Scientific (Child) Psychiatry: An Oxymoron?

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Philosophical issues raised by the title of this address

- an apparent contradiction is implied between science and psychiatry

- Is this a general phenomenon and/or specific to psychiatry?
Science

-involves the branch of knowledge derived from objective principles involving systematic observation of and experiment with phenomena

-also involves systematic and formulated knowledge of a specified type on a specified subject
Psychiatry

-contradiction more apparent because of:

Psychiatry’s central concern with mental phenomena of the mind reflected in the codified diagnostic nosologies (eg DSM-IV, ICD-10)

Psychiatry’s further concern with mental processes and theoretical models of mental mechanisms of the mind (eg empirically based: neuropsychological models through to theoretically based: psychodynamic and systems theory models)

-yet strong empirical base evident (eg Kandel et al.’s work)
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)
In child psychiatry,

- contradiction even more apparent because the empirical base grounded in basic neurosciences relatively undeveloped, and the theoretical models informing the definition, understanding and treatment of mental phenomena are more prominent

-Hence a re-focus of this presentation on the existing biological empirical base of child and adolescent psychiatry and its relationship with the dominant theoretical models in the field
Biological Child Psychiatry: An Oxymoron?
Presentation Outline

- Overview of the field of child and adolescent psychiatry

- Overview of the theoretical influences in the field of child and adolescent psychiatry

- Historical overview of the biological contributions to the field of child and adolescent psychiatry

- Overview of current biological contributions to the field of child and adolescent psychiatry

- Possible future directions noted for discussion

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Three broad strands of the field can be discerned:

- ‘Psychiatric aspects of paediatric medical disorders’
- ‘Child psychiatric disorders’
- ‘Early onset of adult psychiatric disorders’
Psychiatric aspects of paediatric medical disorders

Epilepsy as an example

-approximately 30% cases have one or more psychiatric disorders (Rutter et al., 1970)
-approximately 35%-oppositional defiant disorder; 45% emotional disorders; 7% ADHD-CT (combined type)
-predictors of psychiatric disorder:
  early age of onset; seizure type (TLE) and frequency; focal neurological abnormalities; cognitive impairments; high expressed emotion; parental dysfunction; divorce; social stigmatisation; peer rejection (Taylor, 2001)
-assessment and treatment of psychiatric disorder and the prioritisation of specific goals and their achievement occurs in the context of the primary management of the epilepsy

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Child psychiatric disorders

ADHD-CT as an example

- 3%-5% prevalence in primary school age children
- co-occurring conditions include reading, writing, spelling and arithmetic difficulties, oppositional defiant patterns of behaviour, conduct problems, anxiety and depressive syndromes, and developmental coordination difficulties
- assessment and treatment focuses on delineation of risk factors and resilience factors—biologically (eg, executive function deficits; good arousal regulation) psychologically (eg, externalise blame; balanced critical self-reflection) and socially (eg, hostile critical interpersonal environment; confiding, nurturing consistent interpersonal environment)
- monitoring of these risk and resilience factors and their response to treatment through developmental phases

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Early onset of adult psychiatric disorders

Schizophrenia as an example

-0.8-1% prevalence and incidence of 0.1% per year with peak incidence in males 15-25 years and females 25-35 years (Torrey, 1987)
-early onset cases primarily disorganised type (hebephrenic) schizophrenia, characterised by disorganised speech, disorganised behaviour and flat or inappropriate affect
-assessment and treatment focuses on delineation of risk factors and resilience factors-biologically, psychologically and socially
-monitoring of these risk and resilience factors and their response to treatment through developmental phases
-Goals for assessment, treatment and monitoring are similar across the three broad strands of the field, although the context(s) in which the assessment and treatment occur(s) has a primary effect on the management priorities.

-Developmental context is fundamental to all of the above strands:
  * Assessment and treatment focuses on delineation of risk factors and resilience factors biologically, psychologically and socially.
  * Monitoring of these risk and resilience factors and their response to treatment through developmental phases.

-Theoretical influences are a further key influence on the process of assessment and treatment, the determination of goals for assessment and treatment, the type of assessment and treatment, and the monitoring of assessment and treatment.
Three broad theoretical influences in the field of child and adolescent psychiatry

- Psychodynamic theory and practice
- Family and social systems theory and practice
- Developmental psychopathology
Psychodynamic theory and practice

-for example, Structural theory of the mind (Freud, 1923)
  Id-reservoir of unorganised instinctual drives
  Ego-executive apparatus of the mind with abstract thinking and verbal expression the conscious and preconscious aspects and defense mechanisms the unconscious aspects
  Superego-unconscious internalised system of ideals and values internalised from an individual’s parents
-free association and interpretation are key assessment and treatment tools, respectively
-monitoring of treatment resides primarily with the individual in the treatment process rather than with the clinician
-no clear biological risk factors or resilience factors identified
Family and social systems theory and practice

