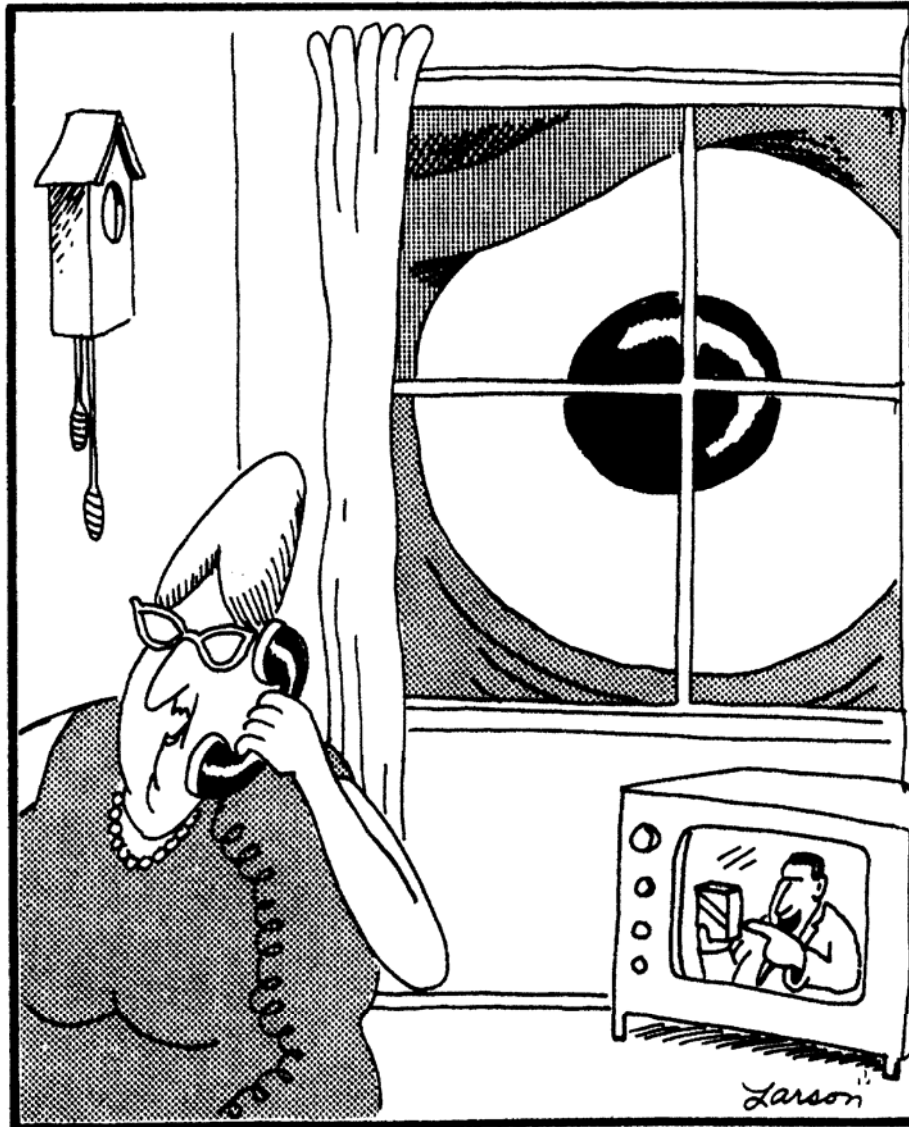


ADHD: biology and environment in interaction

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**"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?"**

‘Man is a riddle
not because he is an animal,
not because he is a social being,
not as part of nature and society.

It is as a person that he is a riddle – just that precisely;
it is because he possesses personality’

Nikolai Berdyaev (1944)

Scientific Child Psychiatry: An Oxymoron?

science objective (observer independent of system)

psychiatry subjective (observer affects system)

Is this a *general* phenomenon or *specific* to child psychiatry?

Science

**both systematic observation
experiments**

systematic and formulated knowledge

Psychiatry

subjective (observer affects system)

central concerns

mental phenomena

mental processes

psychotherapy

‘ideographic’

Kandel

Nobel prize 2000

Sea slugs and rats

molecular switch short to long-term memory

CREB-1 transactivator

CREB-2

PKA signaling pathway

hippocampus

neuropsychological models

In child psychiatry,

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

‘Practically, what is child psychiatry?’

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*

Philosophical issues raised by the title of this address

-human beings as subject, as object, inter-subjective states and interpersonal systems are the field of enquiry of child psychiatry

“How has this subject - object problem in human beings been addressed in the field of child psychiatry?”

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

Case studies: anecdotal, unrepeatabe, uncontrolled, unrepresentative, subjectively interpreted

Farmer A. The demise of the published case report-is resuscitation necessary? B J Psychiatry 1999; 174: 93-94

Individual history examination may identify pattern(s) that are predictive of future behaviour, feelings and attitudes (ideographic approach), while examination of group differences (nomothetic approach) may not be applicable to the individual because psychological causation is always personal and never actuarial-generalisations are not binding on the individual

Allport GW. 1947. The use of personal documents in psychological science.

