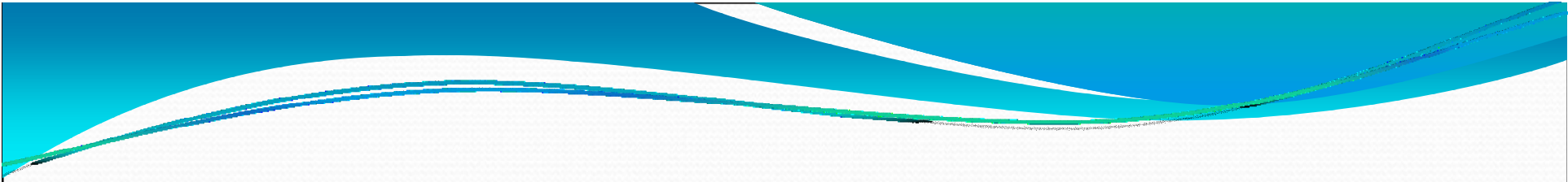
Faraone and Biederman 1999

History of ADHD

- 1902 – Clinical report of children with markedly hyperactive and disruptive behaviours (Still, Lancet)
- 1930's – Minimal brain damage, minimal brain dysfunction, hyperactive child syndrome
- 1968 – Hyperkinetic reaction of childhood (DSM-II)
- 1980 – Attention deficit disorder (DSM- III)
 - ADD with hyperactivity, without hyperactivity, residual type
- 1986 – Attention deficit hyperactivity disorder (DSM- IIIR)
 - No subtypes
- 1994 – Attention deficit/hyperactivity disorder (DSM-IV)
 - Predom inattentive, predom hyperactive, combined

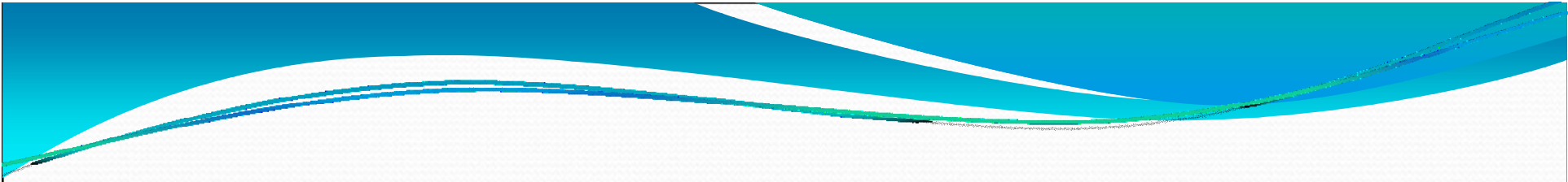
DSM-IV Diagnostic Criteria

- A. Six (6) or more symptoms of either category of inattention or hyperactivity-impulsivity of at least 6 months duration
- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of 7 years
- C. Some impairment from the symptoms is present in two or more settings (e.g. home, school, work)
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
- E. The symptoms are not better accounted for by another mental disorder (PDD, Schizophrenia, Mood or Anxiety Disorder etc)



Inattentive Symptoms

- Fails to pay close attention to detail or makes careless mistakes
- Has difficulty sustaining attention
- Does not seem to listen when spoken to
- Does not follow through on instructions or complete tasks
- Has difficulties organising activities and tasks
- Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
- Often loses things needed for tasks or activities
- Easily distracted by extraneous stimuli
- Forgetful in daily activities

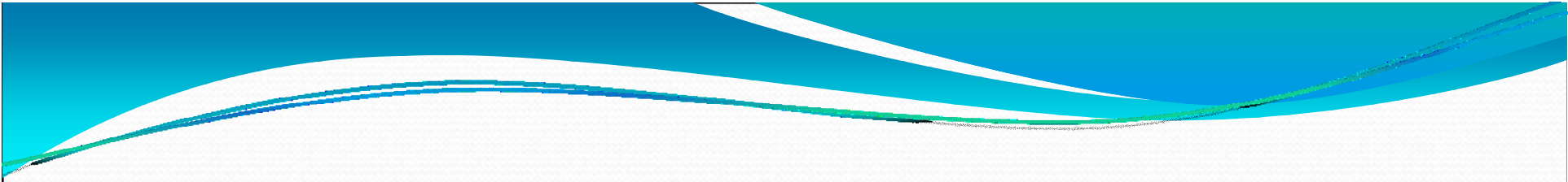


Hyperactive-Impulsive Symptoms

- Fidgets with hands or feet and squirms in seat
- Leaves seat in classroom or in other situations where this is inappropriate
- Runs about or climbs excessively
- Has difficulty playing or engaging in activities quietly
- “On the go” or as if “driven by a motor”
- Talks excessively
- Blurts out answers before question is completed
- Difficulty waiting turn
- Interrupts or intrudes on others

Subtypes of ADHD

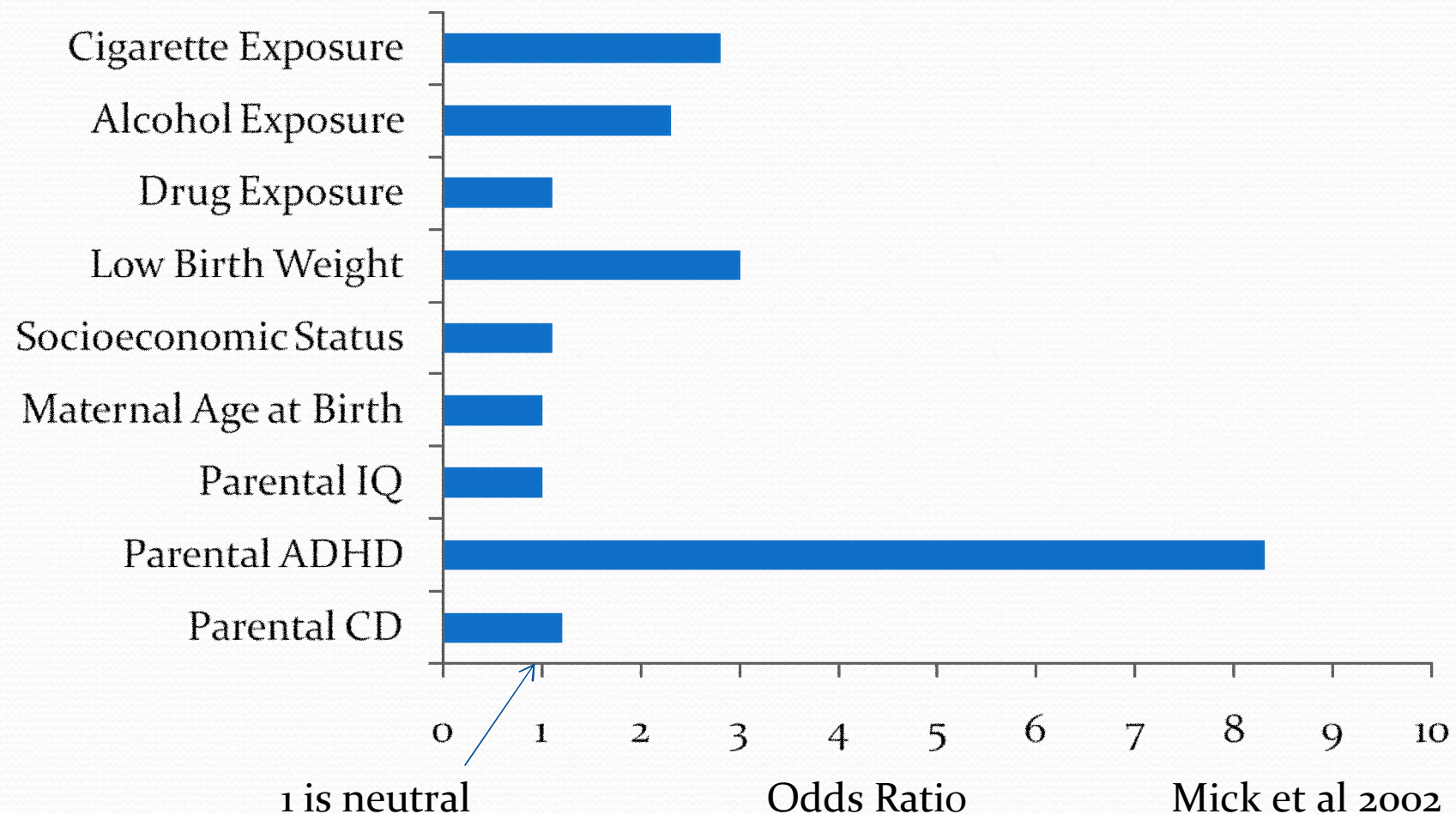
- Combined type : 6 or > of both inattentive and hyperactive –impulsive symptoms
- Predominantly Inattentive type: 6 or > inattentive symptoms but <6 hyperactive-impulsive symptoms
- Predominantly Hyperactive-Impulsive type: 6 or > hyperactive-impulsive symptoms but <6 inattentive symptoms

