

Neurodevelopmental Disorders

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ABSTRACT

Recent technological advances allow us to measure how the infant brain functions in ways that were not possible just a decade ago. Although methodological advances are exciting, we must also consider how theories guide research: what we look for and how we explain what we find. Indeed, the ways in which research findings are interpreted affects the design of policies, educational practices, and interventions. Thus, the theoretical approaches adopted by scientists have a real impact on the lives of children with neurodevelopmental disorders (NDDs) and their families, as well as on the wider community. Here, we introduce and compare two theoretical approaches that are used to understand NDDs: the *neuropsychological account* and *neuroconstructivism*. We show how the former, adult account is inadequate for explaining NDDs and illustrate this using the examples of 'Williams syndrome' and 'specific language impairment'. Neuroconstructivism, by contrast, focuses on the developing organism and is helping to change the way in which NDDs are investigated. Whereas neuropsychological static approaches assume that one or more "modules" (e.g., visuospatial ability in Williams syndrome) are impaired while the rest of the system is spared (e.g., language in Williams syndrome), neuroconstructivism proposes that basic-level deficits have subtle cascading effects on numerous domains over development. Neuroconstructivism leads researchers to embrace complexity by establishing large research consortia to integrate findings at multiple levels (e.g., genetic, neural, cognitive, environmental) across developmental time.

INTRODUCTION

Dramatic increases in the availability of data on neurodevelopmental disorders (NDDs; see Table 1) are providing new and exciting opportunities for understanding the infant brain and the factors that shape its development. Much of the excitement in this field can be traced to technological advances that, in ways that were not possible just a decade ago, allow us to measure how the infant brain functions. Although these methodological advances are exciting, we must also consider how theories guide research: what we look for and how we explain what we find. Here we compare two very different theoretical approaches for explaining NDDs—the *neuropsychological account* and *neuroconstructivism*—and explain why we believe that the latter approach is more likely to lead to better treatments and outcomes.

To illustrate the differences between the two approaches, consider Williams syndrome. Researchers have documented the fact that children with Williams syndrome have problems with number processing. If we adopt a neuropsychological approach^{1, 2} and posit that the brain is composed of independently functioning modules, one of which is a number-processing module, then interventions will be focused specifically on the number domain once the deficit is identified in middle childhood. In contrast, if we adopt a neuroconstructivist (or other developmental) approach and posit that number processing is an emergent property of a self-organizing system that interacts with the environment, then we will focus our intervention efforts much earlier in development to identify those influences that set number processing on an atypical developmental trajectory³. Indeed, differences in basic-level processes (e.g., poor sustained attention)

might affect the way in which infants with Williams syndrome scan numerical displays, faces, and other visual stimuli. So, adopting a neuroconstructivist or other developmental approach, we would target those basic-level processes with the aim of improving developmental processes and outcomes.

THEORETICAL APPROACHES: THE NEUROPSYCHOLOGICAL VERSUS THE NEUROCONSTRUCTIVIST APPROACH

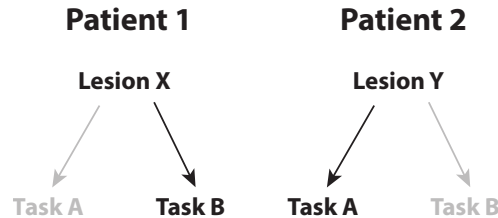
Understanding NDDs requires not only describing differences between typically developing individuals and individuals with NDDs, but also understanding how these differences emerge over developmental time. This entails tracking differences as early in development as possible and on multiple levels of description (e.g., genetic, neural, cognitive, environmental). Up until recently, progress has been limited by the absence of suitable methodologies for infants and young children. Recent technological advances (e.g., new infant-friendly electroencephalography [EEG, Figure 1]) allow us to measure how the infant brain functions (for a comparison of different methods used to measure infant brain activity, see Figure 2). This enables researchers to elucidate how changes on the neural level are associated with changes on other levels of description – such as cognition or behaviour. Furthermore, EEG and neuroimaging approaches have the potential to help identify important early markers of neurodevelopmental disorders of unknown origin (e.g., attention-deficit/hyperactivity disorder, autism) before the behavioural symptoms emerge later in development. This could potentially have high clinical significance since it would provide an opportunity for timely interventions. EEG and neuroimaging approaches can further be used as tools for assessing the impact of

these interventions.

Although methodological advances are exciting, we must also consider how theories guide research: what we look for and how we explain what we find. The interpretation of the research findings then affects the design of policies, educational practices, and interventions. Thus, the theoretical approaches adopted by scientists have a real impact on the lives of many children with NDDs and their families, as well as on the wider community.

