Cerebellar abnormalities in infants and toddlers with Williams syndrome

Wendy Jones* PhD, The Salk Institute for Biological Studies, La Jolla;
John Hesselink MD, Department of Radiology, University of California at San Diego Medical Center, San Diego;
Eric Courchesne PhD, Laboratory for Research on the Neurosciences of Autism, La Jolla;
Tim Duncan MD;
Kevin Matsuda MD, Department of Radiology, University of California at San Diego Medical Center, San Diego;
Ursula Bellugi EdD, The Salk Institute for Biological Studies, La Jolla, CA, USA.

**Correspondence to first author at* Laboratory for Cognitive Neuroscience, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA.
E-mail: jones@crl.ucsd.edu

One commonly observed neuroanatomical abnormality in adults with Williams syndrome is an enlarged cerebellum relative to a small cerebrum. Our study is the first to examine neuroanatomy in young children with Williams syndrome. Clinical brain MRI was examined in nine young children with Williams syndrome (mean age 21 months, range 7 to 43 months) relative to nine age- and sex-matched normally developing control children (mean age 29 months, range 20 to 42 months), and two children with undiagnosed developmental disorders (6 and 41 months). Two neuroradiologists who were blinded to participant classification, hypotheses, and regions of interest for the study, sorted the brain scans into two groups on the basis of six neuroanatomical criteria. The raters placed more of the MR scans from children with Williams syndrome into a separate group when they analyzed features of the cerebellum, but not when they analyzed other brain regions. Based on their written comments, the raters focused on the large size of the cerebellum in the children with Williams syndrome. The results lead us to suggest that abnormal cerebellar enlargement is evident in those with Williams syndrome at an early age. Our results are discussed relative to the cognitive delays observed in Williams syndrome versus other disorders such as autism, leading us to suggest that the cerebellum may play a role in cognition.

Individuals with a variety of developmental disorders display cerebellar abnormalities. Patients with autism, for instance, who have clearly defined abnormalities within the cerebellum, also have severe deficits in the use of language as well as in social and other communicative abilities (Courchesne et al. 1988, Ciaranello and Ciaranello 1995, Rapin and Katzman 1998, Akshoomoff 2000). Similarly, patients with fetal alcohol syndrome (FAS) have decreased cerebellar volumes, and also exhibit abnormalities in language as well as in spatial and general cognitive abilities (Mattson et al. 1994, Ponnappa and Rubin 2000). Animal models of FAS show abnormalities in cerebellar Purkinje cells (Gruol 1991). Patients with other developmental disorders, including patients with Rett syndrome (Bauman et al. 1995), Asperger syndrome (El-Badri and Lewis 1993, Ciaranello and Ciaranello 1995), and fragile X syndrome (Reiss and Freund 1990, Mostofsky et al. 1998) exhibit cerebellar abnormalities and deficits in specific cognitive domains.

Adolescents and adults with Williams syndrome (WS) also show abnormalities within the posterior fossa. Distinct medical, genetic, and cognitive features distinguish WS from other disorders (Table I), and abnormalities involving the cerebellum distinguish the disorder neurologically. Cerebellar structures are comparable, or sometimes large, in adults with WS relative to age-matched normally developing control individuals (Jernigan et al. 1993, Jones et al. 1999, Reiss et al. 2000). Cerebellar hemispheres are within normal size limits in adults with WS, despite an overall decrease in cerebral volume, suggesting that cerebellar and cerebral cortices are affected differentially in adults with WS. The surface area of various regions within the cerebellar vermis, however, is not uniformly affected; neocerebellar vermal areas are more intact than paleocerebellar areas in adults (Wang et al. 1992, Jernigan et al. 1993, Jones 2001).