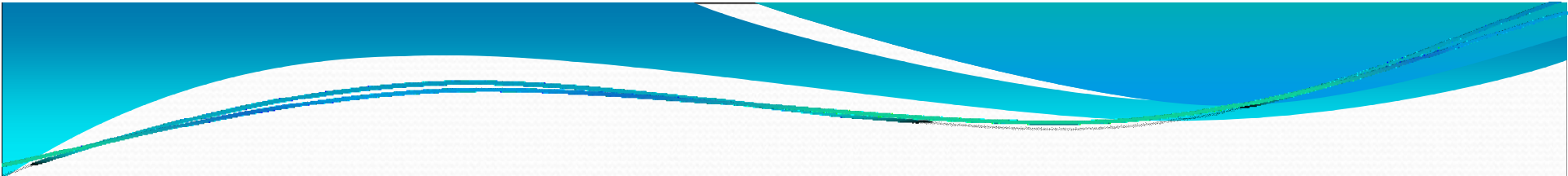


Aetiology of ADHD

- May involve at least four classes of causal agents
 - Genes
 - Pregnancy and delivery complications
 - Psychosocial adversity
 - Exposure to toxins

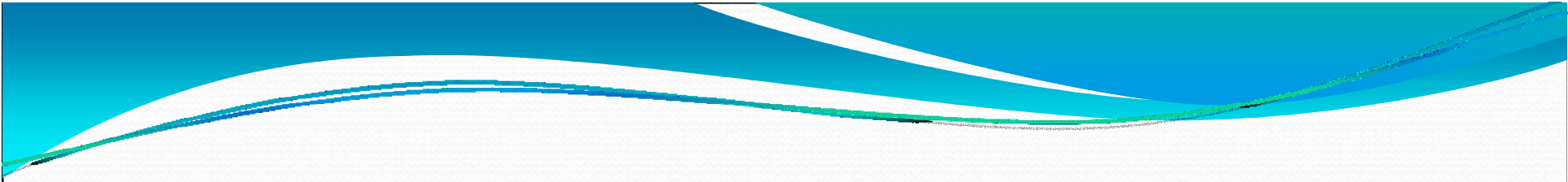
Odds Ratios for Prenatal and Perinatal Risk Factors for ADHD vs Controls





Clinical Epidemiology

- Among the most frequent neurobehavioural disorders in the paediatric age group
- Prevalence of 8-12% worldwide (Faraone et al 2003)
- Males affected 4 times more than females

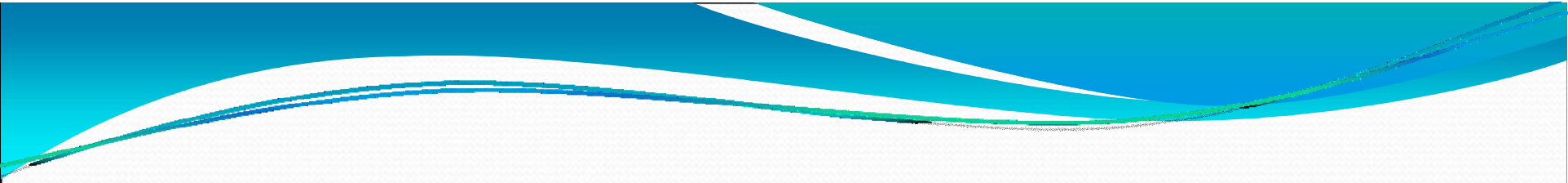


Genetic Epidemiology

- Genetics play an important aetiological role
- Based on multiple lines of investigation
 - Twin and adoption studies
 - Genomewide scans
 - Candidate gene studies

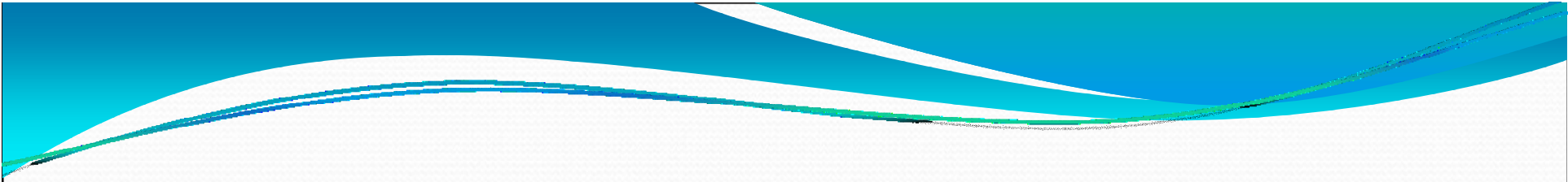
Family Studies

- Increased hyperactivity in relatives of hyperactive children vs controls
- Demonstrate vertical transmission within families
- Structured interviews of relatives of ADHD males – 31.5% vs 5.7% in controls (Biederman et al 1986)
- Risk among parents of ADHD children - increased between two and eightfold
- Increased risk of ADHD associated with parental substance use disorders and low birth weight
- Family studies cannot disentangle genetic and environmental factors



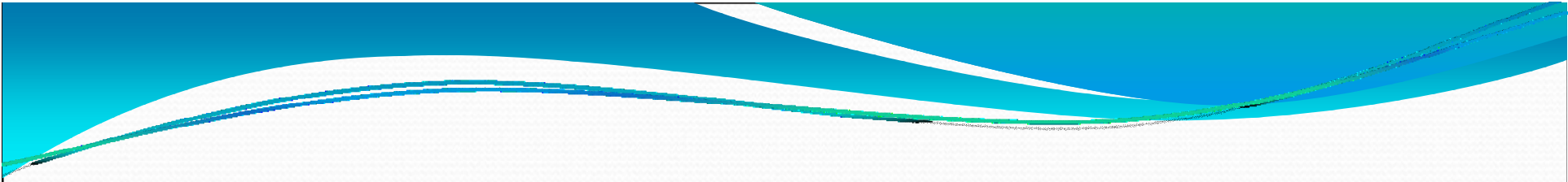
Twin Studies

- Approximately 20 ADHD twin studies conducted in United States, Europe, and Australia (Faraone 2004)
- The mean heritability estimate from these studies calculated to be 74% (Faraone 2004)



Twin Studies- contd

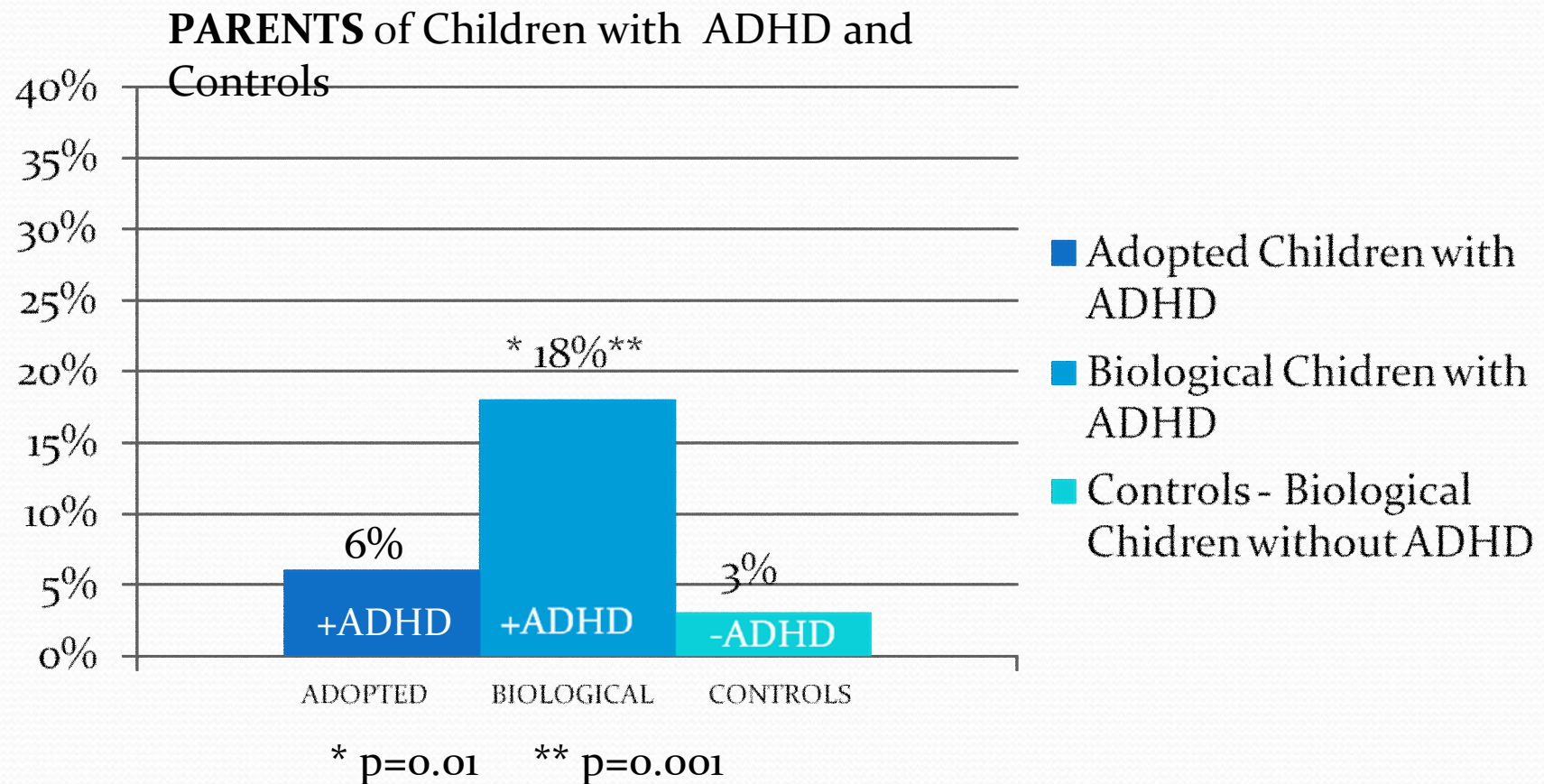
- Goodman and Stevenson (1989) – large study of 102 MZ twins and 111 same-sex DZ twins
 - Heritability accounted for 30-50% of variance of the inattentive and hyperactive symptoms
 - Common environment effects accounted for <30% of the variance