The **neuropsychological account** views the brain as if it were a Swiss Army knife⁴, containing built-in, separate, special-purpose tools. Proponents of this approach argue that the brain has discrete parts, often referred to as *modules*, each of which has a specific, evolved cognitive function. They use the existence of adult neuropsychological patients to support the modularity view. One example given by advocates of this approach invokes patients with damage to the Fusiform Face Area (FFA), which is a part of the cerebral cortex located in the temporal lobe. The FFA is selectively activated when adults perceive faces^{5, 6}. When the FFA has been damaged in adult patients, the ability to identify faces is particularly impacted to the point that otherwise normally functioning patients are unable to recognize their partner or even themselves in the mirror^{7, 8} ([link – Prosopagnosia Research Centers - <http://www.faceblind.org>]). This is the basis for the claim that there exists an independently functioning face-processing module.

Indeed, theorists using data from neuropsychological patients and embracing the *modularity* hypothesis take the existence of *double dissociations* in adults to make strong claims about the functional architecture of the human mind/brain (e.g.,⁹⁻¹¹; see discussion in Shallice¹²). A double dissociation is established when a specific brain lesion X in Patient 1 relates to poor performance on Task A but not Task B, whereas a different brain lesion Y in Patient 2 relates to poor performance on Task B but not Task A¹³:



The usual assumption is that the brain lesion is the direct cause of poor performance, leading to the conclusion that the cognitive function necessary to perform well on Task A is linked to the brain region damaged in Patient 1, and vice versa for Patient 2. Hence, double dissociations for different cognitive abilities in brain-damaged adults are used to relate brain and cognitive data directly, thereby elucidating the architecture of the adult cognitive system and how brain lesions affect it.

Returning to the Swiss Army knife analogy, according to the neuropsychological account, it is possible to selectively break one of the parts (e.g., the can opener) without affecting the other parts (e.g., the corkscrew). But does this analogy provide insight into the functioning of the brain? We think not. Indeed, a growing body of evidence suggests

that adult brain networks display large-scale patterns of interconnectivity that are inconsistent with the notion that there exist independently functioning modules *per se* (for more detail, see¹⁴). Because it is questionable that the neuropsychological framework is useful for explaining even adult neural and cognitive processes, it is unlikely to have any explanatory or predictive power when applied to NDDs in children. We will explain why this is the case using examples from Williams syndrome and specific language impairment in the next section.

When the adult neuropsychological approach is applied to children with NDDs, it is assumed that individual differences in cognitive ability are the result of a deficit in one or more innately specified modules, perhaps due to faulty genes. For example, a “specifically impaired” phonological processor has been purported to be the root cause of dyslexia¹⁵ and an impaired ‘theory of mind’ module has been suggested to be a major causal factor in autism¹⁶.

The static neuropsychological approach contrasts with developmental approaches such as the developmental systems approach¹⁷, the dynamic systems approach¹⁸, and neuroconstructivism¹⁹. These developmental approaches share the view that development is a process of self-organization that results from interactions between multiple subsystems within a context. Intrinsic factors (e.g., physiological, psychological, neural) as well as extrinsic factors (e.g., informational cues, social context) constrain each other and shape the developmental process. **Neuroconstructivism** is the developmental approach that has most often been applied to explain NDDs, **and thus**

will be the one we focus on hereinafter.

In contrast to the neuropsychological approach described above, proponents of the **neuroconstructivist approach** argue that adults with acquired brain lesions cannot be compared to children with NDDs. Although specific patterns of network activation in the brain are relatively stable (highly specialized) in adults, they do not necessarily start out that way. Patterns of activation become increasingly specialized over developmental time (see Figure 3) through interactions between various brain regions and through processing different types of input²⁰⁻²³. Thus, although any brain injury is likely to impair multiple cognitive functions, it is more likely to cause a relatively specific deficit in the highly specialized adult brain than in the less specialized (and more plastic) infant brain^{19, 23}. Therefore, the brain of a child with an NDD cannot be described as composed of a set of damaged versus intact parts (see discussions in²⁴⁻²⁶). Instead, it can be better characterized as an *atypical system developing under different constraints*.

One surprising consequence of the neuroconstructivist view is that even behavioural performance that falls within the normal range may be supported by atypical brain processes in children with NDDs²⁷. For example, despite their low IQ, individuals with Williams syndrome fall in the normal range on two tests measuring face processing^{28, 29}. Yet the cognitive and neural processes that support this performance in the Williams syndrome children are very different from those used by typically developing children²⁷. Furthermore, task performance by children with NDDs can sometimes surpass

performance by typically developing children on the same task (e.g.,³⁰). Children with autism spectrum disorder are actually faster and more accurate than typically developing children in finding hidden shapes embedded in larger meaningful pictures (e.g., finding a triangle within the drawing of a pram). Why? Because those with autism spectrum disorder focus on local details and are less distracted than neurotypicals by the meaning of the whole picture³⁰.

