Studies of brain function in children with ADHD

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Outline of presentation

-What is ADHD?

-Why investigate brain function?
“Hello, Emily. This is Gladys Murphy up the street. Fine, thanks . . . Say, could you go to your window and describe what’s in my front yard?”
Attention Deficit Hyperactivity Disorder (ADHD)

Key DSM-IV CRITERIA

-inattention dimension and/or hyperactivity-impulsivity dimension

-maladaptive/inconsistent with developmental level with impairment social, academic, occupational functioning

-combined type, predominantly inattentive type
“Well, well, King . . . looks like the new neighbors have brought a friend for you, too.”
"Rub his belly, Ernie! Rub his belly!"
Two key reasons

-high rates of *comorbidity* including reading, writing, spelling and arithmetic difficulties, oppositional defiant patterns of behaviour, conduct problems, anxiety and depressive syndromes, and developmental coordination difficulties

-variable effects of primary treatment - stimulant medication immediate dosage versus *short-term* (4-6 weeks) dosage versus *longer-term* dosage (> 3 months) effects on
*core symptoms versus those of comorbid conditions
*cognitive functions such as working memory
*neurophysiological systems such as activation of fronto-striatal neural networks (fMRI)
"All right, Billy, you just go right ahead! . . . I've warned you enough times about playing under the anvil tree!"
Nomothetic aspects of phenomena:

-those features of a given, particular phenomenon that are able to be *validly and reliably demonstrated* in groups of individuals with a particular disorder or a range of disorders

-*amenable* to the science of systematic observation and experiment

Ideographic aspects of the individual:

-those features of a given, particular individual that are not able to be validly and reliably demonstrated in groups of individuals with a particular disorder or a range of disorders

*that is*

aspects of an individual can be *truly unique*

-*not easily amenable* to the science of systematic observation and experiment
Current biological contributions

Clinical phenotyping

-current need to be more *specific* with key phenomena defined:

-putative primary core symptoms/signs of a given disorder associated with its putative core *pathophysiology* versus secondary comorbid symptoms/signs associated with *maladaptive* pathophysiological responses to the primary disorder
Current biological contributions

Neurophysiology

-currently, visual and auditory evoked potential techniques and quantitative EEG approaches have the advantage of excellent temporal resolution but the extreme disadvantage of poor spatial resolution; over-interpretation of data common

-key future directions:
- autonomic nervous system (adrenergic tone and reactivity) investigation through postural blood pressure assessment; ultrasound assessment of forearm blood flow, and novel CNS approaches (eg Esler’s);
- oculomotor pro-and antisaccade tasks: contextual changes

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Mean saccade latency (±SE) of healthy adults and healthy children in the 20% and 80% target probability conditions for overlap and gap trials.
Mean saccade latency (±SE) for healthy children, ADHD and ADHD-M groups in the 20% and 80% target probability conditions for overlap and gap trials.
Current biological contributions

Cognitive Neuroscience

- *ongoing process of refining* measures of verbal and visuospatial working memory, motor response inhibition as the most robust of executive function constructs

- increased recognition of *non-human primate derived models* of executive function, given well defined brain behaviour relationships through single neuronal firing rate studies and high prevalence of language-based learning difficulties in psychiatric clinical populations

- more *targeted* use of specific measures of executive function (eg visuospatial working memory in children with ADHD-CT given 30%+ rates of language based learning difficulties)

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Between Search Errors (BSE) (mean) at each level of difficulty across the three groups, covarying for age

Level of difficulty (number of boxes)

[a] Wilks’ $\lambda = .80$, $F(12, 363) = 1.77$, $p = .05$, partial $\eta^2 = .07$

[b] ADHD-CT+DYS, ADHD-CT>controls $F(3, 122) = 5.27$, $p = .002$, partial $\eta^2 = .14$, cohen’s $d = .81$
Current biological contributions

Neuroimaging

- aided the *localisation* and investigation of these neurodevelopmental anatomical processes

- structural imaging (primarily MRI) has consistently implicated particular brain regions (caudate nucleus, DLPFC, AC, H, cerebellum) in a range of disorders, the most robust studies suggesting that there are *ongoing* neuropathological changes in disorders such as schizophrenia while there are *discrete* changes in others such as ADHD

