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Evidence from Two Genetic Syndromes for a Dissociation between Verbal and Visual-Spatial Short-Term Memory

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ABSTRACT

Williams and Down syndromes, two genetic syndromes of abnormal neurodevelopment, are characterized by specific neuropsychological profiles and unique patterns of brain morphology. We find that the superior language ability of subjects with Williams syndrome is accompanied by significantly better performance on a verbal short-term memory task. Conversely, subjects with Down syndrome perform significantly better on a visual-spatial short-term memory task. This double dissociation provides neurogenetic evidence for the distinction between short-term storage for verbal and for visual-spatial stimuli.

In Down syndrome and Williams syndrome, genetic etiologies manifest themselves in characteristic medical, neuroanatomical, and neuropsychological profiles. The mental retardation, typical facial features, and medical stigmata of Down syndrome (DS) are well known. In 95% of cases, they derive from a trisomy of chromosome 21 (Smith & Jones, 1982). Williams syndrome (WS) is another genetic syndrome of abnormal neurodevelopment. It too is characterized by mental retardation, and by its own distinctive facial appearance and group of medical anomalies, including supravalvar aortic stenosis and infantile hypercalcemia (Jones & Smith, 1975; Morris, Demsey, Leonard, Dilts, & Blackburn, 1988). Abnormal regulation of the hormone calcitonin (which is involved in calcium metabolism) has been found in WS, and serves as a diagnostic marker (Culler, Jones, & Deftos, 1985). Molecular geneticists are actively pursuing identification of the chromosomal locus of this rare autosomal dominant disease (Morris, Thomas, & Greenberg, in press).

As part of a systematic program of investigation, our laboratory has elucidated a striking preservation of linguistic abilities in subjects with WS, despite their general cognitive impairment (Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Bellugi, Bihrle, Neville, Jernigan, & Doherty, 1992; Bellugi, Wang, & Jernigan, in press; Reilly, Klima, & Bellugi, 1991). Syntactic, semantic, affective prosodic, and meta-linguistic abilities all are remarkably preserved in adolescents and young adults with WS, despite IQs ranging from 40 to 60, and despite the failure to understand such fundamental concepts as Piagetian conservation. In contrast, subjects with DS who are matched for age, sex, IQ, and educational status show significant impairment on the same linguistic tasks. On tests of visual-spatial cognition WS and DS subjects both fare poorly, though with distinctive patterns of performance (Bellugi, Sabo, &

Vaid, 1988; Bihrle, 1990; Bihrle, Bellugi, Delis, & Marks, 1989). Specifically, on tests of hierarchical processing WS subjects show a bias toward the local level, whereas DS subjects are biased toward the global level. In addition, subjects with WS show a unique preservation of facial perceptive abilities. These experiments thus have provided extremely interesting data on the fault lines that may exist among language and other cognitive abilities.

Magnetic resonance imaging (MRI) studies of WS and DS have revealed characteristic patterns of brain morphology in association with the syndromes' neuropsychological profiles (Jernigan & Bellugi, 1990; Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993; Wang, Doherty, Hesselink, & Bellugi, 1992a). While overall cerebral volume is reduced in both WS and DS, there is relative preservation of the basal ganglia in DS. In WS, there is proportional preservation of anterior and temporal limbic cortices, and of anterior portions of the corpus callosum. Subjects with WS also show an intriguing preservation of the neocerebellum (Jernigan & Bellugi, 1990; Wang, Hesselink, Jernigan, Doherty, & Bellugi, 1992b). Unlike phylogenetically older parts of the cerebellum, the neocerebellum is well-connected to association areas of the cerebral cortex, and may participate in (nonmotor) higher cortical functions (Leiner, Leiner, & Dow, 1991).