Adoption Studies

- Sprich et al (2000) – study of 25 adopted children with ADHD, 101 nonadopted probands with ADHD and 50 nonadopted, non- ADHD controls
- Compared rates of ADHD and associated disorders in first-degree adoptive relatives of adopted probands versus first-degree biological relatives of nonadopted probands with ADHD and of control probands
- 6% of adoptive parents of adopted probands with ADHD had ADHD
- 18% of biological parents of probands with ADHD had ADHD
- 3% of the biological parents of the controls had ADHD

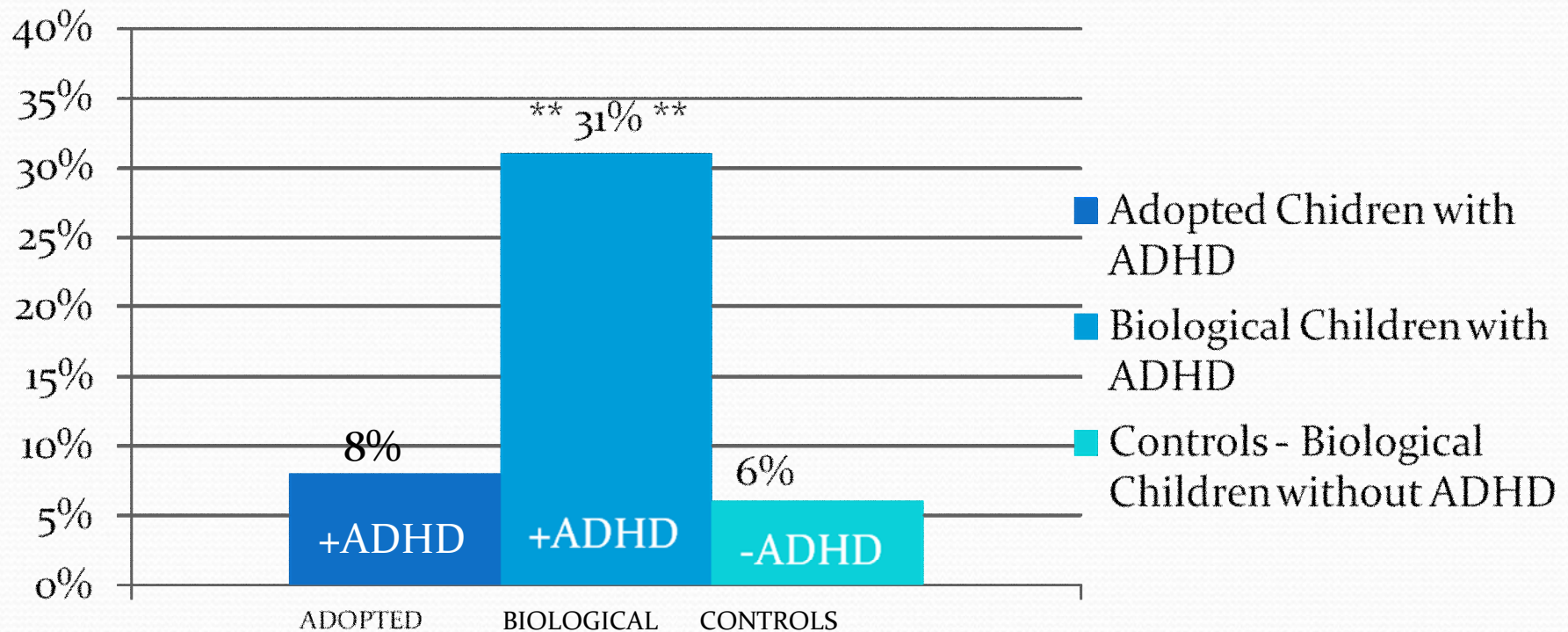
Rates of ADHD in Relatives



Sprich et al 2000

Rates of ADHD in Relatives

SIBLINGS of Children with ADHD and Controls



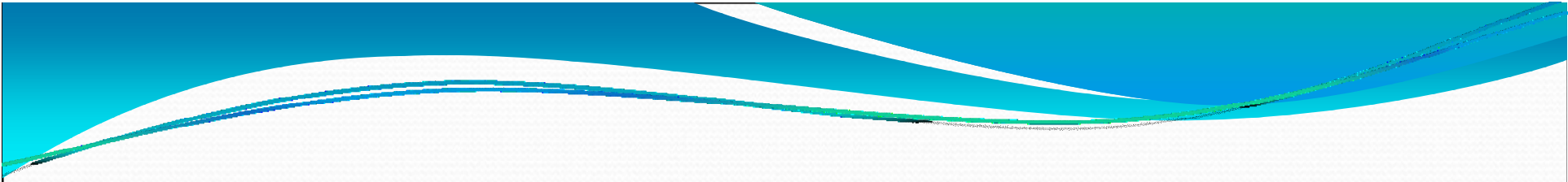
** $p=0.001$

Sprich et al 2000

ADHD compared with other Psychiatric Disorders

Psychiatric Disorder	Relative Risk (RR)	Heritability
Autism	22	93
Tourette's Syndrome	12	90
Bipolar Disorder	8	85
Schizophrenia	12	84
ADHD	4	75
Anorexia Nervosa	14	71
Major Depression	4	37
Alcohol Abuse	2	36
Generalised Anxiety Disorder	6	32
Social Phobia	4	25

Glatt et al 2008



Molecular Genetics

- Linkage Studies

Peak Regions – LOD>3: 5q15, 7p13, 16p13
LOD>2: 9q33

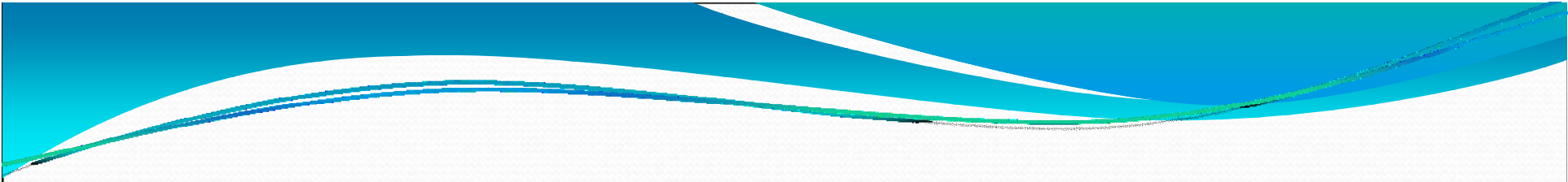
- Candidate Genes with Prior Positive Reports

DAT/SLC6A3, DRD4, DRD5, DBH, HTR1B, 5-HTT, SNAP-25

- Genetic Syndromes with Similar Symptoms

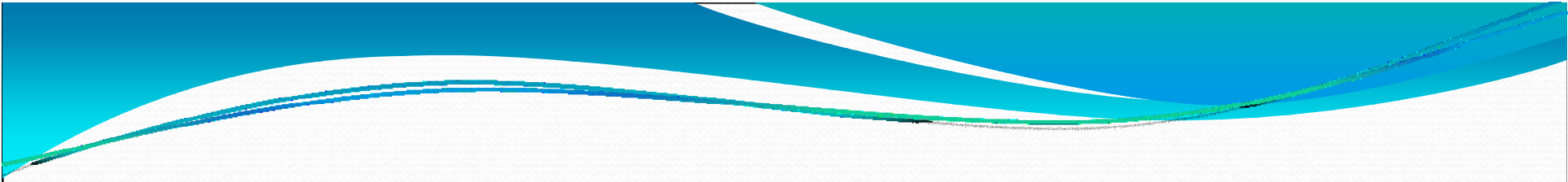
Fragile X Syndrome, Neurofibromatosis, Klinefelter's Syndrome, Turner's Syndrome, Prader-Willi Syndrome, Williams Syndrome, Smith Magenis Syndrome, X-linked adrenoleukodystrophy

Stewart and Pauls 2008



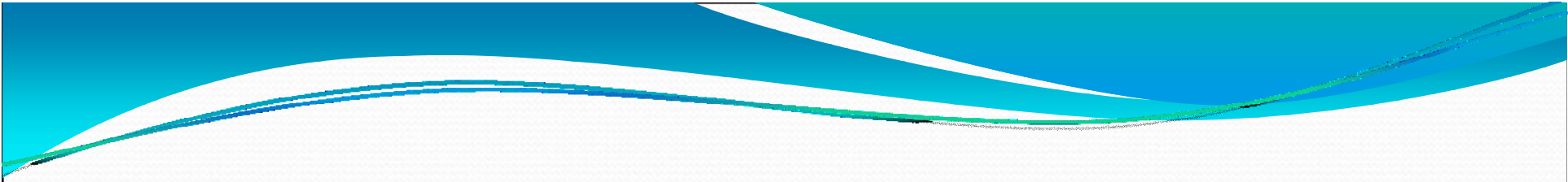
Summary of ADHD Genetics

- ADHD is a clinically heterogeneous disorder. This suggests that the genotype will also be heterogeneous.
- Genetic factors play an important role in the aetiology of ADHD.
- Genetic studies indicate that transmission patterns result from the presence of multiple genes of small effect.
- It is clear that the phenotypic expression is considerably influenced by gene-environment interaction.



