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

ANNETTE KARMILOFF-SMITH *plays detective to unravel the genetic basis of Williams syndrome.*

JAMES Watson's contribution to the discovery of the structure of DNA in the 1950s and to the sequencing of the human genome half a century later cannot fail to excite all those fascinated by human development. Each day we learn more about genes and the human brain. As we do, there is a temptation to seek one-to-one relationships between (on the one hand) complex behaviours like altruism, aggression, intelligence or language, and (on the other hand) specific genes or locations in the brain. In a series of popular books, Steven Pinker (1994, 1997, 1999) has repeatedly supported such assumptions by using data from adult neuropsychology and genetic disorders.

In this article I argue that the interpretation of such data is flawed. It is based on a static model of the human brain, ignoring the complexities of gene expression and the dynamics of postnatal development. I will illustrate this through studies of infants, children and adults with the genetic disorder Williams syndrome. Understanding the complex pathways from gene to brain to cognitive processes to behaviour is like a Sherlock Holmes and Dr Watson detective story, in which seemingly unimportant clues early in development play a vital role in the final outcome.

The 'Swiss Army knife' brain?

Many theorists of a nativist persuasion claim that human infants are born with genetically programmed brains that contain specialised components: not only for low-level perceptual processes, but also for higher-level cognitive modules like language, mathematics and face processing. A direct link is then sought between these specialised modules and specific genes. In other words, the infant brain is claimed to be like a Swiss Army knife, with the notion that evolution has created increasingly complex, uniquely specialised genes (Cosmides & Tooby, 1994).

But are the two sources of data used to bolster these claims – adult neuropsychology and genetic disorders – 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 that may then result in an isolated impairment. For instance, patients with prosopagnosia have normal language, are able to recognise different categories of objects, yet show an isolated impairment in recognising faces. Other adult patients may process faces well and use a wide variety of words, but have difficulty putting words together into grammatical form.

However, it is vital to recall that these selective deficits in neuropsychological patients come from adults who had developed normally until their brain insult. Their brains had by adulthood already become specialised and were subsequently damaged. One cannot simply assume that the infant start-state is organised in the same way as the adult end-state. Brains develop dynamically, not as a series of juxtaposed, isolated parts. Therefore, it could well be that the specialisations for face processing, language and the like in adults are the result of a developmental process, not its starting point (Karmiloff-Smith, 1992, 1998; Paterson *et al.*, 1999). Isolated impairments in adulthood may tell us relatively little about the infant brain and its relationship with gene expression.

While adult neuropsychology patients may be uninformative about innateness, there are a number of genetic disorders that at first blush seem to fit the nativist model. Specific language impairment (SLI) is a disorder with a genetic basis which by its very name suggests that language alone is impaired, with the rest of the child's skills argued to be intact. Williams syndrome (discussed in more detail below) has been hailed by many, including Pinker, as the prime example of impaired and intact cognitive modules directly linked to mutated and intact genes. Indeed, in comparing SLI and Williams syndrome, Pinker argues for a clear-cut dissociation between the two disorders at both the genetic and cognitive levels, appealing to the logic of adult neuropsychology:

> *Overall, the genetic double dissociation is striking… 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, p.262)

By contrast, I argue that there is no one-to-one direct mapping between specific sets of genes and cognitive-level outcomes. Rather, there are very indirect mappings, with the regulation of gene expression more likely to contribute to very broad differences in the timing of maturation, and neuronal characteristics (e.g. type, density, firing thresholds, transmitter type). In the 'neuroconstructivist' framework for which I argue, gene–gene interaction, gene–environment interaction and – crucially – the process of development are all considered to play a vital role in how genes are expressed and how the brain progressively sculpts itself, slowly

WEBLINKS

The Williams Syndrome Foundation (UK): *www.williams-syndrome.org.uk*

The Williams Syndrome Foundation (USA): *www.wsf.org*

Institute of Child Health, Neurocognitive Development Unit: *www.ich.ucl.ac.uk/ich/html/academicunits/neurocog_dev/n_d_unit.html*

becoming specialised over developmental time. The infant brain is not simply a miniature version of the adult brain.

The neuroconstructivist framework

The genetic disorder Williams syndrome (WS) serves as an example of the neuroconstructivist approach to genotype–phenotype relations. A great deal is known about both the WS genotype and the WS phenotype (the physical and behavioural outcome). Yet despite such evidence, the relationship between genotype and phenotype is far from obvious.

The box (right) gives some key facts about WS, and refers to evidence showing a clear-cut disparity between face and space processing in Williams syndrome. Geneticists working on the identification of the functions of the genes in the deleted WS region used these psychological data to make specific claims about genotype–phenotype relations (Frangiskakis *et al.*, 1996). The geneticists discovered some members of one family with a deletion of two genes (elastin and limkinase1) in the same region of chromosome 7 as people with WS. Since the limkinase1 gene (LIMK1) is expressed in the brain, and since those members of this family with the genetic mutation displayed some spatial deficits, the geneticists leapt to the conclusion that only having one copy of LIMK1 was directly linked to the spatial impairment seen in WS (Frangiskakis *et al.*, 1996). It took little time for the press to hail these findings in terms of the discovery of 'a gene for spatial cognition' or even 'a gene for intelligence'.

