

42 Research into Williams Syndrome: The State of the Art

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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, 887)

In sum, brain volume, brain anatomy, brain chemistry, hemispheric asymmetry, and the temporal patterns of brain activity are all atypical in people with Williams syndrome. How could the resulting system be described in terms of 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, which has subtle, widespread repercussions at the cognitive level. (Karmiloff-Smith, 1998, 393)

The striking difference between these two quotations not only encapsulates early research into the neurodevelopmental disorder Williams syndrome (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 window on the nature/nurture debate.

Williams syndrome 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: narrowing of the aorta (supravalvular aortic stenosis: SVAS), distinctive facial dysmorphology, slow physical growth, and learning difficulties. It took another couple of decades before the syndrome started to be extensively investigated by cognitive psychologists and neuroscientists, hoping thereby to gather data that might contribute directly to the question of whether or not the human mind/brain starts out with innately specified, cognitive-level modules (like grammar, face processing, spatial cognition, number, and the like) that operate independently of one another and of general intelligence. The widely held view was and still is to some extent that WS involves a juxtaposition of intact and impaired modules—that is, fluent language, excellent face-processing abilities, and a very friendly social disposition, alongside very poor spatial, problem-solving, and numerical abilities. But, as we shall see later, the real picture of the WS profile is far more complex.

At the level of the brain, WS is characterized by structural abnormalities, with total brain volume being about 80 percent of normal brains (Neville, Mills, and Bellugi, 1994). Once overall brain volume is controlled for, structural imaging studies point to specific reductions in parietal cortex (Eckert et al., 2005) as well as in the brain stem (Reiss et al., 2000). The corpus callosum is particularly small (Schmitt et al., 2001), but primary auditory cortex is proportionally large, with atypical cytoarchitecture (Holinger et al., 2005). While the cerebellum is also large in WS brains (Jones et al., 2005), this is an area in which we identified abnormal brain biochemistry (Rae et al., 1998). Atypical neuronal size, orientation, and density have also been identified (Galaburda et al., 2002), as well as increased cortical gyrification in the right parietal and occipital regions, as well as the left frontal areas (Schmitt et al., 2002). Gray matter volume is close to that found in normal controls, but white matter volume is reduced (Reiss et al., 2000). Finally, the hippocampus in WS brains appears to have an atypical shape (Meyer-Lindenberg et al., 2005). Apart from these structural abnormalities, other studies using functional magnetic resonance imaging (Meyer-Lindenberg et al., 2005) and high-density event-related potentials (Grice et al., 2001, 2003; Mills et al., 2000) point to atypical functioning in the WS brain. It is worth noting, however, that most of the studies of the WS brain structure and function have been based on adult brains. We have as yet little understanding of the developmental mechanisms that yield these brain abnormalities.

Paradoxically, and despite agreement on the abnormalities of the WS brain, some researchers continue to portray the WS brain in terms of a juxtaposition of intact and impaired cognitive modules, while others refute the possibility of intact modules in such a generally atypically developing brain. So, let's first describe the agreed-upon facts about the genotype and noncognitive features of WS and then examine the more controversial cognitive-level phenotype.

The Williams syndrome genotype

It is now known that in the vast majority of individuals with WS at least 28 genes are deleted on the long arm of one copy of chromosome 7q11.23 (Donnai and Karmiloff-Smith, 2000; Tassabehji et al., 2005). In most cases the

1

2

3

deletion is sporadic, although a few cases of parent-to-child transmission and concordant monozygotic twins have been reported (Morris, Thomas, and Greenberg, 1993; Pankau et al., 1993). No indication of parental age effects has emerged, and deletions occur with equal frequency on both maternally and paternally inherited chromosomes. For a long time, the prevalence of WS was estimated to be between 1 in 20,000 and 1 in 50,000 (Morris et al., 1998), but more recently a Norwegian study has situated the prevalence much higher, at closer to 1 in 7,500 (Stromme, Bjornstad, and Ramstad, 2002).

