

SPECIAL LECTURE  
*to mark the centenary of the British Psychological Society*

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

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### Introduction

THE SEEMINGLY LIGHT-HEARTED, yet in fact serious, title of my lecture requires some 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 both the Humanities (Archaeology, Modern Languages, Literature, History, Theology, Philosophy, etc.) and the Social Sciences (Law, Economics, Social Anthropology, Geography, Sociology, Politics, Psychology, etc.). Even the Psychology Section of the Academy covers a wide range of disciplines: social psychology, cognitive psychology, adult neuropsychology, health psychology, emotional psychology, primate cognition, etc. And my own speciality—developmental cognitive neuroscience—is probably one of the furthest from the Humanities. So the problem the lecture posed was to link my interest in genotype/phenotype relations with the interests of these other disciplines, and the name ‘Watson’ came to mind. On the science side: James Watson contributed to the discovery of the structure of DNA in the 1950s and, half a century later, to the sequencing of the human genome. On the humanities side: although Arthur Conan Doyle is hardly one of Britain’s greatest literary figures, the sidekick of his famous character, Sherlock Holmes, is also called Watson. In fact, the

Read at the Academy 5 November 2001.

*Proceedings of the British Academy*, 117, 525–543. © The British Academy 2001.

Watson link turns out to be less tenuous than it might seem, because understanding the complex pathways from gene-to-brain-to-cognitive processes-to-behaviour is not unlike a detective story, in which seemingly unimportant clues very 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 even in some of the psychological, linguistic and philosophical literature, to seek one-to-one relationships between specific genes (or specific sets of genes) and complex higher-level behaviours like altruism, aggression, intelligence, spatial cognition, or language. In a series of popular books, Steven Pinker has repeatedly supported such assumptions by using data from neuropathology (Pinker, 1994, 1997, 1999; see also Temple, 1997). 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, spatial cognition, face processing, and the like. 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). Data used to bolster such claims come from adult neuropsychological patients and from 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 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 present with an isolated impairment in recognising faces. Other adult patients may process faces well, use a wide variety of words, but present with difficulties putting words together into grammatical form, and so forth. However, it is vital to recall that these selective deficits in neuropsychological patients come from adult patients who had previously developed normally throughout their lives until their brain insult. Their brains had by adulthood already become specialised and subsequently damaged. But their brains were not damaged in early childhood. Thus, 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).

Thus, isolated impairments in adulthood may tell us relatively little about the infant brain and its relationship with gene expression.

While adult neuropsychology patients may therefore be uninformative about innateness, there are a number of genetic disorders that at first blush seem to fit the nativist model. Dyslexia is a disorder with a clear genetic component. The syndrome appears to present with impairments solely in reading. A similar case holds for Specific Language Impairment, SLI, 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 (1994, 1997, 1999), 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, suggesting that language is both a specialisation of the brain and that it depends on generative rules that are visible in the ability to compute regular forms. 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. (1999, p. 262)

By contrast, in the lecture I challenge such assumptions and 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 developmental timing, neuronal type, neuronal density, firing thresholds, neurotransmitter types, etc. 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 a vital role in how genes are expressed and how the brain progressively sculpts itself, slowly becoming specialised over developmental time. The infant brain is not simply a miniature version of the adult brain.

### The neuroconstructivist framework

A 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 this, the relationship between genotype and phenotype is far from obvious. WS occurs in approximately 1 in 25,000 live births and involves the deletion of some 17 genes on the long arm of one copy of chromosome 7q11,23 (Donnai & Karmiloff-Smith, 2000). People with WS present with atypical brain anatomy (Jernigan *et al.*, 1993) and atypical brain chemistry (Rae *et al.*, 1999). Their brains are about 20 per cent smaller in volume than normal brains, with abnormal size, orientation and density of neurons, and atypical proportional volumes of several brain regions. Structural abnormalities of genetic origin are likely to be subtle and diffuse, not like adult neuropsychological patients, and this seems to hold for WS. Such subtle but widespread abnormalities give rise to atypical patterns of interactions between different brain regions. The WS brain is not a normal brain with parts intact and parts impaired.

