



Perspectives on the dynamic development of cognitive capacities: insights from Williams syndrome

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Purpose of review

This article identifies an increasing change from rather static approaches to neurodevelopmental disorders and the search for 'intact' and 'impaired' domain-specific modules, to more recent dynamic perspectives that take account of cross-domain interactions and changes over developmental time.

Recent findings

Research on Williams syndrome is taken as a model, used to demonstrate the static versus dynamic perspectives, covering new work on social cognition, spatial cognition, and sleep-related consolidation of memory in neurodevelopmental disorders, as well as hypothesis-driven cross-syndrome comparisons. Many previously considered 'intact' domains have now been shown to harbour subtle deficits because of the cross-domain interactions typical of early periods of infant development. Sleep architecture has been found to be atypical in all syndromes hitherto assessed, with consequent impact on learning. This has opened avenues for sleep intervention which may impact on subsequent cognitive development.

Summary

Cross-syndrome associations, and not merely cross-syndrome dissociations or comparisons with typical development, are shown to be particularly relevant for advancing theory and research. These comparisons reveal that clinical intervention strategies should aim at syndrome-specific remediation as early in the developmental trajectory as possible.

Keywords

neurodevelopmental disorders, sleep, social cognition, spatial cognition, Williams syndrome

INTRODUCTION

Studies of cognitive development have been undertaken from both static or dynamic perspectives, with these opposing approaches continuing throughout recent years. Static approaches stem from theoretical perspectives based on Nativism and the search for innately specified core knowledge [1–3]. When extended to neurodevelopmental disorders, the approach is inspired by adult neuropsychological models of the mature brain, treating cognitive domains as operating independently of one another and as being 'impaired' or 'intact' [2,4^{***}]. The dynamic perspective, by contrast, takes a Neuroconstructivist approach [5] and explains cognitive-level outcomes in terms of basic-level processes in infancy, focusing on, rather than negating, cross-domain interactions [6^{***},7^{***},8]. This review will examine recent research on neurodevelopmental disorders, taking Williams syndrome (also known as Williams–Beuren syndrome) as a

model of the contrasting static versus dynamic approaches.

WILLIAMS SYNDROME

Williams syndrome is caused by a hemizygous deletion of 26–28 genes on chromosome 7q11.23, characterized by facial dysmorphology, cardiovascular abnormalities, mild/moderate mental retardation, and an uneven cognitive profile of serious deficits and relative proficiencies [9]. Williams syndrome is considered to be a compelling model for

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KEY POINTS

- Cross-syndrome comparisons can reveal more subtle details of the trajectory of development than the focus on single syndromes and comparisons with typical development.
- Cross-domain comparisons can be more informative than the focus on single cognitive domains.
- Sleep plays a critical role in the consolidation of learning and has been found to be atypical in many neurodevelopmental disorders.
- Computational modelling of developmental disorders allows researchers to explore how multiple interacting parameters contribute to phenotypic outcomes over developmental time.

genotype–phenotype relations and has been a major focus of research and theory in neurodevelopmental disabilities. This is due to significant progress made at multiple levels: in candidate gene identification and gene expression, in brain structure, function and biochemistry, and in the cognitive phenotype [5,10^a,11,12^a,13–17]. New research is challenging the hitherto widely held but static view that ‘Williams syndrome can be explained in terms of selective deficits to an otherwise normal modular system’ [18]. Nonetheless, this static theoretical enterprise continues to dominate some Williams syndrome research [4^{aa},19–22]. Such a strong contrast in theoretical approaches is also typical of specific language impairment research. Whilst it has been argued that ‘grammatical neural circuitry underlying language is a *developmentally unique system* ...[that] can be *selectively impaired*’ (italics added) [23], other researchers have examined the dynamic factors that contribute over developmental time to the phenotypic outcome [24].

Initial research on Williams syndrome highlighted severe deficits in spatial cognition, number and problem-solving alongside apparent strengths in language, face processing and social cognition. However, recent studies [15,25–27] have revealed deficits also in these so-called ‘intact’ domains, due to the identification of cross-domain interactions over developmental time. This is not surprising, given that the neonate brain does not start out highly specialized; rather, numerous regions of cortex initially compete to process different types of inputs. It is only with time that the brain becomes progressively specialized and localized. In neurodevelopmental disorders such as Williams syndrome, gene mutations are likely to be expressed across several brain regions and thus cause widespread, albeit sometimes subtle, deficits across several

cortical networks, rather than targeting single functions, as might hold for focal lesions in normal adults.