New York: Social Science Research Council

Three broad theoretical influences in the field of child and adolescent psychiatry

Ideographic models

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

Nomothetic model

- Developmental psychopathology

Psychodynamic theory and practice

- *valid focus* on the human being as subject and inter-subjective states
- primarily concerned with the *interaction between* the conscious and unconscious aspects of the human mind
- systematic, formulated and scientific knowledge base
- 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

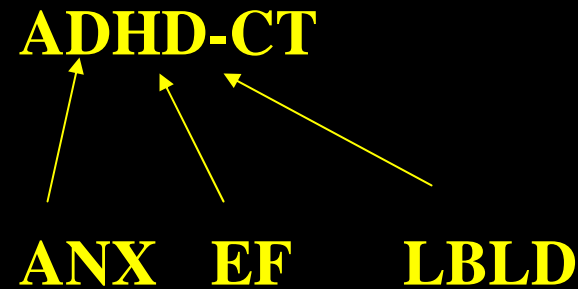
Family and social systems theory and practice

- *valid focus* on human interpersonal systems
- primarily concerned with the *interdependence of relationships* in an interpersonal system governed by processes of circular causality and homeostasis
- systematic, formulated and scientific knowledge base
- 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

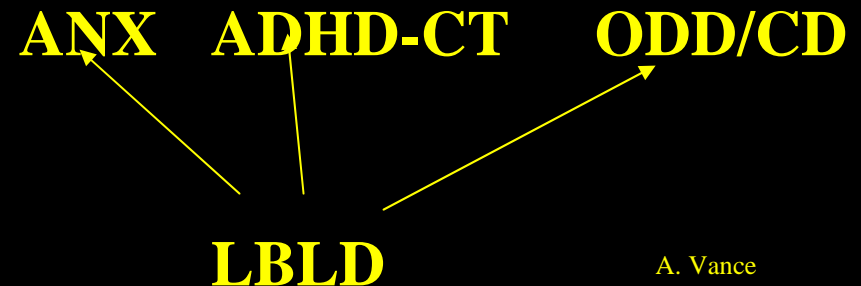
- equifinality:

more than one precursor/antecedent being associated with a given factor



-multifinality:

a given precursor/antecedent being associated with multiple factors



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 ideographic theoretical influences are in the ascendancy in the field although the nomothetic developmental psychopathology model is gaining credibility

its credibility is primarily due to its consonance with the international movement towards understandable and complimentary modes of service delivery in paediatric, youth and adult psychiatric services

further, biologically informed advances have a history in the field of child psychiatry

Historical overview of the biological contributions

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

Historical overview of the biological contributions

However, the complexity of equifinality and multifinality was emphasized by biological researchers

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

as was the interaction between biological and psychosocial factors across developmental stages

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

Current examples of these complexities include

-high rates of *comorbidity* between autistic spectrum disorders, disruptive behaviour disorders (eg ADHD-CT), anxiety and depressive disorders, among others

-*variable* effects of medication, such as 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)

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

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

Developmental neuroanatomy

-key current questions:

- *primary disorder phenotype specific abnormalities versus secondary comorbid disorders,