If the developing infant brain starts out highly interactive, then an initial impairment in one cognitive component is likely to have *cascading effects* on other parts of the developing system. That is, a basic-level deficit in the cognitive system will constrain the emergence of several higher-level cognitive functions, because these functions emerge from complex interactions in the brain^{24, 26}. This early basic-level cognitive deficit may be underpinned initially by small variations in one or more factors including gene expression, neuronal growth and migration, synaptogenesis, and synaptic pruning^{20, 25}; (for a comprehensive account of early neural development, see³¹). These initial small alterations interact with other genetic and environmental events that, over time, give rise to the resulting phenotype. Such complexities make it challenging to elucidate developmental causes in complex, dynamic, multi-level systems. To understand NDDs, it is thus critical to account for these dynamic, complex interactions between and within all levels of organization across time, from genes to environment³². Simple explanations may seem more tractable but they do not suffice; we must embrace complexity.

As a result of cascading effects and multilevel interactions, children with NDDs are likely

to develop *atypical* neural and cognitive trajectories with numerous widespread impairments^{24, 26}, rather than a set of *impaired* and *intact* modules. A single deficit may have differential cascading effects on the system, with some functions being more affected than others. Thus, some atypicalities may be subtle and difficult to detect, using standardized measures designed for children with typically developing brains³³. Because these subtle differences are hard to identify, they lead some theorists to claim that impaired modules co-exist with “intact” modules in NDDs, even though fine-grained analyses have revealed this not to be the case.

DOES THE NEUROCONSTRUCTIVIST APPROACH EXPLAIN THE DATA BETTER?

One example that illustrates the advantages of the **neuroconstructivist approach** is that of Williams syndrome ([links - Williams Syndrome Association: <http://www.williams-syndrome.org>; Williams Syndrome Foundation: <http://www.williams-syndrome.org.uk>]).

Within the **neuropsychological framework**, Williams syndrome is often invoked as a model NDD. This is because of its known genetic etiology and its uneven cognitive profile, with seemingly intact and impaired components. Proponents of the neuropsychological approach characterize this syndrome as having specific impairments in spatial and numerical cognition modules³⁴ alongside “intact” language and face recognition modules³⁴⁻⁴¹. Consequently, Williams syndrome is often compared with other NDDs in an attempt to delineate double dissociations not only in adults but also in children.

For example, a double dissociation has been repeatedly proposed between Williams syndrome and ‘specific language impairment’ (SLI), a developmental disorder that—as its name suggests—appears to target language development in a highly specific manner. Researchers point to this double dissociation as evidence that language is the product of a stand-alone cognitive module (e.g.,^{38, 42, 43}). Accordingly, proponents of this double dissociation describe Williams syndrome as a disorder in which the “system for language is selectively spared” (³⁶; p. 193) and SLI as a disorder characterized by a single impairment in the language domain in an otherwise intact brain^{37, 38, 44-46}. Furthermore, the proposed double dissociation is used to support the notion that “a grammar module” develops normally in Williams syndrome alongside low IQ while being selectively impaired in SLI alongside normal IQ, suggesting that syntax is a cognitive module operating independently of nonverbal cognitive abilities in children (e.g.,^{38, 42, 43}).

In fact, however, the purported double dissociation between Williams syndrome and SLI does not exist. Rather, as proposed by the **neuroconstructivist approach**, several aspects of the brain and cognitive system in both Williams syndrome and SLI develop atypically^{25, 47-49}. For example, when the purported double dissociation was tested by *directly* comparing individuals with Williams syndrome and SLI on a battery of verbal and non-verbal tests, no double dissociation emerged. Although children with Williams syndrome did perform significantly worse on non-verbal tasks, their performance in the verbal domain did not differ from that of individuals with SLI⁵⁰. Furthermore, despite the fact that language is a relative strength in individuals with Williams syndrome, it still falls well below the level of proficiency expected of a typically developing child of a similar

chronological age. In other words, within Williams syndrome, language ability may be strong relative to other domains (e.g., visuospatial ability), but it cannot be considered to represent an intact language module because it develops atypically. Most aspects of language, including the lexicon⁵¹, morphosyntax⁵² and pragmatics⁵³, are atypical in Williams syndrome when compared to typically developing children.

Even the claim that SLI entails a selective impairment of language alongside preserved non-verbal intelligence (e.g.,⁵⁴⁻⁵⁶) is controversial. Although individuals with SLI perform within the normal range on non-verbal intelligence tests, they have been shown to perform significantly worse than their siblings⁴⁷, which points to subtle, more widespread impairments⁵⁷. Moreover, SLI has been associated with numerous other (subtle) cognitive, sensory, and motor difficulties^{47, 58-64}. Finally, the double dissociation is proposed purely on behavioural evidence whereas, as predicted by the neuroconstructivist approach, widespread brain atypicalities are found in both Williams syndrome and SLI (see review by^{49, 65}).

HOW THEORETICAL APPROACHES INFLUENCE RESEARCH STRATEGIES

As mentioned earlier, the theoretical approaches that scientists adopt influence the type of research questions they ask, which in turn determine the studies they carry out and the way that they interpret their findings. These decisions have consequences for health and social policies as well as for education and intervention.

