

INTRODUCTION

WILLIAMS SYNDROME: A MODEL FOR THE NEUROCONSTRUCTIVIST APPROACH

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Introduction: Why Williams Syndrome?

There was a time when most of the research into neurodevelopmental syndromes was merely based on a brief clinical assessment and a few standardised tests. However, with the huge technological advances in subtle in-depth phenotyping at the cognitive level as well as in genetics and brain imaging, multi-disciplinary research into neurodevelopmental disorders is now the rule rather than the exception. This book provides just such an approach, taking the neurodevelopmental disorder, Williams syndrome, as a model syndrome, with the aim that the book will serve as a paradigm for multidisciplinary, Neuroconstructivist approaches to a wide range of other syndromes.

But why Williams syndrome (WS) as our model disorder? After all, it is a rather rare, sporadic disorder occurring in only some 1 in 15,000-20,000 births (although one study yielded an estimate of 1 in 7,500 births, Stromme, Bjornstad & Ramstad, 2002). Although WS was first described by two cardiology groups (Williams, Barrett-Boyes, and Lowe, 1961; Beuren, Apitz, and Harmjanz, 1962), both identifying the association of several clinical features in affected individuals, it took another couple of decades before the syndrome started to be extensively investigated by cognitive psychologists and neuroscientists. Our choice for this book of such a rare syndrome as a model for studying neurodevelopmental disorders from a Neuroconstructivist viewpoint was based on two crucial reasons. The first is the fact that WS has been extensively

researched from multiple levels of description: genes and gene expression, brain structure and function, the electrophysiology of the brain, brain chemistry, cognitive processing across multiple domains as well as the social and everyday practical problems of growing up with WS. The second is the fact that WS has been studied across the lifespan, with now a growing number of studies on infants and toddlers with WS as well as a large bulk of research on children, adolescents and adults.

The Neuroconstructivist approach to neurodevelopmental disorders

Given its rarity, what made the study of WS so popular in the research community? Interestingly, the reasons were initially rooted in a theoretical debate about whether domain-specific abilities were modular, i.e., whether they functioned independently of one another (e.g., number having nothing to do with language, face processing having nothing to do with navigation, etc.), and could be shown to be dissociated in cases of adult neuropsychological patients, but also in neurodevelopmental syndromes. The initial descriptions of WS (e.g. Bellugi, Sabo & Vaid, 1988) highlighted the seemingly extraordinary language abilities of adolescents and adults with WS, their extreme social friendliness and their normal scores on standardized face-processing tasks. These proficiencies sat alongside serious impairments in visuo-spatial cognition and number processing. So, the claims went, the WS uneven profile was the perfect example of cognitive modules operating independently of one another, as can be seen in the following quotations:

“For instance, children with Williams syndrome have a barely measurable general intelligence and require constant parental care, yet they have an exquisite mastery of syntax and vocabulary. They are, however, unable to understand even the most immediate implications of their admirably constructed sentences.” (Piattelli-Palmarini, 2001)

“the linguistic performance of [individuals with] WS can be explained in terms of selective deficits to an otherwise normal modular system” (Temple & Clahsen, 2003)

“...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)

Contrast these with the following Neuroconstructivist-inspired quotations, which surprisingly are describing the same syndrome but this time with a focus on the dynamics of development:

“In sum, brain volume, brain anatomy, brain chemistry, hemispheric asymmetry, and the temporal patterns of brain activity are all atypical in people with WS. How could the resulting system be described as a normal brain with parts intact and parts impaired, as the popular view holds? Rather, the brains of infants with WS develop differently from the outset, with subtle, widespread repercussions...” (Karmiloff-Smith, 1998)

“We argue that rather than being the paradigm case for the independence of language from cognition, Williams syndrome provides strong evidence of the interdependence of many aspects of language and cognition.” (Mervis & Baccara, 2007)

The striking difference between these sets of quotations not only encapsulates early research into WS, but also continues to illustrate the theoretical differences guiding current research into this fascinating syndrome. And there is no doubt that debates will continue to rage over the extent to which WS is a direct window on the nature/nurture debate.

Williams syndrome is not alone in having quite opposing theoretical positions that guide cognitive and neural research. Autism Spectrum Disorders (ASDs) are another set of

neurodevelopmental syndromes for which researchers either abide by a strictly modular view or take the Neuroconstructivist stance, as the following quotations nicely illustrate.

