A142

NeuroReport 10, 1653–1657 (1999)

Towards the neural basis for hypersociability in a genetic syndrome

Ursula Bellugi,[CA] Ralph Adolphs,[1] Cindi Cassady and Michael Chiles

Laboratory for Cognitive Neuroscience, The Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037; [1]Department of Neurology, Division of Cognitive Neuroscience, University of Iowa, Iowa City, IA, USA

[CA]Corresponding Author

WILLIAMS syndrome (WMS), a rare disorder with a distinctive profile of medical, psychological, neurophysiological and neuroanatomical characteristics, results from hemizygous deletion of about 20 genes. The phenotype exhibits specific dissociations in higher cognitive functions: general cognitive deficits but spared linguistic abilities; extreme spatial cognitive deficits, but intact face processing. Of special interest is an unusual social phenotype in WMS: an overly friendly, engaging personality and excessive sociability with strangers. In this first experimental study of social behavior in WMS, we report that WMS subjects show an abnormal positive bias in their social judgments of unfamiliar individuals, consistent with their behavior in real life. Our findings contribute to an understanding of the neural and genetic bases of human social behavior. *NeuroReport* 10:1653–1657 © 1999 Lippincott Williams & Wilkins.

Key words: Dissociations in cognitive functions; Experimental study of approachability; Genetic disorder; Neural and genetic basis of social behavior; Social behavior; Williams syndrome

Introduction

Williams syndrome (WMS) is a rare genetic disorder that carries a distinctive profile of medical, psychological, neurophysiological and neuroanatomical characteristics [1]. WMS results from the deletion of one copy of a small/restricted set of genes on chromosome 7, including the genes for elastin, LIM-1 kinase and syntaxin 1a among others [2–5]. Previous findings from our group and others have mapped out a neuropsychological profile for WMS that shows peaks and valleys of cognitive abilities [1,6–9]. The syndrome gives rise to specific dissociations in higher cognitive functions, including impaired IQ co-occurring with relatively spared linguistic abilities and extreme deficits in spatial cognition co-occurring with excellent face processing. We focus in this paper on an experimental investigation of the hypersociability which is characteristic of individuals with this genetically based disorder.

A cognitive profile for Williams syndrome

Most subjects with WMS studied are classified as mild to moderately mentally retarded, with a mean IQ of 60; they have difficulty with aspects of general problem solving, arithmetic, even making change, and are thus typically unable to achieve fully independent living. Despite their low IQs, individuals with WMS display characteristic patterns of cognitive performance with peaks and valleys of abilities. Especially striking is a well documented dissociation between relatively spared language abilities and severely impaired visuospatial capacities. In addition, face processing is essentially intact [10,11].

We have found distinct developmental trajectories across these three major cognitive domains (lexical knowledge, spatial cognition, and face processing) in studies involving more than 50 WMS subjects aged 3–23. Children with WMS, unlike those with Down syndrome (DNS), showed different developmental trajectories in these major cognitive domains [12,13] (Fig. 1). While individuals with DNS showed an essentially uniform developmental trajectory across the three domains (i.e. uniformly impaired in each domain), individuals with WMS showed three distinctly different trajectories, with different starting points and ending points. Planned contrasts showed that performance on the three tests differed significantly within the WMS group, even when controlled for age. No between-test differences are found in the DNS group. A two (WMS, DNS) by three (Benton, VMI, PPVT) analysis of covariance with chronological age entered as the covariate revealed a significant group × test interaction ($p < 0.0001$) [9].

