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Fulfilling the Promise of the Cognitive Neurosciences

The paper by Meyer-Lindenberg and colleagues in this issue of *Neuron* provides strong evidence that the absence of one or more genes in Williams syndrome leads to highly circumscribed pathology in the dorsal visual stream. This program of research demonstrates that neurocognitive architecture follows the same principles in typical and atypical development.

For more than two decades, cognitive scientists have studied Williams syndrome, in the hopes that this genetically based neurodevelopmental disorder would reveal insights into how cognitive systems are structured and organized (Bellugi et al., 1992). Children and adults with Williams syndrome share a unique and striking profile, characterized by peaks in verbal fluency and social engagement and valleys in visuospatial construction and mathematical skills. Surely this unusual pattern of cognitive and behavioral characteristics could quickly settle theoretical debates over whether the mind is structured in a relatively modular or more generalized organizational system (e.g., Pinker, 1994)? For the most part, cognitive research on Williams syndrome failed to settle these kinds of questions, instead leading to new arguments about whether a neurodevelopmental disorder, even one as remarkable as Williams syndrome, could ever reveal anything of significance about cognitive architecture, given that from the earliest stages the *development* of the brain is fundamentally altered (Karmiloff-Smith, 1998).

The article in this issue of *Neuron* by Meyer-Lindenberg and colleagues (2004) is significant because it ushers in a new era of research on Williams syndrome and offers clear evidence that we can indeed learn a great deal by studying this fascinating population. Their research takes us beyond behavioral and cognitive investigations, adding in brain imaging methodologies that reveal unambiguous evidence about the neurobiological substrate for one key feature of the Williams phenotype: visuospatial construction. The converging findings presented in this paper come from behavioral performance and reaction time measures on simple but elegant cognitive tasks, functional activation patterns, regional volumetric measures, and an analysis of the pathways connecting the hierarchical levels in the dorsal stream of the visual system. Together, these methods, noteworthy for their rigor and sensitivity to the specific concerns of analyzing images from a special population, identified a localized region within the dorsal pathway located at and around the *intraparietal sulcus* that is responsible for the highly specific deficits in visuospatial processing that are characteristic of people with Williams syndrome (Mervis et al., 1999).

Unlike many other studies of Williams syndrome, this study pays careful attention to numerous design issues that plague this area of research. By selecting adults with Williams syndrome in a relatively narrow age range who have the classic deletion on chromosome 7 but have normal range intelligence scores, the investigators reduce the considerable heterogeneity that may confuse interpretation of findings from this population. More importantly, the study compares the group (and individuals) with Williams syndrome to a comparison group that is very well matched to the adults with Williams syndrome, not only on age and sex but also on handedness and IQ scores. By controlling for all these variables, the authors preclude the possibility that factors such as mental retardation or developmental level could explain the results. Regrettably, few other studies in either the behavioral or the neuroimaging literature on Williams syndrome, or indeed on most other neurodevelopmental disorders, follow such a well-controlled research design.

To some extent, it is because of methodological problems that there is still so much controversy in interpreting aspects of the behavioral phenotype of Williams syndrome. What might be viewed as a striking ability in a group of children with Williams syndrome, for example, social relatedness and empathy, may or may not turn out to reflect genuine sparing in the cognitive mechanisms that underlie these behaviors (Karmiloff-Smith et al., 1995; Tager-Flusberg and Sullivan, 2000). People with Williams syndrome engage in conversations with ease, using complex grammatical constructions and a rich vocabulary. Initially, these observations were taken to suggest that the phenotype includes spared language ability (e.g., Bellugi et al., 1992), but later studies showed that there are residual subtle linguistic deficits, which are likely to be related to intellectual disability, (Grant et al., 2002) and pragmatic problems that have been documented but are not well understood (Laws and Bishop, 2004). Several studies using standardized measures have documented the preserved skill of people with Williams syndrome in identifying faces. Nevertheless, in spite of strong evidence that they rely on the same cognitive mechanisms to process faces as controls (Tager-Flusberg et al., 2003), bolstered by the functional imaging findings in this paper by Meyer-Lindenberg et al. that faces activate the same region of the fusiform gyrus as in controls, several research groups continue to claim that in Williams syndrome faces are processed in atypical ways (e.g., Mobbs et al., 2004) that are the result of aberrant developmental patterns (Karmiloff-Smith, 1998).

