

VICTORIA UNIVERSITY OF WELLINGTON
Te Whare Wananga o te Upoko o te Ika a Maui



School of Biological Sciences

The Genetics of Neurological Disorders

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Genetics Seminar

18 May 1998



Caveats and Assumptions

CAVEATS

Genetic Fallacy — current function *cannot* be inferred from ancestral function

Naturalistic Fallacy — a moral consequent *cannot* be inferred from solely factual premises

ASSUMPTIONS

NOT the Standard Social Science Model — The SSSM asserts that at birth all human minds are a clean slate, and individual differences (and similarities) are products of the environment.

NOT Descarte's Dualism — Descartes argued that there is a fundamental difference between the physical realm in which the body exists and the realm of the soul

CAVEATS

Examples:

Saying that the function of the bones of the mammalian middle ear — which evolved from (some) jaw bones of fish — are explained by describing the piscine jaw is a *genetic fallacy*.

Saying that since, through the course of hominid history, the most successful reproductive strategy for males was a polygamous one, men should now be allowed to have affairs is a *naturalistic fallacy*.

ASSUMPTIONS

The SSSM denies any role for evolution. Refer “The Adapted Mind”.

Only by assuming a physical basis for the mind can we study it scientifically. Chomsky started the cognitive revolution in the 1950's with his theory of an innate universal grammar.



Areas not Covered

The body of work which can shed light on the question of the mind is enormous, thus there are many areas of relevance which cannot be covered, but should be noted.

- linguistics/cognitive psychology
- non-human primate studies
- age-onset neurodegenerative disorders
- trauma-related disorders in adults
- neural development
- neurophysiology
- sensory/motor processing

linguistics/cognitive psychology — language of thought; behavioural phenotypes
non-human primate studies — comparative studies; refinement of our theory of mind

~~age onset neurodegenerative disorders — neural mechanics and their effects~~

trauma-related disorders in adults — localisation of function in the brain

neural development — ontogeny of brain architecture

neurophysiology — neural mechanics

sensory/motor processing] — sets of neurons which provide input/output function to the mind



Computational Theory of Mind I

EVOLUTION OF THE BRAIN

- environmental complexity
- social complexity
- communication needs
- intra-specific arms-race

WHAT IS THE MIND?

- ‘mind’ is what the brain does
- brain transforms **inputs** → **outputs**
- interactions of neurons are *sufficient* explanation
- mind can therefore be studied scientifically

The brain evolved as a response to specific environmental pressures, and so can best be explained by keeping those forces in mind. One possible explanation for the development of cognitive ability in primates relies on environmental complexity, social complexity, communication needs, and, in the case of hominids, an intra-specific arms race.

The Computational Theory of Mind (CTM) asserts that the brain is an entity which transforms input states into output states in much the same way as a modern digital computer. The mind is ‘what the brain does’ and programs are ‘what silicon hardware does’. The brain is composed of (many) neurons, and these are all that is required to explain the mind. Thus, properties and functions of brains, therefore minds, can be subjected to scientific study, just as properties and functions of livers, flowers, and sub-atomic particles can be.



Computational Theory of Mind II

FODOR

- Internal Representation — symbols
- Symbol Manipulation — rule-based, a la serial computer
- Task-specific Modules

CHURCHLANDS

- Internal Representation — (distributed) symbols
- Symbol Manipulation — one possible cognitive skill
- Highly Connected, Massively Parallel

BROOKS

- Situated Agency — no internal representation

One view, based on the work of J.A. Fodor, holds that the mind has internal representations for states of the world. These internal symbols are a mapping from specific internal neural (firing) arrangements to specific features of the world. The mind operates on these symbols in the same way that a digital computer operates on its internal symbols. The mind is composed of various modules, evolved to perform specific tasks, which have the ability to communicate with each other. Examples might be a module for spatial positioning, a module for communication (language), or a module for facial recognition.

The Churchlands feel that this view does not reflect biological reality sufficiently. The emphasis here is that the brain is a collection of massively parallel neurons with a high order of connectivity — a neural network, in contrast with the serial architecture of modern computers — which strongly influences computational algorithms. They agree that there is a level of symbolic representation, but they feel that rule-based symbol manipulation is one *possible* skill a neural network may acquire. Also acceptable is the modular view, with the proviso that the brain is a collection of neural networks. It has been shown that neural networks do not satisfy certain constraints such as those present in language which the mind does.

Brooks, on the other hand, feels that brains have no internal representations. The real world is better than any objective model. But in this case, how to decide what current percepts are relevant (frame problem).