The deletion occurs at the outset of pregnancy during meiosis and is due to the existence of identical repeats on the regions flanking the deletion, thereby allowing for the chance misalignment of segments (Peoples et al., 2000; Urban et al., 1996). The genetic basis of the syndrome started to be identified in the early 1990s when it was found that the elastin gene (ELN) at 7q11.23 was disrupted by a translocation associated with SVAS (Curran et al., 1993), leading to the hypothesis that hemizyosity at the elastin locus might help situate the extent of the full deletion in individuals with WS (Ewart et al., 1993), who suffer from SVAS (Hallidie-Smith and Karas, 1988). The discovery of the ELN deletion in WS supported the view that haploinsufficiency for ELN causes the vascular abnormalities of WS such as SVAS (Ewart et al., 1993) and perhaps prematurely aging skin, but subsequent research has challenged the role of ELN in the WS facial dysmorphism (Hammond et al., 2005; Tassabehji et al., 2005) and in other physical or cognitive anomalies of the syndrome (Li et al., 1997; Tassabehji et al., 1999, 2005).

Since then, a great deal of progress has been made in identifying several of the other genes responsible for the full-blown WS phenotype (for reviews see Franke, 1999; Donnai and Karmiloff-Smith, 2000; Meyer-Lindenberg et al., 2005). The microdeletion is approximately 1.5 Mb, with ELN being midway between the two break points (Perez-Jurado et al., 1996). Adjacent to ELN, the Limkinase-1 gene (LIMK1), which is expressed in the brain, was found to be deleted in all patients with full-blown WS (Tassabehji et al., 1996). Notable is the fact that defects in the expression of LIMK1 may well affect axonal guidance during central nervous system development (Arber et al., 1998). Moreover, changes in the expression levels of the genes neighboring the deletion in WS may also play a role (Merla et al., 2006). Other genes are currently under investigation, often helped by the identification of patients with partial deletions in the WS critical region (Frangiskakis et al., 1996; Gray et al., 2006; Karmiloff-Smith et al., 2003; Tassabehji et al., 1996, 2005). But, because of the complexities of both gene expression and human ontogeny, no genotype-phenotype relations, apart from the role of ELN in SVAS, have yet been unequivocally identified. Nonetheless, studies of partial deletion (PD)

patients do point to testable hypotheses about possible genotype/phenotype relations. For example, Frangiskakis and colleagues identified a family, some of whose members had ELN and LIMK1 deleted and others who did not. It turned out that PD family members displayed spatial deficits similar to those encountered in individuals with WS, whereas those without the PD showed no spatial deficits (Frangiskakis et al., 1996). Based also on findings from a LIMK1 knockout mouse model, which resulted in spatial deficits in the Morris Maze (Meng et al., 2002), Frangiskakis and colleagues concluded that the LIMK1 gene deletion in individuals with WS caused their spatial impairment. However, subsequent studies of PD patients, using first the same tasks as in the Frangiskakis study (Karmiloff-Smith et al., 2003; Tassabehji et al., 1999) and then a very wide range of 16 different tasks to detect subtle spatial impairments (Gray et al., 2006), demonstrated that the deletion of LIMK1 could not alone explain the spatial deficits, since our ELN/LIMK1 PD patients were completely unimpaired across all these studies. How does this finding sit with the fact that the mouse LIMK1 knockout does show spatial deficits?

It is important to note that the LIMK1 mouse knockout model was tested in the Morris Maze, in which the mouse must represent the changing positions of its body in space, whereas the human tests had targeted tabletop constructions during which participants remain seated and stationary. It thus remained crucial to test PD and WS patients in navigational tasks in which they also had to mentally represent their changing positions in space. Karmiloff-Smith and collaborators (submitted) therefore devised child and adult human versions of the Morris Maze measuring navigational abilities. Our ELN-LIMK1 PD patients continued to show no spatial deficits, whereas the WS controls were very impaired. However, a patient with a much larger PD (24 of the 28 WS genes) turned out to be just as impaired as the WS controls on the navigational task, highlighting the importance of two genes (CYLYN2 and GTF2IRD1) at the telomeric end of the WS critical region as the most likely contributors to spatial cognition. Interestingly, this patient had a much milder social phenotype compared to the typical overly friendly disposition of those with full-blown WS, suggesting that one or more of her four nondeleted genes contribute, probably with many other genes, to the development of normal social cognition (Karmiloff-Smith et al., submitted).