There are, however, several problems with the direct mapping of the LIMK1 gene to spatial cognition. Firstly, to reiterate, direct one-to-one mappings between specific genes and specific higher-level cognitive outcomes like spatial cognition are highly unlikely. Genotype–phenotype relationships are exceedingly indirect. It is one thing to state that a mutated gene contributes to the disruption of a cognitive outcome, but quite another to claim that this is the 'gene for' that outcome. Secondly, drawing such strong conclusions from the study of a single family who may have other genetic impairments is premature. Thirdly, using the adult outcome to draw such genotype/phenotype conclusions negates the role of ontogenetic development in gene expression.

My team and I thus decided that three approaches were required to explore the genotype–phenotype relationship in WS. I will now deal with these in turn.

WILLIAMS SYNDROME

Williams syndrome occurs in approximately 1 in 25,000 live births. It involves the deletion of some 17 genes on the long arm of one copy of chromosome 7q11,23 (Donnai & Karmiloff-Smith, 2000).

Characteristics:

- Atypical brain anatomy and chemistry: subtle and diffuse, in keeping with structural abnormalities with a genetic origin.
- Facial dysmorphology.
- Cardiac abnormalities.
- Renal abnormalities.
- IQs in the 50–65 range.
- Proficient at recognising and remembering faces.
- Serious impairment on spatial tasks. Serious deficit continues throughout adulthood.

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Genotype–phenotype studies

Studies with colleagues at St Mary's Hospital, Manchester, of patients with partial deletions in the WS critical region on chromosome 7 have thus far covered four patients who have been examined in detail (Karmiloff-Smith *et al.*, in press; Tassabehji *et al.*, 1999). Despite having deletions of varying sizes (but all including elastin and limkinase1), none had the facial dysmorphology of WS, all had intelligence in the normal range and none showed the typical uneven profile of language scores outstripping spatial scores. Our results make it clear that deletion of LIMK1, a mutation characteristic of all our patients in this study, cannot alone explain the particularly serious spatial deficits in WS. Our detectives Holmes and Watson may conclude that the direct one-to-one genotype–phenotype relation between LIMK1 and spatial impairments claimed by previous researchers was erroneous. A more complex story about genotype–phenotype relations is required.

In-depth studies of behavioural proficiency in WS Our second approach was to undertake in-depth studies of the ostensibly proficient domains of face processing, language and social cognition in older children and adults with WS. These were of particular interest because the literature is replete with claims that these domains represent intact modules in WS. Yet our neuroconstructivist approach regarding the dynamics of overall brain development suggests that we should find subtle deficits even in proficient domains.

Face processing is a domain in which people with WS seem to excel. They score in the normal range on the Benton Face Processing Task (Benton *et al.*, 1983) and the Rivermead Face Processing Task (Wilson *et al.*, 1990), indicating a particular proficiency with face identity matching in this clinical population (e.g. Karmiloff-Smith, 1997). However, do behavioural scores 'in the normal range' necessarily entail normal cognitive processes and normal gene expression?

We set out to examine this question in a series of behavioural and brain-imaging studies. We first replicated the findings that, on the Benton Face Processing Task, people with WS score surprisingly well. We then tested our WS group on other, more detailed face-processing tasks (Bruce *et al.*, 2000). For example, participants were asked to match faces in terms of their emotional state, lip reading, eye-gaze direction and identity.

At first blush, the WS group seemed to perform well. However, once we examined separately those items which could be solved by looking simply at one of the features of a face and those for which the whole configuration of the face had to be taken into account, a striking difference emerged in the WS data. For featural processing, the WS group performed like normal controls. However, their scores

were at chance when they had to analyse the face configurally (Karmiloff-Smith, 1997). They also do not show the typical inversion effect by which normal controls perform more slowly and less accurately when faces are presented upside down (Deruelle *et al.*, 1999). So the WS behavioural scores 'in the normal range' on standardised face-processing tasks like the Benton and the Rivermead must be arrived at via a different cognitive process, compared with normal controls.

Such differences also hold for our studies of the functioning of WS brains. We decided to use high-density event-related potentials because this method is totally non-invasive and our patients enjoy participating. While normal controls process faces predominantly with the right hemisphere, people with WS show bilateral or predominantly left hemisphere processing (Mills *et al.*, 2000). Furthermore, normal controls differ in brain electrophysiology when processing human faces, monkey faces or cars, whereas people with WS process all three in the same way (Grice *et al.*, 2001). So it is not the case that face processing is intact and spatial processing is impaired: both follow atypical pathways in WS, compared with controls, once experimental design delves beneath the surface of behavioural scores.

Our other cognitive-level studies reveal the same subtle impairments with respect to language and social cognition (e.g. Karmiloff-Smith *et al.*, 1997, 1998; Laing *et al.*, 2002). These are two further domains that some researchers argue to be intact in WS. Yet our in-depth studies of children and adults with WS reveal serious delays as well as numerous deficits in both language and social cognition (see also Jarrold *et al.*, 1998; Mervis *et al.*, 1999; Tager-Flusberg & Sullivan, 2000).