The **neuropsychological approach** generates research questions such as “By what

age does each module come online?”, “Which modules are impaired and which are intact?”, and “Where are these modules located in the brain?” Such questions necessarily lead to the search in children with NDDs for specifically impaired modules in an otherwise intact brain. This type of research tends to generate interventions that target one specific cognitive system in isolation of others (e.g., language in SLI; number in dyscalculia). However, as argued above, it cannot be assumed that the infant brain is modular. Brain circuits interact across different regions at every age, but especially in early development when they are more plastic and less specialized. Thus, the static research questions that are generated by the neuropsychological approach are now giving way to new, more dynamic questions such as “How do neural circuits and cognitive functions emerge and change over developmental time?”, “Will an early, low-level deficit be followed by compensation or compounding of effects?” “Which domains interact across developmental time?”, and “What aspects of the ever-changing environment affect gene expression and cognitive development?”

Neuroconstructivists are helping to change the way in which NDDs are investigated. Whereas neuropsychological approaches assume that basic-level deficits directly impair one or more “modules” while sparing the rest of the system, neuroconstructivism suggests that basic-level deficits have cascading effects that alter interactions within and between networks. These cascades act to constrain the emergence of many higher-level (interactive) functions. In other words, a basic-level deficit that affects one functional domain (e.g., in visual attention) may constrain the emergence of functions in other domains (e.g., in language) because the developing system is highly interactive; it

is not composed of isolated, minimally interactive brain parts. Thus, neuroconstructivism requires that researchers adopt a truly developmental approach, focused on change over time, to gain insight into interactions among the genetic, cellular, neural, cognitive, behavioral, and environmental levels of description. This is critical in order to discover how an initial perturbation in one domain, and at one level of analysis (e.g., genetic), may over time influence other domains at other levels of analysis.

The neuroconstructivist approach has also helped to engender a shift in research from small domain-focused research teams (focused, for example, on numerical cognition) to large collaborative networks of multidisciplinary teams that include geneticists, cellular and molecular biologists, neuroscientists, social scientists, and psychologists as well as computational modelers and others. To facilitate this collaboration, large cross-scientific consortia are being established (e.g., British Autism Study of Infant Siblings [BASIS] [<http://www.basisnetwork.org>], European Autism Interventions - A Multicentre Study for Developing New Medications [EU-AIMS] [<http://www.eu-aims.eu>], London Down Syndrome Consortium [LonDownS] [<http://www.ucl.ac.uk/londowns>], and Pediatric Imaging, Neurocognition and Genetics [PING] [<http://pingstudy.ucsd.edu>]).

Furthermore, the neuroconstructivist view, like all developmental approaches, highlights the importance of tracking *developmental trajectories*⁶⁶, beginning as early in development as possible, in order to unpack how interactions at multiple levels give rise to the resulting NDDs. For example, in the case of Williams syndrome, the genetic deletion likely affects basic-level processes that have cascading effects on various

domains over developmental time^{25, 48}. Being able to ascertain how tiny variations interact with factors early in development provides greater insight into the emerging phenotype. Examining developmental trajectories is also important for identifying possible *protective* factors (factors that improve outcome) and *risk* factors (factors that worsen outcome). Uncovering the cascading effects of a basic-level perturbation, as well as any protective and risk factors, are critical for the design of early diagnostic tests and intervention strategies.

To be able to tailor early diagnostic tests and interventions, it is necessary to compare children with NDDs not only with typically developing children, but also with children with other NDDs, conducting *cross-syndrome comparisons*^{3, 67-71}. This is especially important because initial perturbations may be very similar across syndromes, yet tiny subsequent differences may ultimately yield very different developmental outcomes.

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REFERENCES

1. Butterworth B. *The Mathematical Brain*. London, England: Macmillan; 1999.
2. Butterworth B. Foundational numerical capacities and the origins of dyscalculia. *Trends Cogn Sci* 2010, 14:534-541.
3. Karmiloff-Smith A, D'Souza D, Dekker TM, Van Herwegen J, Xu F, Rodic M, Ansari D. Genetic and environmental vulnerabilities in children with neurodevelopmental disorders. *Proceedings of the National Academy of Sciences of the United States of America* 2012, 109:17261-17265.
4. Cosmides L, Tooby J. Beyond Intuition and Instinct Blindness - toward an Evolutionarily Rigorous Cognitive Science. *Cognition* 1994, 50:41-77.
5. Kanwisher N, McDermott J, Chun MM. The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience* 1997, 17:4302-4311.
6. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society B-Biological Sciences* 2006, 361:2109-2128.
7. Barton JJ. Structure and function in acquired prosopagnosia: lessons from a series of 10 patients with brain damage. *J Neuropsychol* 2008, 2:197-225.
8. Barton JJ, Press DZ, Keenan JP, O'Connor M. Lesions of the fusiform face area impair perception of facial configuration in prosopagnosia. *Neurology* 2002, 58:71-78.
9. Coltheart M. *Attention and Performance XII: The Psychology of Reading*. Hillsdale, NJ: Erlbaum; 1987.
10. Dunn JC, Kirsner K. Discovering functionally independent mental processes: the principle of reversed association. *Psychol Rev* 1988, 95:91-101.
11. Vallar G. The methodological foundations of neuropsychology. In: Denes F, Pizzamiglio L, eds. *Handbook of Clinical and Experimental Neuropsychology*. Hove, UK: Psychology Press; 1999, 95-131.
12. Shallice T. *From Neuropsychology to Mental Structure*. Cambridge, England: Cambridge University Press; 1988.
13. Dunn JC, Kirsner K. What can we infer from double dissociations? *Cortex* 2003, 39:1-7.
14. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn Sci* 2010, 14:277-290.
15. Frith U. Can we have a shared theoretical framework? *Educational and Child Psychology* 1995, 12:6-17.
16. Leslie AM. Pretense, Autism, and the Theory-of-Mind Module. *Current Directions in Psychological Science* 1992, 1:18-21.
17. Oyama S, Griffiths P, Gray R. *Cycles of Contingency: Developmental Systems and Evolution*. Cambridge, MA: MIT Press; 2001.
18. Thelen E, Smith L. *A Dynamic Systems Approach to the Development of Cognition and Action*. Cambridge, MA: MIT Press; 1994.
19. Mareschal D, Johnson MH, Sirois S, Spratling M, Thomas MSC, Westerman G. *Neuroconstructivism: How the Brain Constructs Cognition* Oxford: Oxford University Press; 2007.