Other neuroanatomical abnormalities also exist in adults with WS. Past studies document a lengthening of the skull (Trauner et al. 1989), as well as mild microcephaly in adolescents and adults with WS (Jones et al. 1975, Jernigan and Bellugi 1990). Like individuals with other developmental disorders, adults with WS have reduced cerebral volume relative to normally developing control individuals (Jernigan et al. 1993, Reiss et al. 2000). The general shape of the adult brain in WS appears to be unusual (Schmitt et al. 2001a) and reductions in total brain volume appear to result from greater reductions in white matter than in gray matter within specific brain regions (Reiss et al. 2000). Anterior regions show less volume reduction than posterior regions (Jernigan et al. 1993, Galaburda et al. 1994). The total surface area of the corpus callosum is also reduced in WS, relative to age-matched normally developing control individuals (Wang et al. 1992). Although the shape of the corpus callosum was comparable to that of control participants in one study (Wang et al. 1992), it was more elongated than in control participants in another (Schmitt et al. 2001b), and thin in the preoccipital portion in a third (Galaburda and Bellugi 2000). Brainstem structures, the caudate nuclei, and basal ganglia also appear to be reduced in size and volume relative to age-matched adult normally developing control individuals (Jernigan et al. 1993, Reiss et al. 2000). Although many of the neuroanatomical differences must be quantified to be evident, increased cerebellar size is frequently readily evident on the WS adult brain scan.

No neuroanatomic studies of abnormalities like those reported in adults have been conducted in young children with WS. Studies using in-vivo MRI have been difficult to perform because individuals with WS exhibit a high level of anxiety, as well as specific fears of doctors, hospitals, and loud noises (Davies et al. 1998). The complex cardiac problems in WS make the use of sedation difficult, and full sedation is dangerous because sudden death can occur (Bird et al. 1996). Obtaining research MRI of adults with WS, let alone young children, has thus been difficult. Most neuroanatomical research studies of WS have used small numbers of participants (generally 10 to 20) in the adolescent and adult age range.

For the current study, we examined the brain in infants and toddlers with WS to identify cerebellar and other neuroanatomical abnormalities that may exist in early development. We used clinical mid-saggital brain MRIs of infants and toddlers with WS to examine abnormalities associated with specific brain structures. We hypothesized that particular neuroanatomical features in children with WS would differ from those of age- and sex-matched control children without WS. We predicted that, like adolescents and adults with WS, young infants and toddlers with WS would also show evidence of a large cerebellum as a distinguishing neuromorphological feature. We examined whether abnormalities were specific to a particular brain region (such as the cerebellum) or if they were more pervasive, affecting, for example, the whole cerebrum.

Table I: Williams syndrome phenotype

Medical	
Deletion of contiguous genes along chromosome 7	Ewart et al. 1993, Joyce et al. 1996, Osbourne and Pober 2001
Characteristic 'elfin' facies	Jones and Smith 1975, Lashkari et al. 1999
Cardiac and pulmonary abnormalities	Chowdhury and Reardon 1999, Lashkari et al. 1999, Sadler et al. 1998
Growth Delays	Lashkari et al. 1999
Hypercalcemia[a]	McTaggart et al. 1999, Rodd and Goodyer 1999
Anxiety	Davies et al. 1998, Levine and Wharton 2000
Hyperacusis[a]	Van Borsel et al. 1997
Colic; Feeding difficulties[a]	Sarimski 1996
Cognitive	
Mild mental retardation[b]	Bellugi et al. 1999b, Howlin et al. 1998, Kaplan et al. 2001
Delays in language milestones	Singer-Harris et al. 1997
Visuospatial delays across age span	Bertrand et al. 1997
Motor delays and abnormalities	Masataka 2001, Kaplan et al. 2001
Language relative strength in adolescence/adulthood	Bellugi et al. 1999b, Howlin et al. 1998, Jarrold et al. 1998
Social, outgoing personality	Bellugi et al. 1999a, Jones et al. 2000, Mervis et al. 2001

[a]Specific age-related changes occur. [b]UK usage: learning disability.