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Recall, however, that 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 earlier quote from Pinker illustrates. Differentiating between superficial behavioural scores and underlying cognitive processes reveals that this is not the case.

Comparing the infant start-state with the adult phenotypic outcome

Our third line of experimental attack was to explore whether the pattern of deficits and proficiencies found in adults is the same in infants with Williams syndrome. In other words, can one simply assume that the uneven profile in the outcome will have been identical in the start-state in infancy? We tested this assumption in the domains of face processing, language, social cognition and number, and also examined whether the typical language/spatial cognition imbalance in adulthood was already apparent in very young children. In each domain, we endeavoured to keep the experimental stimuli the same for very young children as those that we had used in our adult studies. Obviously, the actual methodologies had to be adapted to the age of the infants and toddlers.

In order to assess their face-processing abilities, we showed infants and toddlers a series of schematic faces. Some of these were identical, whereas others had been modified either in terms of features (round eyes were changed to triangular or square eyes) or of configuration (a face was stretched or squashed so that the distance between features was altered). Our results suggest that infants with WS notice both featural and configural changes in faces, but, unlike control infants, they prefer to focus on features if given a choice between the two (Humphreys *et al.*, 2002). Using the same stimuli, we had earlier found that adults with WS are significantly less accurate and take significantly longer to notice configural changes compared with normal control adults (Humphreys & Karmiloff-Smith, 2000). So the tendency in adulthood to focus on features seems to be a function of an early developmental tendency in Williams syndrome.

To test whether children with WS notice differences in number, two monitors displayed pairs of pictures of two objects and then, after familiarisation, one image suddenly displayed three objects. Normal controls always look longer at the display containing the altered number. This turned out also to be true of infants with WS. They noticed small changes in numerosity, whereas infants with Down's syndrome (DS) of the same chronological and mental age did not (Paterson *et al.*, 1999). Yet in adulthood, the opposite pattern obtains: people with DS turn out to be less impaired in arithmetic tasks than those with WS (Paterson *et al.*, 2002). So the pattern in the WS infant start-state is different from the adult phenotypic outcome in the number domain.

We also tested infants with WS and infants with DS on early language comprehension. Here, the results were very different. The infants with WS turned out to be just as seriously delayed as those with DS and significantly worse than both mental age-matched and chronological age-matched controls (Paterson *et al.*, 1999; see also Laing *et al.*, 2002, for studies of atypical prelinguistic interaction in infants with WS). This stands in sharp contrast to adulthood, when it is those with WS who clearly outstrip adults with DS in the language domain.

Thus, once again, the pattern in the adult outcome cannot be used simply to assume what the infant start-state is like or to make claims about gene expression. Yet nativist arguments using adult profiles from genetic disorders to make claims about impaired and intact innate modules would require that the infant profiles look

similar to the phenotypic outcome. But they do not.

Finally, we examined a number of low-level mechanisms in WS, with the hypothesis that subtle impairments early on in development impact over time on the final outcome. We were able to identify atypical eye-movement planning in infants with WS (Brown *et al*., in press) and atypical sychronisation of oscillatory brain activity in adolescents and adults with WS (Grice *et al*., 2001). These basic impairments affect fundamental processes that have a cascading impact on development from early infancy onwards.

At present my team is carrying out the same exercise with other genetic disorders, such as velocardiofacial syndrome (another microdeletion disorder like WS, but on chromosome 22), DS, autism and fragile-X syndrome. We dissect the cognitive profile at both the behavioural and brain levels, and trace development back to its origins in infancy. Yet even in a syndrome with a single mutated gene, like fragile-X syndrome, the same story holds: we are discovering subtle deficits across numerous aspects of the developing system. Irrespective of whether one focuses on multiple or single gene disorders of genetic origin, direct relations between specific genes and cognitive-level outcomes turn out to be highly unlikely.

Development is the key

In this article I have argued against the assumption that children with genetic disorders present with brains like adult neuropsychological patients; that is, a pattern of intact and impaired cognitive modules. The adult neuropsychological model is a static one of the structure of the human brain, because it focuses on adults whose brains are already fully formed. But pre- and postnatal brain development is a dynamic process which involves interactions across the whole brain. The range of findings from our studies of infants, children, adolescents and adults with Williams and other syndromes suggests that it cannot be taken for granted that the infant start-state is necessarily the same as the phenotypic outcome.

Thus, claims about innate modules and how they relate to mutated and intact genes must be constrained by knowledge of the profile of abilities and impairments found in early childhood as well as the subsequent developmental trajectory over time. Furthermore, neuropsychological cases (normal adults who suffer a brain insult) cannot be used to make claims about evolution and the ontogenetic start-state, because the structure of the normal adult brain is the end product of a non-static process over developmental time. Both these sources of data need to be treated with extreme caution if used to bolster claims about genetically programmed, modular specialisations of the human brain. My contrasting view is that our aim should be to understand how genes are expressed through development. The major clue to genotype–phenotype relations is not simply in the genes, or simply in the interaction between genes and environment, but in the very process of development itself.

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