- *whether deviant or delayed development,

- *developmental stage specific or generalised

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

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*

**noradrenaline : anxiety disorders*

**serotonin : anxiety disorders, depressive disorders*

COMTval/met : anxiety disorders, schizophrenia

-*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

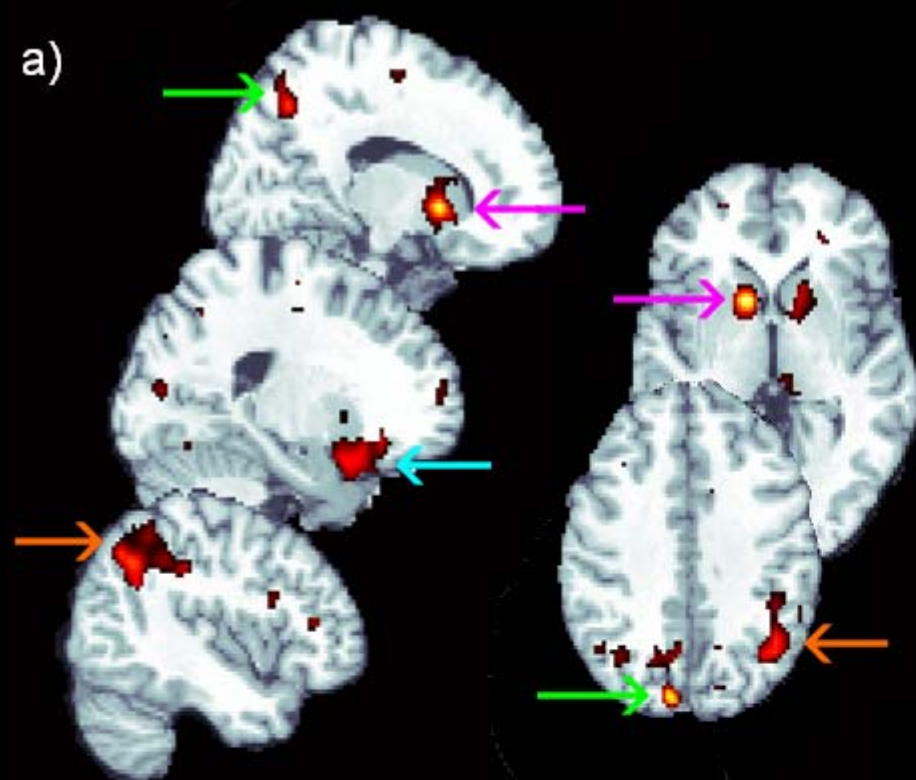
Molecular genetics

- 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

Current biological contributions

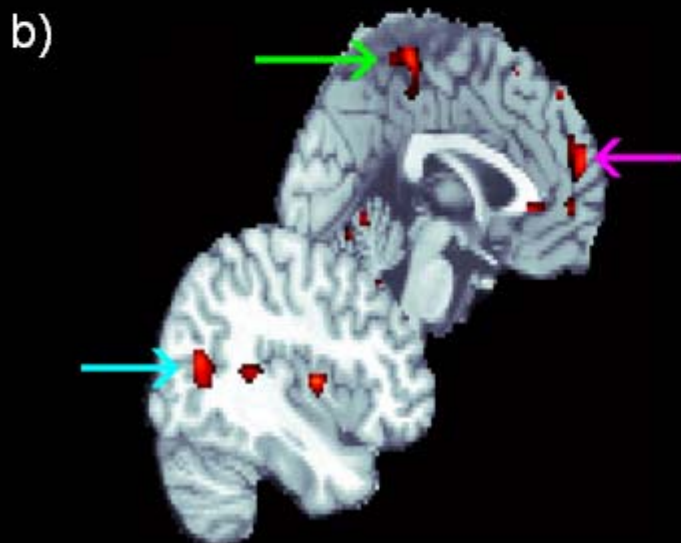
Neuroimaging

- 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)



Greater activation for Control than ADHD group.

Region	BA	x	y	z
● Left Prefrontal				
Caudate Head		-15	12	0
Sup Frontal Gyr.	10	-27	54	3
Inf Frontal Gyr.	46	-30	30	12
● Right Prefrontal				
Ventral Inf Frontal Gyr.	47	18	12	-21
● Right Parietal				
Inf Parietal Lob.	40	42	-57	39
Sup Parietal Lob.	7	36	-60	51
● Occipital				
Left Precuneus	19	-12	-81	42
Right Cuneus	19	15	-84	33



Greater activation for ADHD than Control group.

Region	BA	x	y	z
● Medial Sup Frontal Gyr.	10	-9	63	15
● Posterior Cingulate Gyr.	31	18	-24	30
● Left Temporal				
L Sup Temporal Gyr.	13	-36	-27	6
L Mid Temporal Gyr.	39	-48	-60	9

Current biological contributions

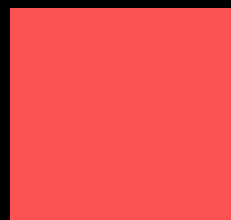
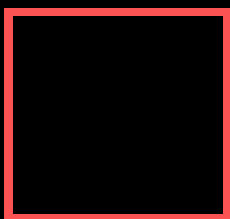
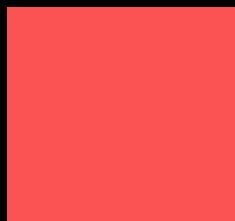
Neuroimaging

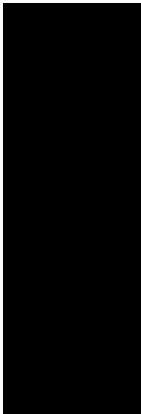
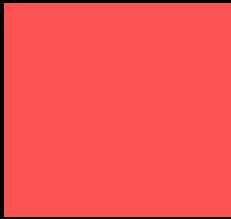
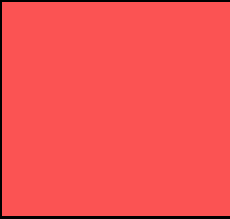
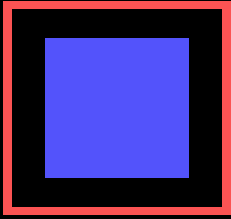
- key future step: (ab)/normal developmental trajectories mapped which will aid the determination of
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Current biological contributions