Method

PARTICIPANTS

We compared clinical MRI data from nine infants and preschool-age children with WS to imaging data from nine chronological age- and sex-matched normally developing control children. We included scans from children with WS in the study if the child had a clinical MRI of the brain before age 4 for one of two reasons: (1) the MRI was done to rule out other disorders and to aid in diagnosis before being formally diagnosed with WS, or (2) the MRI was done to rule out the presence of the Arnold Chiari Type 1 malformation in a child with known WS, as this condition may lead to neurological difficulties (Wang et al. 1992). We located the children with WS after they were screened for participation in a study of language and cognitive development in young children. Parents of those children with WS who met the criteria listed above were asked to sign a consent form to release medical records, so that we could obtain a copy of the clinical MRI films. We identified nine children with clinical and genetic diagnoses of WS whose parents agreed to participate in the study. Table II identifies the age and sex breakdown of the children with WS whom we studied, as well as the ages and sexes of those individuals who were in the two control groups. Of the nine WS MR scans included in the study, two were accompanied by clinical reports of abnormalities. Specifically, two of the children with WS exhibited the Arnold Chiari Malformation, Type 1. One of the children went on to have surgical correction of the malformation. The remaining seven MRIs were read as clinically normal by radiologists before entry into the current study.

Nine children were included as a normally developing control group. These children were matched to the WS group on the basis of chronological age (within 12 months) and sex. A control match could not be located for the youngest child with WS. As a result, one older child with WS was assigned two control participants matched for age and sex. Scans of all normally developing control children resulted from their participation in previous research studies. These participants were carefully screened for any evidence of developmental delay, neurological abnormality, or medical disorder before their MRI. Their MRIs were read as clinically normal before participation in the current study.

Table II: Participant characteristics

Characteristics	*WS (n=9)*	*Normal control children (n=9)*	*Control children with developmental delay (n=2)*
Age (months) and sex of participants	7 M 10 M 14 F 18 M 19 M 20 F 29 M 34 F 43 M	– 20 M 26 F 23 M 26 M 27 F 30 M 35 F, 34 F 42 M	6 M 41 M
Sex breakdown	6M, 3F	6M, 3F	2M
Mean age (months)	21.6	29.2	23.5

A 'developmentally delayed' contrast group consisted of two individuals from the University of California at San Diego MRI center. They presented with anecdotal evidence of developmental delay, but their brain scans were subsequently judged to be clinically normal. These children were included in the study to examine the impact of developmental delay on WS brain ratings.