People with WS present with a facial dysmorphology, as can be seen in Figure 1, as well as cardiac and renal abnormalities. Their IQs are in the 50–65 range, with an uneven cognitive profile in which language scores usually outstrip scores on spatial tasks.

The difference in WS between the very impaired spatial skills and the seemingly proficient face processing skills is particularly striking. Participants are given the Benton Face Processing Task (Benton *et al.*, 1983) which requires them to select from six faces, shown in different orientations, the three that are identical to a model face. On this task, children and adults with WS tend to score in the normal range, indicating a particular proficiency with face identity matching in this clinical population (Bellugi *et al.*, 1988; Bellugi, Wang & Jernigan, 1994; Karmiloff-Smith, 1997). This peak of ability is also evident using the Rivermead Face Processing Task (Wilson, Cockburn, & Baddeley, 1990), one in which patients have to recall which faces they have already seen presented amongst other, new faces. Here, too, patients with WS perform well (Udwin & Yule, 1991). In sum, children and adults with WS are especially proficient at recognising and remembering faces. In stark contrast to this stands their serious impairment when asked to match the orientation of one line amongst a choice of others on the Benton Line Orientation Task (Benton *et al.*, 1983). Here, people with WS score at floor, and this serious deficit continues throughout adulthood (Bellugi *et al.*, 1988; Rossen *et al.*, 1996).

The clear-cut disparity between face and space processing in Williams syndrome led a number of psychologists of a nativist persuasion to claim that the syndrome presents with an intact face processing module and an



**Figure 1.** WS infants, children and adolescents

impaired space processing module (Bellugi *et al.*, 1994). 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 one family some members of which had 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 haploinsufficiency (one copy only) 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. Moreover, 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) together with colleagues in Clinical Genetics at St Mary’s Hospital, Manchester, we studied a larger number of patients with partial gene deletions in the WS critical region; (ii) we carried out in-depth studies of those domains which other research teams had deemed to be intact in WS (face processing, language and social cognition), by dissecting the phenotype in detail; and, (iii) we explored the phenotypic start-state by studying infants with WS and comparing them to the phenotypic end-state in adults with WS as well as to infants with other genetic disorders. It is the second and third approaches that particularly illustrate the Neuroconstructivist framework, but first we will turn to the studies of patients with partial deletions in the WS critical region who do not have Williams syndrome.

### Studies of the relationship between genotype and phenotype in Williams syndrome

Our studies 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 (Tassabehji *et al.*, 1999; Karmiloff-Smith *et al.*, 2002). Two brothers in their thirties presented with a deletion of 80kb which included the two genes (Elastin and LIMK1) on which the claims of Frangiskakis *et al.* (1996) were made. Although the brothers had similar heart problems to people with WS (supravalvular aortic stenosis, SVAS), they did not have a dysmorphic face, nor did they show any imbalance between language and spatial cognition or between the latter and face processing. Their IQs were in the normal range. The third patient, in his late twenties, had a slightly larger deletion, around 100 kb, including ELN, LIMK1 and the WBSCR1 gene. He, too, had the SVAS heart abnormality, but no facial dysmorphism. He was a student of engineering at Athens University, with IQ in the normal range. The fourth patient, an 8-year-old girl, had a much larger deletion, stretching some 800 kb along the WS critical region, with 13 of the 17 genes deleted, including, ELN and LIMK1. Despite this huge deletion and very serious heart problems, the young girl was well above normal intelligence in all domains and displayed no imbalances whatsoever in her cognitive profile. Figures 2 and 3 illustrate how our patients differed from even our highest functioning woman with WS. Note that even when one of our SVAS patients was at the lower end of the normal range of intelligence and could be matched in terms of overall cognitive ability with our high-functioning WS patient (Fig. 2), the pattern of