A social behavioral profile for Williams syndrome: hypersociability

A prime characteristic of the social behavior of typical individuals with WMS is their strong impulse

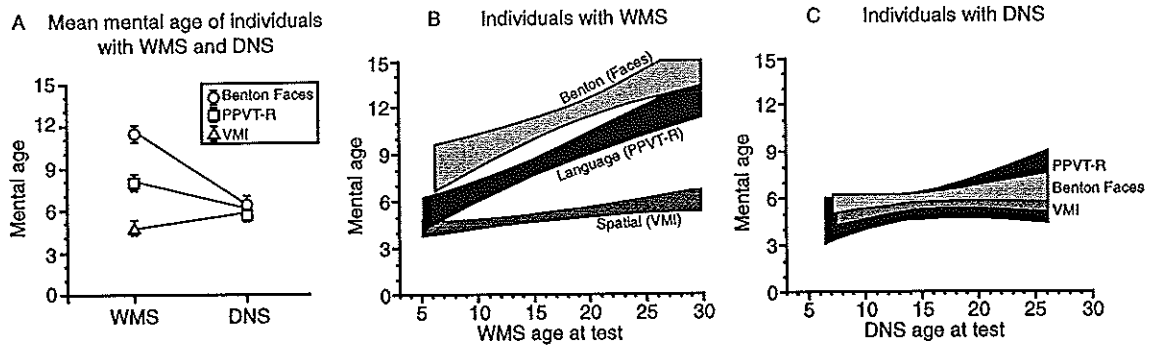

FIG. 1. Dissociations between language, face and space processing in Williams syndrome. **Left:** WMS subjects (age 7–23) show three distinctly different trajectories across cognitive domains: lexical knowledge, spatial cognition and face processing. On a standardized test of vocabulary (Peabody Picture Vocabulary, Revised, PPVT-R), subjects with WMS start low, and then show a sharp increase in score with age. On a probe of spatial cognition that involves copying geometric shapes (Visual Motor Integration task, VMI), subjects with WMS are consistently below the subjects with DNS and plateau early on. On a task of face processing (Benton Test of Facial Recognition), the WMS group starts high even at the early ages and is consistently high across the age range. **Right:** subjects with DNS show equivalent low trajectories in the three domains across age.

towards social contact and affective expression [1,7–9], although their social behavior is not always appropriate [14]. Through a series of tasks, we have been investigating aspects of their dramatic story telling, which is peppered with ways of engaging their audience through a series of narrative tasks [15,16]. Language may be emotionally enriched through the use of affective prosody as well as through the use of evaluative words. In their narrations, WMS subjects use affective prosody far more frequently than do normal children of the same mental age. We concluded that, despite their cognitive impairments, subjects with WMS are not only sociable and affectively sensitive, but that they also show an abundance (or overabundance) of affectivity in both prosodic and lexical devices, and appear to be able to manipulate affective linguistic devices for the purposes of story-telling. This pattern is strikingly different from DNS subjects, and also from normal individuals at any age (see examples in Fig. 2). Moreover, this pattern of abnormally high linguistically encoded affect may in some ways be the inverse of that seen in autistic individuals [17]. Comparisons between individuals with WMS and those with autism are now beginning to emerge [18] and may provide an especially powerful entry into studying the neural and the genetic bases of social cognition.

Interest in the social behavior of individuals with WMS stems from numerous accounts of a personality type described as friendly, outgoing, engaging, and sometimes excessively social. This includes a degree of fearlessness and an inner drive with regard to social interaction with strangers that may far exceed that of other clinical populations. The ten-

(M. Mayer, "Frog Where are You")

WMS age 10

Lo and behold, they find him... with a lady. Then they found him and another frog. But then lo and behold he knew why his... frog had ran away. It was time for him... to have children. And lo and behold... some frogs came out of the bushes. And there the boy and his dog are walking away. The boy got another frog. There they are walking away.

DNS age 11

And there his frog. This is his frog. Yeah. And he say goodbye.