It is interesting to note that Meyer-Lindenberg and colleagues chose one aspect of the Williams syndrome phenotype that is not so plagued by controversy: there is general agreement that visuospatial construction skills are profoundly impaired in this population. Moreover, there is growing consensus that these deficits are linked to the dorsal visual stream, but the most conclusive evidence for this hypothesis is presented by Meyer-Lindenberg et al., because they document the impairment using multiple converging methods. Thus,

the findings presented here are not likely to be challenged on either empirical or interpretative grounds.

The significance of this paper lies in the discovery that the neurobiological substrate for the visuospatial constructive impairment in Williams syndrome is localized to a small region in parietal cortex. This finding is consistent with everything we know about the organization of the visual system in the brain, so this localized pathology is, therefore, precisely what one would have predicted, based on knowledge of the normal brain. This study suggests that the brain in Williams syndrome does *not* develop in completely different ways than in people without genetic disorders, conflicting with views held by some in the field (e.g., Karmiloff-Smith, 1998). On the contrary, the localized and predictable neuropathological substrate of visuospatial constructive impairments in Williams syndrome shows that neural development is a highly constrained process; the impact of genetic alterations can be quite specific in the brain, as they are in the heart (note that Williams syndrome is also characterized by numerous physical features such as supravalvular aortic stenosis; Morris and Mervis, 1999).

The neurocognitive architecture of the visual system in Williams syndrome demonstrates striking dissociations between the dorsal and ventral streams, as illustrated in this study, for example, in the contrasting brain activation patterns to a spatial localization task and face recognition. These dissociations, nevertheless, reveal that people with Williams syndrome still have fundamentally the same complex system and pathways in the visual system as others, but with one region that is significantly reduced in volume that selectively disrupts higher-level processing along the dorsal pathway. This pattern of visual system organization revealed in Williams syndrome suggests that a genetically based developmental disorder might have more in common with acquired brain lesions than we might have predicted. In this way, the research presented by Meyer-Lindenberg and colleagues goes a long way to advancing the field of cognitive neuroscience by bringing together cognitive and brain imaging research from typical and atypical populations. It confirms our faith that Williams syndrome can teach us a great deal about links between brain and behavior, and ultimately links to specific genes (Bellugi and St. George, 2000).

Future investigations need to explore the neurocognitive underpinnings for other components of the Williams syndrome behavioral phenotype. Our understanding of the mechanisms that underlie social engagement, face processing, and language in Williams syndrome will be significantly advanced if studies follow the same exemplary methodological approach taken by Meyer-Lindenberg et al. These aspects of the phenotype, however, represent relative strengths rather than impairment, and it is therefore not surprising that their definition has been more controversial and less easily interpreted. In a parallel way, Meyer-Lindenberg et al. point out that other aspects of the neural phenotype of Williams syndrome highlighted in structural brain imaging studies show less consistency across different research groups than has been found for visuospatial constructive skill. It remains to be seen whether other unique aspects of behavior in Williams syndrome, for which we can expect to find connections to specific genes in the critical region on chromosome 7, can be directly linked to relatively localized neural abnormalities or are the result of more widely distributed pathologies that span both cortical and subcortical brain regions.

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Selected Reading

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Food for Thought: Essential Fatty Acid Protects against Neuronal Deficits in Transgenic Mouse Model of AD

Interactions between environmental and genetic factors may contribute to neurodegenerative disease. In this issue of *Neuron*, Calon et al. report that a diet low in an essential omega-3 polyunsaturated fatty acid (docosahexaenoic acid) depletes postsynaptic proteins and exacerbates behavioral alterations in a transgenic mouse model of Alzheimer's disease.

Alzheimer's disease (AD) results in a progressive dementia and a loss of neurons and synapses in the brain. Available treatments aim to improve the communication between surviving brain cells, which is also impaired by AD. Sadly, none of the current treatments have been