It is obvious from the previous discussion that while PD patients help narrow hypotheses about the contribution of particular genes to the resulting WS phenotype, these are rare cases and the story always turns out to be extremely complex at both the genotypic and phenotypic levels. Given the pleiotropic nature of most genes, it is highly unlikely that scientists will end up with neat one-to-one mappings between mutated genes and phenotypic outcomes at the cognitive or social levels.

The Williams syndrome phenotype

First let us note a general point. To understand any developmental syndrome, it is essential to distinguish between the behavioral phenotype (based on scores from standardized tests of overt behavior) and the cognitive phenotype (based on in-depth analyses of the mental processes underlying the overt behavior) (Karmiloff-Smith, 1998). For instance, it can happen that equivalent behavioral scores camouflage very different cognitive processes, as we shall see when we examine in detail some aspects of the WS phenotypic profile.

Apart from the physical abnormalities in WS (facial dysmorphism, SVAS, small stature, and hyperacusis), the personality profile of people with WS is very specific to the syndrome. Even in early infancy, children with WS fixate the faces of others and smile very frequently. As they reach middle childhood onward, individuals with WS tend to be overly friendly with strangers and to lack social judgment skills (Einfeld, Tonge, and Florio, 1997; Gosch and Pankau, 1997). While tending not to be shy in new surroundings, they also display extreme anxiety where unexpected things happen. This clinical population also shows empathy toward others' emotions, although they have difficulty in interpreting some more complex facial expressions, such as anger and fear, compared to controls (Tsirempolou et al., 2006). They are also less skilled at understanding human intentionality than originally thought. In other words, their social-affective understanding seems relatively proficient, but their social-cognitive understanding of other minds is clearly impaired (Tager-Flusberg, Boshart, and Baron-Cohen, 1998).

Most studies suggest that individuals with WS exhibit a relatively uneven cognitive-linguistic profile (although see meta-analysis in Brock, in press, arguing for a more even profile in this syndrome), together with mild to severe mental retardation. Their WS full intelligence quotient is estimated at 51–70, with a mean of 56 (Mervis et al., 1999; Udwin and Yule, 1991). To be noted, however, is the fact that the full IQ score camouflages marked differences in specific cognitive abilities. The pioneering work of Bellugi and her collaborators suggested some clear-cut dissociations in the cognitive architecture of WS. Language and face processing appeared to be preserved in the face of both general retardation and particularly serious problems with visuospatial cognition (Bellugi, Wang, and Jernigan, 1994). However, the notion that abilities in developmental disorders are “preserved” or “intact” takes overt behavior in the adult as if it were a direct index of underlying cognitive processes, which it clearly is not (Karmiloff-Smith, 1998). In-depth analyses of the language and face processing in adults with WS—two areas purported to be “intact”—strongly suggest that their behavioral proficiencies are supported by different cognitive processes compared with normal controls. Moreover,

analyses of the WS infant cognitive profile demonstrate that the latter differs from the adult phenotypic outcome. In other words, it is critical to examine full developmental trajectories from infancy to adulthood at the level of cognitive processes rather than merely recording overt behavior (Karmiloff-Smith, 1998; Annaz, Karmiloff-Smith, and Thomas, in press).

Let us start historically with what is known about the adult cognitive phenotype in WS, since studies of infants with the syndrome are only recently being undertaken. All researchers agree that WS presents with serious deficits in spatial cognition and number (Ansari et al., 2003; Ansari and Karmiloff-Smith, 2002; Bellugi, Wang, and Jernigan, 1994; Mervis et al., 1999). It is therefore of interest to focus mainly on face processing and language, the two areas on which much of the debate continues to hinge.