20. Elman J, Karmiloff-Smith A, Bates E, Johnson M, Parisi D, Plunkett K. *A Connectionist Perspective on Development*. Cambridge, MA: MIT Press; 1996.
21. Fair DA, Dosenbach NUF, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL. Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences of the United States of America* 2007, 104:13507-13512.
22. Johnson MH. Functional brain development in humans. *Nature Reviews Neuroscience* 2001, 2:475-483.
23. Johnson MH. *Developmental Cognitive Neuroscience*. 3rd ed. Oxford: Wiley-Blackwell; 2011.
24. Bishop DV. Cognitive neuropsychology and developmental disorders: uncomfortable bedfellows. *Q J Exp Psychol A* 1997, 50:899-923.
25. Karmiloff-Smith A. Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences* 1998, 2:389-398.
26. Karmiloff-Smith A. Crucial differences between developmental cognitive neuroscience and adult neuropsychology. *Developmental Neuropsychology* 1997, 13:513-524.
27. Karmiloff-Smith A, Thomas M, Annaz D, Humphreys K, Ewing S, Brace N, Van Duuren M, Pike G, Grice S, Campbell R. Exploring the Williams syndrome face-processing debate: the importance of building developmental trajectories. *Journal of Child Psychology and Psychiatry* 2004, 45:1258-1274.
28. Benton AL, Hamsher K, Varney NR, Spreen O. *Contributions to Neuropsychological Assessment*. New York: Oxford University Press; 1983.
29. Wilson B, Cockburn J, Baddeley A. *Rivermead Behavioural Memory Test*. Reading, UK: Thames Valley Test Co; 1985.
30. Frith U. *Autism: Explaining the Enigma*. 2nd ed. Oxford: Wiley-Blackwell; 2003.
31. Stiles J, Jernigan TL. The Basics of Brain Development. *Neuropsychology Review* 2010, 20:327-348.
32. Gottlieb G. Probabilistic epigenesis. *Developmental Science* 2007, 10:1-11.
33. Karmiloff-Smith A, Scerif G, Ansari D. Double dissociations in developmental disorders? Theoretically misconceived, empirically dubious. *Cortex* 2003, 39:161-163.
34. Bellugi U, Wang P, Jernigan TL. Williams syndrome: an unusual neuropsychological profile. In: Broman S, Grafman J, eds. *Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function*. Hillsdale, NJ: Erlbaum; 1994, 23-56.
35. Bellugi U, Marks S, Bihrlé A, Sabo H. Dissociation between language and cognitive functions in Williams syndrome. In: Bishop D, Mogford K, eds. *Language Development in Exceptional Circumstances*. London: Churchill Livingstone; 1988, 177-189.
36. Clahsen H, Almazan M. Syntax and morphology in Williams syndrome. *Cognition* 1998, 68:167-198.
37. Pinker S. *The Language Instinct: How the Mind Creates Language*. New York: W. Morrow; 1994.
38. Pinker S. *Words and Rules: The Ingredients of Language*. New York: Basic Books; 1999.
39. Rossen M, Klima ES, Bellugi U, Bihrlé A, Jones W. Interaction between language and cognition: Evidence from Williams syndrome. In: Beitchman JH, Cohen NJ, Konstantarea MM, Tannock R, eds. *Language, Learning, and Behavioural Disorders: Developmental, Biological, and Clinical Perspectives*. New York, NY: Cambridge University Press; 1996, 367-392.