-for example, structural, strategic and systemic family therapy
-family and social unit is greater than the sum of their parts
-interdependence of relationships in the system leads to circular causality
-homeostasis in the system is a primary process
-aims of treatment are symptom removal from an identified individual; decreased family distress; improved communication; increased flexibility; increased problem solving
-monitoring of treatment resides primarily with the individual in the treatment process rather than with the clinician
-no clear biological risk factors or resilience factors identified (Hayes, 1991)
Developmental psychopathology
- ‘an evolving interdisciplinary scientific perspective that elucidates the interplay between the biological, psychological and social contexts of normal and abnormal development across the life course’ (Cicchetti, 2001)
  - equifinality:
    more than one precursor/antecedent being associated with a given factor
    - ADHD-CT
      - ANX  EF  LBLD
  - multifinality:
    a given precursor/antecedent being associated with multiple factors
    - ANX  ADHD-CT  ODD/CD
      - LBLD

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Developmental psychopathology

-risk factors and resilience factors are interdependent in a given individual (eg a hostile critical primary caregiver relationship may be a risk factor at age 3 and a resilience factor at age 13 in a given individual)

-assessment and treatment involves [1] identifying biological, psychological, social, cultural and developmental risk and resilience factors and their relative importance in a given individual and [2] biological and psychological treatments used alone or in conjunction to achieve specific goals informed by the relative priorities of these risk and resilience factors

-monitoring of treatment resides primarily with the clinician in association with the individual in the treatment process
-clear biological risk factors or resilience factors identified
Currently,
the first two theoretical influences are in the ascendancy in the field although the last model is gaining credibility however, biologically informed advances have a history in the field
Historical overview of the biological contributions

In 1937, Bradley published the findings of their investigation of children with hyperactivity using pneumoencephalography. The adverse feature of the procedure was headache, which was treated with benzedrine, an amphetamine psychostimulant. Subsequently, some hyperactive children had noted improvement in their behavior and school performance along with a rise in intelligence scores for some of these children.
Historical overview of the biological contributions

In 1943, Kanner described 11 children with ‘an inability to relate themselves in the ordinary way to people and situations from the beginning of life’. Other features included an inability to use language to communicate, an obsessively anxious focus on maintaining sameness, an excessive focus on objects and/or pictures, and good cognitive potential in contrast to childhood onset schizophrenia.

In 1944, Asperger described a group of children who had difficulties with social integration in groups, but had preserved language function and appeared more intelligent than Kanner’s infantile autism group. His work was not translated from German into English and was largely unknown until 1981 when Lorna Wing popularised the term Asperger’s Syndrome.
Historical overview of the biological contributions

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

Problems of Method (1960)

‘In reality, psychology teaches us at every step that though two types of activity can have the same external manifestation, whether in origin or essence, their nature may differ most profoundly.’

Vygotsky, Lev Semyonovich

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Problems of Method (1960)

‘We believe that child development is a complex dialectical process characterised by periodicity, unevenness in the development of different functions, metamorphosis or qualitative transformation of one form into another, intertwining of external and internal factors, and adaptive processes which overcome impediments that the child encounters….most workers in child psychology ignore those turning points, those spasmodic and revolutionary changes that are so frequent in the history of child development.’

Vygotsky, Lev Semyonovich
Relevance of Vygotsky’s critique shown by

- interface between autistic spectrum disorders, disruptive behaviour disorders (eg ADHD-CT), anxiety and depressive disorders, among others

- immediate dosage versus short-term (4-6 weeks) dosage versus longer-term dosage (> 3 months) effects of psychostimulant medication, among others on core symptom dimensions, cognitive functions, neurophysiological measures, among others
Current biological contributions

Developmental neuroanatomy

- key epigenetic principles are as follows:
  - adult maturity required for the establishment of anatomical structure of regions of the central nervous system (CNS)
  - neural crest segmental arrangement determines cortical layer to which a cell will belong
  - neuroblast migration is an interactive process involving neurotransmitters, neuromodulators, radial glial cells and contact with surfaces of neighbouring cells
  - neuronal differentiation influenced by contact with other cells and levels of circulating hormones
  - abnormalities at this stage of development involve migration and/or proliferation problems (eg HLD mutant/Dreher mutant) (Nowakowski, 1991)

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Current biological contributions

Developmental neuroanatomy

-apoptosis is a ‘spontaneous’ cascade of degenerative changes leading to cell death involving shrinkage of the nucleus, condensation of the chromatin, increased electron opacity of the cell, loss of the golgi apparatus, endoplasmic reticulum, disaggregation of the polyribosomes, and nuclear membrane breakdown (Hamburger & Levi-Montalcini, 1949); biphasic process; accelerated or retarded by metabolic factors, eg thyroxine level (direct proportional relationship), glutamate/aspartate (direct proportional relationship), lactic acidosis, ammonia, electrolyte and calcium imbalances (direct proportional relationship), other environmental factors, eg synaptic relationships (inverse proportional relationship)
Current biological contributions

Developmental neuroanatomy

-cell-cell interactions, cell-substrate interactions and chemotactic interactions guide the process of axonal outgrowth projection which must occur prior to dendritic proliferation

-neuronal pruning abnormalities 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)

-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

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Current biological contributions