FIG. 2. Increased linguistic affect in Williams syndrome. Individuals with WMS use more affective prosody, more linguistic affective devices than do normals or individuals with DNS at any age. Subjects are asked to tell a story from a wordless picture book and the WMS subjects tend to be dramatic story tellers. The figure shows samples of a story telling task by age- and Full Scale IQ-matched individuals with WMS and DNS. The WMS sample is from a 17-year-old individual (Full Scale IQ = 50, Verbal IQ = 54, Performance IQ = 55). The DNS sample is from an individual who is 18 years old (Full Scale IQ = 54, Verbal IQ = 59, Performance IQ = 53).

dency for hypersociability toward strangers is apparent from an early age, and is a major concern for parents of WMS children [19]. The anecdotal stories told by parents of children with WMS overwhelmingly describe a personality type characterized by fearlessness in social interactions with strangers, excessive desire for social contact, and a great facility to readily connect with and engage strangers in conversation. The desire for social contact is perhaps best exemplified in the words of an 8-year-old child with WMS: 'There are no strangers, there are only friends'. It is this hypersocial behavior, including the abnormally high linguistic affect evident in story telling and biographical interviews, that may be a hallmark of WMS, and therefore a candidate for mapping across levels including behavior, brain and molecular genetics.

In the present study, we investigated social cognition experimentally with a set of stimuli that permit comparison with other studies. The stimuli, and the task, were derived from a procedure that has been used to investigate social judgment in subjects with bilateral amygdala damage [20]. The results of this experiment can provide both a quantitative assessment of social judgment in WMS, and a comparison with social judgment shown by subjects with amygdala damage.

Materials and Methods

Subjects with WMS were recruited from those who had previously participated in a large set of other studies involving cognitive, neural and genetic probes. All subjects were diagnosed with WMS by medical genetic testing (absence of one copy of the gene for elastin on chromosome 7), and all exhibited the associated medical and clinical phenotype. For this study we tested 26 subjects with WMS (16 female, 10 male; mean age 23.6 ± 8.6), and 26 normal control subjects of similar gender ratio and age (15 female, 11 male; mean age 25.5 ± 7.7). All participants were tested individually. All subjects with WMS participated in extensive neuropsychological testing, including assessment of IQ, language function and perceptual function using standardized tests. We collected measures of receptive vocabulary (the Peabody Picture Vocabulary Test), expressive vocabulary (the Expressive One-Word Picture Vocabulary Test), visuospatial function (the Developmental Test of Visual Motor Integration), intelligence (from the WISC-R or WAIS-R) and face perception (the Benton Test of Facial Recognition).

To assess subjects' social judgment of other individuals, we modified a task that had been previously used successfully with both normal and brain-damaged populations [20]. We selected 42 photographs of unfamiliar human faces, chosen from an original set of 100 stimuli so as to span the entire rating range. Stimuli were chosen with an emphasis on those from the original 100 that had previously received the most negative, and the most positive, ratings from normal subjects; thus, there was an overrepresentation of stimuli at extremes of the normal rating scale. Printed black-and-white photographs of the 42 final stimuli were shown to subjects, one at a time and without time limit. Subjects rated the 42 faces on a 5-point Likert scale, by pointing to an analog representation of the scale (Fig. 3). Subjects were asked to indicate how approachable they found the face stimulus, in terms of how much they would like to approach the person and strike up a conversation with them.

Results

We divided our analysis into two parts: data for the 21 faces that normal controls gave the most negative ratings, and data for the 21 faces that normal controls gave the most positive ratings (cf [20]). An examination of the mean ratings given to each block of 21 faces showed that subjects with WMS gave more positive ratings overall than did normal subjects. For the 21 most negative faces, WMS subjects gave mean ratings of -0.54 ± 1.39, while normal controls gave mean ratings of -0.96 ± 0.96; and for the 21 most positive faces, WMS gave mean ratings of 1.32 ± 1.1, while normal controls gave mean ratings of 0.84 ± 1.12.