Pathophysiologic Models of ADHD

- Similarities between clinical presentation of ADHD and neurological patients with frontal and especially prefrontal lesions
- This suggests that ADHD is a brain disorder substantially affecting the prefrontal cortex
- Evolving models of pathophysiology
 - Deficits in response inhibition
 - Deficits in multiple related neural circuits



Deficits in Response Inhibition

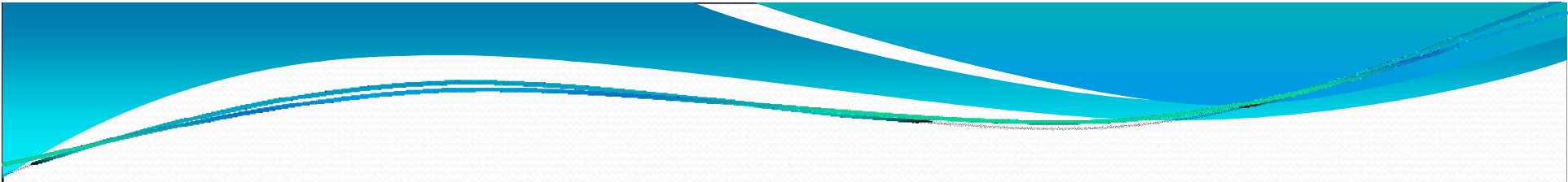
- **Response inhibition** refers to the ability to suppress a cognitively or behaviourally primed response
- Lesions in animals and imaging studies in humans implicate the **medial and ventral aspects of the frontal lobes**, including components of the **orbitofrontal cortex and cingulate gyrus**
- Such a **ventral defect** thought also to **disrupt more dorsal executive functions** related to regulation of behaviour, cognition, and emotion
- Therefore, **ventral and medial prefrontal** disturbances in ADHD thought to **give rise to impulsivity, distractibility, and hyperactivity** characteristic of this disorder

Deficits in multiple related neural circuits

- **ADHD considered heterogeneous group of syndromes related to disturbances in multiple related neural circuits**
- **Ventral prefrontal deficit** thought to produce **hyperactivity and impulsivity**
- This model places more emphasis on **attentional** deficits
- Abnormalities in **right dorsolateral prefrontal and parietal cortices** posited as basis for **poor sustained attention** (lesion and imaging studies)
- Third circuit connecting **parietal lobes, superior colliculus, and pulvinar nucleus** implicated in **distractibility**

Brain Systems Mediating Attention

- **Different cortical areas make distinct contributions to attentional experience**
- The inferior temporal cortex (ITC) focuses attentional resources on particular detail – such as the colour red
- The posterior parietal association cortex (PAC) “pays attention”, allowing us to orient attention in time and space
- The prefrontal cortex (PFC) regulates attention, inhibiting processing of irrelevant stimuli, sustaining attention over long delays, and dividing and coordinating attention



Brain Systems Mediating Attention

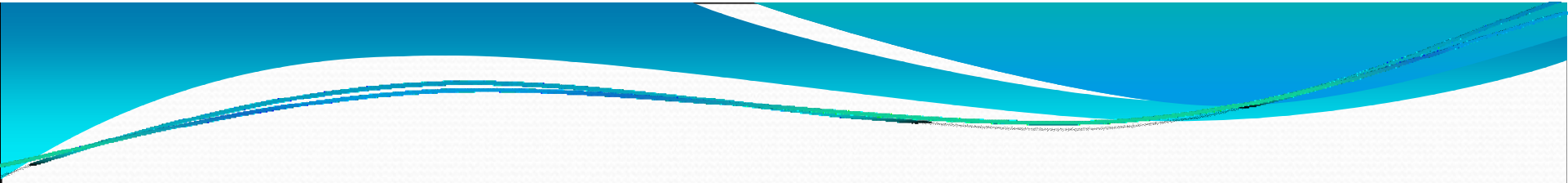
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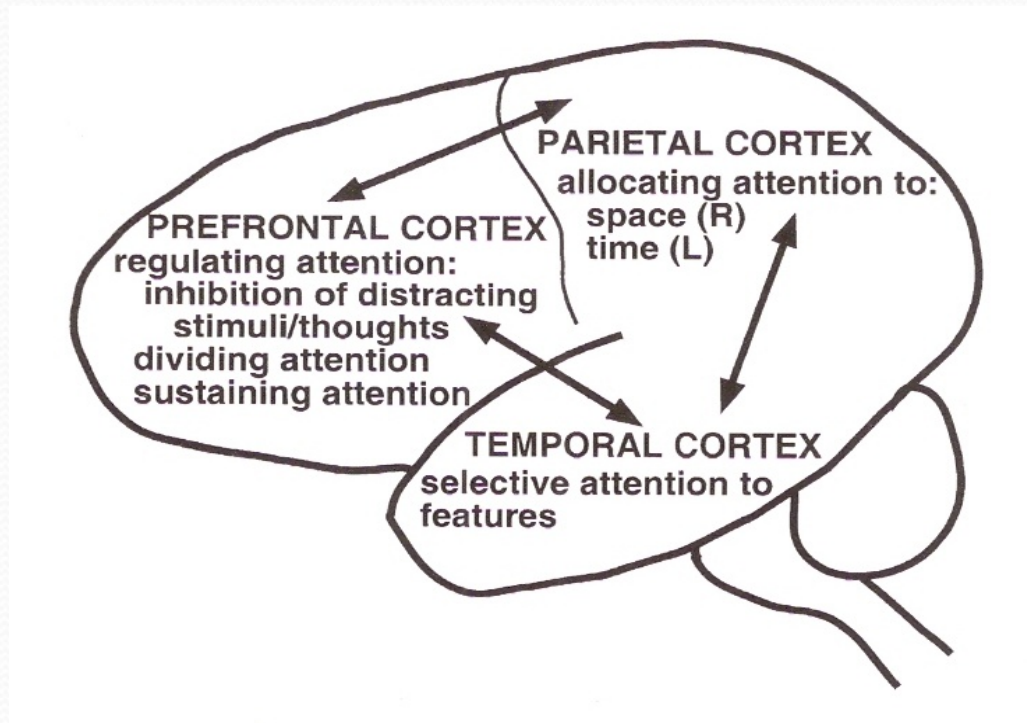
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Brain Systems Mediating Attention

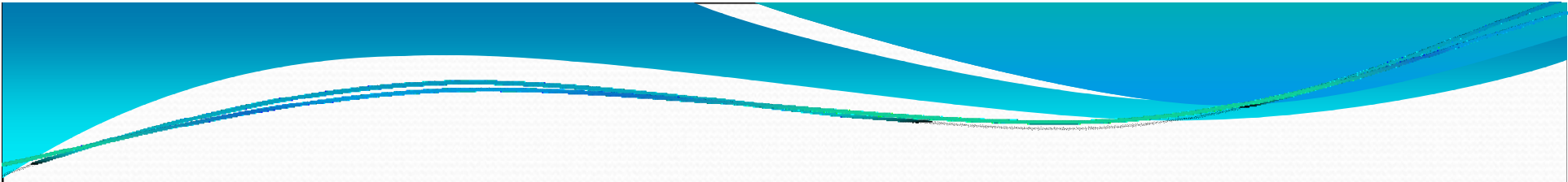
- The PFC, PAC, and ITC are intricately interconnected, creating both feed-forward and feedback loops that work together to provide a unified attentional experience

Network of Association Cortices for Attention



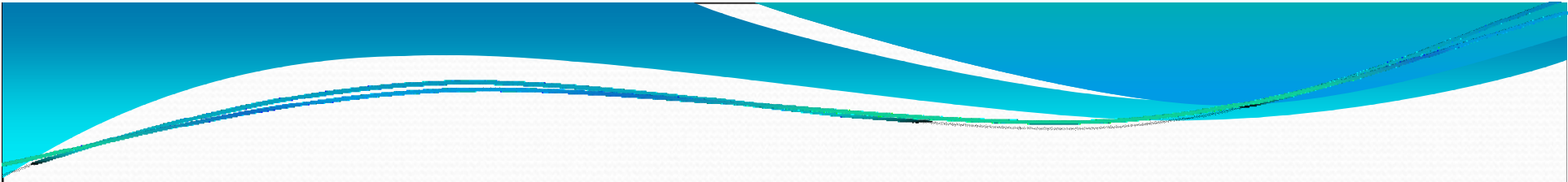
The prefrontal, parietal, and temporal association cortices form interconnected networks that play complementary roles in attention processing

Arnsten and Castellanos 2003



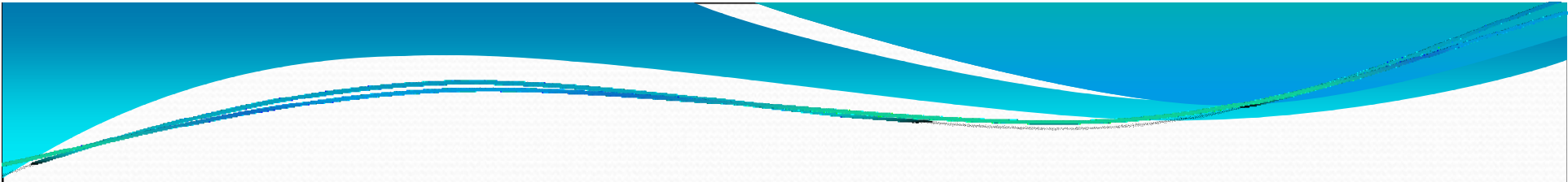
ADHD and Executive Function

- Barkely has proposed an integrated model of **executive dysfunctions located in the prefrontal cortex** to explain the cognitive and behavioural deficits of ADHD
- Model comprises 5 major executive functions that enable individuals to recognise and control their actions to achieve a goal:
 - Response inhibition – most important deficit in ADHD
 - Nonverbal working memory
 - Verbal working memory
 - Self-regulation of emotion and motivation
 - Reconstitution