- functional imaging (fMRI and MRS) is increasingly useful to investigate in vivo activation of *neural networks* associated with defined cognitive neuroscience tasks (fMRI) and in vivo *markers of neurochemistry* (MRS)

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Current biological contributions

Molecular Genetics

-primarily association studies have shown a moderate
strength association between
key catecholamine transporter polymorphisms and
high and low prevalence psychiatric disorders
*dopamine : ADHD

-imprecise phenotyping is the primary limitation
Current biological contributions

Molecular Genetics

- A few gene-environment interactions have been reported
  * MAO_A : maltreatment : CD/ASPD
  * 5HTT : lifelong stress events : depressive disorders and suicide
  * COMT : cannabis : psychotic symptoms, schizophreniform disorder
- Again specificity of the definition of the environmental event and the resultant phenotypic expression are the primary limitations

- Association studies of cognitive neuroscience constructs and fMRI neural network activation patterns have begun:
  * verbal working memory : COMT
  * verbal working memory fMRI : DLPFC activation
- Again specificity of the definition of the cognitive neuroscience construct is the primary limitation
Current biological contributions

Nevertheless the quest is ongoing to isolate key physiological processes and their dysfunction at key developmental stages that may help us understand and treat such complexities in a more targeted fashion.
Current biological contributions

Developmental neuroanatomy

-processes of *neuroblast migration* and *neuronal differentiation*

are interactive involving
*neurotransmitters, neuromodulators, levels of circulating hormones*
*radial glial cells and*
*contact with surfaces of neighbouring cells*

-abnormalities at this stage of development involve migration and/or proliferation problems (eg HLD mutant/Dreher mutant) (Nowakowski, 1991)
Current biological contributions

Developmental neuroanatomy

-**dendritic proliferation** processes are interactive and involve
  *cell-cell interactions,
  *cell-substrate interactions and
  *chemotactic interactions
  that guide the process of axonal outgrowth projection
  prior to dendritic proliferation

-**neuronal pruning** involves similar interactions and

-**myelination** increases the speed of electrical conduction between mature neurones and other cells, mature neurones requiring (1) an electrically polarised and excitable membrane and (2) a secretory function
Current biological contributions

Developmental neuroanatomy

-abnormalities of all three may be relevant for biological risk factors such as verbal and visuospatial span and/or working memory deficits, response inhibition and neurological subtle signs deficits (Taylor, 2001)

“deficits of neuronal connectivity”
Current biological contributions

Neurophysiology, Cognitive neuroscience, Neuroimaging, Molecular Genetics, Developmental neuroanatomy

-key future step: (ab)/normal developmental trajectories mapped which will aid the determination of
*whether deviant or delayed development,
*developmental stage specific or generalised,
*primary disorder phenotype specific abnormalities versus secondary comorbid disorders

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Kandel

-Nobel prize for medicine and physiology 2000 for advances in the understanding of signal transduction in the central nervous system

-procedural memory studies in *invertebrates*-Drosophila and Aplysia led to identification of a *common molecular switch* for converting short-into long-term memory: coordinated expression of CREB-1 transactivator and concomitant relief of repression of CREB-2 that lowers the threshold for memory storage (Bartsch et al., 1995)

-both are part of the PKA signaling pathway that was shown to be required for the formation of long-term explicit memory (L-LTP) in the CA1 area of the hippocampus in mice, where the memory type was contextual rather than aversive (Rotenberg et al., 1996)
Current biological contributions: Summary

-Progressively better definition of
  * clinical phenotyping, particularly of primary versus secondary phenomena (aided by theoretical models)
  * cognitive neuroscience and neurophysiological constructs
  * functional and structural neuroimaging
  * molecular genetic candidate gene polymorphisms

-will aid the definition of (ab)/normal developmental trajectories, whether development is deviant or delayed, and whether alterations are developmental stage specific or generalised

-and will aid the determination of threshold effects and primary risk factors (core pathophysiology) versus secondary (absent) resilience factors ((mal)/adaptive physiological processes)
Current biological contributions : Summary

-in turn, the process of illuminating developmental neuroanatomical physiological processes and their dysfunction will be facilitated