Elementary, my dear Watson, the clue is in the genes … or is it?

On 5 November 2001, **Professor Annette Karmiloff-Smith FBA, FMed.Sci**, *Head of the Neurocognitive Development Unit at University College London, delivered a special lecture at the Academy to celebrate the Centenary of the British Psychological Society. In the edited extract below, she outlines the theme of her lecture.*

The full text of this lecture will be published in the *Proceedings of the British Academy* Volume 117.

My seemingly light-hearted, yet serious, lecture title requires explanation. This lecture celebrated the Centenary of the British Psychological Society, hosted by the British Academy (whose Centenary is but one year later). The British Academy covers the humanities (including archeology, ancient and modern languages and literature, history, theology) and the social sciences (including law, economics, geography, anthropology, politics, psychology). Even within the Academy's Psychology Section there is a wide range of expertise: social psychology, health psychology, cognitive psychology, etc. And my own speciality – developmental cognitive neuroscience – is probably the furthest from the humanities. My problem was thus to link my interest in genotype/phenotype relations with those of these other disciplines, and the name 'Watson' came to mind. On the science side: James Watson contributed to the discovery of DNA's structure in the 1950s and, half a century later, to the human genome sequencing. On the humanities side: although Conan Doyle is hardly a great literary figure, the sidekick of his famous character, Holmes, is also called Watson. And the Watson link turns out to be less spurious than it seems, because understanding the complex pathways from gene-to-brain-to-cognitive processes-to-behaviour is like a detective story, in which seemingly unimportant clues early in development play a vital role in the final outcome.

As we learn more about genes, there is a temptation, not only in the press but in the scientific literature, to seek one-to-one relationships between specific genes and complex behaviours like altruism, aggression, intelligence, or language. Steven Pinker has repeatedly supported such assumptions, using data from adult neuropsychology and genetic disorders. Many psychologists and linguists of a Nativist persuasion claim that human infants are born with genetically specified brains that contain specialised components, not only for low-level perceptual processes, but also for higher-level cognitive modules like language, mathematics, spatial cognition, face processing and the like. A direct link is then sought between specialised modules and specific genes. The infant brain is thus claimed to start out like a Swiss Army knife. Data used to bolster such claims come from adult neuropsychological patients and children with genetic disorders. But are these two sources of data as straightforward as they seem? It is indeed the case that adults who suffer stroke or accident can damage a specific part of the brain which results in isolated impairments. Patients with prosopagnosia have normal language, are able to recognise different categories of objects, yet present with an impairment in recognising faces. Other patients process faces well, but present with difficulties with grammar. However, it is vital to recall that these are adults who developed normally throughout their lives until their brain insult. One cannot simply assume that the adult end-state is organised in the same way as the infant start-state. It could be that specialisation for face processing or language are the *result* of a developmental process, not its starting point. Thus, isolated impairments in adulthood may tell us nothing about gene expression in the infant brain.

At first blush, there are a number of genetic disorders that may fit the Nativist model. Dyslexia is a disorder with a clear genetic component. The syndrome appears to present with impairments solely in reading. Likewise for Specific Language Impairment (SLI), which is claimed to affect language alone, with the rest of the child's skills intact. Williams Syndrome, discussed below, has been hailed by many, including Pinker, as the prime example of impaired and intact cognitive modules directly linked to genes. Indeed, in comparing SLI and Williams Syndrome (WS), Pinker argues for a dissociation between the disorders at both the genetic and cognitive levels, appealing to the logic of adult neuropsychology: 'Overall, the genetic double dissociation is striking, suggesting that language is [both] a specialisation of the brain.… The genes of one group of children [SLI] impair their grammar while sparing their intelligence; the genes of another group of children [WS] impair their intelligence while sparing their grammar' (Pinker, 1999).

By contrast, I argue that there is no one-to-one direct mapping between a specific gene and a cognitive-level outcome. Rather, there are many-to-many indirect mappings, with the regulation of gene expression contributing to broad differences in developmental timing, neuronal type, neuronal density, neuronal firing, neurotransmitter types, and so on. In the Neuroconstructivist framework for which I argue, gene/gene interaction, gene/environment interaction and, crucially, the process of ontogeny itself (pre- and post-natal development) are all considered to play vital roles in how the brain progressively sculpts itself and *becomes* specialised over developmental time. Infant brains are not miniature versions of adult brains.