The phenotypic outcome in adults: Face processing

There is no doubt that people with WS are very proficient at recognizing faces. They score in the normal range on at least two standardized face-processing tasks (Bellugi, Wang, and Jernigan, 1994; Udwin and Yule, 1991). As we shall see with respect to the case of WS language, initial hypotheses about face processing in WS suggested an intact, innately specified face-processing module (Bellugi, Wang, and Jernigan, 1994; Rossen et al., 1996). However, as mentioned earlier, it is vital to distinguish between the behavioral phenotype and the cognitive phenotype (Karmiloff-Smith, 1998). Several studies have replicated Bellugi's earlier work revealing normal or near normal WS scores on standardized face-processing tasks (Deruelle et al., 1999; Karmiloff-Smith, 1998; Karmiloff-Smith et al., 2004). However, this work has also seriously challenged the notion that the behavioral success displayed in WS face processing is normal. Rather, it has been shown that, whereas normal controls tend to use configural processes to recognize faces, people with WS use predominantly featural or holistic processes (Annaz, 2006; Annaz and Karmiloff-Smith, 2006; Deruelle, et al., 1999; Karmiloff-Smith, 1998; Karmiloff-Smith et al., 2004; Nakamura et al., 2006). Moreover, the tendency to use greater featural than configural processing in WS, as compared to, say, patients with Down syndrome and normal controls, is seen not only with respect to faces, but also in other visuospatial tasks such as drawing and construction (Bellugi, Wang, and Jernigan, 1994; Deruelle et al., 1999; Mervis et al., 1999).

Imaging studies focusing on the electrophysiology of face processing in WS also support the notion that different cognitive processes sustain the WS behavioral proficiency. Thus, using high-density event-related potentials (ERPs), we discovered abnormalities in the early waveforms of WS patients (Grice et al., 2003) not found in any of our healthy controls.

For example, whereas normal adult brains show differences in both amplitude and latency when processing faces compared to cars, the individuals with WS displayed the same brain signatures for both faces and cars. Moreover, in contrast to normal controls, there was less right-hemisphere lateralization in WS brains when processing faces. Other ERP laboratories have found similar differences in WS adults compared to controls (Mills et al., 2000), particularly with respect to the normally different brain signatures for upright and inverted faces, which are less differentiated in participants with WS. These various data refute the idea of an “intact” face-processing module and instead suggest that people with WS may use a general “object processor” to process all visual stimuli. Furthermore, a comparison of 40-hertz gamma-band activity in WS, autism, and healthy controls yielded interesting cross-syndrome differences (Grice et al., 2001). The adolescents and adults with autism displayed bursts of activity similar to those of the controls, except that they were not closely tied to stimulus onset in the group with autism. By contrast, the adolescents and adults with WS displayed almost no gamma bursts, with their brain patterns resembling those of normal 2-month-old infants (Grice et al., 2001; see, also Farran, 2005, regarding deficits in perceptual integration in WS). This finding yet again points to a lack of a normal developmental trajectory over time in the WS brain.

The phenotypic outcome in adults: Language

Despite claims to the contrary (Bellugi, Wang, and Jernigan, 1994; Piatelli-Palmarini, 2001; Pinker, 1994; Rossen, et al., 1996; Smith and Tsimpli, 1995), it is questionable whether any aspect of language—syntax, semantics, phonology, or pragmatics—is intact in WS. Indeed, an abundance of empirical studies from numerous laboratories across the world now challenge intactness claims with respect to all aspects of WS language (e.g., the lexicon: Jarrold et al., 2000; Temple, Almazan, and Sherwood, 2002; morphosyntax: Grant, Valian, and Karmiloff-Smith, 2002; Karmiloff-Smith et al., 1997; Thomas et al., 2001; Volterra, Capirci, and Caselli, 2001; phonology: Grant et al., 1997; Laing et al., 2001; pragmatics: Laws and Bishop, 2004). In a report by Clahsen and Almazan (1998), they tried to retain the innateness hypothesis but for an aspect of morphosyntax rather than a whole cognitive module. These researchers argued for a dissociation of innate mechanisms, on the basis of their claim that in WS memory for vocabulary is impaired but grammar is intact. However, their arguments were based on a very small sample of children with WS ($N = 2$ for $MA = 5$ years, and $N = 2$ for $MA = 7$ years), with considerable individual variation between the few participants. By contrast, a much broader, in-depth study using the same tasks (Thomas et al., 2001) compared the performance of