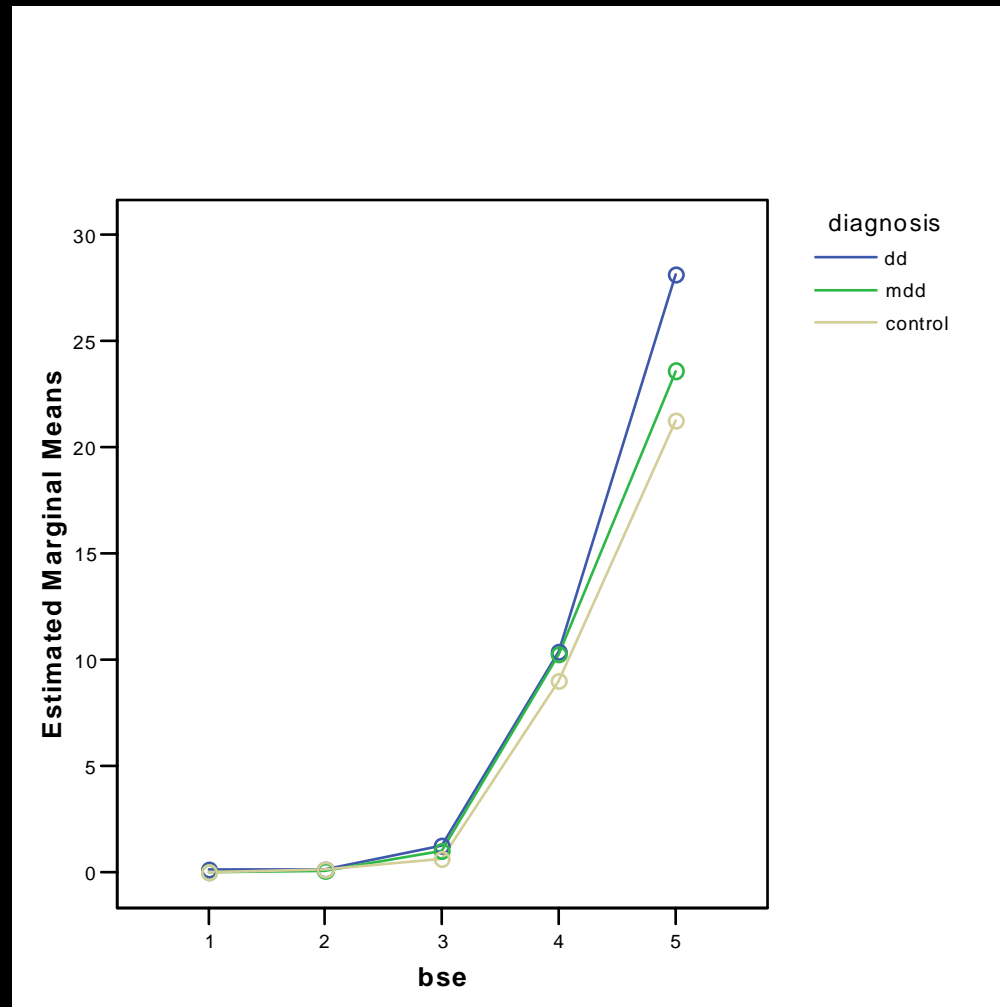
Cognitive Neuroscience

- 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)





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



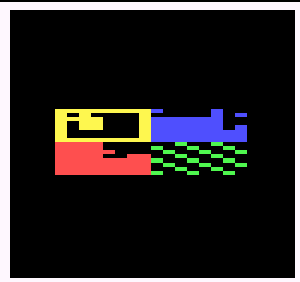
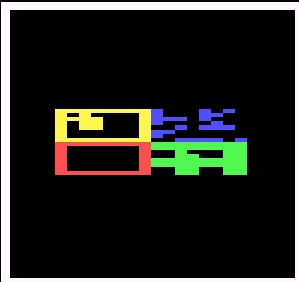
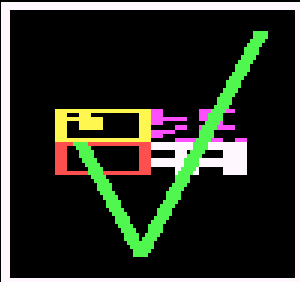
Level of difficulty (number of boxes)

[a] Wilks' $\lambda = .89$, $F(8, 272) = 1.77$, $p = .05$, partial $\eta^2 = .06$

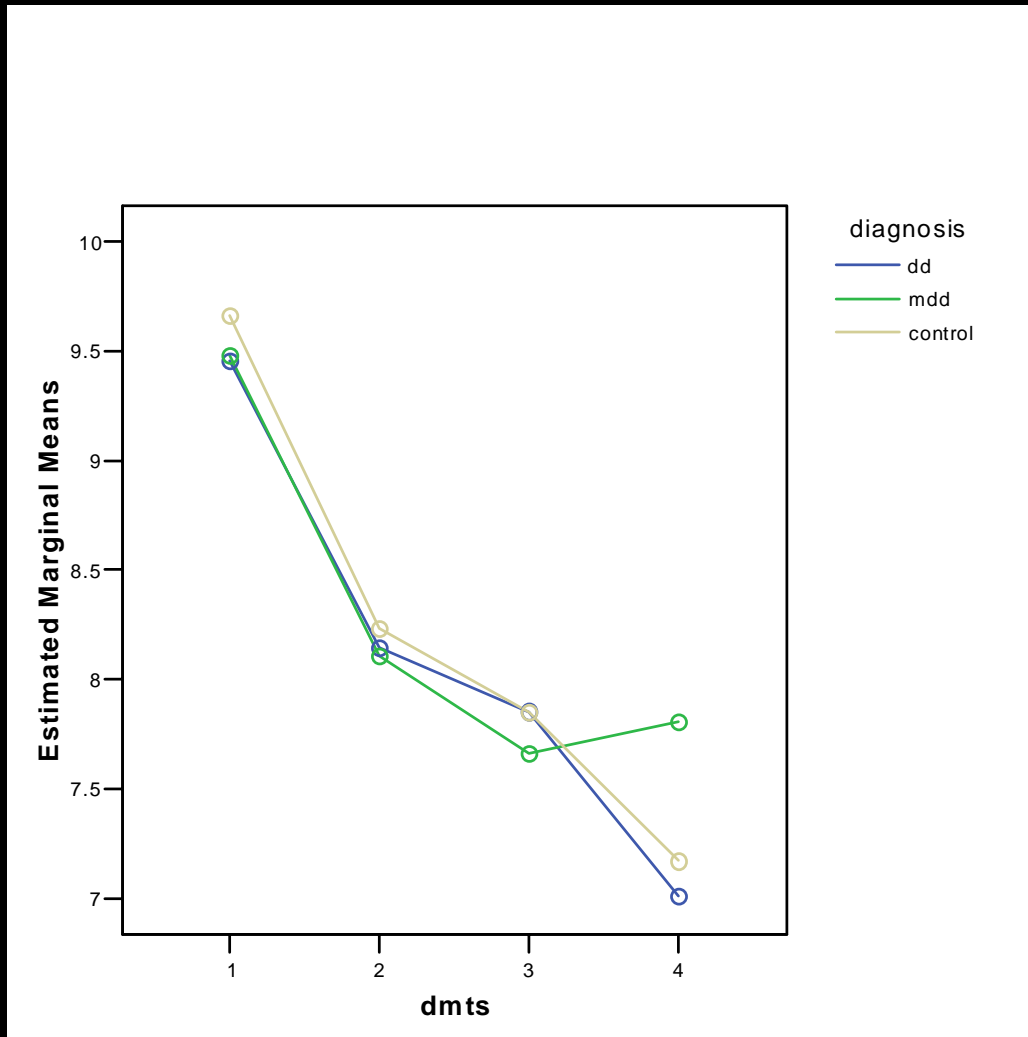
[b] Dysthymic disorder > controls $F(2, 176) = 3.32$, $p = .04$,