There have been suggestions both from our studies and from other investigators that verbal memory skills may be preserved in WS (Bennett, LaVeck, & Sells, 1978; Udwin & Yule, 1991). These studies have included tasks such as sentence repetition and recall of short prose passages, but none has examined memory in a systematic fashion. Other studies on the importance of memory resources, particularly working memory resources, to language and other cognitive processing (Just & Carpenter, 1992; Siegel & Ryan, 1989) add to our motivations for such systematic investigation.

We therefore began a comprehensive examination of memory in WS and DS, by focusing on short-term storage for verbal and for visual-spatial stimuli. According to Baddeley and Hitch's model (1974), these functions are served by two distinct storage mechanisms: a "phonological loop" for verbal and other phonological information, and a "sketchpad" for visual-spatial information. We hypothesized that the phonological store, which is thought to be involved in language processing, would be better preserved in WS than in DS.

The dissociability of these two storage mechanisms has been supported by two types of evidence. First, case studies of adults with focal brain lesions have demonstrated deficits apparently restricted to one store or the other. Subject PV [Basso, 1982 #171] is argued to have had damage specific to the phonological mechanism, whereas subject ELD [Hanley, 1991 #172] is argued to have sustained damage to only the visual-spatial store. Second, concurrent psychological tasks have shown differential interference with phonological and visual-spatial working memory tasks in normal subjects (Baddeley, 1986; Logie, Zucco, & Baddeley, 1990). The current study takes a new approach: We examined whether two genetically specified neurodevelopmental disorders, each with a specific brain morphology and a specific neuropsychological profile, also would evidence a dissociation between short-term storage of verbal and of visual-spatial stimuli.

METHODS

Subjects.

Nine subjects with DS (6 female, 3 male) and 10 subjects with WS (5 female, 5 male) were recruited for a large, multidisciplinary study of the neurobiological basis of language and cognitive development (Bellugi et al., 1990; Bellugi et

al., 1992; Bellugi et al., in press). All diagnoses of DS had been confirmed by karyotyping. For the WS subjects, diagnoses had been established by a pediatric geneticist on the basis of major stigmata. One of the male subjects with WS did not take part in the study reported here because he had moved away from the site of our laboratory. The remaining members of each group were matched for age (DS: 15.4 ± 4.5 years, WS: 13.4 ± 2.1 years) and IQ (DS: 47.8 ± 7.6, WS: 51.3 ± 7.1; Wechsler Intelligence Scale for Children - Revised (Wechsler, 1974)), and were in comparable educational placements. As part of the larger study, MRI of the brain had been performed on 7 of the DS subjects and on 8 of the WS subjects. None showed any mass or cystic lesions or any focal atrophy (Jernigan & Bellugi, 1990; Jernigan et al., 1993). Mild diffuse atrophy was noted in one female subject with DS.

Tests and Procedures.

Short-term storage for both verbal and visual-spatial material was probed in each subject. The Digit Span subtest of the WISC-R was employed as a measure of short-term storage for verbal material. It was administered according to standard protocol, usually during the same session as the remainder of the WISC-R. The Corsi blocks test was employed as a measure of visual-spatial storage (Milner, 1971). The apparatus consisted of 9 identical 1.2 x 1.2 in. black wooden blocks affixed randomly to an 8 in. x 10.5 in. black base board. The examiner touched a predetermined sequence of these blocks and then asked the subject to touch the same blocks in the same order. Each subject began with two practice sequences of two blocks each. Subsequent administration and scoring were identical to that for the digit span.

Analysis.

Three scores were determined for each subject on each of the tests. "Test score" was identical to the WISC-R "raw score": 1 point was awarded for each correct response. "Longest span" refers to the longest sequence for which the subject responded correctly at least once. In addition, an "unordered score" was calculated for the forward digit span and Corsi tasks. That is, trials were regarded as correct if the set of response items matched the set of stimulus items. Multivariate analysis of variance (MANOVA) procedures were employed to test for group differences across tasks. Where significant group effects were found, univariate results were examined for each specific task.