Whereas previous Williams syndrome research has covered numerous cognitive domains, a few areas have witnessed particular focus in the recent past: social cognition, spatial cognition, sleep-related consolidation of memory, as well as hypothesis-driven cross-syndrome comparisons. We cover each of these in turn below.

THE SOCIAL DOMAIN

Understanding the social brain is a major recent focus of developmental cognitive neuroscience in general, with individuals with Williams syndrome considered of special relevance because they display an unusual fascination with social interaction, a lack of social fear, alongside heightened nonsocial anxieties. Indeed, Williams syndrome produces abnormally elevated amygdala responses to threatening nonsocial stimuli (e.g. spiders, buildings). In typically developing individuals, amygdala activity is inhibited through dense, reciprocal white matter connections with prefrontal cortex. A recent study used diffusion tensor imaging to investigate prefrontal–amygdala white matter integrity in Williams syndrome and typically developing individuals [10^a], with the hypothesis that prefrontal–amygdala inhibition might be uncoupled in Williams syndrome. White matter pathways between amygdala and several prefrontal regions were isolated using probabilistic tractography, and within each pathway, white matter integrity differences were examined. Compared to controls, individuals with Williams syndrome had lower fractional anisotropy in several prefrontal–amygdala pathways, indicating a reduction in white matter integrity. This was explained by significantly higher radial diffusivity, suggestive of lower fibre density or axon myelination in prefrontal–amygdala pathways. This indicates that deficits in the structural integrity of these pathways are likely to underlie the increased amygdala activity and the extreme nonsocial anxieties observed in Williams syndrome, which are so different from their social disinhibition.

The nature of the Williams syndrome social phenotype remains a question of debate, however. An earlier study had suggested that the Williams syndrome unusual social disinhibition led to a lack of race bias and racial stereotyping [28]. However, a new study [29^a], designed to investigate the neural correlates of other-race face perception, reached a different conclusion. Caucasian Williams syndrome and typically developing participants performed a sex identification task with own-race (White) and

other-race (Black) faces while event-related potentials (ERPs) were recorded. Nothing unusual emerged from the ERP signature of the Williams syndrome group. Indeed, in Williams syndrome and controls alike, other-race faces elicited larger-amplitude ERPs within the first 200 ms following face onset, demonstrating that individuals with Williams syndrome process own-race faces differently from other-race faces at early perceptual stages just as in typical development. This warrants a reconsideration of claims that the syndrome is characterized by insensitivity to race, although it is worth considering the fact that implicit processing is of course not the same as responding to explicit questioning as in the earlier study. Nonetheless, the new findings do not detract from other work demonstrating that the cognitive/neural processes underlying the Williams syndrome proficient face processing are atypical. Their processing is more featural compared to configural processing in controls [30] and has now been shown to involve different spatial frequency biases over time [31].

Despite the Williams syndrome fascination with faces, earlier work had demonstrated that toddlers with Williams syndrome were atypical in joint attention tasks, failing to use others' eye gaze direction [32]. But eye gaze control is not only important for social interaction, it also is used for nonsocial functions. Indeed, during face-to-face questioning, typically developing individuals use gaze aversion while thinking about their answers, with gaze aversion increasing with question difficulty and greater gaze aversion resulting in improved response accuracy. This is due to the problem of the shared resources required for thinking while simultaneously processing faces. A new cross-syndrome study compared gaze and the management of cognitive load in individuals with Williams syndrome and autism spectrum disorder (ASD) [33]. Like typically developing individuals, children with Williams syndrome and ASD increased their gaze aversion as question difficulty increased. However, those with ASD showed significantly more gaze aversion than controls when simply listening to interlocutors. In other words, two different neurodevelopmental disorders, both characterized by significant executive problems and atypical social interaction, exhibited typical patterns of gaze aversion, except that those with ASD showed elevated levels of gaze aversion while listening to questions, but not while thinking about their responses. The findings have important implications for how professionals interpret gaze aversion in these populations as well as for social skills training.