Developmental neuroanatomy

-key questions about disorder/phenotype specific abnormalities, whether deviant or delayed development, versus generalised non-specific conferring of risk remain

-constructs of equifinality/multifinality and pleiotropism/heterogeneity have been formulated to aid the understanding of these questions

-neuroimaging has been used to investigate structural and more recently functional abnormalities within and across disorders such as ADHD-CT, Autistic disorder and Schizophrenia
Current biological contributions

Neuroimaging

-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) are increasingly useful techniques to investigate in vivo alterations in functional neuronal activity associated with defined neuropsychological tasks (fMRI) and imaging procedures (MRS)

-key future step: (ab)/normal developmental trajectories mapped

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Current biological contributions

Neuropsychology

- 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)
Current biological contributions

Neuropsychology

- short- and longer-term monitoring of medication and/or psychological treatment outcome a key future role

- key future step: (ab)/normal developmental trajectories mapped
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 investigation through postural blood pressure assessment; ultrasound assessment of forearm blood flow, and novel central nervous system approaches (eg Essler’s); oculomotor pro- and antisaccadic contextual changes
Future directions

- Further refining of functional and structural neuroimaging, neuropsychological and neurophysiological measures with well understood brain behaviour relationships to enable normal and abnormal developmental trajectories to be mapped across a range of high and low prevalence disorders

- Single dosage, short-term and longer-term monitoring of medication and/or psychological treatment outcomes using refined neuropsychological/neurophysiological constructs

- Further refining of clinical phenomena, at a symptom level, interpersonal level and at a system level (family unit, peer group unit) through systematic investigation across high and low prevalence disorders
Future directions

- continued investigation of primary relationships between phenomena across developmental stages but also innovative study of the second order relationships between phenomena across development, given the polymorphism noted by Vygotsky

- molecular genetics as a primary investigative aim for epidemiological and clinical studies, phenomenological, neuroimaging, neuropsychological and neurophysiological studies

- current examples are conceptually grounded in models of endophenotypes: ‘heritable, quantitative traits that index an individual’s liability to develop or manifest a given disease’ (Castellanos and Tannock, 2002)
Future directions

-22q11, COMT gene contains an evolutionarily recent G to A missense mutation that translates into a substitution of Met for Val at codon 108/158 (Val 108/158 Met polymorphism)

it is known that the Met allele is associated with 4x less dopamine catabolism that the Val allele

Val allele associated with significantly worse working memory performance that Met allele (4.1% variance); Met allele associated with a significantly more efficient DLPFC activation during working memory task; Val allele significantly increased in adults with schizophrenia (OR 1.5) recently demonstrated in adults with schizophrenia (Egan et al., 2001)
**Future directions**

- Linkage studies of COMT gene polymorphism in children with ADHD have been equivocal to date (4 studies) and no studies have looked at working memory performance in a systematic manner.

-Caspi et al., 2002 have published the first gene-environment interaction study, investigating VNTR polymorphism at the promoter of MAOA gene (Xp11.23-11.4) leading to high and low MAOA activity.

*MAOA activity x maltreatment associated with antisocial index
low MAOA x maltreatment
*adolescent conduct disorder (OR 2.8)
adult violent conviction (OR 9.8)
self reported violence and/or ASPD symptoms (significantly increased antisocial scores)
Future directions

-two genome-wide scans published so far indicate two linkage peaks at chromosomal locations 2q24 and 16p13 associated with both ADHD (Fisher et al., 2002) and Autism (IMGSAC, 2001) *an example of heterogeneity and pleiotropism noted earlier

-allelic association studies of ten-repeat allele of an untranscribed variable tandem-repeat region in the dopamine transporter gene (DAT1) and seven-repeat allele of dopamine receptor D4 in ADHD; replicated findings
*current estimates OR 1.2-1.4 for both
*DAT1 allele alters the density and not the structure of the dopamine transporter

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In summary:

Philosophical basis:
Science → Psychiatry → Child Psychiatry  Yes
Breadth field Child Psychiatry  Yes
Theoretical influences  Yes
Developmental context (equi/multifinality, risk/resilience)  Yes

Psychopharmacology  No
Phenomenology (clinical/interpersonal)  No
Neuroanatomy  No
Neuroimaging  No
Neuropsychology  No
Neurophysiology  No
Molecular genetics  No

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Current experimental paradigms
Between Search Errors (BSE) (mean) at each level of difficulty across the four groups

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 $\eta^2 = .14$
CORRECT
Delayed Matching To Sample (DMTS) (mean correct responses) at simultaneous and three delay conditions across the four groups

Level of delay (simultaneous, 0, 4, 12 seconds)

[a] Wilks’ $\lambda = .83$, $F(9, 366) = 1.94$, $p = .05$, partial $\eta^2 = .06$

[b] controls > ADHD-CT, ADHD-CT+DYS, DYS > ADHD-CT+DYS

$F(3, 122) = 6.31$, $p = .001$, partial $\eta^2 = .17$ (controls > DYS, Cohen’s $d = .79$)
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 condition for overlap and gap trials.