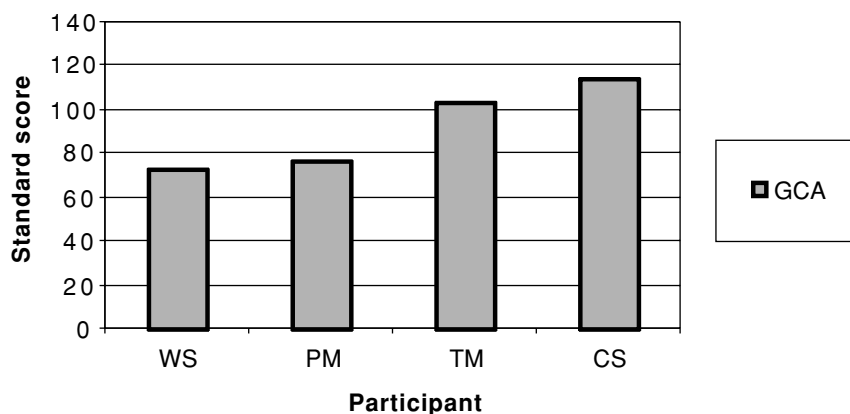
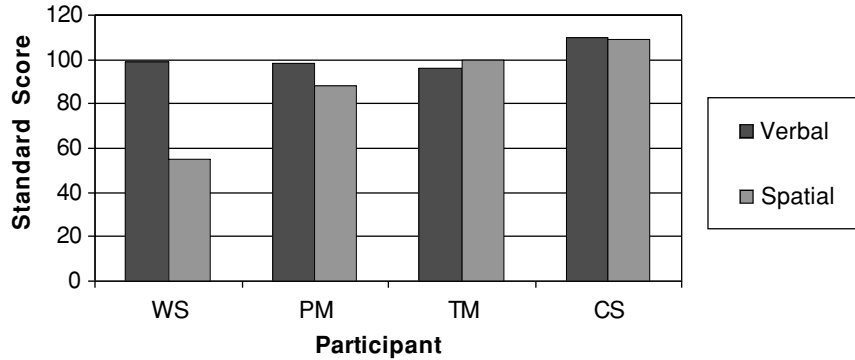


Figure 2. WS/SVAS individual patients' General Cognitive Ability (GCA).



**Figure 3.** WS/SVAS individual patients' verbal/spatial abilities (excluding non-verbal reasoning).

language versus spatial abilities differed radically between all the SVAS patients and the one with WS (Fig. 3). The difference between the profiles is striking, with the WS patient showing the pattern typical of this clinical group. Our results make it clear that deletion of *LIMK1*, a mutation characteristic of all our SVAS and WS patients, cannot alone explain the particularly serious spatial deficits in WS. The in-depth study thus demonstrated that the direct one-to-one genotype/phenotype relation between *LIMK1* and spatial impairments claimed by previous researchers was erroneous and cannot alone explain the atypical developmental pathway seen in Williams syndrome.

#### **In-depth studies of behavioural proficiency in Williams syndrome**

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 Williams syndrome. These were of particular interest for two reasons. First, the literature is replete with claims that these domains represent intact modules in Williams syndrome (Bellugi, Wang & Jernigan, 1994; Pinker, 1994, 1997, 1999; Rossen *et al.*, 1996). Yet our neuroconstructivist approach regarding the dynamics of overall brain development suggests that we should find subtle deficits even in proficient domains. Second, it is none the less unquestionable that people with Williams syndrome show far greater proficiency in these domains compared to their seriously impaired spatial cognition. Such strikingly uneven cognitive profiles are unusual in developmental disorders and are thus worthy of further study.

Face processing is, as mentioned above, a domain in which people with WS seem to excel. 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 (Karmiloff-Smith, 1997). We then tested our WS group on other, more detailed face processing tasks. For example, participants were asked to match faces in terms of their emotional state, lip reading, eye gaze direction and identity. We also varied whether stimuli were presented full face or three-quarters, whether the eyes were covered or the hairline masked (Bruce *et al.*, 2000). 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 (the eyes, the cheek bone, the shape of the ears, etc.) and those for which the whole configuration of the face had to be taken into account, a striking difference appeared 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). Here their data were very different from the controls who processed the faces configurally, i.e., the controls looked at the whole face and the relationships between the parts. People with Williams syndrome processed the faces featurally: they focused on single details in each face and performed poorly when they needed to rely on configural information (see Fig. 4). They also do not show the typical inversion effect that normal controls display when faces are presented upside down (Deruelle *et al.*, 1999). In