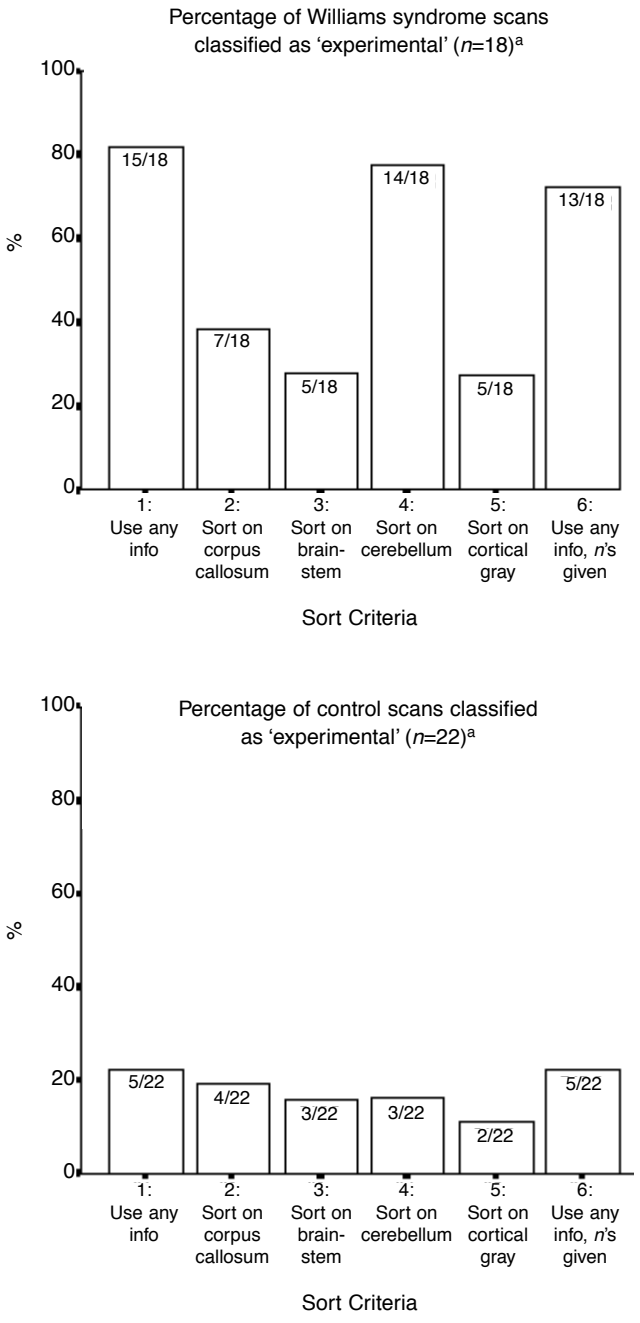

Figure 1: *Percentage of scans classified as 'experimental' by group. [a]n=9 for WS group (18 total across two raters); n=11 for control participants (22 total across two raters).*

MRI RATING SCALES

All analyses used the T_1-weighted saggital MRI series. Identifying information, including name, sex, date of birth, scan site, and scan series was removed from each film, and scans were subsequently identified using only the child's first and last initial and age in months (e.g. HM7).

Due to the fact that the scans were not collected using a research or standardized protocol, the measures used in this study were qualitative, not quantitative. Two medical neuroradiology resident physicians participating in training fellowships at the University of California at San Diego MRI center in the USA served as the raters for the study. Without knowledge of the hypotheses of the study, regions of interest in the study, and diagnosis of each child, they sorted the films into 'control' versus 'experimental' groups, based on six sorting criteria. First, the raters sorted the scans into two groups using any salient information from the scan. Next, they sorted the scans by the appearance and relative size of the corpus callosum, then by the relative size and shape of the brainstem, the relative size and shape of the cerebellum, and the relative amount and appearance of cortical gray matter. Finally, they were told the number of participants in the experimental ($n=9$; WS) versus control groups ($n=11$), and sorted the scans into two such groups, based again on any salient information. The raters were asked to indicate if they 'guessed' during any of the six sorts, and to comment on information from the scan that helped them to separate the two groups. In addition, after separating the scans into two groups, the raters sorted the experimental group based on magnitude of abnormality. Appendix I contains the sorting cover sheet, including the directions given to each rater. Appendix II presents an example of one of the specific rating sheets. The interrater reliability was in the moderate range (Pearson's $r=0.75$, $p<0.01$; Spearman's $r=0.74$, $p<0.01$). Data from both raters were averaged for formal analyses.

Results

The raters placed children with WS in the experimental group more often that they did the control children across all six sorting criteria (one-way ANOVA with group by mean rating: $F(1,19)=17.9$, $p<0.001$). They placed those with WS in the control group 46 percent of the time (averaged across all six sortings), and control children in the control group 80% of the time.

When the ratings were assessed by specific sorting criteria, the neuroradiologists rated participants with WS in the experimental group more often when they used three specific sorting criteria (Fig. 1). When the raters used any salient information to sort the scans (sort 1), they placed 15 of 18 WS MRIs into the experimental group (seven of nine participants for rater 1; eight of nine participants for rater 2). Similarly, when they used any salient information to sort the scans and knew the correct number of participants in the experimental group (sort 6), they placed 13 of 18 WS scans into the experimental group (seven of nine for rater 1; six of nine for rater 2). Finally, when they paid attention only to features of the cerebellum, they placed 14 of 18 WS scans into the experimental group (sort 4; six of nine for rater 1; eight of nine for rater 2).

When the raters used the corpus callosum, brainstem, or cortical gray matter as the sorting criteria, they placed the WS scans in the control group more often than the experimental group (number of WS scans classified as experimental across

both raters 7, 5, 5, respectively; $n=18$ total possible). In addition, the raters were less likely to place control scans in the experimental group, irrespective of the sorting criteria they used (number control scans classified in experimental group 5, 4, 3, 3, 2, 5 across the six sortings; $n=22$ total possible; see Fig. 1).