The Neuroconstructivist Approach

I take Williams Syndrome as an example of the Neuroconstructivist approach. Much is known about both the WS genotype and phenotype (the behavioural outcome). Despite this, the genotype/phenotype relationship is far from obvious. WS involves the deletion of 20 genes on one copy of chomosome 7. People with WS have atypical brain anatomy and atypical brain chemistry. Their IQs are in the 50–65 range, with an uneven cognitive profile in which language usually outstrips scores on spatial tasks. The difference between impaired spatial skills and seemingly proficient face processing skills in WS is particularly striking. Children and adults score in the normal range on standardised face processing tasks, yet are in the seriously impaired range on spatial tasks. This led a number of psychologists of a Nativist persuasion to claim that the syndrome presents with an intact face processing module and an impaired space processing module. Geneticists working on the syndrome discovered one family with two genes deleted (Elastin and Limkinase1) in the WS critical region. They leapt to the claim that Limkinase1, expressed in the brain, was directly linked to spatial deficits. It took little time for the press to hail the discovery of 'a gene for spatial cognition' or 'a gene for intelligence'. However, several problems arise with the direct mapping of Limkinase1 to spatial cognition. Firstly, to reiterate, direct one-to-one mappings between specific genes and specific higher-level cognitive outcomes like spatial cognition are extremely unlikely. Secondly, drawing such conclusions from the study of a single family is questionable. Thirdly, using adult outcomes to draw genotype/phenotype conclusions negates the role of development in gene expression.

My team and I decided that three approaches were required to explore genotype/phenotype relationships in WS: (i) together with clinical geneticists at St. Mary's Hospital, Manchester, we studied partial gene deletion cases in the WS critical region; (ii) we made in-depth studies of those areas which other research teams had deemed to be intact in WS, by dissecting the phenotype; and (iii) we explored the WS infant start-state with infants with other genetic disorders. It is the second and third approaches that particularly illustrate the Neuroconstructivist framework.

Studies of the relationship between genotype and phenotype in Williams Syndrome

Given the space limitations of this summary, I merely point to the findings from our three approaches, and direct readers to relevant publications. Our studies of four patients with partial deletions in the WS region on chromosome 7 showed that even when 13 of the 16 WS genes (including Limkinase1) were deleted, the outcome was normal intelligence and no linguistic/spatial imbalance. Thus, the earlier claims about the relation between Limkinase1 and spatial impairments were erroneous and could not alone explain the atypical developmental pathway in Williams Syndrome.

Our in-depth studies of the seeming proficient domains of face processing, language and social cognition in older children and adults with Williams Syndrome reveal subtle impairments, not intact modules. Scores 'in the normal range' do not necessarily entail normal cognitive processes nor normal gene expression. For example, normal controls process faces configurally – they look at the whole face and relationships between parts. By contrast, people with Williams Syndrome process faces featurally – they focus on local details. Their scores in the normal range are arrived at via different cognitive processes. Such differences also hold for our studies of the functioning of WS brains. While normal controls process faces predominantly with the right hemisphere, people with WS show bilateral or predominantly left hemisphere processing. While normal controls differ in brain electrophysiology when processing human faces, monkey faces or cars, people with WS process all three similarly. It is not the case that face processing is intact and spatial processing is impaired: *both* are impaired in WS. And our studies reveal similar subtle impairments for language and social cognition, two other domains which some

argue to be intact in WS. Yet Nativist claims, and the use of a genetic disorder like Williams Syndrome to support those claims, require a pattern of intact versus impaired modules formed from intact versus mutated genes, as the above citation from Pinker illustrates.

Our third line of experimental attack was to ask whether patterns of impairments found in adulthood look analogous in infants with WS. Our results showed that for faces, infants with WS notice both featural and configural changes, but, unlike control infants, they prefer to focus on features if given a choice between the two. For number, infants with WS notice small changes in numerosity, whereas infants with Down's Syndrome (DS) of the same age and IQ do not. Yet in adulthood, people with DS are less impaired in arithmetic tasks than those with WS. With respect to language, infants with WS are just as impaired as those with DS. Yet, by adulthood, WS clearly outstrips DS in the language domain. Again, Nativist arguments require that infant profiles resemble phenotypic outcomes, and they do not.

Finally, we examined low-level mechanisms in WS and found atypical eye movement planning in infants and atypical sychronisation of oscillatory brain activity in adolescents and adults. We are also carrying out similar exercises at the brain, cognitive and infancy levels with other genetic disorders. Yet, even in a syndrome with a single mutated gene (Fragile-X syndrome), the same story holds: subtle impairments across *multiple* aspects of the developing system.

My conclusion is that data from adult neuropsychology and genetic disorders cannot be used by Nativists to bolster claims about genetically specified, modular specialisations of the human brain. We need to understand how genes are expressed *through development*, because the major clue to genotype/phenotype relations turns out to be the very process of development itself.

Further Reading

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