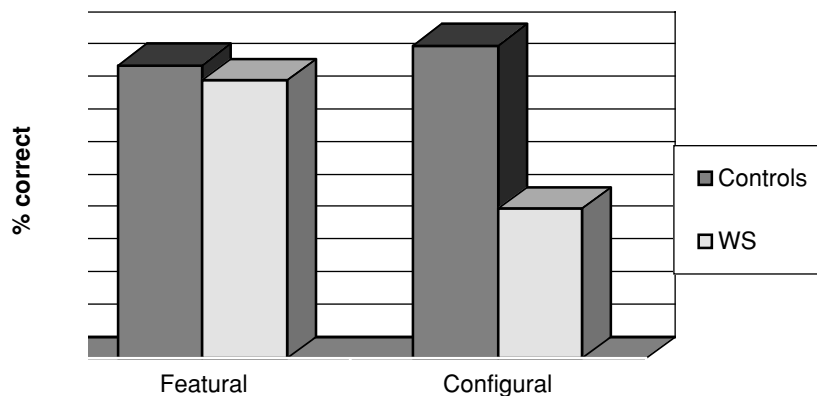


Figure 4. Featural and configural processing in WS and controls.

other words, WS patients perform equally well on upright and inverted faces, whereas controls are significantly worse on inverted faces. This is because normal controls use two different processes—configural for upright faces, featural for inverted faces—whereas the WS group use featural processing whichever way the face stimuli are presented. 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 to normal controls.

Such differences between normal controls and WS patients also hold for our studies of the functioning of WS brains. Over the past decade, powerful new tools for imaging the workings of the brain have become increasingly available. Some of these methods are based on measures of blood oxygenation and flow (Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI)), while others detect the magnetic or electrical fields generated when groups of neurons fire synchronously within the brain (Magneto-encephalography (MEG), Event Related Potentials (ERP)). In general, methods related to blood flow are thought to have better spatial resolution (of the order of millimetres), whereas the other methods have better temporal resolution (of the order of milliseconds). With the advent of event-related fMRI and High-Density ERP, both types of method are now working towards better spatial and temporal resolution within a single approach. We decided to use HD-ERP because this is easy to administer, is totally non-invasive and our patients enjoy participating (see Fig. 5). While normal controls process faces predominantly within 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 our research showed that people with WS process all three in the same way (Grice *et al.*, 2001). Contrary to claims in the literature, it is clear that people with WS do not have an intact, specialised face processing module. Thus, it is not the case that face processing is intact and spatial processing is impaired: *both* follow atypical pathways in WS, compared to 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 (Böhning, Campbell, & Karmiloff-Smith, 2002; Grant *et al.*, 1996, 1997; Grant, Valian & Karmiloff-Smith, 2002; Karmiloff-Smith *et al.*, 1995, 1997, 1998; Laing *et al.*, 2001, 2002; Stevens & Karmiloff-Smith, 1997; Thomas *et al.*, 2001;



**Figure 5.** WS adolescent in HD-ERP geodesic net.

Tyler *et al.*, 1997). These are two further domains which some researchers argue to be intact in WS. Yet, 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, Baddeley & Hewes, 1998; Mervis, Bertrand, & Robinson, 1999; Tager-Flusberg & Sullivan, 2000; Vicari *et al.*, 1996). 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 citation 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, and for this we used either the preferential looking technique (Fig. 6) or the head-turn technique (Fig. 7).

In order to assess their face processing abilities, infants and toddlers were shown a series of schematic faces. Some of these were identical to one another 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, Ewing & Karmiloff-Smith, 2002). Using the same stimuli, we had earlier found that adults with WS are significantly less accurate (see Fig. 8) and take significantly longer (see Fig. 9) to notice configural changes compared to 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, infants were shown on two monitors (see Fig. 6) 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 syn-