40. Tager-Flusberg H, Boshart J, Baron-Cohen S. Reading the windows to the soul: Evidence of domain-specific sparing in Williams syndrome. *Journal of Cognitive Neuroscience* 1998, 10:631-639.
41. Tager-Flusberg H, Plesa-Skwerer D, Faja S, Joseph RM. People with Williams syndrome process faces holistically. *Cognition* 2003, 89:11-24.
42. Clahsen H, Ring M, Temple C. Lexical and morphological skills in English-speaking children with Williams Syndrome. In: Bartke S, Siegmüller J, eds. *Williams Syndrome Across Languages*. Amsterdam: Benjamins; 2004, 221-244.
43. Fonteneau E, van der Lely HKJ. Electrical Brain Responses in Language-Impaired Children Reveal Grammar-Specific Deficits. *Plos One* 2008, 3.
44. Pinker S. Talk of genetics and vice versa. *Nature* 2001, 413:465-466.
45. Smith N. *Noam Chomsky: New Horizons in the Study of Language and Mind*. Cambridge: Cambridge University Press; 1999.
46. Smith N, Tsimpli IM. *The Mind of a Savant: Language, Learning and Modularity*. Oxford: Blackwell; 1995.
47. Chiat S. Mapping theories of developmental language impairment: Premises, predictions and evidence. *Language and Cognitive Processes* 2001, 16:113-142.
48. Farran EK, Karmiloff-Smith A. *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. Oxford: Oxford University Press; 2012.
49. Martens MA, Wilson SJ, Reutens DC. Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry* 2008, 49:576-608.
50. Stojanovik V, Perkins M, Howard S. Williams syndrome and specific language impairment do not support claims for developmental double dissociations and innate modularity. *Journal of Neurolinguistics* 2004, 17:403-424.
51. Temple CM, Almazan M, Sherwood S. Lexical skills in Williams Syndrome: a cognitive neuropsychological analysis. *Journal of Neurolinguistics* 2002, 15:463-495.
52. Grant J, Valian V, Karmiloff-Smith A. A study of relative clauses in Williams syndrome. *Journal of Child Language* 2002, 29:403-416.
53. Laws G, Bishop D. Pragmatic language impairment and social deficits in Williams syndrome: a comparison with Down's syndrome and specific language impairment. *International Journal of Language & Communication Disorders* 2004, 39:45-64.
54. Gopnik M, Crago MB. Familial Aggregation of a Developmental Language Disorder. *Cognition* 1991, 39:1-50.
55. Rice ML. A unified model of specific and general language delay: Grammatical tense as a clinical marker of unexpected variation. In: Levy Y, Schaeffer J, eds. *Language Competence Across Populations: Toward a Definition of Specific Language Impairment*. Mahwah, NJ: Erlbaum; 2002, 63-95.
56. VanderLely HKJ. Language and cognitive development in a grammatical SLI boy: Modularity and innateness. *Journal of Neurolinguistics* 1997, 10:75-107.
57. Clegg J, Hollis C, Mawhood L, Rutter M. Developmental language disorders a follow-up in later adult life. Cognitive, language and psychosocial outcomes. *Journal of Child Psychology and Psychiatry* 2005, 46:128-149.
58. Benasich AA, Spitz RV. Insights from infants: Temporal processing abilities and genetics contribute to language impairment. In: Whitmore K, Hart H, Willems G, eds. *A*

- Neurodevelopmental Approach to Specific Learning Disorders*. London: Mac Keith Press; 1999, 191-210.
59. Bishop DV. Motor immaturity and specific speech and language impairment: evidence for a common genetic basis. *Am J Med Genet* 2002, 114:56-63.
 60. Botting N. Non-verbal cognitive development and language impairment. *J Child Psychol Psychiatry* 2005, 46:317-326.
 61. Hick R, Botting N, Conti-Ramsden G. Cognitive abilities in children with specific language impairment: consideration of visuo-spatial skills. *International Journal of Language & Communication Disorders* 2005, 40:137-149.
 62. Hill EL. Non-specific nature of specific language impairment: a review of the literature with regard to concomitant motor impairments. *International Journal of Language & Communication Disorders* 2001, 36:149-171.
 63. Johnston J. Cognitive deficits in specific language impairments: decisions in spite of uncertainty. *Journal of Speech-Language Pathology and Audiology* 1999, 23:165-172.
 64. Norbury CF, Bishop DVM, Briscoe J. Does impaired grammatical comprehension provide evidence for an innate grammar module? *Applied Psycholinguistics* 2002, 23:247-268.
 65. Watkins KE, Vargha-Khadem F, Ashburner J, Passingham RE, Connelly A, Friston KJ, Frackowiak RSJ, Mishkin M, Gadian DG. MRI analysis of an inherited speech and language disorder: structural brain abnormalities. *Brain* 2002, 125:465-478.
 66. Thomas MSC, Annaz D, Ansari D, Scerif G, Jarrold C, Karmiloff-Smith A. Using Developmental Trajectories to Understand Developmental Disorders. *Journal of Speech Language and Hearing Research* 2009, 52:336-358.
 67. Annaz D, Karmiloff-Smith A. Cross-syndrome, cross-domain comparisons of development trajectories. *Cahiers De Psychologie Cognitive-Current Psychology of Cognition* 2005, 23:44-48.
 68. Brown JH, Johnson MH, Paterson SJ, Gilmore R, Longhi E, Karmiloff-Smith A. Spatial representation and attention in toddlers with Williams syndrome and Down syndrome. *Neuropsychologia* 2003, 41:1037-1046.
 69. D'Souza D, Kyjonkova H, Johnson MH, Gliga T, Kushnerenko E, Scerif G, Karmiloff-Smith A. Are Early Neurophysiological Markers of ASD Syndrome-Specific? Preliminary Results from a Cross-Syndrome Study. In: *International Meeting for Autism Research, IMFAR* San Sebastian, Spain May, 2013.
 70. Paterson SJ, Brown JH, Gsodl MK, Johnson MH, Karmiloff-Smith A. Cognitive modularity and genetic disorders. *Science* 1999, 286:2355-2358.
 71. Scerif G, Cornish K, Wilding J, Driver J, Karmiloff-Smith A. Visual search in typically developing toddlers and toddlers with Fragile X or Williams syndrome. *Developmental Science* 2004, 7:116-130.
 72. Bishop DVM. Which Neurodevelopmental Disorders Get Researched and Why? *Plos One* 2010, 5.
 73. Lloyd-Fox S, Blasi A, Elwell CE. Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. *Neurosci Biobehav Rev* 2010, 34:269-284.
 74. Passarotti AM, Paul BM, Russiere JR, Buxton RB, Wong EC, Stiles J. The development of face and location processing: an fMRI study. *Developmental Science* 2003, 6:100-117.