The neuroradiologists detected abnormalities in participants with WS more often when they used any salient information (sorts 1 and 6) or attended only to the cerebellum (sort 4), relative to when they attended to the corpus callosum, brainstem, or cortical gray areas. According to the ratings, sorting based on the cerebellum did not increase detection above that based on using 'any salient information' (14 of 18 WS scans placed in experimental group based on cerebellum; 15 and 13 of 18 WS scans placed in experimental group using any sorting criteria and any sorting criteria with correct group numbers, respectively). In their written comments, the raters identified the contour of the cerebellum as one of the most salient features they used to help sort the two groups when they used any salient information. Table III lists the written comments of the two raters.

The raters were also asked to sort scans within the experimental group based on degree of abnormality. When attending to features of the cerebellum (sort 4), both neuroradiologists overlapped in their placement of six WS participants into the experimental group. The two raters were consistent in their ordering of the degree of abnormality in these six participants, with only one exception (Spearman's $r=0.43$, $p=ns$). The degree of abnormality did not vary as a function of age in the participants with WS , although sex may have been a factor (Table IV). The two WS participants with Arnold Chiari Malformation, Type 1 (evident from past radiological report) were consistently placed into the experimental group by both raters.

Two of the control participants had histories of developmental delay, but clinically normal MR scans (by past radiological report). The neuroradiologists' assignments of these individuals were variable for all sorting criteria but one (Fig. 2). Both consistently placed these control participants in the control group based on features of the cerebellum.

Table III: Comments written by radiological raters as a function of sorting criteria. Answers by neuroradiologists to the questions: 'What aspects were you using to sort the two groups? Were there other clues that you used?'

Sort criteria	*Rater A (TD)*	*Rater B (KM)*
1. Use any salient information	Large size of cerebellar structures; unusual shape of midline structures	Unusual shape of corpus callosum & brainstem; unusual gyral patterns, Unusual cerebellum size
2. Corpus callosum	Thickness	Contour irregularities, thickness
3. Brainstem	Shape of brainstem	Contour irregularities, abnormalities for age
4. Cerebellum	Low position; large size of cerebellum and tonsils	Size and over-occupation of space, contour irregularities, downward extension of tonsils
5. Cortical gray matter	Gyral size	Sulci, signal contrast, abnormalities for age
6. Use any salient information (*n*'s given)	Large size of cerebellar structures; unusual shape of midline structures	Unusual corpus callosum and cerebellar contours

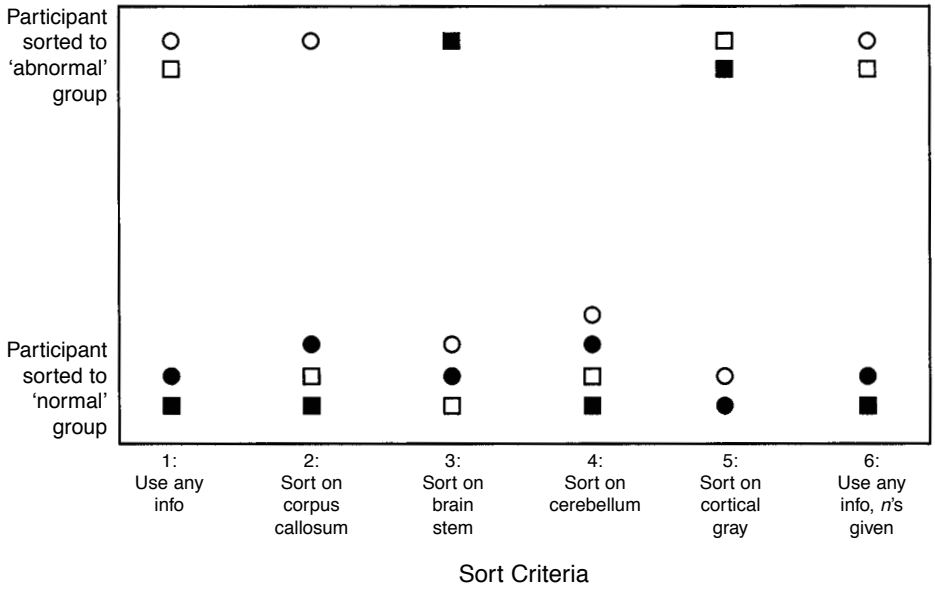

Figure 2: *Ranking of developmental delay (DD) participants (n=2) by radiologist (n=2).* ○●, *Rater 1 (TD);* □■, *Rater 2 (KM);* □○, *DD participant 1;* ■●, *DD participant 2.*

Cerebellar abnormalities in individuals with WS appeared to be specific to WS, as opposed to developmental delay. The limited number of developmentally delayed participants studied suggests that these findings should be generalized with caution.