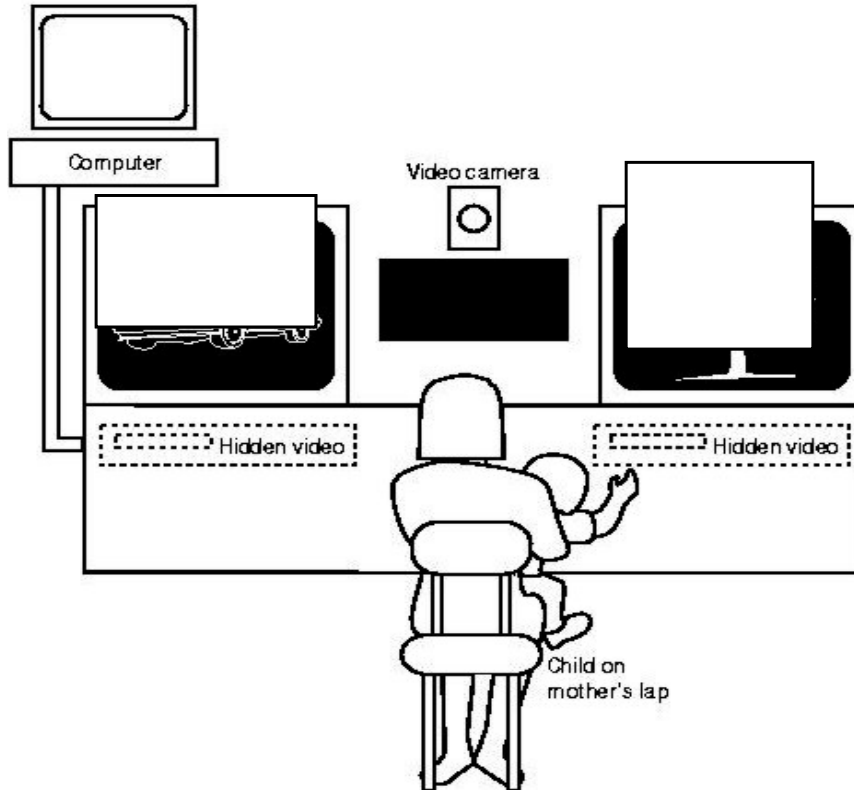


Figure 6. Preferential looking technique.

drome (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.

Finally, we tested infants with Williams syndrome and Down's syndrome with respect to their 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). 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. The process of development modifies such patterns.

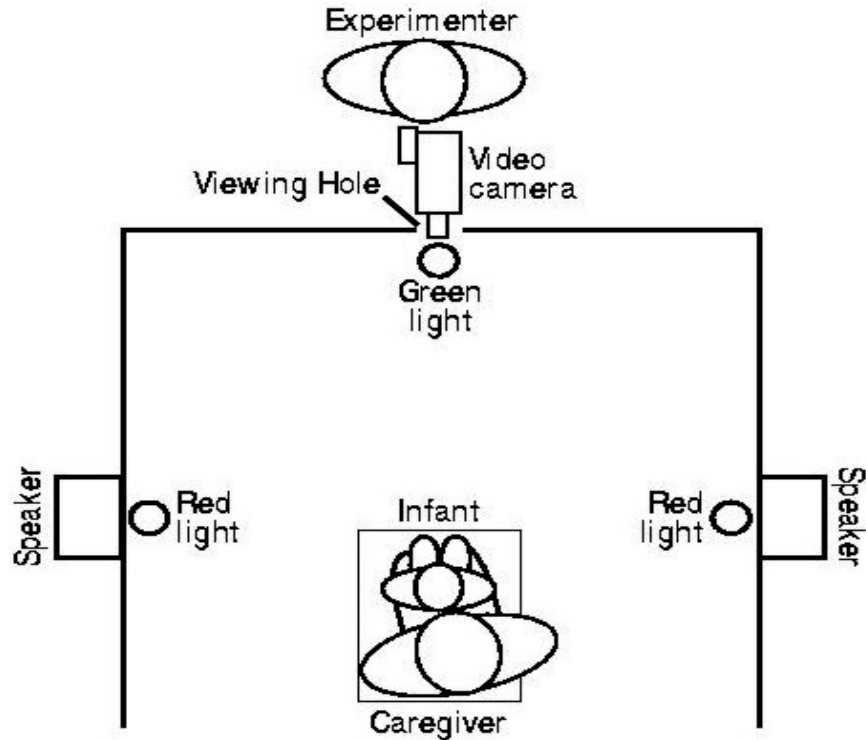


Figure 7. Head-turn preference technique.