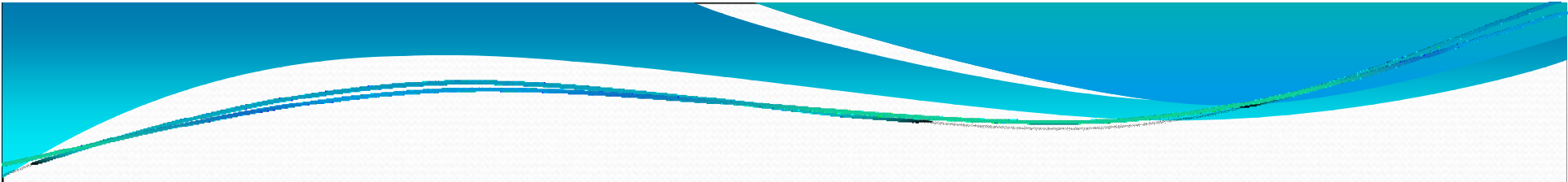
Neurobiology of ADHD

- **Frontolimbic hypothesis of ADHD** – Satterfield and Dawson (1971)
 - Suggested that weak cortical inhibitory controls over limbic functions may lead to ADHD
 - Similarities of children with ADHD to adults with frontal lobe damage
 - Neuropsychological testing supports this hypothesis
 - Impairment of **frontosubcortical** or **frontostriatal function** more accurately reflects the deficit of ADHD



Neuroimaging Studies of ADHD

- Many neuroimaging studies support links between brain structure and function and cognitive and behavioural control deficits of ADHD
- 10 of 11 early structural imaging studies (CT or MRI) found evidence of abnormalities
 - 4 found abnormalities in the frontal cortex, usually limited to the right side
 - Some findings supported smaller subcortical structures
- 5 of 5 early functional imaging studies of either regional blood flow (rCBF) or glucose metabolism (PET) found evidence for brain abnormalities with hypoactive frontal and prefrontal cortices
- Structural and functional studies consistent and implicate **frontosubcortical dysfunction** in ADHD



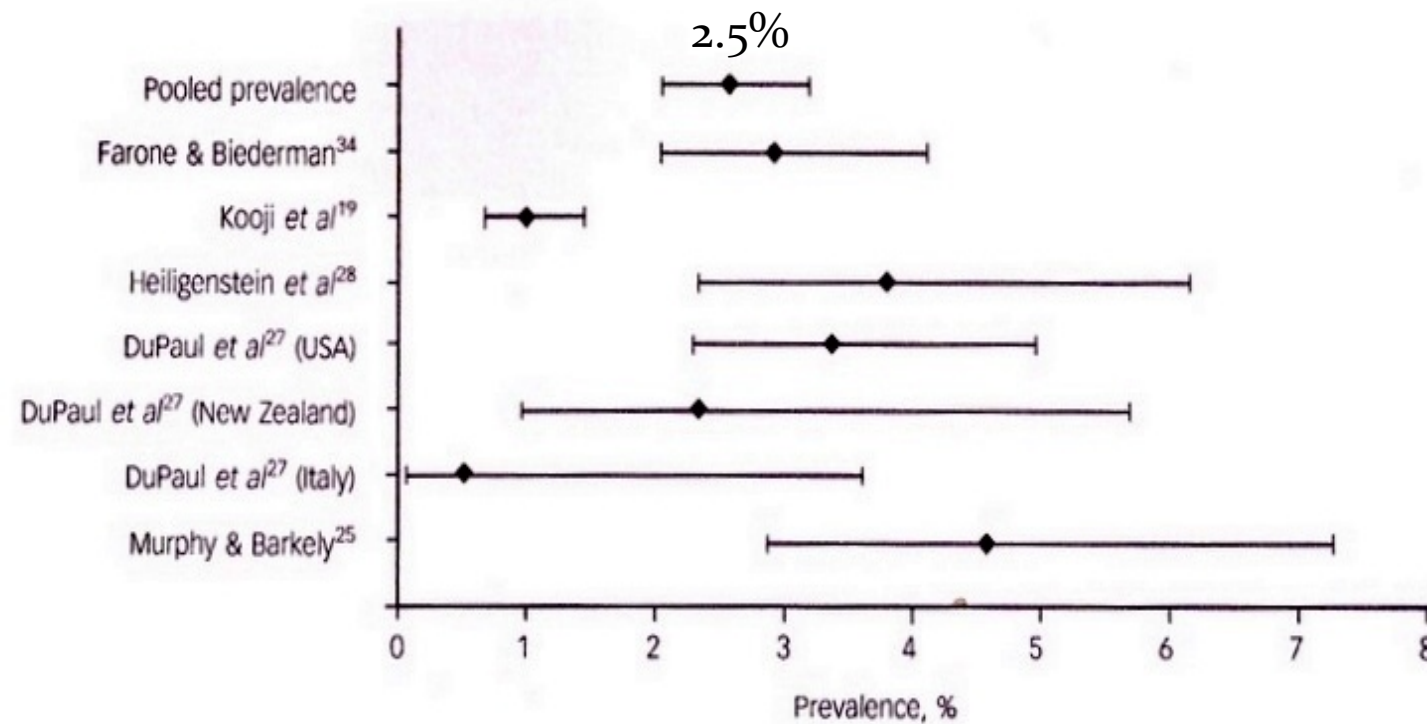
Recent Neuroimaging Studies

- Casey et al 2007 used functional imaging maps from a go/nogo task to identify portions of the ventral prefrontal cortex and striatum in suppressing an inappropriate action
- Compared responses of 20 parent-child dyads (N=40) with ADHD with 10 parent-child dyads (N=20) without ADHD using diffusion tensor images
- Fractional anisotropy in right prefrontal fiber tracts correlated with functional activity in the IFC and caudate nucleus and with performance on go/nogo task in parent-child dyads with ADHD
- These findings support heritability of frontostriatal structures among individuals with ADHD and suggest disruption in frontostriatal tracts as one possible pathway to the disorder

Recent Neuroimaging Studies - contd

- Narr et al 2009, using high resolution MRI, found that subjects with ADHD (compared with controls) exhibited significant reductions in:
 - Overall brain volume
 - Gray matter volume
 - Mean cortical thickness
- They concluded that:
 - Widespread reduction of cortical thickness presents a robust neuroanatomical marker of child/adolescent ADHD
 - Neurobiological underpinnings of ADHD extend beyond the prefrontal and subcortical circuits

Prevalence of Adult ADHD



Simon et al 2009

US National Comorbidity Survey Replication

- Epidemiological study with representative sample of over 3000 respondents
- Sample of those identified with possible Adult ADHD and controls interviewed by blinded clinicians
- Imputation of these findings yielded a population prevalence of Adult ADHD of 4.4%

Kessler et al

Prevalence of Adult ADHD – Study Limitations

- Adult ADHD only assessed comprehensively in clinical reappraisal subsample
- Initial survey and clinical reappraisal based on self-reports
- Other studies have demonstrated a general pattern of underestimation in self-reports by adults (as in children)

Prevalence of Adult ADHD - Caveats

- Important limitation is that DSM-IV criteria for ADHD were developed with children in mind
- These criteria offer only minimal guidance regarding diagnosis among adults
- Clinical studies indicate that ADHD in adults more heterogeneous and subtle than in children
- Suggestions for increase in variety of symptoms to be assessed, reduction of severity criteria, or reduction of number of required DSM-IV symptoms