We analyzed these data with a repeated-measures ANOVA, with factors of subject group (WMS or normal) and stimulus valence (in the 21 most positive faces, or in the 21 most negative faces), and with an interaction term, subject group by stimulus

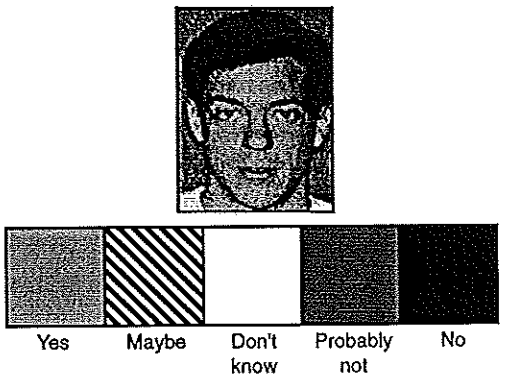

FIG. 3. Ratings of unfamiliar faces: approachability task. Depiction of the experimental task. Subjects were shown faces of unfamiliar individuals, such as the one at the top, one at a time and without time limit. The faces were rated from −2 (very unapproachable) to +2 (very approachable) by pointing to the analog scale shown at the bottom (adapted from [20]).

valence, to examine the possibility that WMS subjects might be disproportionately impaired for the most negative, or the most positive, faces. Individual stimuli, and individual subjects, differed significantly among one another (both $p < 0.0001$). There was a significant effect of stimulus valence ($F = 275.5$, $p < 0.0001$), and a significant effect of subject group ($F = 11.27$, $p < 0.002$), but no interaction between the two ($p > 0.5$). Thus, the main finding is that subjects with WMS tended to give abnormally positive ratings of approachability to all faces (Fig. 4), consistent with their real-life social behavior. It is important to note that WMS subjects were still able to generate a normal rank-order of approachability for the faces (Fig. 4). That is, their judgments regarding which person was more approachable relative to another were normal, even though the absolute ratings had a global positive bias.

To examine the possibility that impaired social judgment might result from low IQ, or from impaired visual processing of faces, we calculated the correlations between subjects' scores on our task with IQ, with their scores on a task of face discrimination (the Benton Test of Facial Recognition), as well as with other tasks of language and visuospatial function (see Methods for a list of these). There was no significant correlation between performance on our experimental task of social judgment and any of these other neuropsychological measures ($r < 0.1$ in all cases).

Discussion

The principal finding in this study was that subjects with WMS judged unfamiliar individuals to be abnormally approachable. The effect was significant for our sample sizes, and is consistent with the hypersocial behavior exhibited by WMS subjects in real life. The intact face-processing abilities of our subjects, together with the lack of correlation with other task measures, argue that the social impairment we report could not be attributed simply to low IQ, or to impaired early visual processing of the stimuli. The findings from this laboratory task, together with observations in everyday life, provide strong evidence for an abnormal tendency towards excessively social behavior in WMS. Below we discuss the relation of the finding to other impairments of social behavior, the specificity of the impairment, and its implication for a genetic contribution to human social behavior.

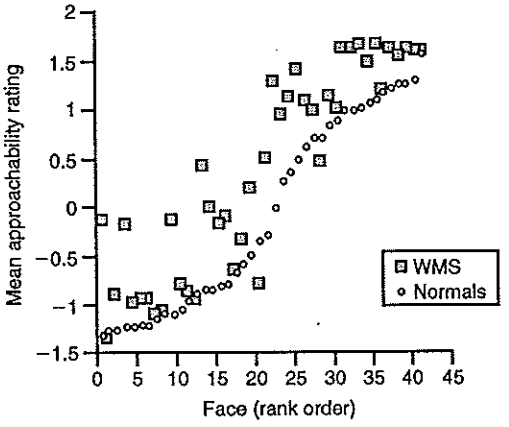

FIG. 4. Ratings of approachability given by subjects with WMS (filled squares) and by normal controls (small open circles). The stimuli are rank-ordered on the x-axis according to the mean approachability they received from normal controls; thus, very unapproachable-looking faces are at the far left, and very approachable-looking faces are at the far right. Subjects with WMS generated a normal rank-order of approachability ratings for the faces, but exhibited an abnormal overall positive bias.