75. Osborne LR. Genes: The gene expression approach. In: Farran EK, Karmiloff-Smith A, eds. *Neurodevelopmental Disorders Across the Lifespan: A Neuroconstructivist Approach*. Oxford: Oxford University Press; 2012, 59-81.
76. Meyer-Lindenberg A, Mervis CB, Sarpal D, Koch P, Steele S, Kohn P, Marengo S, Morris CA, Das S, Kippenhan S, et al. Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *Journal of Clinical Investigation* 2005, 115:1888-1895.
77. Andrus BM, Blizinsky K, Vedell PT, Dennis K, Shukla PK, Schaffer DJ, Radulovic J, Churchill GA, Redei EE. Gene expression patterns in the hippocampus and amygdala of endogenous depression and chronic stress models. *Mol Psychiatry* 2012, 17:49-61.
78. Cohen MM, Tottenham N, Casey BJ. Translational Developmental Studies of Stress on Brain and Behavior: Implications for Adolescent Mental Health and Illness? *Neuroscience* 2013, 249:53-62.
79. Lisowski P, Juszczak GR, Goscik J, Wieczorek M, Zwierzchowski L, Swiergiel AH. Effect of chronic mild stress on hippocampal transcriptome in mice selected for high and low stress-induced analgesia and displaying different emotional behaviors. *European Neuropsychopharmacology* 2011, 21:45-62.
80. Leyfer O, Woodruff-Borden J, Mervis CB. Anxiety disorders in children with Williams syndrome, their mothers, and their siblings: Implications for the etiology of anxiety disorders. *Journal of Neurodevelopmental Disorders* 2009, 1:4-14.

FURTHER READING

Karmiloff-Smith A. An alternative to domain-general or domain-specific frameworks for theorizing about human evolution and ontogenesis. *AIMS Neurosci* 2015, 2:91-104.
doi: [10.3934/Neuroscience.2015.2.91](https://doi.org/10.3934/Neuroscience.2015.2.91)

Karmiloff-Smith A. Development itself is the key to understanding developmental disorders. *Trends Cogn Sci* 1998, 2:389-398. doi:[10.1016/S1364-6613\(98\)01230-3](https://doi.org/10.1016/S1364-6613(98)01230-3)

Karmiloff-Smith A, Al-Janabi T, D'Souza H, Groet J, Massand E, Mok K, Startin C, Fisher E, Hardy J, Nizetic D, et al. The importance of understanding individual differences in Down syndrome. *F1000Research* 2016, 5:389. doi: [10.12688/f1000research.7506.1](https://doi.org/10.12688/f1000research.7506.1)

Mareschal D, Johnson MH, Sirois S, Spratling M, Thomas MSC, Westerman G.

Neuroconstructivism: How the Brain Constructs Cognition. Oxford: Oxford University Press; 2007.