Faces, of course, are stimuli with multiple functions. It has been long claimed that from early

infancy onwards, individuals with Williams syndrome are fascinated with faces and spend more time fixated on faces than on objects [34]. However, a recent experiment asked whether this continued over developmental time. The study focused on older children and adolescents with Williams syndrome and measured attention capture by upright faces, task interference through face distraction, face bias and engagement versus disengagement from faces and objects [35]. No qualitatively different patterns of attention to faces emerged in this older Williams syndrome group compared to typically developing controls. Nonetheless, individuals with Williams syndrome tended to take longer to disengage from faces than from objects, suggesting that the infant inability to disengage continues in a milder form in subsequent development.

As mentioned, individuals with Williams syndrome have been consistently described as showing heightened sociability, gregariousness, and interest in people. To explore the mechanisms underlying this unusual social phenotype, a new study [36] measured likeability ratings and autonomic responsiveness (pupil dilation) to emotionally laden images with social or nonsocial content. Adolescents and adults with Williams syndrome were compared to chronological age-matched and nonverbal mental age-matched groups. The participants with Williams syndrome looked significantly longer at the social images compared to images without social content and had reduced arousal to the negative social images compared to the control groups. Furthermore, in contrast to the comparison groups, the explicit likeability ratings in the Williams syndrome group did not correlate with the differences in their self-selected viewing time of the images; instead, the explicit ratings tended to fall at one or other of the extremes of very likeable or very aversive. This distinctive pattern of implicit viewing interest, explicit likeability ratings, and autonomic arousal to images with social content in the Williams syndrome group suggests that their heightened social drive may be related to atypical functioning of reward-related brain systems reflected in autonomic reactivity measures, but not in explicit ratings.

Finally, atypical social interaction, whether it be hypersociability (typical of Williams syndrome) or withdrawal (typical of ASD), contributes to social vulnerability. New research has shown that, despite their different social profiles, the lives of individuals from both syndromes are marred by risks of social isolation, bullying, employment difficulties and abuse [37]. In other words, the cognitive phenotype is not only relevant in and of itself but has significant implications for everyday life. In

neurodevelopmental disorders, it will be critical to bridge the gaps between experimental observations and real-life experiences. Whereas evidence exists that individuals with Williams syndrome or ASD are socially vulnerable, it remains unclear whether this is attributable to atypical interaction styles and/or to socio-cognitive deficits. A recent Williams syndrome study addressed this point [38]. Indiscriminate approachability is a consistent trait in the Williams syndrome developmental trajectory, the exact basis of which was unknown. The new study revealed an association between high self-reported approachability ratings and perceptual deficits in affect identification in Williams syndrome. This not only provides clues to what underlies their atypical behaviour, but also has implications for intervention, as do studies that employ multiple modalities on the same population [36[■]], for example, neuropsychological assessment, experimental tasks, imaging, and self/teacher questionnaires.

THE ROLE OF SLEEP

Quality and quantity of sleep are essential to physical and mental health, with important implications for cognition. An interest in sleep-related consolidation of learning has been emerging over recent years [30–32,33[■],34,35,36[■],37–41], with neurodevelopmental disorders the focus of new research [42]. Variable sleep architecture turns out to be a hallmark of neurodevelopmental disorders, because it involves finely tuned multidimensional processes involving gene expression, brain biochemistry, and psychological processes in response to environmental stimuli. Here, too, it is opportune to move away from the static focus on the sleep state and focus on the dynamic processes occurring during sleep.

Quantitative data were lacking until two recent Williams syndrome studies examined overnight sleep patterns in laboratory settings [43[■],44], concluding that Williams syndrome sleep architecture is atypical, also confirmed by a recent large-scale questionnaire survey of sleep in Williams syndrome children [45]. These studies identified longer latency for sleep onset, decreased sleep efficiency, increased respiratory-related arousals as well as increased slow wave sleep on overnight polysomnography, compared to controls. EEG recordings in Williams syndrome were characterized by region-independent decreases in 10.50–12.50 Hz and central increases in 14.75–15.75 Hz EEG power [43[■]]. These atypical patterns highlight a decrease in alpha/low sigma power, as well as a redistribution of non-rapid eye movement (NREM) sleep 8–16 Hz EEG power toward the higher frequencies and/or a higher

frequency of NREM sleep thalamocortical oscillations in Williams syndrome [43[■]]. Rather than simply making comparisons with typical controls, detailed cross-syndrome sleep studies are necessary to understand the relationships between these atypical patterns of sleep architecture and the resulting failures to consolidate learning.