Discussion

This study is the first to examine systematically the neuroanatomy of young children with WS. We examined cerebellar ratings from MR scans of infants and toddlers with WS relative to age- and sex-matched control participants. Two neuroradiologists who were blinded to the goals of the study, regions of interest, and participant information (sex, diagnosis, reason for scanning) used assigned criteria to sort the scans into two groups. The neuroradiologists placed participants with WS in the experimental group more often overall than control participants. This classification was specific to the type of sorting criteria used; when using features of the cerebellum, the neuroradiologists placed WS participants in the experimental group more consistently then when they used anatomical features such as the corpus callosum, brainstem, or cortical gray matter. Both neuroradiologists commented in writing that the large size of the cerebellum was the most salient feature they used as sorting criterion, even when they were allowed to include other anatomical information. Thus, they reliably identified the cerebellum of infants and toddlers with WS as structurally abnormal for their ages and sexes. The magnitude of cerebellar abnormalities did not vary as a function of age in the WS group. In addition, results from two children with developmental delays, but not WS, suggested that the unusual appearance of the cerebellum was not related to an attendant history of developmental delay in WS.

The observation that the cerebellum is abnormally large from a relatively young age in children with WS leads us to speculate about the role of the cerebellum in specific domains of cognition. While disproportionate enlargement of the cerebellum appears to be a stable neuroanatomical feature across development in WS, the cognitive profile in WS changes significantly during early childhood. As a result, a cerebellar–cognition correlation in WS may be specific to those domains of cognition which are most stable across development. Social, visual–spatial, and face processing abilities are developmentally stable in WS, while language and motor abilities change significantly as individuals with WS mature (Bertrand et al. 1997, Singer-Harris et al. 1997, Jarrold et al. 1998, Jones et al. 2000). It may be those cognitive domains that are most stable which are controlled, at least in some sense, by cerebellar brain regions. Our results suggest that it will be useful for future investigators to consider the relation between developmental changes in neuroanatomy and cognition in WS participants as one avenue of better understanding brain–behavior links.

Interestingly, the brain regions that are large in individuals with WS throughout development appear to be small in those with autism throughout development. In autism, the volume of the brain as a whole appears to be normal (Piven et al. 1995), but cerebellar volume is reduced in size, apparently as a result of extensive neuronal loss (Courchesne et al. 1994). Of particular significance is the discrepancy between sizes of neocerebellar vermal regions VI and VII in adults with WS versus autism, as these regions give rise to the output pathways that eventually connect the cerebellum with the cerebral cortex. These regions are enlarged in adults with WS, but are selectively reduced in size in adults with autism (Courchesne and Singer 1995). The findings from the current study suggest that these same regions are atypical beginning in early development, although quantitative study is necessary to show this definitively.

Indeed, behavioral contrasts between individuals with WS and autism are striking. One characteristic of the WS phenotype is a strong impulse towards social contact and affective expression (Bellugi et al. 1999a, p754), Jones et al. 2000). For example, Galaburda and colleagues (1994) described a child with WS as drawing '…people to him as though he had a social magnet in him.' Language abilities are relatively strong in individuals with WS on average. In contrast, the cardinal features of autism are profound deficiencies in social knowledge, affective expression, and linguistic communication. Such a contrast suggests that cerebellar regions may be an underlying neuroanatomical basis for the linguistic and social strengths seen in the individual with WS, but absent in the individual with autism.