RESULTS

The test scores of each group on digit span, Corsi blocks, and reverse digit span are illustrated in Figure 1A, and the unordered scores are shown in Figure 1B. The average tests scores (mean±SD) for the two groups (WS vs. DS) were: 4.33±1.12 versus 2.00±0.87 (forward digit span), 1.22±0.83 versus. 2.89±1.69 (Corsi blocks), and 2.67±1.66 versus. 1.44±1.01 (reverse digit span). Unordered test scores for forward digit span and Corsi blocks differed only slightly. The longest span scores were similarly illustrative (WS vs. DS): 4.56±0.53 versus 2.89±0.93 (forward digit), 3.00±0.71 versus 3.78±1.09 (Corsi), and 2.67±1.00 versus 2.00 ±0.71 (reverse digit).

A 2 group x 3 task MANOVA on the test scores showed a significant difference between groups (Hotelling's $T^2 = 2.51$, exact $F(3,14)=11.71$, $p<.001$). Univariate results showed a significant differences on both digit span ($F(1,16)=24.50$, $p<.001$) and Corsi blocks ($F(1,16)=7.03$, $p<.05$), consistent with a double dissociation between the two tasks. The group

difference on reverse digit score did not reach significance ($F(1.16)=3.56$, $p>.05$). A second MANOVA (2 group x 2 task) on the unordered test scores also showed a significant group difference (Hotelling's $T^2=1.95$, exact $F(2,15)=14.62$, $p<.001$), with significant univariate statistics for both digit span ($F(1,16)=27.66$, $p<.001$), and Corsi blocks ($F(1,16)=6.28$, $p<.05$). The statistical analysis of longest span scores was similar.

DISCUSSION

We find a double dissociation in the performance of two genetically defined groups on short-term storage for phonological and for visual-spatial information. The patterns of performance found here for WS and DS subjects are consistent with those reported in previous studies, although the latter have not focused on short-term storage. For example, Bennett et al. reported relatively good composite memory scores in WS subjects on a battery which included digit span (Bennett, et al., 1978). Udwin and Yule (1991) reported a higher "verbal memory index" in WS subjects than in their controls, and poor visual-spatial memory on longer-term, supraspan measures. Similarly for DS subjects, previous work demonstrated deficits on auditory span tasks, even in conditions designed to minimize auditory processing confounds, and when manual rather than verbal responses were elicited (Marcell & Weeks, 1988). Also, Haxby (1989) found that subjects with DS performed no differently on digit span and on a block-tapping task similar to the Corsi blocks, whereas his control subjects performed much better on the digit span task.

Although a number of authors recently have stressed the point that a double dissociation is not logically sufficient to demonstrate the independence of any two functions (e.g., Caramazza, 1986), it is still recognized that double

dissociations constitute strong evidence for such separability (Shallice, 1988). Weiskrantz (1991) has emphasized the importance of corroborative evidence from multiple study populations and from multiple levels of neuroscience for such arguments. The findings reported here thus represent important evidence on the separability of short-term memory for verbal and for visual-spatial information.

We note also the relation between our short-term memory tasks and current conceptions of working memory. Auditory span tasks, such as the digit span, comprise the most commonly used class of tasks for testing the integrity of Baddeley and Hitch's phonological loop (see Baddeley, 1986, 1992 for a review). As the term implies, this mechanism is thought to be sensitive to phonological similarity, as well as to word length and other stimulus characteristics. For the assessment of the visual-spatial sketch pad, a variety of tasks has been employed, including the Corsi blocks (e.g., Hanley et al., 1991). While many of these incorporate the confounding task of constructing a mental image from verbal input, the Corsi task does not. In addition, subjects PV and ELD, discussed above, showed a double dissociation on digit and Corsi spans. Further studies are needed to determine to what extent the properties of short-term memory in WS and DS are similar to the properties of the storage components of working memory, and whether the results here contribute to arguments on the dissociability of those components.