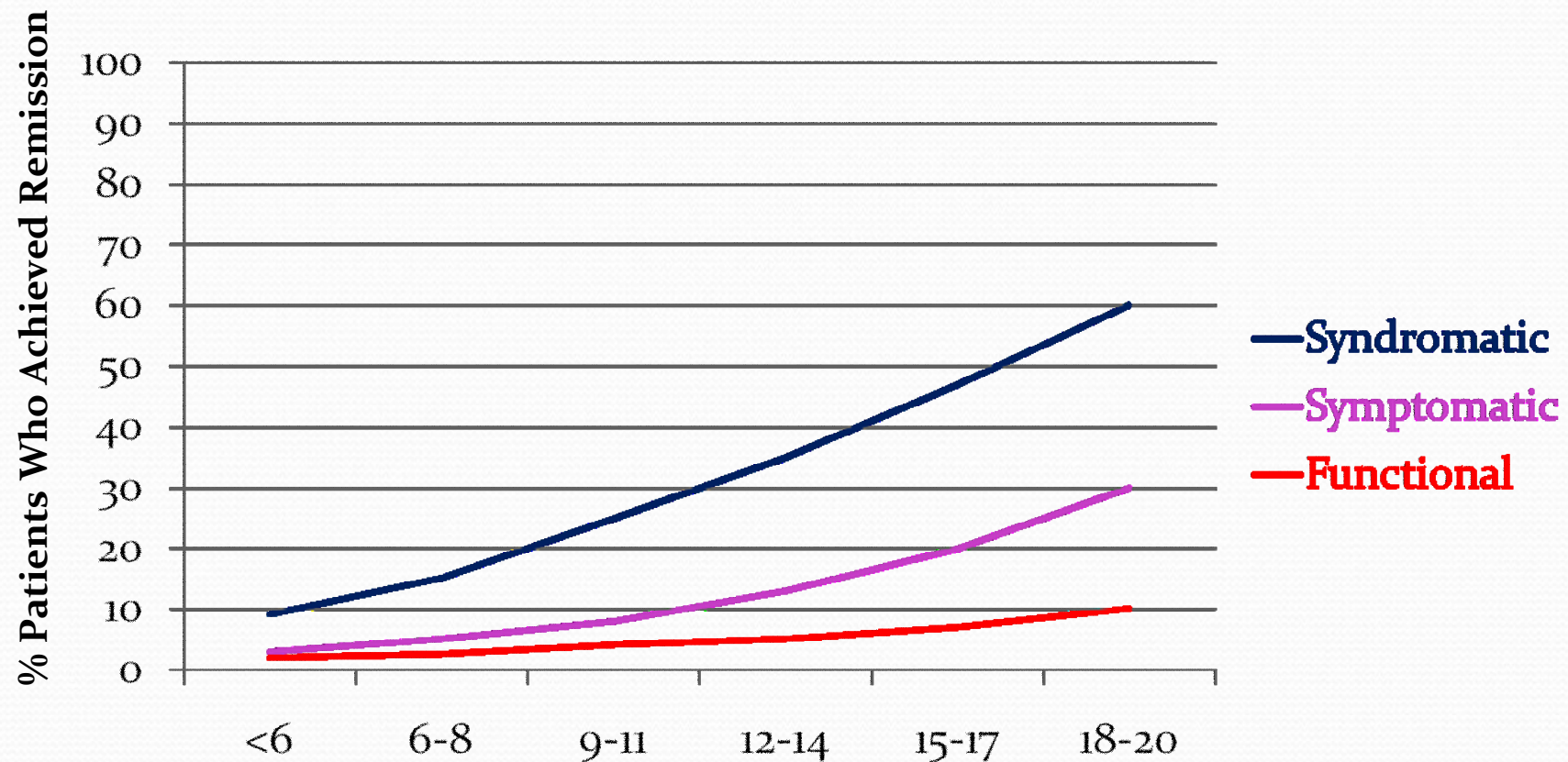
US National Comorbidity Survey Replication – Summary

- Adult ADHD is common
- Often produces serious impairment
- Adult ADHD has a high level of overall comorbidity with other DSM-IV disorders
- Only 10% of those diagnosed with adult ADHD had received treatment

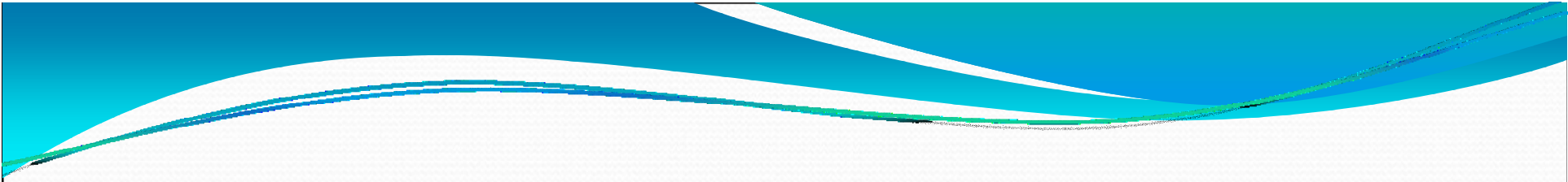
Persistence of ADHD into Adulthood

- Depends on criteria used and how these are measured
- Barkley et al compared DSM criteria with developmentally referenced criteria and reports by others
 - DSM-IV criteria - **58%** still met ADHD criteria at 21 years
 - Developmentally referenced criteria and reports by others – rate of persistence was **66%**

Age-Dependent Remission from Symptoms of ADHD (DSM-III-R)



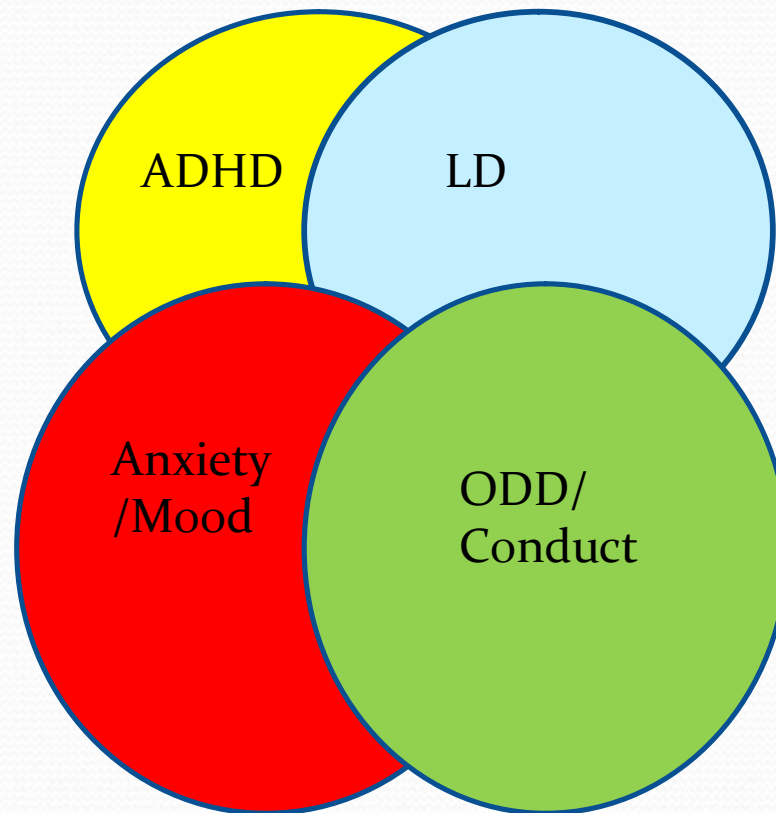
Biederman et al 2000



Comorbidity of ADHD

- Throughout the life cycle, a key clinical feature is comorbidity with conduct, depressive, bipolar, and anxiety disorders
- Notably in children, high level of comorbidity with other neurodevelopmental disorders such as specific learning disorders, autistic spectrum disorders, and of course Tourette's

Comorbidity of ADHD - Children



ADHD +
LD = 20-30%

ADHD +
Anxiety/Mood = >30%

ADHD +
ODD/Conduct = >30%

Comorbidity of Adult ADHD

TABLE 3. Comorbidity of Adult ADHD With Other DSM-IV Disorders in the National Comorbidity Survey Replication (N=3,199)^a

Comorbid Disorder During Previous 12 Months	Prevalence of ADHD ^b				Prevalence of Other Disorders ^c				Analysis ^d	
	Among Respondents With Other Disorders		Among Respondents Without Other Disorders		Among Respondents With ADHD		Among Respondents Without ADHD			
	%	SE	%	SE	%	SE	%	SE	Odds Ratio	95% CI
Mood disorders										
Major depressive disorder	9.4	2.3	3.7	0.5	18.6	4.2	7.8	0.4	2.7*	1.5–4.9
Dysthymia	22.6	5.8	3.7	0.5	12.8	3.4	1.9	0.2	7.5*	3.8–15.0
Bipolar disorder	21.2	3.9	3.5	0.5	19.4	3.8	3.1	0.3	7.4*	4.6–12.0
Any mood disorder	13.1	2.3	2.9	0.5	38.3	5.5	11.1	0.6	5.0*	3.0–8.2
Anxiety disorders										
Generalized anxiety disorder	11.9	3.9	4.0	0.5	8.0	2.5	2.6	0.3	3.2*	1.5–6.9
PTSD	13.4	3.4	3.8	0.5	11.9	3.0	3.3	0.4	3.9*	2.1–7.3
Panic disorder	11.1	3.0	3.9	0.5	8.9	2.5	3.1	0.3	3.0*	1.6–5.9
Agoraphobia	19.1	9.0	4.0	0.5	4.0	2.0	0.7	0.1	5.5*	1.6–18.5
Specific phobia	9.4	1.9	3.6	0.5	22.7	4.2	9.5	0.6	2.8*	1.7–4.6
Social phobia	14.0	2.5	3.2	0.5	29.3	4.3	7.8	0.5	4.9*	3.1–7.6
Obsessive-compulsive disorder	6.5	5.2	4.2	0.5	2.7	2.0	1.3	0.4	1.5	0.2–9.4
Any anxiety disorder	9.5	1.4	2.8	0.5	47.1	5.0	19.5	0.7	3.7*	2.4–5.5
Substance use disorders										
Alcohol abuse	9.5	4.2	4.0	0.5	5.9	2.5	2.4	0.2	2.5	0.9–6.6
Alcohol dependence	11.1	5.9	4.0	0.5	5.8	2.9	2.0	0.4	2.8	0.8–9.8
Drug abuse	7.2	6.6	4.1	0.5	2.4	2.3	1.4	0.2	1.5	0.2–10.5
Drug dependence	25.4	11.7	4.0	0.5	4.4	2.3	0.6	0.1	7.9*	2.3–27.3
Any substance use disorder	10.8	3.6	3.8	0.5	15.2	4.8	5.6	0.6	3.0*	1.4–6.5
Impulse control disorders:										
intermittent explosive disorder	12.3	2.5	3.6	0.5	19.6	3.8	6.1	0.5	3.7*	2.2–6.2

^a Among respondents ages 18–44 years who met the criteria for at least one disorder assessed in part 1 of the survey or were included in part 2 as part of a probability subsample of other respondents.