Cohen's $d = .81$

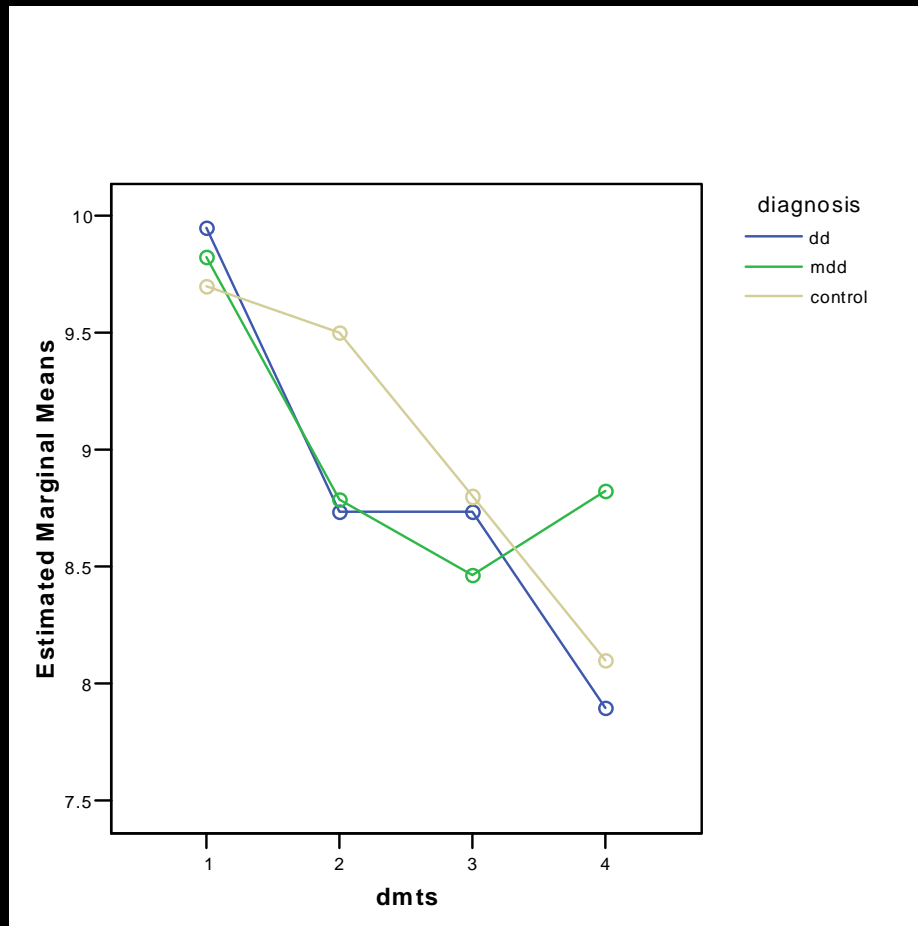
CORRECT



Delayed Matching To Sample(DMTS) (mean correct responses) at simultaneous and three delay conditions across the three groups, covarying for age



Delayed Matching To Sample(DMTS) (mean correct responses) at simultaneous and three delay conditions across the three groups: Age \geq 13 years