It is of interest to compare the present findings with those previously reported for subjects with bilateral amygdala damage [20]. Like subjects with WMS, subjects with bilateral amygdala damage appear unusually friendly in real life, and will tend to approach people that would normally be avoided. On a task similar to the one used in the present study (which included the same stimuli), subjects with bilateral amygdala damage gave abnormally positive approachability ratings to unfamiliar faces. An interesting difference between subjects with WMS and subjects with bilateral amygdala damage is that subjects with WMS gave abnormally positive ratings across all the stimuli, both those normally judged to be unapproachable and those normally judged approachable. Subjects with bilateral amygdala damage, on the other hand, gave abnormally positive ratings only for those faces that normally receive the most negative ratings (normally judged to be the most unapproachable). One interpretation of these disparate results is that amygdala damage impairs a normal ability to judge unapproachability (to detect potentially dangerous or threatening people), whereas WMS augments a strong social tendency to approach other individuals. Possibly, these two processes, a tendency towards sociability, and a tendency towards caution, normally operate in tandem as we navigate the social environment.

Also notable is the finding that recognition of facial identity is remarkably preserved in both subjects with bilateral amygdala damage and WMS. One of us has previously described a subject with complete bilateral amygdala damage, who is impaired in making social judgments from faces, but who has no difficulty recognizing identity whatsoever [20,21]. Similarly, subjects with WMS show preserved ability to recognize unfamiliar individuals from their faces [10]. These observations are consistent with the idea that perception of the social and emotional relevance of stimuli can be selectively

disrupted, with sparing of the ability to process other types of information. This view is corroborated by our finding that there was no correlation between the performance of WMS subjects on social judgment, and their ability to perceive faces, or their IQ. All WMS subjects underwent a range of testing across cognitive domains (face processing, IQ, spatial cognitive ability, language ability), none of which correlated with performance on our experimental task of social judgment.

Studies of the neuroanatomical characteristics of WMS provide some suggestions regarding specific neural structures that may contribute to social cognition. Quantitative MRI imaging suggests a relative sparing of the limbic system and of frontal and neocerebellar areas [1,9], structures that are likely to play a critical role in the processes that underlie social behavior. Analysis of WMS brains from autopsy suggests that there is posterior curtailment of the amygdala in WMS brains [22] and in one case a significant reduction in volume of the amygdala [23], implicating defects in visual processing and social behavior. These initial neuroanatomical findings are thus compatible with the impaired social cognition we report in WMS.

Towards a neural and genetic basis for sociability? Bellugi, Korenberg and colleagues [3–10] are currently engaged in studies that may begin to provide links between specific genes in the small deleted region in WMS on chromosome 7 and specific characteristics of the WMS phenotype: clinical, neural, cognitive and social [3–5]. By studying individuals with WMS who have deletions of slightly different sizes, there are already clues available. There is a strong link between the specific heart defect found in WMS and absence of one copy of the elastin gene, as well as a suggested link between the visuospatial deficit characteristic of WMS and absence of one copy of the LIM-1 kinase gene. We argue that in the near future we may be able to link other specific genes or regions deleted in WMS with the specific personality characteristics of the syndrome and to the neural systems underlying them [5,9]. Of special interest will be the investigation of the differential contribution of specific genes to specific aspects of social behavior. The present study is the first in a series aimed at elucidating such possible links.

Conclusion

The findings provide, for the first time, a quantitative assessment of the unusual personality involving hypersociability in WMS. Like subjects with bilateral amygdala damage [20], individuals with WMS give abnormally positive ratings to unfamiliar people. However, unlike subjects with amygdala damage, subjects with WMS are still able to rank-order unfamiliar individuals normally; they just exhibit an abnormally positive bias across the board. The results offer an intriguing link between the levels of gene, brain, and human social behavior.

The personality of individuals with WMS is notable for a lack of fear of strangers, heightened empathy, and a tendency towards excessive friendliness in real life. This is the first experimental investigation of the profile of excessive sociability in WMS. The finding of a distinct definable temperament in a genetically based syndrome is intriguing with respect to the contribution of genes to the neural systems underlying social behavior.