21 patients with WS with that of four typically developing control groups at ages 6, 8, 10, and adult. Thomas and colleagues argued that it is not sufficient to demonstrate that one aspect of language is relatively poorer than another, because this also obtains at younger stages in normal development. One cannot take a relative comparison and make an absolute claim. Rather, it is necessary to demonstrate that the level of a specific aspect of language is poorer than would be expected in WS given the subjects’ overall level of language development. The Thomas and colleagues study showed that when verbal mental age was controlled for, the WS group not only was generally impaired, but also displayed no selective deficit across vocabulary and morphosyntax. Results of a subsequent study of rapid naming in WS (Thomas et al., submitted) also pointed to atypicality in WS: slower and less accurate naming in the clinical group compared with both chronologically age-matched and receptive-vocabulary age-matched controls. In fact, Mervis and her collaborators (e.g., Klein and Mervis, 1999) have concluded that the best way to characterize WS language is that it is delayed, revealing patterns typical of considerably younger children. Indeed, a meta-analysis of a large number of language studies reveals that WS language is neither intact nor at the level expected for chronological age; rather, it is often no better than would be expected for nonverbal mental age (Brock, in press).

A number of other empirical findings suggest that the WS language system not only is delayed, but actually develops along a different trajectory compared to healthy controls (Karmiloff-Smith et al., 1997; Klein and Mervis, 1999; Mervis et al., 1999; Stevens and Karmiloff-Smith, 1997; Thomas and Karmiloff-Smith, 2003; Thomas et al., 2001, submitted). For example, unlike healthy controls, young children with WS use pointing *after* the appearance of naming. Exhaustive sorting follows the vocabulary spurt in WS, rather than preceding it as in typical development (Mervis et al., 1999). Sensitivity to the sound patterns of the language may act as a greater constraint in WS language than sensitivity to meaning (Grant et al., 1997; Klein and Mervis, 1999; Laing et al., 2001). Finally, several studies across different languages (e.g., Karmiloff-Smith et al., 1997; Klein and Mervis, 1999; Levy and Bechar, 2003; Lukas, Pleh, and Racsmany, 2004; Vicari et al., 1996; Volterra et al., 1996, 2003) now suggest that the subtle problems that people with WS have with semantics, morphosyntax, and pragmatics are often camouflaged by their good verbal memory, challenging the popular belief that their language is intact.

Taken together, these and many other studies point to the fact that when learning language as children, as well as when processing language as adults, individuals with WS follow a deviant developmental trajectory. Behaviorally, WS language may appear to be relatively proficient, but cognitively,

it seems increasingly likely to involve different cognitive processes from the language of normally developing controls.

The infant start state versus the phenotypic outcome

Let us now turn briefly to the infant start state and how it relates to the phenotypic end state in WS. Early assumptions, made on the basis of the adult behavioral phenotype, held that the pattern of abilities and deficits found in the end state would also characterize the infant start state, leading to claims about the innate specification of certain WS abilities. We challenged these assumptions and addressed directly the relationship between the end state and the start state in, for example, a study of two cognitive domains, one of relative proficiency in the phenotypic end state—language—and one of serious impairment—number. Infants, toddlers, children, and adults with WS were compared with infants, toddlers, children, and adults from another syndrome, Down syndrome (Paterson et al., 1999, 2006), matched for mental age and chronological age. The findings were very clear. For adults, the WS and DS groups had significantly different scores on a vocabulary test, with the WS adults outstripping the DS adults. For number, the pattern of performance of the DS adults, although delayed, resembled that of the normal controls. By contrast, the WS adults performed far more poorly on number tasks than the DS adults and showed signs of a deviant trajectory (Paterson et al., 2006; see also Ansari et al., 2003). So the phenotype in the adult end state was as follows: DS significantly worse than WS on vocabulary, WS significantly worse than DS on number. If the start state could be directly derived from the end state and used to make claims about innateness and genotype/phenotype relations, then atypical infants should show the same profile of cognitive abilities and impairments as the atypical adults. But this was not the case. The infancy studies revealed a very different pattern from the adult studies when comparing WS to DS. For the vocabulary task, the WS and DS infants were equally impaired (at approximately half their chronological age), despite the fact that WS adults are significantly better than the DS adults. By contrast, for number, although the WS adults are more impaired than the DS adults, in infancy the group with WS was unimpaired on a numerosity judgment task. The WS infants performed like the chronological-age controls, whereas the DS infants were seriously impaired and did not even reach the level of the mental-age controls. Again, the pattern in infancy differed considerably from that observed in adulthood across the two syndromes.