Hitherto, the effects of architectural atypicalities on sleep-related consolidation of learning have not been measured, but just such a study was recently undertaken [42]. Six to 12-year-old children with Williams syndrome were first trained in the evening, and then retested the following morning and afternoon, to use their left hand to repeatedly type a five-digit number sequence on a computer keyboard. Speed and accuracy were recorded across time points. The researchers found a dramatic overnight improvement in the controls, but no evidence of sleep-related learning in the Williams syndrome group. This kind of research is likely to become prevalent in the coming years because, if sleep disturbance affects the consolidation of memory, then an important intervention strategy for learning disability might lie in first remediating sleep architecture. Indeed, a new study examining melatonin intervention in neurodevelopmental disorders had positive results for sleep [46], although it did not measure the effects on sleep-related consolidation of learning, a topic of critical relevance to individuals with learning difficulties.

SPATIAL COGNITION

Individuals with Williams syndrome have long been shown to have serious visuo-spatial deficits. This finding derives mainly from performance on small-scale laboratory tasks. A recent study [47] investigated large-scale route learning in Williams syndrome and two matched control groups (a moderate learning difficulty group and typically developing). In a nonlabelling condition and one in which verbal information was provided, participants were guided along two unfamiliar 1-km routes with 20 junctions, and then retraced the routes themselves. The Williams syndrome participants performed more poorly than the other groups, but improved in the verbal labelling condition. The study revealed that individuals with Williams syndrome can learn a route, but store inflexible route knowledge, that is they are able to follow a fixed route, but do not understand the spatial relationships between locations. This means that they can neither work out a short-cut nor re-orient themselves when lost.

Further work explored navigational cognition in Williams syndrome using virtual reality [48]. In

addition to comparing route-learning ability, this study focused on whether participants differentiate between 'useful' and 'less useful' landmarks. Both the Williams syndrome and typically developing controls (matched on Ravens Coloured Progressive Matrices) learnt each route to criterion. However, during the learning phase, the Williams syndrome group took longer than controls to reach criterion and produced numerous perseverative errors. When tested on their recall of the landmarks, individuals with Williams syndrome realized that landmarks at critical junctions are the most useful. However, the lower the Williams syndrome scores on the Ravens [49[¶]], the more limited was their use of landmarks, a pattern not observed in the typically developing group, despite being matched on nonverbal abilities.

CONCLUSION

One important avenue of future research will, in my view, be a focus on cross-syndrome comparisons very early in the developmental trajectory. Much of the research on neurodevelopmental disorders uses typically developing controls or concentrates on cross-syndrome dissociations. However, the identification of cross-syndrome associations in infancy may lead to a subtler understanding of how and why developmental trajectories deviate from one another over time as well as from the typically developing trajectory [6^{¶¶}]. Williams syndrome and ASD share many similar deficits in early infancy, for example, problems with saccadic eye movement planning and with attentional disengagement, atypical eye gaze direction following and atypical pointing, as well as heightened sensitivity to sound. When researchers compare a syndrome to typically developing controls, differences are usual major. However, when they compare two syndromes in which both have a seemingly similar deficit, it is often possible to reveal much more subtle changes over time. Such discoveries should lead to better syndrome-specific intervention strategies at a very early stage in infant development. A second avenue of future research should engage in the computational modelling of developmental disorders, since this allows researchers to explore the multiple interacting parameters contributing to the phenotypic outcome the influence of which changes over developmental time [50^{¶¶}]. Dynamic changes, together with multidirectional interactions, occur over developmental time in gene expression, in brain structure, function and biochemistry, in cognitive processes, in overt behaviours and in the environment. Indeed, nothing in biology or psychology is static, and a focus on

dynamic change should be the hallmark of all research into neurodevelopmental disorders.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
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