^b These numbers can be interpreted as, for example, 9.4% of individuals with major depressive disorder have ADHD and 3.7% of those without major depressive disorder have ADHD.

^c These numbers can be interpreted as, for example, 18.6% of individuals with ADHD have major depressive disorder and 7.8% of those without ADHD have major depressive disorder.

^d Based on multivariate logistic regression analysis controlling for age by using two-sided design-based multiple-imputation tests.

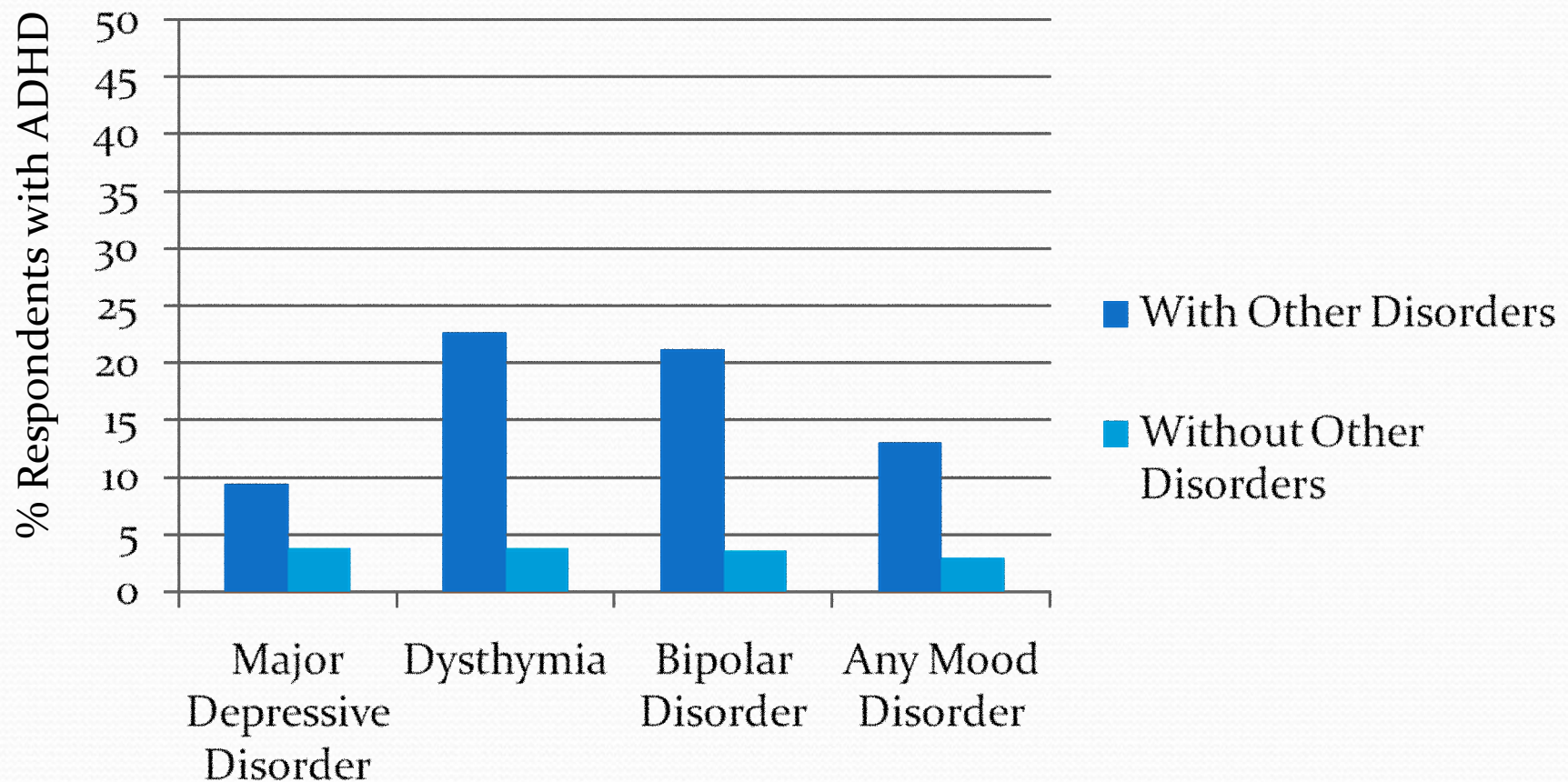
*p<0.05.

Comorbidity of Adult ADHD with other 12-month DSM-IV Disorders

	Odds Ratio
• Mood Disorders:	2.7 – 7.5
• Anxiety Disorders:	1.5 – 5.5
• Substance Use Disorders:	1.5 – 7.9
• Intermittent Explosive Disorder:	3.7