The role of the cerebellum in cognition has recently received increased attention. Based on the results of structural and functional neuroimaging studies, some investigators now support a role for the cerebellum in various aspects of cognition, including language and social–emotional abilities. In functional imaging studies, for instance, the cerebellum can be activated by a wide variety of language paradigms, including word generation tasks (Petersen et al. 1989, Pardo and Fox 1993, Raichle et al. 1994), semantic decision measures (Binder et al. 1997), verbal retrieval versus verbal recall tasks (Cabeza et al. 1997), verb substitution and grammar paradigms (Petersen et al. 1989), synonym generation, and general semantic processing measures (Klein et al. 1995). Animals with cerebellar lesions exhibit deficits in emotional control (Berman 1997), and humans with cerebellar lesions exhibit deficits in affective control (Schmahmann and Sherman 1998) and executive functioning (Hallet and Grafman 1997). Most studies of cerebellar functioning in cognition examine adults. That those with WS show strengths in many of the cognitive domains now shown to be driven by cerebellar brain areas suggests that this region is important in WS not only from a neuroanatomical perspective, but also from a cognitive perspective. Our finding that the

Table IV: Participants with Williams syndrome ordered by degree of cerebellar abnormality (most to least abnormal)

Age of participant (m)	*Sex of participant*	*Order by rater 1*	*Order by rater 2*
43	M	1	1
7	M	2	3
19	M	3	4
10	M	4	5
20	F	5	6
18	M	6	2

Six WS participants were placed in experimental group by both neuroradiologists. The two neuroradiologists were generally consistent in their assigned order of WS participants based on degree of cerebellar abnormalities. Degree of abnormality did not appear to vary as a function of age. Five of six 'experimental' participants were male, suggesting a possible effect of sex (two WS participants considered 'normal' were female, one was male).

region is atypical starting at a young age in WS suggests that this region plays a role in cognition starting in early development.

While intriguing, we acknowledge that the findings from this study were limited by their qualitative rather than quantitative nature. The MR scans used in the study were collected using a clinical, non-standardized protocol, and scan quality was limited by participant movement, making direct measurement of the size of cerebellar and other neuroanatomical regions unreliable. In addition, the study was limited by small sample sizes. Only further study will confirm whether the cerebellar effects observed are typical of a wider sample of children with WS. Despite these limitations, the results of the current study are intriguing and represent the first steps in understanding the development of the brain in WS. Taken in combination with studies on the role of the cerebellum in cognition, researchers can now use these results to develop specific hypotheses about the etiologies of behaviors observed in people with WS relative to other disorders.

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Appendix I: Instruction sheet given to neuroradiologists

Instructions for Toddler MRI Sorting Study

You will be sorting brain MRI scans from normal children and children with a rare genetic disorder. To aid you in your ratings, each child's age in months is marked in the upper corner on the scan, however all other identifying information has been removed. The scans are ordered randomly and there are *unequal* numbers of subjects in the groups.

You will perform 6 independent sorts of the scans. You will be sorting both on structures of interest to our study, as well as on structures not of interest to our study.

For reliability purposes, multiple radiologists are being asked to sort the scans. You may also be asked to rate the scans again at a later date to check our findings.

You should be blind to the diagnosis of each child. If you are biased or unblinded for any reason, please make a comment about this on one of the score sheets below.

Don't worry if you feel like you are frequently guessing, we expect that this will be the case. We will inform you as to the purpose of the study after you have completed all 6 sorts.

In order to minimize errors in judgment, we ask that you begin by looking at the MRIs first without sorting. As you look at each scan, keep in mind the child's age. Look for any obvious abnormalities that may suggest group differences. Feel free to record notes as you go along. After you have looked at each scan, please turn to the next page and begin your ratings.

You may contact *first author and phone number* or *sixth author and phone number* at any time if you have questions or comments on the study. We appreciate your help, and will keep you informed of the results.

Appendix II: Example sorting sheet used for MRI sorting study

Rating Number 2

Rater Name and Date: _____

Look through all scans and attempt to separate them into two groups based on the appearance of the corpus callosum. Does the size, shape, length, width or color of the corpus callosum appear normal or abnormal for the child's age? Once you have separated the stack into two groups, order each stack by degree of abnormality and record your results below. Mark a "G" (for "guess") next to any scan that you feel unsure about.

Group 1 **Group 2**

Put a mark here if you feel like you guessed more often than not: _____

What aspects of the corpus callosum were you using to sort the two groups? Were there other clues that you used?

_____