The infancy/adult data suggest that the learning trajectories of the two syndromes, WS and DS, differ across developmental time. This finding highlights the need to consider the process of development itself when studying

developmental disorders, by building full developmental trajectories. It also underlines the fact that claims about innateness and genotype/phenotype relations cannot be based on patterns found in phenotypic outcomes in adults (Annaz, Karmiloff-Smith, and Thomas, in press; Karmiloff-Smith, 1998; Paterson et al., 1999).

Building full developmental trajectories within domains and across domains

The healthy infant cortex starts out as highly interconnected, and it is only with time that areas of the brain become increasingly specialized (progressively restricting the inputs that a particular circuit processes) and increasingly localized (Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997; Johnson, 2001; Neville, 2006). Timing plays a crucial role in human ontogeny, and it is possible that in individuals with WS this progressive modularization of function does not occur (Karmiloff-Smith, 1992). We have seen in an earlier section how face processing in WS, despite its superficial proficiency, involves brain processes that do not differentiate between, say, cars and faces, or between upright and inverted faces, and that the typical right-hemispheric specialization for faces does not obtain in WS. This finding indicates that, despite the behavioral proficiency on some standardized tasks, the gradual process of modularization may fail to occur in this syndrome. This observation suggests that the atypical brain may remain more interconnected over time with less progressive modularization than in the normal case. Preliminary analyses of our recent data comparing the symbolic-distance effect and the semantic-distance effect in WS and controls yielded interesting results in this respect (Scerif et al., submitted). 17 The symbolic distance effect measures participants' reaction time when they compare two numbers and click on the larger of the two: the closer the two numbers, the slower the reaction time. The semantic distance effect measures participants' reaction time when they compare two words/images and judge whether they are the same or different: the closer the words/images are semantically, the slower the reaction time. Our initial analyses point to correlations across the numerical and lexicosemantic domains in the adults with WS, whereas healthy controls showed no such correlations. This result suggests that in the normal case domains like number and vocabulary become progressively modularized (i.e., localized and specialized), whereas in our adults with WS more commonality of processing remains across domains. Of course, it will next be essential to examine these questions in younger children (for whom such tasks are suitable) in order to build full normal and atypical developmental trajectories, and to pinpoint when and how in normal development these two domains become increasingly specialized.

Multiple developmental factors contributing to lexical development in Williams syndrome

An attempt to understand the early interplay across domains is often missing from developmental studies, and yet this issue is crucial. Our current research program aims to address this issue further in the case of early lexical development in WS infants and toddlers. How does our developmental approach sit with earlier claims about an intact language module in WS (Bellugi, Wang, Jernigan, 1994; Pinker, 1994, 1999; Smith and Tsimpli, 1995)? Interestingly, language onset in WS children is very late. Indeed, despite the superficially fluent language peppered with erudite-sounding words of adolescents and adults with WS, language production in this clinical population often does not occur until the 5th or 6th year (Singer-Harris et al., 1997). Why is language so delayed in this population? Is the delay simply due to a late-maturing language module? Or is there a developmental explanation?