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

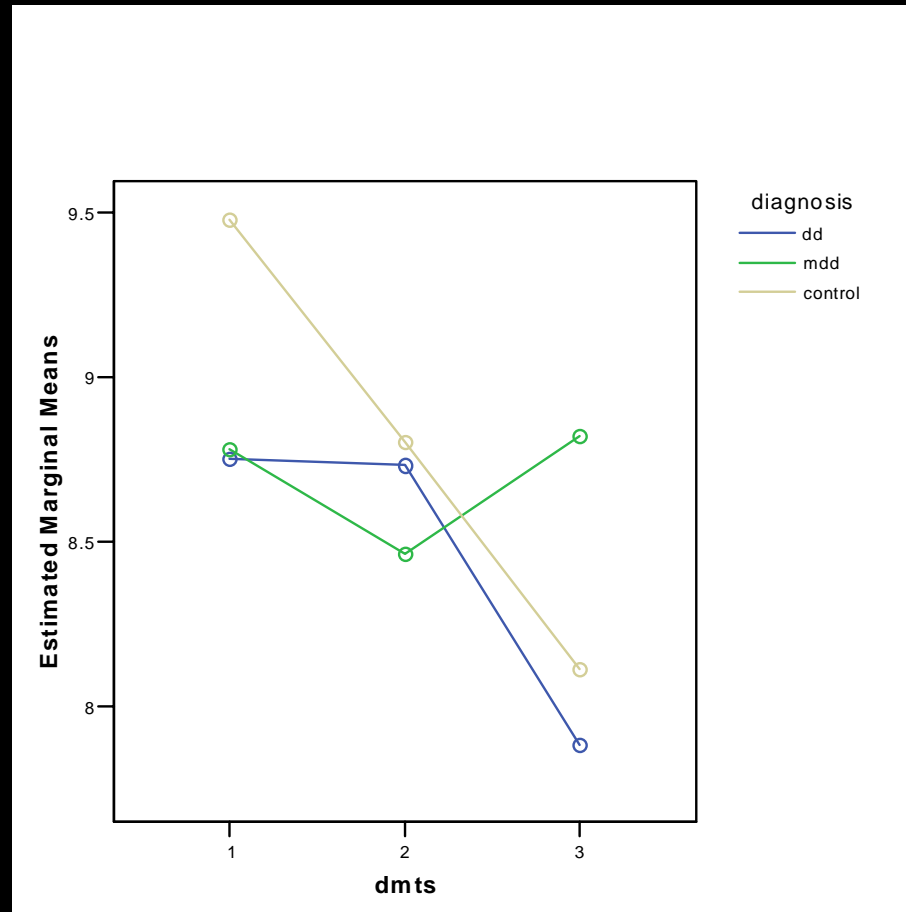
[a] Wilks' $\lambda = .76$, $F(6, 104)=2.62$, $p=.02$,

0: controls $>$ DD, MDD; 12: MDD $>$ DD

cohen's d = .66/.65; .73

Delayed Matching To Sample(DMTS) (mean correct responses) of the three delay conditions across the three groups, covarying for the simultaneous matching to sample:

Age \geq 13 years



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

[a] Wilks' $\lambda = .80$, $F(4, 104)=3.17$, $p=.02$,

[b] 0: controls > DD, MDD; 12: MDD > DD

cohen's d = .66/.65; .73

Current biological contributions

Cognitive neuroscience

- 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

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:

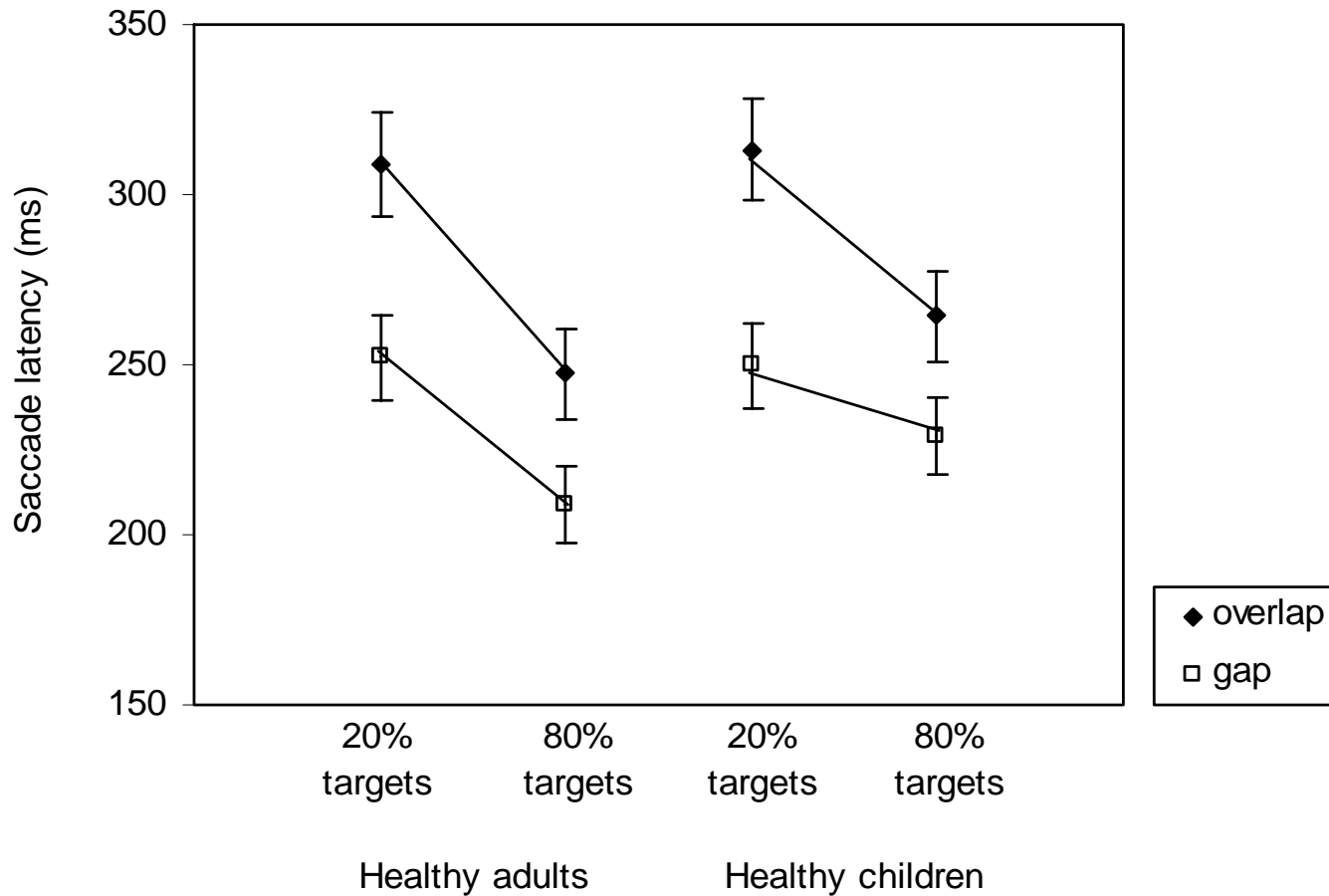
autonomic nervous system (adrenergic tone and reactivity)