Interpreting the CTM I

Features of the CTM which must map to biological structure/function

- modules
- symbolic representations and rule-based transformations
- neural network accounts

A symbol-rule type system would require certain *logical* constructs built on underlying physical neuronal strata, whereas emergent properties of neural networks do not necessarily rely on such arrangements.



Interpreting the CTM II

Genetic Influences

- morphology
- metabolic profile of neuron
- neurotransmitter profile of neuron

Examples of heritable features which require an account

- innate language ability
- anecdotal evidence from twin studies



Issues in Behavioural Studies

DATA

Can only measure naturally occurring genetic variation [in humans] through concordance studies, twin/adoption studies, and pathologies, of which only severe syndromes are reported.

BEHAVIOURAL PHENOTYPES

- qualitative (gross abnormality) vs. quantitative (normal distribution)
- are qualitative traits merely tail ends of normal distribution?
- there are inherent difficulties in determining phenotype

ROLE OF THE ENVIRONMENT

- cannot separate V_G from V_E easily
- longitudinal studies: genetic component increases with age
- fixed genotype in sample cannot be determined
- non-shared environment has greater effect than shared environment



Types of Pathology I

STRUCTURAL ABNORMALITIES

e.g. OMIM 303350 Clasped Thumb and Mental Retardation

- point mutation in L1CAM gene — cell adhesion molecule
- specific brain morphology abnormality

ENZYMATIC DEFICIENCIES

e.g. OMIM 300032 α -Thalassemia/Mental Retardation Syndrome, X-Linked

- mutations in Helicase 2 locus — gene expression
- profound effects

e.g. OMIM 261600 Phenylketonuria

- lack of phenylalanine dehydroxylase — metabolic deficiency
- progressive mental retardation and self-mutilating behaviour



Types of Pathology II

NEUROTRANSMITTER/RECEPTOR DEFICIENCIES

e.g OMIM 126451 Dopamine Receptor D3

- loss of function mutation - normally ~ 1% of dopamine receptors
- possible role in schizophrenia/bipolar disorder

e.g OMIM 137150 Gamma-aminobutyrate transaminase

- loss of function mutation
- severe brain disorder

POLYGENIC PHENOTYPES

All these examples are single locus abnormalities. Less well understood, and probably more important in terms of behavioural variation in the 'normal' ranges are the incremental effects of the many genes which contribute to the final composition of the brain.



Causes of Pathology

As well as 'common' mutation events, such as point mutations, the following mechanisms are found to be involved in abnormal phenotypes.

cytogenetic abnormalities — affects contiguous loci.

e.g. Down's Syndrome

tri-nucleotide repeats — affects particular locus.

e.g. Huntington's Disease

imprinting — affects expression of particular locus.

e.g. Turner Syndrome

Cognitive Disabilities I

SPCH1 — Speech and Language Disorder with Orofacial Dyspraxia

- localised to 7q31
- autosomal dominant with full penetrance
- originally associated with specific grammar disorder
- subsequently shown to affect functional ability in motor-related areas of frontal lobe
- affects intellectual, linguistic, and orofacial praxic functions generally

CGF1 — Social Cognitive Function

- located on Xq or proximal Xp
- imprinted — 45, X_{pat} less affected
- associated with aptitude for spatial visualisation
- males (who only have X_{mat}) more susceptible to language and social disorders → synergistic action with other loci



Cognitive Disabilities II

dyslexia — Specific Reading Disability

- possible located in 1p36-p34
- inability to identify phonetic elements embedded in speech
- results in impaired learning — no molecular/cellular learning defects

Autism — Infantile Autism

- inability to form the usual affective contact with *people*
- regions on 6 chromosomes found to be significant, 7q > distal 16p
- strong evidence of multifactorial causation
- possible 5-HT (serotonin) involved (abnormally high levels)
- possible correlation with cerebellar vermis lobules VI and VII
- possible correlation with RFLP polymorphism of *engrailed-2* home-box gene
- autistic behaviour also associated with FRAX, Angelman, and phenylketonuria

Issues

- What is meant by penetrance?
- What is meant by quantitative traits?
- Why are so many cognitive functions X-linked?
- Does a computational theory of mind account for these findings?
- Can we accept a modular view?
- Does the mind appear to be a logical function sitting on neural substrate?
- If the evidence suggests a ‘neural network’ architecture, how are inherited behaviours ‘programmed’?
- If the CTM holds, and specific behavioural phenotypes are (partially) inherited, is it fair to treat people as if they were born with ‘clean slate’ and *must* these phenotypes be accepted in society?
- Do we care, or this something we can leave for a few hundred more years?