18

In my view, the roots of the delay reside in deficits in multiple interacting earlier processes. For example, infants and toddlers with WS are extremely delayed in hand movements and babbling (Matsataka, 2001). They are also seriously delayed in segmenting the speech stream (Nazzi, Paterson, and Karmiloff-Smith, 2003), a capacity seen as early as 8 months in typically developing infants but still impaired at 20 months in WS toddlers. Second, unlike typical controls, toddlers and young children with WS rely more on perceptual cues than on linguistic labels when identifying new objects (Nazzi, Gopnik, and Karmiloff-Smith, 2005). Furthermore, early categorization abilities in WS are impaired (Nazzi and Karmiloff-Smith, 2002), and, as mentioned previously, exhaustive sorting follows word onset rather than preceding it as in the normal case (Mervis and Bertrand, 1997). Pointing is also atypical in WS toddlers. Whereas in typical development, referential pointing precedes the onset of language, in WS this order is unusually reversed (Mervis and Bertrand, 1997). Moreover, our recent studies revealed that WS toddlers do not use or follow eye gaze for referential communication and do not properly understand the referential function of pointing (Laing et al., 2002). They are good at dyadic attention but poor at triadic attention—shared attention to an external object or event. Finally, in normal language acquisition, young children’s comprehension outstrips their levels of production. This clear-cut asymmetry does not hold for WS (Paterson et al., 1999). In sum, many different aspects of communication show an early, unusual pattern in WS, jointly contributing in complex ways to the explanation of the late onset of their language.

19

However, an even earlier deficit outside the domain of language may offer a compelling explanation of some of these early deficits: atypical eye movement planning. In a

study of saccadic planning in infants and toddlers with WS and DS compared to mental-age and chronological-age controls, we found that although children with DS resembled controls, apart from being somewhat slower, the infants and toddlers with WS displayed a range of impairments in planning saccadic eye movements (Brown et al., 2003). Some stayed fixated on one stimulus without moving their eyes to the second stimulus at all, whereas others made one saccade to a new stimulus, but failed to make the second saccade that all the controls and young children with DS made. For the infants with WS who did make a double saccadic movement, two errors appeared: either they failed to update their retinal image after the first eye movement and ended in the wrong location after their second saccade (the retinocentric error); or they summated the two saccades before moving their eyes, thus making the vector summation error, typical of normal 2-month-olds. In other words, planning visual attention and making saccadic eye movements to explore the environment, as well as to follow another’s eye gaze and pointing gestures, turns out to be atypical in infants and toddlers with WS. Recall that in normal interaction, many vocabulary items are learned through triadic interaction with caregivers, which involve saccadic eye movements to follow the partner’s focus of attention. Thus early visuospatial deficits in the WS developmental trajectory *outside the domain of language* can have cascading developmental effects over time on several *emerging* higher-level linguistic and cognitive domains. Moreover, infants and toddlers with WS show specific impairments in visual search tasks when looking for targets among distractors. Their errors differ from the errors of young children with fragile X syndrome, for instance (Scerif et al., 2004). Moreover, the fact that domains (like visual cortex and auditory cortex) are highly interrelated in early cortical development (Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997; Neville, 2006) turns out to play a critical role in the formation of more general, albeit sometimes subtle, deficits in later development.

20

Concluding thoughts

It has become increasingly clear that the uneven profile of abilities and impairments at the behavioral level in WS must be reanalyzed at the cognitive level if we are to begin to adequately relate genotype to phenotype and gain a deeper understanding of the WS cognitive phenotype. Debates are likely to continue to rage. Notable is the fact that the choice of control group can influence the way in which data from individuals with WS are interpreted. Often, when reporting levels of WS performance consistent with mental-age controls, researchers then tend to conclude that the ability is “intact,” despite being several years behind the typical child. We must not dismiss delay as irrelevant or count a “relative”

advantage of one system over another as an “absolute” one, leading to claims of intactness (see discussion in Karmiloff-Smith, 1998; Karmiloff-Smith, Scerif, and Ansari, 2003). Moreover, 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, we should not directly relate the effects of deleted genes to cognitive-level outcomes in adults. In fact, genetic mutations are more likely to affect low-level cognitive processes that will have differing, cascading effects on different domains as development proceeds over time. Indeed, timing plays a critical role in normal development, and its effects on atypical development must be center stage when we endeavor to build a comprehensive theory of Williams syndrome in particular, and of developmental disorders in general.

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