investigation through postural blood pressure assessment;

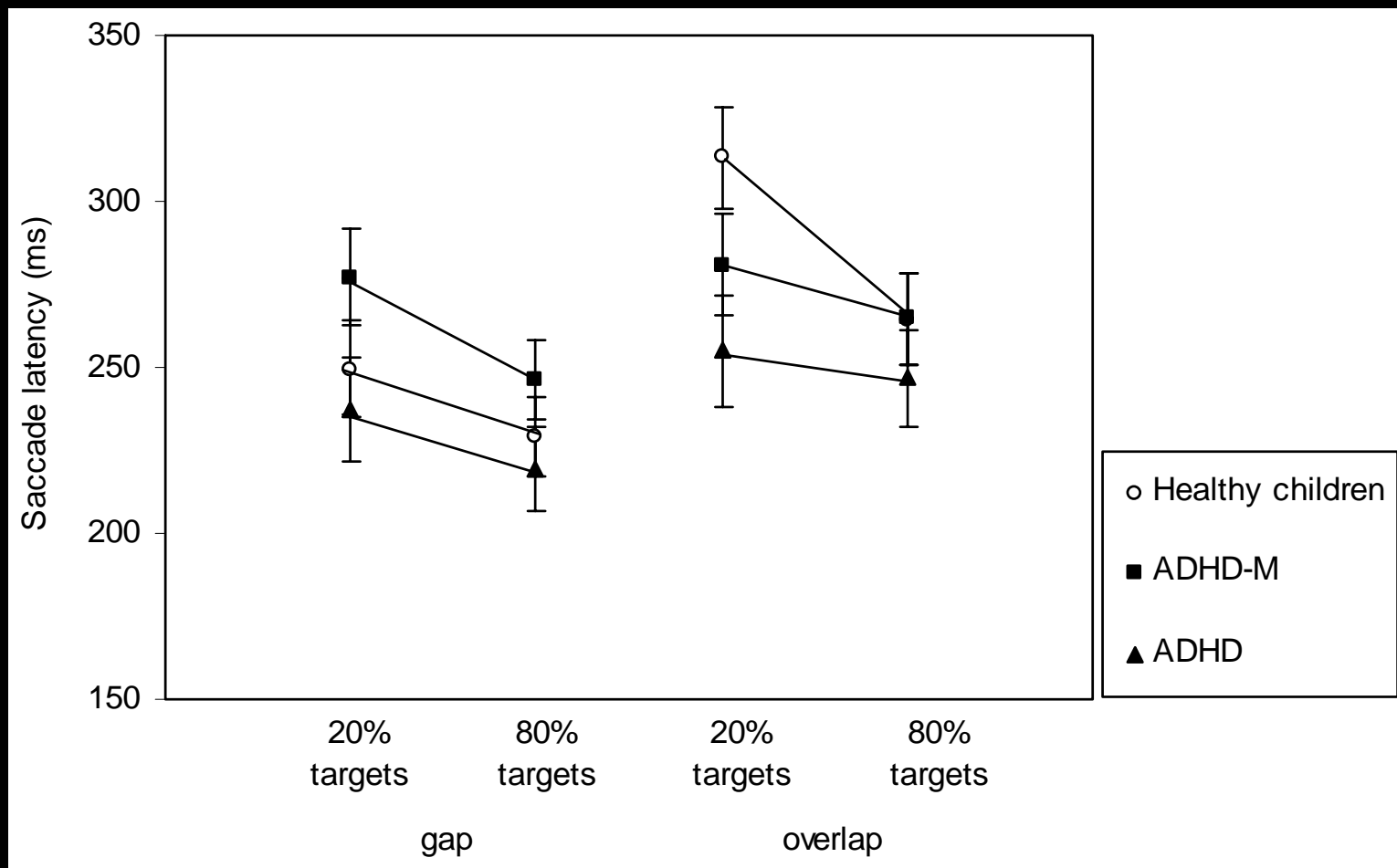
ultrasound assessment of forearm blood flow, and novel CNS approaches (eg Essler's);

oculomotor pro-and antisaccade tasks: contextual changes

Mean saccade latency (\pm SE) of healthy adults and healthy children in the 20% and 80% target probability conditions for overlap and gap trials.