“Autism is due to a deficit in an innately-specified module that handles theory-of-mind computations only” (Leslie, 1992)

“...a module that is localized in the orbito-frontal cortex” (Baron-Cohen et al., 1999)

Again, contrast these with the following three Neuroconstructivist-inspired quotations:

“Autism affects the interconnectivity among and within various cognitive systems.”

(Carpenter et al., 2001)

“In autism, functional brain development goes awry such that there is increased intra-regional specialization and less inter-regional interaction” (Johnson, Halit, Grice &

Karmiloff-Smith, 2002)

“... examine the crucial role of unbalanced excitatory-inhibitory networks... leading to ASD through altered neuronal morphology, synaptogenesis and cell migration”.

(Persico & Bourgeron, 2006)

It quickly becomes obvious that the Nativist, modular view of the mind/brain of WS and of ASD differs radically from the Neuroconstructivist view of the mind/brain. The former calls upon the existence of uneven cognitive profiles to support a static view based solely on the endstate and the assumption that the brain is modularised from the start, whereas the latter focuses on the uneven profile being the resultant product of dynamic processes of development over time.

While arguing against the strictly modular, Nativist view, it is important to stress that the Neuroconstructivist approach does not imply that the neonate brain is a blank slate with no

structure, as Empiricists would claim. Nor does it entertain the possibility that just any part of the brain can process any and all inputs. On the contrary, Neuroconstructivism maintains that the neonate cortex has some regional differentiation in terms of types of neuron, density of neurons, firing thresholds, etc. These differences are not domain-specific aimed at the sole processing of proprietary inputs, but nor do they amount to more domain-general constraints. Rather, they are ‘domain-relevant’, i.e., different parts of the brain have small differences, which turn out to be more appropriate/relevant to certain kinds of processing over others. But initially, brain activity is widespread for processing all types of input and competition between regions gradually settles which domain-relevant circuits *become* domain-specific over time (Karmiloff-Smith, 1998). So, starting out with tiny differences across brain regions in terms of the patterns of connectivity, the balance of neurotransmitters, synaptic density, neuronal type/orientation and the like, some areas of the brain are somewhat more suited (i.e. more *relevant* in terms of their computational properties) than others to the processing of certain kinds of input, and over time they ultimately win out. In other words, the computational properties of a particular brain circuit may be more relevant to certain types of processing (e.g. holistic vs. componential processing) than others, although they are initially not specific to that type of processing only. It is only after developmental time and repeated processing that such a circuit *becomes* domain specific as ontogenesis proceeds (Karmiloff-Smith, 1992, 1998). There is thus a *gradual* process of recruitment of particular pathways and structures for specific functions (Elman et al. 1996), such that brain pathways that were previously partially activated in a wide range of task contexts increasingly confine their activation to a narrower range of inputs and situations (Johnson et al. 2002).

The Neuroconstructivist position is supported by neuroimaging research showing that the functional specialization of brain regions is highly context sensitive and depends on interactions with other brain regions through feedback processes and top-down modulation (Friston & Price, 2001). This process becomes most evident in brain organization in people who lack one sensory modality. For example, in individuals who have been blind from an early age, visual cortex is recruited for the tactile modality instead, i.e., Braille reading (Sadato, et al., 1996). Moreover, using transcranial magnetic stimulation (TMS) to block processing in this area affects tactile identification of Braille letters in the blind, but not in seeing people who instead display impaired visual processing when stimulated in this area (Cohen, et al.1997). It therefore appears that the functional development of cortical regions is strongly constrained by available sensory inputs and that the final organization of the cortex is an outcome of interactive processes such as competition for space.

Multi-level Analyses

Another issue that arises with respect to the study of neurodevelopmental disorders is the distinction that must be drawn between the behavioural, cognitive and neural levels of description. It is entirely possible that individuals may reveal scores in the normal range on a given test, and yet be achieving that success via different cognitive-level and neural-level processes compared to typically developing controls. This is certainly the case, for instance, for the good face processing scores identified in adolescents and adults with WS but which turn out to be sustained by different cognitive and neural processes. Equally, cross-syndrome comparison can reveal an association at the behavioural level, which is not mirrored at the neural level. Compare Attention Deficit Hyperactivity Disorder (ADHD) and WS; both groups show impaired inhibitory processes, but in ADHD this is associated with increased activation of

dorsolateral prefrontal cortex and dorsal anterior cingulate cortex, but in WS these same areas show an associated decrease in activation (see Chapter 9).