References

1. Bellugi U, Wang PP and Jernigan TL. Williams syndrome: An unusual neuropsychological profile. In: Broman S and Grafman J, eds. *Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function.* Hillsdale, NJ: Lawrence Erlbaum Associates, 1994: 23–56.
2. Frangiskakis JM, Ewart AK, Morris CA *et al. Cell* 86, 59–69 (1996).
3. Korenberg JR, Chen X-N, Mitchell S *et al. Am J Hum Genet*, Suppl. 59, A306 (1996).
4. Korenberg JR, Chen X-N, Lai ZC *et al. Am J Hum Genet* 61, 103 (1997).
5. Korenberg JR, Hirota H, Chen XN *et al. Cogn Neurosci Soc 1998 Annu Meet Abstr Prog.* 11 (1998).
6. Bellugi U, Hickock G, Lai ZC and Jernigan T. Links between brain and behavior: clues to the neurobiology of Williams syndrome. *Int Behav Neurosci Soc Abstr* 6, 57 (1997).
7. Bellugi U, Klima ES and Wang PP. Cognitive and neural development: Clues from genetically based syndromes. In: Magnussen D, ed. *The Life-Span Development of Individuals: Behavioral, Neurobiological and Psychosocial perspectives. The Nobel Symposium.* New York: Cambridge University Press, 1996: 223–243.
8. Bellugi U, Lai ZC and Korenberg JR. Genes, brains and behavior: What genetic disorders reveal about behavior. In: Bizzi E, Calissano P and Volterra V, eds. *The Brain of Homo Sapiens*, Vol. 4, Frontiere della Biologia. Rome, Italy: Enciclopedia Italiana, In Press.
9. Bellugi U, Lichtenberger L, Mills D *et al. Trends Neurosci* (in press).
10. Bellugi U and Wang PP. Williams syndrome: From cognition to brain to gene. In: Edelman G and Smith BH, eds. *Encyclopedia of Neuroscience.* Amsterdam: Elsevier Science Publishers; CD-ROM version.
11. Rossen ML, Jones W, Wang PP *et al. Genet Counseling* 6, 138–140 (1995).
12. Jones W, Hickok G, Rossen ML *et al. Dissociations in Cognitive Development: Differential Effects from Two Genetically Based Syndromes (Technical Report CND-9805).* University of California, San Diego: Center for Research in Language, Project in Cognitive and Neural Development, 1998.
13. Jones W, Rossen ML and Bellugi U. *Genet Counseling* 6, 178–179 (1995).
14. Einfeld SL, Tonge BJ and Florio T. *Am J Psychiatry* 102, 45–53 (1997).
15. Reilly JS, Klima ES and Bellugi U. *Dev Psychopathol* 2, 367–391 (1990).
16. Bellugi U, Losh M, Reilly J *et al. Excessive Use of Linguistically Encoded Affect: Stories From Young Children with Williams Syndrome (Technical Report CND-9801).* University of California, San Diego: Center for Research in Language, Project in Cognitive and Neural Development, 1998.
17. Courchesne E, Bellugi U and Singer N. *Genet Counseling* 6, 144–145 (1995).
18. Tager-Flusberg H, Boshart J and Baron-Cohen S. *J Cogn Neurosci* 10, 631–639 (1998).
19. Udwin O. *Dev Med Child Neurol* 32, 129–141 (1990).
20. Adolphs R, Tranel D and Damasio AR. *Nature* 393, 470–474 (1998).
21. Adolphs R, Tranel D, Damasio H *et al. Nature* 372, 669–672 (1994).
22. Galaburda A, Wang PP, Bellugi U *et al. NeuroReport* 5, 758–787 (1994).
23. Galaburda A. *Cogn Neurosci Soc 1998 Annu Meet Abstr Progr* 10–11 (1998).

ACKNOWLEDGEMENTS: This research was supported by grants to U.B. from NIH (P01 HD33113, P50 NS22343, P01DC01289), the OakTree Philanthropic Foundation, and the James S. McDonnell Foundation; as well as from a Sloan Research Fellowship to R.A. The authors thank the national and regional Williams Syndrome Associations and are grateful to the subjects and their families for participation in these studies.

Received 17 March 1999; accepted 30 March 1999