Mean saccade latency (\pm 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

Neurophysiology

- 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

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 : 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

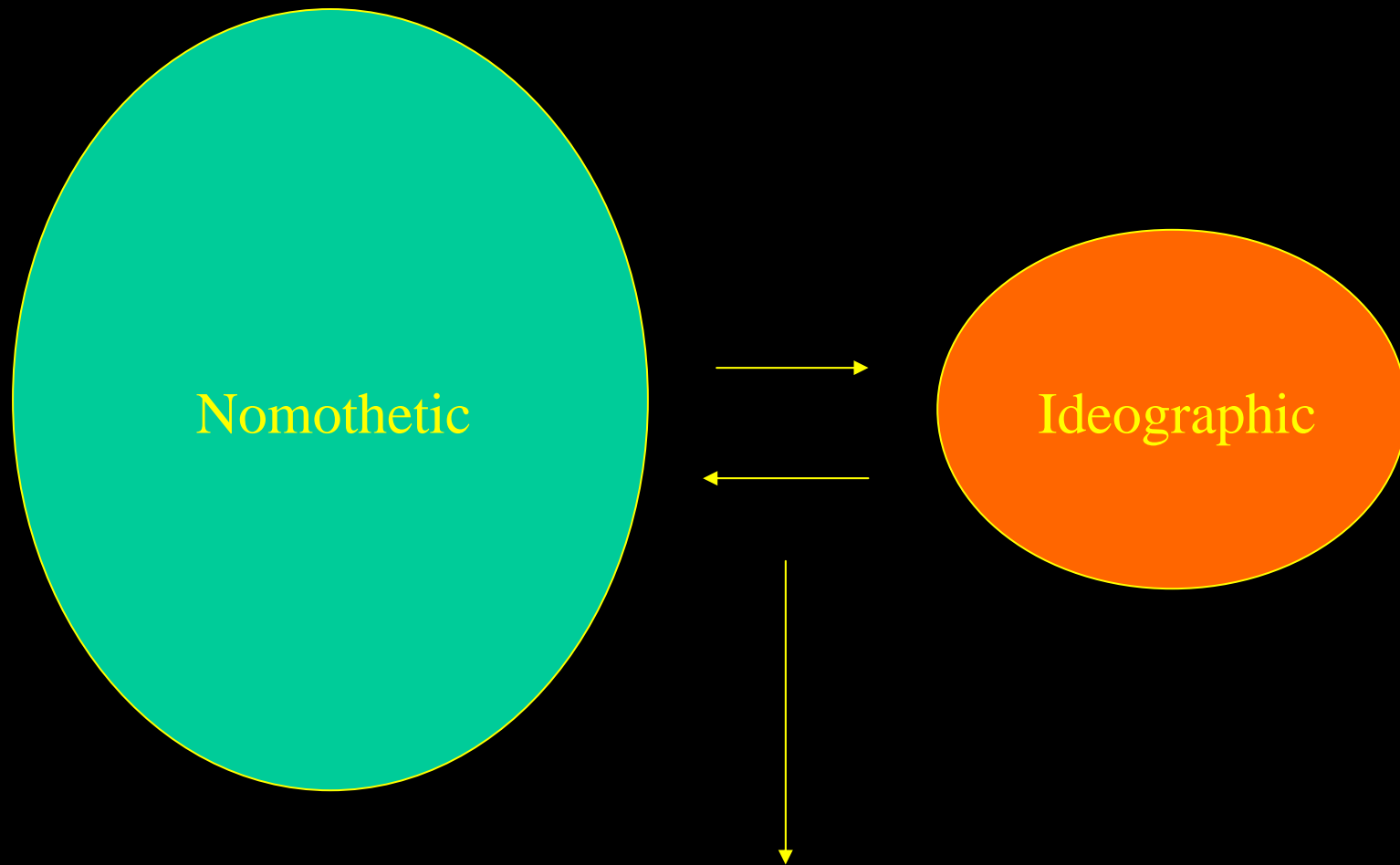
-will aid the *definition* of (ab)/normal developmental trajectories, whether development is *deviant or delayed*, and whether alterations are developmental stage *specific or generalised*

-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*

Thus,
the evidence - based (nomothetic) approach is developing and needs to be in *balance* with the individual - based (ideographic) approach so the subjective, objective, inter-subjective and interpersonal domains form the basis of assessment, treatment and monitoring of treatment



Comprehensive assessment, treatment and monitoring of treatment

But,
social, cultural and political movements affect this nomothetic
and ideographic balance....