Moore DG, George R. ACORNS: A tool for the visualisation and modelling of atypical development. *J Intellect Disabil Res* 2011, 55:956-972. [doi:10.1111/j.1365-2788.2011.01471.x](https://doi.org/10.1111/j.1365-2788.2011.01471.x)

Table 1. A list of neurodevelopmental disorders, ordered by prevalence. Prevalence has been divided by two if reported for one sex only. Adapted from Bishop⁷²

Condition	Prevalence per 100
Lesch-Nyhan syndrome	0.0005
Lowe syndrome	0.0005
Rubinstein-Taybi syndrome	0.0008
Cornelia de Lange syndrome	0.0014
Cri du chat syndrome	0.0020
Galactosaemia	0.0020
Angelman syndrome	0.0040
Williams syndrome	0.0044
Marfan syndrome	0.0067
Prader-Willi syndrome	0.0067
Rett syndrome	0.0080
Phenylketonuria	0.0100
Duchenne muscular dystrophy	0.0143
Tuberous sclerosis	0.0167
Trisomy 18	0.0250
Velocardiofacial syndrome	0.0250
Neurofibromatosis type 1	0.0308
Turner syndrome	0.0400
XYY	0.0545
XXX	0.0550
Noonan syndrome	0.0571
Fragile X syndrome	0.0615
Klinefelter syndrome	0.0860
Fetal alcohol syndrome	0.1000
Cerebral palsy	0.1500
Down syndrome	0.1667
Tourette syndrome	0.5000
Autistic spectrum disorder	0.6500
Developmental dyscalculia	3.0000
Attention deficit hyperactivity disorder	5.0000
Intellectual disability	5.5000
Developmental dyslexia	6.0000
Developmental coordination disorder	6.5000
Specific language impairment	7.4000
Speech sound disorder	10.0000

FIGURE LEGENDS

Figure 1. An infant with Down syndrome wearing a cap that records electrical activity in the brain. Electroencephalography (EEG) is one of the most commonly used methods to measure brain responses in infants.

Figure 2. This figure compares the spatial and temporal resolution of different methods used to measure brain activity in infants. It also illustrates the relative degree of tolerance needed from the infant for each method, ranging from yellow (low) to red (high). EEG = electroencephalography; ERP = event-related potential; MEG = magnetoencephalography; NIRS = near infrared spectroscopy; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; PET = positron emission tomography. From Lloyd-Fox, Blasi, & Elwell⁷³.

Figure 3. Functional magnetic resonance imaging (fMRI) data showing the neural response to faces in 10-12-year-olds and adults. Children show more distributed and bilateral activation than adults. The colored bar to the left represents the percent increase in intensity of activation in the experimental task, as compared to the control task. Note that according to the radiological convention the left side of the brain represents the right hemisphere (RH), and the right side of the brain represents the left hemisphere (LH). Adapted from Passarotti, et al.⁷⁴.

Example of complex interactions

Williams syndrome (WS) is caused by the deletion of some 28 genes on one copy of chromosome 7 (7q11.23), 22 of which are expressed in the brain⁷⁵. This initial deletion at the genetic level is linked to a number of atypicalities at the level of the brain (brain chemistry, brain anatomy, brain volume, hemispheric asymmetry, temporal patterns of brain activity, etc.²⁵), and these are associated with various cognitive and behavioural abnormalities⁴⁸. However, although the genetic deletion is the root cause of WS, this simple fact belies the complexity of how WS emerges over developmental time.



For instance, alterations in many brain areas have been reported in WS. Changes in one of them—the hippocampus—have been linked to deficits in spatial navigation and long-term memory⁷⁶. While hippocampal changes may be in part due to the genetic mutations, it is important to highlight the fact that environmental factors such as chronic stress and anxiety also affect neural development^{75, 77-79}. It is known that stress and anxiety are especially high in WS⁸⁰. Therefore, it is not necessarily the case that it is the genetic mutations that *directly* affect brain development in WS; it could also be a combination of emotional perturbations that also impact the brain. Thus, it is impossible to understand how the WS neuro-cognitive profile emerges without studying it very early in development, across time, and at multiple interacting levels.

How different theories affect assessment and intervention

Neuropsychological approach

- Assessments focus on the identification of impaired and intact parts of cognition and brain.
- Once the “broken” module has been identified, the intervention targets this module specifically (e.g., practicing language in the case of specific language impairment or number in the case of Williams syndrome).
- If the module is identified as being underpinned by specific genes, then gene therapy may be considered the only solution.

Neuroconstructivist approach

- Assessments are broad, mapping the profile of the child’s strengths and weaknesses over time.
- No specific isolated impairment is assumed. Rather, many domains will be more or less affected.
- The ideal intervention is based on prior in-depth syndrome-specific research and usually takes place early in the developmental trajectory, enhancing protective factors and/or reducing risk factors in the child’s development.
- The targeted intervention need not be in the most visibly problematic domain, like language or number. Rather, it can be targeted at basic-level processes that underlie the domain, such as memory, attention, etc. It is

these processes that would be likely to have the most cascading impact on other domains.

- Timely intervention is key. Effective intervention ultimately depends on the timing of various interactions among domains, which is why it is crucial to base the intervention on syndrome-specific research that identifies how systems change over developmental time in a given neurodevelopmental disorder.
- Although the earliest intervention will not necessarily be the most successful one, younger brains are typically more plastic than older ones. Also, early in development, even relatively small perturbations can have cascading effects over developmental time.