Moreover, there is a frequent slippage in the literature from relative differences to absolute ones. So, for example, when comparing two domains, A and B, in which individuals reach levels of performance that are consistent with mental-age-matched controls in domain A but well below those levels in domain B, researchers tend to conclude that ability A is “intact” and B impaired, despite the fact that performance in A is still several years behind the typical child of equivalent chronological age. The Neuroconstructivist view that focuses on interactions between domains across developmental time would never simply dismiss delay as irrelevant or count a “relative” advantage of one system over another as an “absolute” one, leading to claims of intactness (see discussions in Karmiloff-Smith, 1998; Karmiloff-Smith, Scerif, and Ansari, 2003). A process that is vital, say, at Time 2 may no longer play a role at Time 5. Yet its presence at Time 2 may have been crucial to a healthy developmental trajectory and outcome; delay can alter subsequent multilevel interactions, with cascading effects on developmental outcome.

The very notion of “intactness/preservation” has a static connotation and implies genetic *determinism*, as if states in the brain were entirely hard-wired, unchanging and unaffected by developmental or environmental factors. The Neuroconstructivist view, by contrast, considers the brain as a self-structuring, dynamically changing organism over developmental time as a function of multiple interactions at multiple levels, including gene expression (e.g., Casey, 2002; Johnson, 2001). Research on birds and mammals eloquently illustrates this point. Extensive evidence from studies of the neural and epigenetic consequences of song listening and song production in passerine birds (Bolhuis et al., 2000) shows how gene expression changes over developmental time and may be significantly more important during learning than during final

production (see Chapter 3 [Osbourne]). Rather than something fixed and predetermined, gene expression in the birds turned out to be a function of how many elements the bird copied from its tutor. A second example comes from early mammalian development and also underlines the potential role of the environment in shaping long-term patterns of gene expression (Kaffman & Meaney, 2007). These authors studied brain development in rodent pups and traced how differences in maternal grooming behaviour influence patterns of gene expression in their pups, which have lifelong effects. The researchers showed that rather than thinking of gene expression as pre-programmed, differences in the amount of postnatal pup grooming and stroking change the amount of gene expression of genes involved in the body's responses to stress, and that these changes last the pups' lifetime. These kinds of dynamic environment-gene relations are likely to be a pervasive feature of mammalian brain development, including that of humans. In general, epigenesis is not deterministic under tight genetic control. Rather, as Gottlieb stressed (Gottlieb, 2007), epigenesis is probabilistic and only under very broad genetic control.

Neuroconstructivism does not rule out domain-specificity; it argues that it cannot be taken for granted and must always be questioned. Unlike the Nativist perspective, Neuroconstructivism – like Piaget's Constructivism - offers a truly developmental approach that focuses on change and emergent outcomes. And, every aspect of development turns out to be dynamic and interactive. Genes do not act in isolation in a predetermined way. Even the FOXP2 gene, about which there was much excitement regarding its role in human language, must be thought of in terms of the downstream gene targets to which FOXP2 binds. The profiles of those downstream genes suggest roles in a wide range of general, not domain-specific, functions including morphogenesis, neurite growth, axon guidance, synaptic plasticity and neurotransmission (Teramitsu & White, 2007). This is very different from theorizing at the level of cognitive modules and making claims about “a gene for language”, and points to the multi-

level complexities of understanding human development in any domain.