Our studies of infants and toddlers in the domains of face processing, number, and language clearly show a very different cognitive profile in infancy compared to adulthood (Paterson *et al.*, 1999; see, also, Laing *et al.*, 2002 for studies of infant and toddler social cognition in Williams syndrome). 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 Williams syndrome, 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.*, 2002) and atypical synchronisation 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.

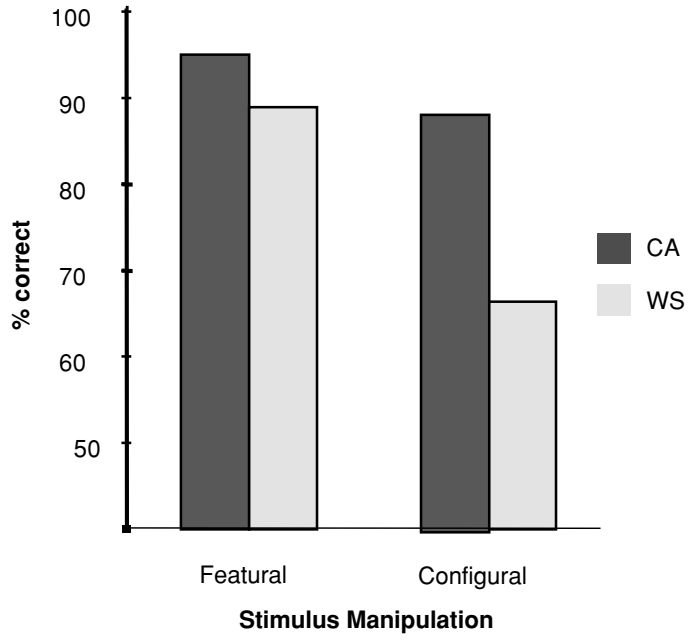


Figure 8. Accuracy of featural versus configural processing.

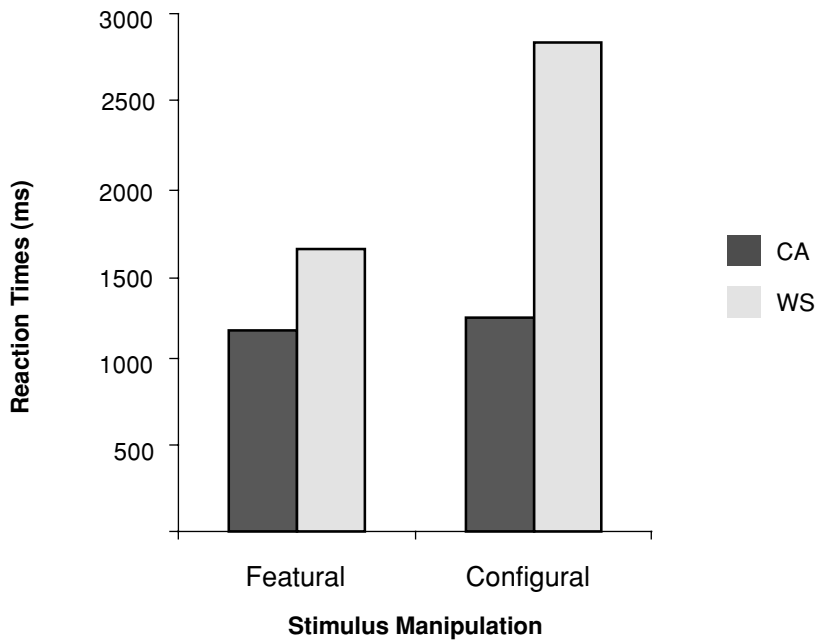


Figure 9. Speed taken to notice featural versus configural changes.

At present, my team is carrying out the same exercise with other genetic disorders, such as Velocardiofacial syndrome (another microdeletion disorder like Williams syndrome, but on chromosome 22), Down's syndrome, 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. So, 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.

### Concluding comments

In this lecture I argued against the assumption that children with genetic disorders present with brains like adult neuropsychological patients, i.e., 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- post-natal 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) also 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. Thus, 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. The contrasting view presented in this lecture is that our aim should be to understand how genes are expressed *through development*, because 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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