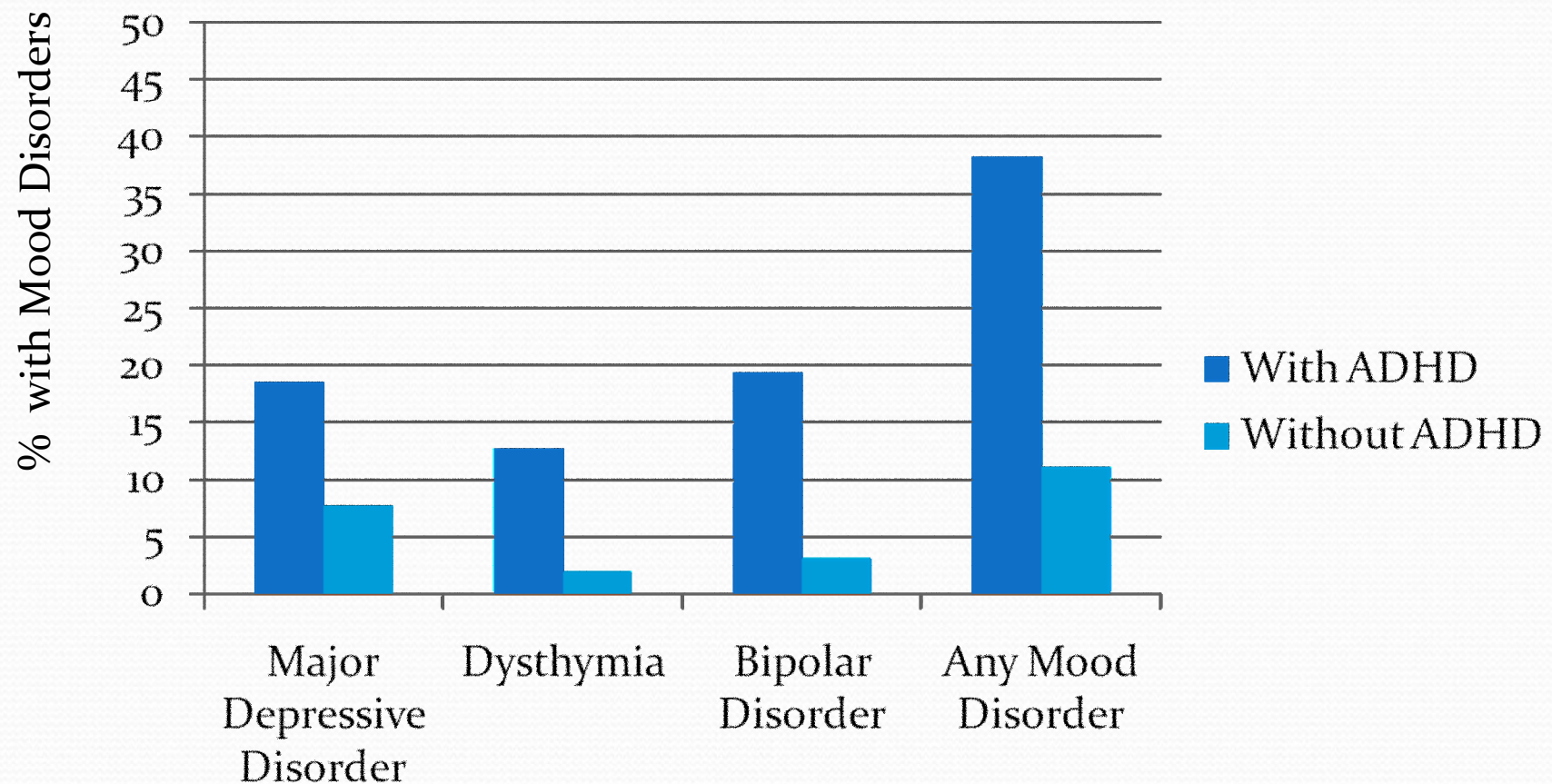
Kessler et al 2006

Prevalence of ADHD among Patients with Mood Disorders



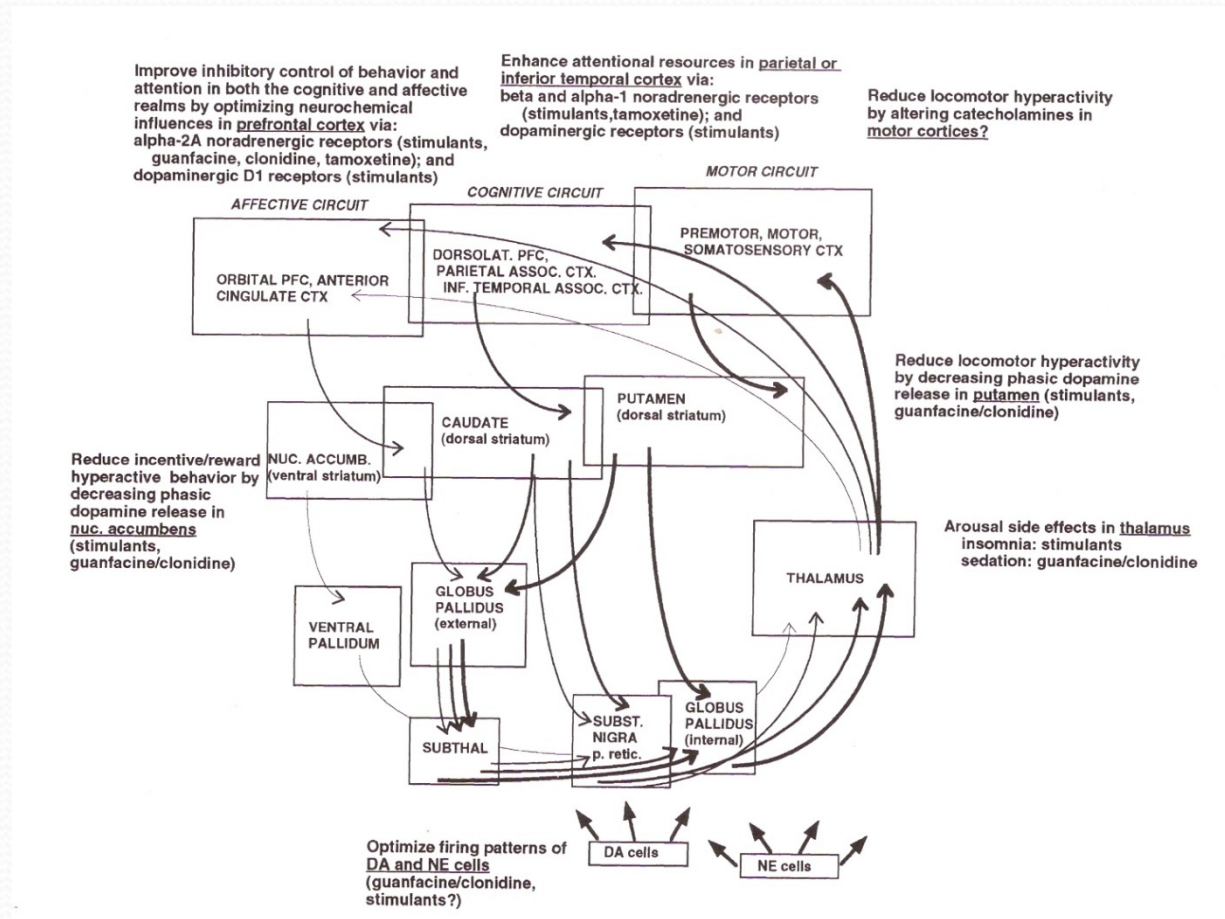
Kessler et al 2006

Prevalence of Mood Disorders among Respondents with ADHD



Kessler et al 2006

Possible mechanisms of action for ADHD medications



Corticostriatal loops that regulate motor, cognitive, and affective behaviours

Arnsten and Castellanos 2003

Possible mechanisms of action for ADHD medications - Inattention

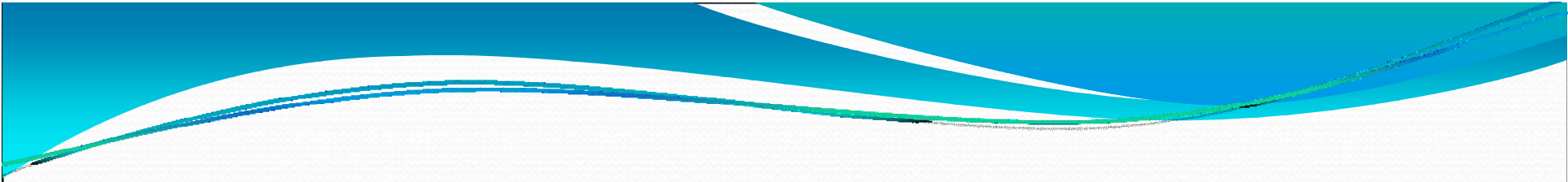
- **Improve inhibitory control** of behaviour and attention in both the cognitive and affective realms by optimising neurochemical influences in **pre-frontal cortex** via: alpha-2A noradrenergic receptors (stimulants, guanfacine, clonidine, atomoxetine); and dopaminergic D₁ receptors (stimulants)
- **Enhance attentional resources** in **parietal or inferior temporal cortex** via: beta- and alpha-1 noradrenergic receptors (stimulants, atomoxetine); and dopaminergic receptors (stimulants)

Possible mechanisms of action for ADHD medications - Hyperactivity

- Reduce locomotor hyperactivity by altering catecholamines in **motor cortices**
- Reduce locomotor hyperactivity by decreasing phasic dopamine release in **putamen** (stimulants, guanfacine/clonidine)
- Reduce incentive/reward hyperactive behaviour by decreasing phasic dopamine release in **nucleus accumbens** (stimulants, guanfacine/clonidine)

Possible mechanisms of action for ADHD medications - Other

- Optimise firing patterns of **DA and NE cells** that are widespread in the **cortices and striatal structures**, or project to these (guanfacine/clonidine, stimulants)
- Arousal side-effects in **thalamus**
 - Insomnia: stimulants
 - Sedation: guanfacine/clonidine



Treatment of Adult ADHD

- Educational therapy and psychotherapy often beneficial for development of skills to cope with the challenge of ADHD
- **Pharmacological treatment is the mainstay** for adults as it is for children
- There are fewer controlled medication studies for adults than for children
- Stimulant medications are the most frequently prescribed
- Atomoxetine, a nonstimulant, has also established an important place in the armamentarium

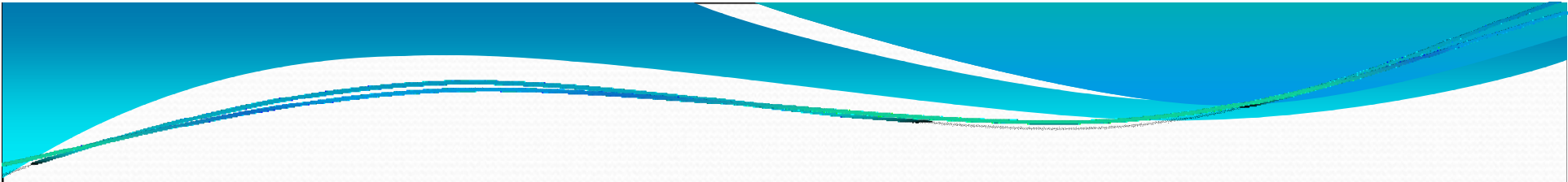
Stimulant Medication for Adult ADHD

- Methylphenidate (MPH), in its various forms, is the most commonly prescribed of the stimulants (especially in NZ)
- Results of earlier studies were inconsistent, probably because of lower doses and less stringent inclusion criteria than later studies
- **Response rates of >75% have been demonstrated for higher doses of MPH (1.0 mg per kg per day) and mixed amphetamine salts**
- **A 2004 meta-analysis of 6 studies (of MPH v placebo) showed a mean effect size of 0.9 ($p < 0.001$)**

Nair R, Moss S 2009, Spencer et al 1995, Faraone et al 2004

Preparations of Methylphenidate

- **Short-acting**
 - Rubifen (5, 10, 20 mg)
 - Ritalin (10 mg)
- **Intermediate-acting**
 - Rubifen SR (20 mg)
 - Ritalin SR (20 mg)
 - Ritalin LA (10, 20, 30, 40 mg)
- **Long-acting**
 - Concerta – OROS MPH (18, 27, 36, 54 mg)



Other Medications for Adult ADHD

- **Other Stimulants**
 - Dexamphetamine (5 mg)
- **Specific Nonstimulant**
 - Atomoxetine (Strattera – 10, 18, 25, 40, 60, 80, 100 mg). This is a selective noradrenergic and dopaminergic agent with a similar structure to tricyclic antidepressants
- **Antidepressants**
 - Desipramine (mostly noradrenergic)
 - Nortriptyline (norepinephrine and serotonin reuptake inhibitor)
 - Bupropion (atypical catecholaminergic – dopamine and norepinephrine)
 - Venlafaxine (noradrenergic and dopaminergic NSRI)

Other Medications for Adult ADHD

- contd

- **Antihypertensive Agents**

- Mostly used to reduce aggression, temper outbursts, and marked hyperactivity
- Propranolol (nonspecific beta-blocker)
- Clonidine (central alpha₂-adrenergic agonist)
- Guanfacine (alpha-adrenergic agonist)

- **Antinarcotic/alertness agent**

- Modafanil (mode of action unknown)

Nonpharmacologic Treatments of Adult ADHD

- Cognitive behaviour therapy has shown some promising results
 - Meta-cognitive therapy has been adapted for treatment of Adult ADHD
 - This is a group administered intervention that incorporates cognitive-behavioural principles and is designed to foster the development of executive self-management skills
- There may also be a role for individual therapy to address self-esteem issues and couple/family therapy for relationship issues

Solanto et al 2010