The importance of full developmental trajectories

Neuroconstructivism argues that if the adult brain is in any way modular, this is the product of an emergent developmental process of modularisation, not its starting point (Karmiloff-Smith 1992, 1998, 2007, 2009; Elman et al. 1996; Johnson et al. 2002; Westermann et al. 2007). A crucial error is to conflate the specialised brains of adults, which have developed normally prior to damage in later life, with those of infants and children, which are still in the process of developing (Karmiloff-Smith et al. 2002). Infancy studies have highlighted the fact that we cannot use the phenotypic outcome in adults to simply assume the pattern of abilities and impairments in the start state. In other words, researchers should not directly relate the effects of deleted genes to cognitive-level outcomes in adults. In fact, as we shall see in this book, genetic mutations are more likely to affect low-level cognitive processes that will have differing, cascading effects on different domains as developmental trajectories emerge over time. Indeed, timing plays a critical role in normal development, and its effects on atypical development must be centre stage when we endeavor to build a comprehensive theory of WS in particular, and of neurodevelopmental disorders in general. Moreover, genetic mutations contributing to neurodevelopmental disorders in infants are likely to affect widespread systems within the brain (Karmiloff-Smith 1998; Chapter 2 [Karmiloff-Smith]; Chapter 3 [Osborne]). This does not preclude that the outcome of the dynamic developmental process could end up with some areas being more impaired than others, but this would not be the pattern necessarily apparent at the outset, but due to the result of processing demands of certain kinds of inputs to those areas and to differences in synaptogenesis across various cerebral regions (Huttenlocher & Dabholkar, 1997). By contrast, the Nativist modular view seriously underestimates the dynamics of the

changing patterns of connectivity within and across different brain areas during development.

Another important issue to bear in mind is that typical development of course also involves change, so matching on mental age can at times be very misleading. Indeed, a neurodevelopmental disorder might show a pattern of performance that appears to be atypical when compared to a matched control group. However, this kind of comparison - to a static point in development - neglects the possibility that the performance of the atypical group might resemble a pattern observed somewhere along the developmental trajectory of typical children. A clear illustration of this comes from the visual domain. As will be discussed in Chapter 13 [Atkinson & Braddick], many neurodevelopmental disorders show a relative deficit in dorsal visual stream processing relative ventral visual stream processing. However, this is the case in typical development, too, in that when young (< 5 years), children also show poorer dorsal stream than ventral stream processing. Care must therefore be taken to determine whether the pattern of performance in an atypical group is delayed or atypical, as this has important implications for our understanding of the constraints on atypical developmental trajectories. This can only be achieved by sampling the whole developmental trajectory in both the typical and atypical case.

Recent technological advances are now enabling us to make the same consideration at the neural level. Imaging of brain activation in children has begun to characterise the developmental trajectories of emerging brain networks. For instance, we will see in Chapter 17 [Camp, Farran & Karmiloff-Smith] that the brain network activated during number processing in young children is different from that activated in adults. This questions whether it is appropriate that we rely on what we know about the brain of typical adults to determine whether atypical groups

show typical brain activation (Karmiloff-Smith, 2010; Chapter 2). It is entirely possible that the pattern of activation observed in a neurodevelopmental disorder is present somewhere along the typical developmental trajectory of emerging brain networks. Currently, knowledge of the *development* of typical brain networks remains quite limited, but there is an emerging body of work to suggest that during the next decade we will be in the position to take developmental trajectories into account, not only in terms of behaviour, but also the development of neural networks.

A Neuroconstructivist view of remediation

Rather than invoking “intact” and “impaired” modules, assessing atypical development in terms of cascading developmental effects of tiny perturbations early in the developmental trajectory should result in a better understanding of genetic disorders in children. However, perhaps the notion of impaired vs. intact brain systems in uneven cognitive profiles might be useful for clinical practice, even if theoretically it underplays the role of development. If a patient has scores in the normal range in a specific domain, surely there is no need to consider remediation in that domain? The Nativist would probably agree and focus solely on the domains of deficit. However, the Neuroconstructivist would not rule out intervention also in a proficient domain. For instance, take a patient who presents with a serious deficit in, say, number, yet scores in the normal range for all other domains. It would be tempting in such a case to tailor remediation solely to the domain of number. But that misses the very point of the Neuroconstructivist framework. First, the scientist would need to trace back to infancy the origins of the number deficit which might not be in the number domain directly; it could be a deficit in the visual system in scanning arrays of objects. A scanning deficit might affect other

domains but to a lesser degree, meaning that these other domains could *look* normal in subsequent development but may camouflage subtle deficits. Once one explores multiple, low-level interacting processes that underpin early development, this leads to a more dynamic, Neuroconstructivist view of remediation also.

Conclusions

It is clear that development – whether typical or atypical, whether human or non-human – is fundamentally characterized by plasticity for learning, with the infant brain dynamically structuring itself over the course of ontogeny. The infant brain is not a collection of static, built-in modules handed down by Evolution. Rather, the infant brain follows developmental trajectories which are the emergent property of dynamic multi-directional interactions between biological, physical and social constraints.