Although we did not find a significant difference on the reverse digit span task, the trend for better performance in the WS group suggests a direction for future investigations. Like Daneman and Carpenter's "reading span" (Daneman & Carpenter, 1980) and other "operation spans," the reverse digit span contains a processing component that forward digit span and Corsi blocks do not. As such, it is more closely related to working memory than to

the other tasks. More specific investigation of working memory will reveal whether the relationship between working memory and other higher cortical functions is the same in WS and DS subjects as it is in normal controls.

The neuroanatomic substrates of short-term memory currently are the subject of experimental scrutiny in nonhuman primates. For example, Colombo, D'Amato, Rodman, and Gross (1990) have suggested that temporal-lobe areas participate in auditory short-term memory. The mesial temporal preservation seen on MRI in WS suggests the availability of such an anatomic resource, though the functional status of these structures is not yet known. Future studies will shed light not only on the cortical basis of memory storage, but also on their relationship to other cortical functions. Baddeley has suggested that the mechanisms for working memory storage and for the perception of phonological and visual-spatial material may be related evolutionarily and may overlap each other in the brain (Baddeley, 1992). As the convergent neuroanatomic and neurobehavioral investigations of WS and DS indicate, genetic neurodevelopmental groups provide a unique window on the study of such brain-behavior relationships.

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REFERENCES

Baddeley, A. (1986). Working memory. Oxford: Clarendon Press.

Baddeley, A. (1992). Working memory. Science, 255, 556-559.

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. A. Bower (Ed.), The psychology of learning and motivation (pp. 47-89). New York: Academic Press.

Basso, A., Spinnler, H., Vallar, G., & Zanobio, M. E. (1982). Left hemisphere damage and selective impairment of auditory verbal short-term memory: A case study. Neuropsychologia, 20(3), 263-274.

Bellugi, U., Bihrle, A., Jernigan, T., Trauner, D., & Doherty, S. (1990). Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. American Journal of Medical Genetics Supplement, 6, 115-125.

Bellugi, U., Bihrle, A., Neville, H., Jernigan, T., & Doherty, S. (1992). Language, cognition, and brain organization in a neurodevelopmental disorder. In M. R. Gunnar & C. A. Nelson (Eds.), Developmental behavioral neuroscience (pp. 201-232). Hillsdale, NJ: Erlbaum Press.

Bellugi, U., Sabo, H., & Vaid, J. (1988). Spatial deficits in children with Williams syndrome. In J. Stiles-Davis, M. Kritchevsky, & U. Bellugi (Eds.), Spatial cognition: Brain bases and development (pp. 273-298). Hillsdale, NJ: Erlbaum Press.

Bellugi, U., Wang, P. P., & Jernigan, T. L. (in press). Williams syndrome: An unusual neuropsychological profile. In S. Broman & J. Grafman (Eds.), Atypical cognitive deficits in developmental disorders: Implications for brain function Hillsdale, NJ: Erlbaum Press.

Bennett, F. C., LaVeck, B., & Sells, C. J. (1978). The Williams elfin facies syndrome: The psychological profile as an aid in syndrome identification. Pediatrics, 61, 303-306.

Bihrle, A. M. (1990). Visuospatial processing in Williams and Down syndromes. Unpublished doctoral dissertation, University of California, San Diego.

Bihrle, A. M., Bellugi, U., Delis, D., & Marks, S. (1989). Seeing either the forest or the trees: Dissociation in visuospatial processing. Brain and Cognition, 11, 37-49.

Caramazza, A. (1986). On drawing inferences about the structure of normal cognitive systems from the analysis of patterns of impaired performance: The case for single-patient studies. Brain and Cognition, 5, 41-66.

Colombo, M., D'Amato, M. R., Rodman, H. R., & Gross, C. G. (1990). Auditory association cortex lesions impair auditory short-term memory in monkeys. Science, 247, 336-338.

Culler, F. L., Jones, K. L., & Deftos, L. J. (1985). Impaired calcitonin secretion in patients with Williams syndrome. Journal of Pediatrics, 107, 720-723.

Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. Journal of Verbal Learning and Verbal Behavior, 19, 450-466.

Hanley, J. R., Young, A. W., & Pearson, N. A. (1991). Impairment of the visuo-spatial sketch pad. Quarterly Journal of Experimental Psychology, 43A(1), 101-125.

Haxby, J. V. (1989). Neuropsychological evaluation of adults with Down's syndrome: Patterns of selective impairment in non-demented old adults. Journal of Mental Deficiency Research, 33, 193-210.

Jernigan, T. L., & Bellugi, U. (1990). Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. Archives of Neurology, 47, 529-533.

Jernigan, T. L., Bellugi, U., Sowell, E., Doherty, S., & Hesselink, J. R. (1993). Cerebral morphological distinctions between Williams and Down syndromes. Archives of Neurology, 50, 186-191.

Jones, K. L., & Smith, D. W. (1975). The Williams elfin facies syndrome: A new perspective. Journal of Pediatrics, 86, 718-723.

Just, M. A., & Carpenter, P. A. (1992). A capacity theory of comprehension: Individual differences in working memory. Psychological Review, 99(1), 122-149.

Leiner, H. C., Leiner, A. L., & Dow, R. S. (1991). The human cerebro-cerebellar system: Its computing, cognitive, and language skills. Behavioral Brain Research, 44, 113-128.

Logie, R. H., Zucco, G. M., & Baddeley, A. D. (1990). Interference with visual short-term memory. Acta Psychologica, 75, 55-74.

Marcell, M. M., & Weeks, S. L. (1988). Short-term memory difficulties and Down's syndrome. Journal of Mental Deficiency Research, 32, 153-162.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. British Medical Bulletin, 27(3), 272-277.

Morris, C. A., Thomas, I. T., & Greenberg, F. (in press). Williams syndrome: Autosomal dominant inheritance. American Journal of Medical Genetics.

Morris, C. A., Demsey, S. A., Leonard, C. O., Dilts, C., & Blackburn, B. L. (1988). Natural history of Williams syndrome: Physical characteristics. Journal of Pediatrics, 113, 318-326.

Reilly, J. S., Klima, E. S., & Bellugi, U. (1991). Once more with feeling: Affect and language in atypical populations. Development and Psychopathology, 2, 367-391.

Shallice, T. (1988). From neuropsychology to mental structure. New York: Cambridge University Press.

Siegel, L. S., & Ryan, E. B. (1989). The development of working memory in normally achieving and subtypes of learning-disabled children. Child Development, 60, 973-980.

Smith, D. W., & Jones, K. L. (1982). Recognizable patterns of human malformation: Genetic, embryologic and clinical aspects (3rd ed.). Philadelphia: W.B. Saunders.

Udwin, O., & Yule, W. (1991). A cognitive and behavioural phenotype in Williams syndrome. Journal of Clinical and Experimental Neuropsychology, 13(2), 232-242.

Wang, P. P., Doherty, S., Hesselink, J. R., & Bellugi, U. (1992a). Callosal morphology concurs with neurobehavioral and neuropathological findings in two neurodevelopmental syndromes. Archives of Neurology, 49, 407-411.

Wang, P. P., Hesselink, J. R., Jernigan, T. L., Doherty, S., & Bellugi, U. (1992b). The specific neurobehavioral profile of Williams syndrome is associated with neocerebellar hemispheric preservation. Neurology, 42(10), 1999-2002.

Wechsler, D. (1974). Wechsler Intelligence Scale for Children – Revised. New York: The Psychological Corporation.

Weiskrantz, L. (1991). Dissociations and Associates in Neuropsychology. In R. G. Lister & H. J. Weingartner (Eds.), Perspectives on cognitive neuroscience (pp. 157-164). New York: Oxford University Press.