About the book

This book places the Neuroconstructivist approach to developmental disabilities at its very heart. We start in Section 1 with three Chapters which take WS as a model syndrome (all studies discussed refer to individuals with the classic WS deletion, unless otherwise stated) for the discussion of Cognition, Brain and Genes. The Cognition chapter focuses on the critical issue of building task-specific developmental trajectories for typical development and then judging whether and how atypical developmental trajectories fit this trajectory, as well as pinpointing how this approach differs from the usual method of matching on the basis of chronological or mental age. The Brain chapter examines how the WS brain in particular, and other atypical developing brains in general, differ from the typical brain in terms of structure,

function, physiology and biochemistry. It particularly stresses the multidirectional interactions between genes, cognition, behaviour and brain raising such questions as to whether, in WS, parietal cortex *starts out* smaller or *becomes* smaller over developmental time because of atypical processing in that region. It bemoans the fact that almost everything we know about the Williams syndrome brain emanates from studies of *adult* brains, and stresses the need to trace brain anatomy, brain biochemistry and brain function across developmental time, i.e., to study the *developing* brain across time from infancy to adulthood, together with the need for in-depth cross-syndrome comparisons at the cerebral level. The Genes chapter goes well beyond the identification of mutated genes that contribute to syndromic outcomes and focuses mainly on the crucial topic of gene expression. It shows how genes cannot be thought of in terms of static one-to-one mappings between gene function and cognitive outcome, because the temporal and spatial expression of genes changes over developmental time.

The first section is followed by two chapters specifically on WS, describing the clinical profile as well as the adult outcomes and the daily problems individuals have in integrating into society. Their fluent language and friendly demeanour is frequently misjudged by others as this can mask their real disabilities. It is clear that a detailed syndrome-specific clinical profile is crucial both for research and for life decisions for individuals with neurodevelopmental disorders, whose problems are not only apparent in early infancy but continue throughout life and into old age. These are concerns of the individuals themselves but also of parents, teachers and policy makers.

Sections 3 and 4 tackle the important issues of how domain-general and domain-specific processes operate in neurodevelopmental disorders. In Section 3 we cover the development of attention, sleep-related learning, memory, executive function and motor planning in WS and other neurodevelopmental disorders. These processes affect specific domains of cognition to

varying degrees. Section 4 goes into the details of specific domains like language, visual perception, visuo-spatial cognition and visuo-motor action, as well as face processing and mental state understanding as they relate to social interaction. One of the particularly interesting cross-syndrome comparisons is between WS and ASD in the social domain, because superficially they seem to present with such different profiles, with WS overly friendly and fascinated by faces, whereas ASD is characterised by aloofness and a distaste for faces. Yet in reality there are many overlaps between the syndromes, both culminating in atypical social interaction. We end Section 4 with an account of the domain-specific processes involved in numeracy and literacy.

Section 5 offers a very timely account of how domain-general and domain-specific processes are integrated over developmental time, pointing to numerous important issues about the dynamics of developmental integration processes. Finally, the editors round off the book with a concluding discussion of how a Neuroconstructivist, multidisciplinary approach enriches our understanding of neurodevelopmental disorders.

Acknowledgements

We have many people to warmly thank for their contributions to this book. First and foremost, our greatest appreciation goes to all our chapter contributors who all did their utmost to follow our editorial guidelines so that the book was not a mere juxtaposition of albeit interesting chapters but conveyed a common cohesive approach. Not only did they take all our detailed comments on board, but they revised their chapters with amazing promptness which meant that we actually met our planned deadline – an incredible feat! Second, all the authors also generously commented alongside the editors on other chapters, again contributing to the book's cohesiveness.

Third, Daniel Ansari, Karen Berman, Brian Haas, Elizabeth Fisher, Allan Reiss and May Tassabehji for their very useful comments on specific book chapters, and Lauren Willmott for help in preparing references. Fourth, we would particularly like to thank Charlotte Green of Oxford University Press who made our task much smoother at multiple levels. Finally, we thank our partners, John Willoughby and Mark Johnson, for their patience while we inundated every home tabletop surface with chapters, reference lists and Post-it notes!

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