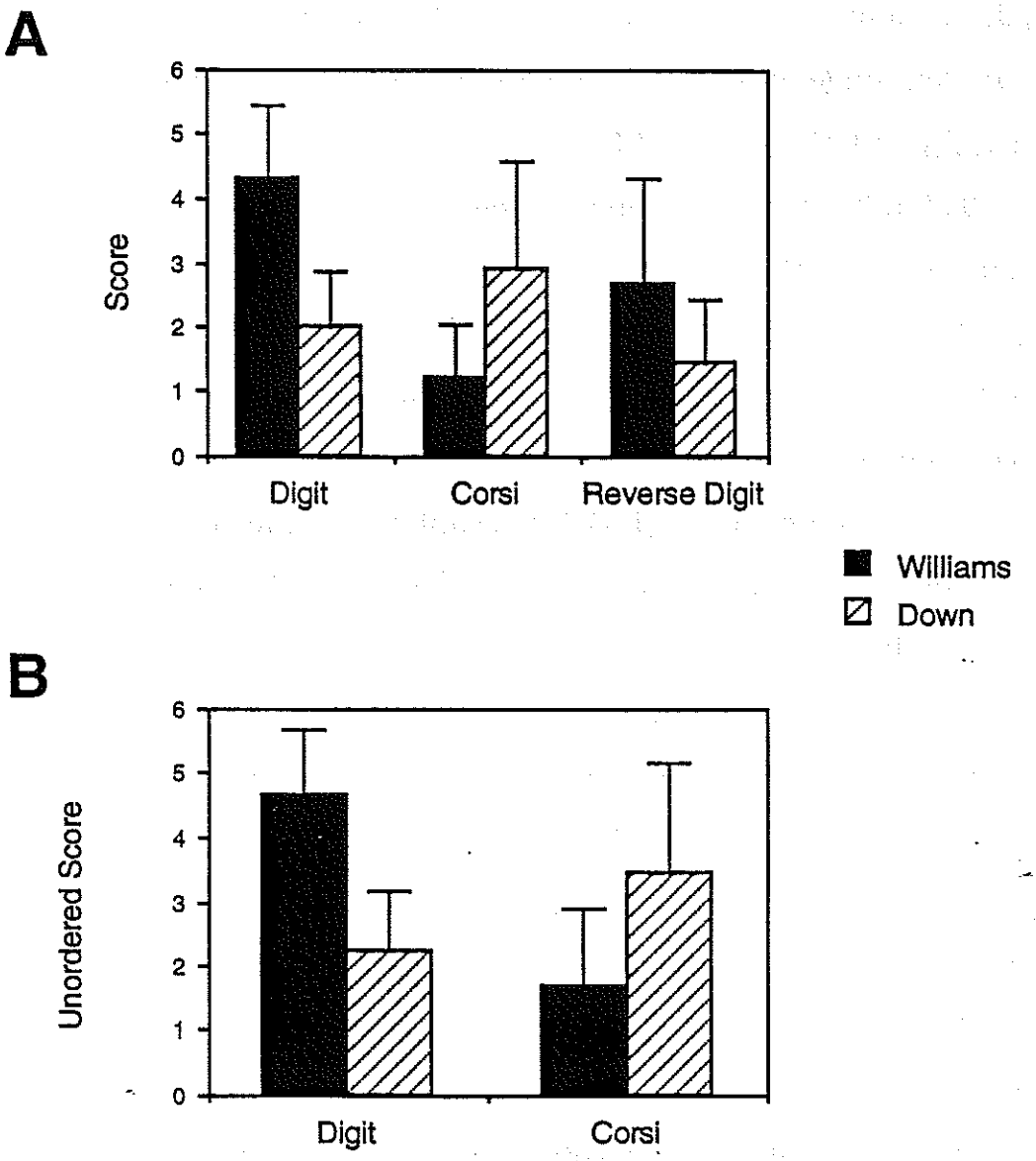

Figure 1

Comparison of test scores (A) and unordered scores (B) in Williams and Down syndromes. Mean and standard deviation bars are shown. The two groups differed significantly on both measures of Digit Span and Corsi Block performance. (See text for details.)