



Enlarged cerebellar vermis in Williams syndrome

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Abstract

Williams syndrome (WMS) is a rare genetic disorder characterized by relative preservations of language ability and facial processing despite deficits in overall intelligence, problem solving, and visuospatial processing. Subjects with WMS also display hypersocial behavior and excessive linguistic affect during conversations and when giving narratives. Neuroimaging studies have shown global reductions in the brain volumes of subjects with WMS compared with normal controls, but with preservations in cerebellar volume. This study examines the neuroanatomic structure of the cerebellar vermis in 20 subjects with WMS and 20 age- and gender-matched controls via high-resolution magnetic resonance imaging. The vermis was divided into lobules I–V, VI–VII, and VIII–X. Lobules VI–VII and VIII–X were both relatively enlarged in the WMS group, and after adjusting for the smaller size of the WMS brain, the posterior vermis was significantly larger in WMS (Mann–Whitney z -value=4.27; $P<0.001$). Given that reductions in posterior vermis size have been implicated in flattened affect and autistic features, increased vermis size in subjects with WMS may be related to the hypersociality and heightened affective expression characteristic of individuals with this genetic condition. © 2001 Published by Elsevier Science Ltd. All rights reserved.

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1. Introduction

It has long been known that the cerebellar vermis plays well-defined roles in motor programming, control, and balance (Andermann et al., 1975; Takagi et al., 1998). However, studies in the last 10 years have demonstrated that the vermis also is involved in a broad spectrum of cognitive and behavioral functions. Recent experiments using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have correlated neural activation in the vermis with the processing of language, music, working memory, and executive function (Ryding et al., 1993; Desmond et al., 1997; Penhune et al., 1998). Previous structural neuroimaging studies also suggest a role of the vermis in higher brain function. For example, decreases in vermal size have been associated with attention deficit hyperactivity disorder (ADHD), fragile X syndrome, and schizophrenia (Holroyd et al., 1991; Mostofsky et al., 1998a; Nopoulos et al., 1999).

In the face of overall reduction in brain volume, cerebellar volumes are conserved in Williams syndrome (WMS), a rare genetic disorder caused by a microdeletion of approximately 30 genes on chromosome 7. This *de novo* deletion, occurring approximately once in 20,000 live births, results in a characteristic neurocognitive profile. Though possessing mild to moderate mental retardation, individuals with WMS have a remarkable preservation of social drive, facial processing, and linguistic abilities (Bellugi et al., 1999, 2000; Jones et al., 2000). Persons with WMS also have a characteristically friendly demeanor and fascination with sound and music. Additionally, WMS is associated with several motor problems, including abnormalities of muscle tone, motor coordination, and gait (Chapman et al., 1996; Trauner et al., 1989).

Previous neuroimaging studies in WMS have shown conserved overall cerebellar tissue volumes despite a 13% reduction in cerebral volume when compared with typically developing controls (Jernigan and Bellugi, 1990; Reiss et al., 2000). The only previous investigation specifically examining the cerebellar vermis in WMS reported a significant increase in the area of vermal lobules VI and VII in six subjects with WMS compared

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with 14 typically developing controls (Jernigan and Bellugi, 1990). Volumetric measurements of the cerebellar tonsils were also found to be proportionally larger in the WMS population (Wang et al., 1992). In order to further localize neuroanatomic differences in WMS, the present study examined the cerebellar vermis using high-resolution structural magnetic resonance imaging in a large sample, and is the first to measure the most posterior region of the vermis (lobules VIII–X) in WMS. Given evidence of relatively increased posterior cerebellum size as well as the known neurocognitive profile of WMS, we hypothesized that the posterior vermis would be proportionally increased in this condition.

2. Methods and materials

2.1. Subjects

Twenty subjects diagnosed with WMS [13 women and seven men, mean age: 28.5 (8.3), range 19–44 years] and 20 healthy, typically developing volunteers individually matched for age [mean age: 28.5 (8.2), range 19–48 years], gender, and ethnicity were recruited by the Laboratory for Cognitive Neuroscience at the Salk Institute as part of a multisite study investigating genetics, neuroanatomy, and behavior in WMS. The diagnoses of WMS were made by confirming hemizygoty for ELN, a gene consistently found in the critical deletion region associated with WMS, via fluorescent in-situ hybridization (Korenberg et al., 1997, 2000). Control subjects were volunteers from the University of California at San Diego community and were recruited via email mailing lists. All controls were in good health and had no evidence of neurological or mental problems. Each subject gave informed consent for his or her participation via protocols approved by the institutional review board at the Salk Institute.

2.2. Imaging

High resolution magnetic resonance images (MRI) of each subject's brain were acquired using a 1.5 T GE-Signa Scanner (General Electric, Milwaukee, Wisconsin). The images were acquired in the sagittal plane with a volumetric 3D-radio frequency spoiled gradient echo (SPGR) pulse sequence (TR = 24 ms, TE = 5 ms, flip angle = 45°, NEX = 2, matrix size = 256 × 192, field of view = 24 cm, slice thickness = 1.2 mm). Thirty-eight of the scans were acquired at the University of California, San Diego (UCSD) Medical Center. The remaining two scans, both controls, were acquired using an identical scanner and pulse sequence at Stanford University Medical Center.

All scans were imported into the program *BrainImage 3.X* for blinded image processing and analysis (Reiss,

2001). Measurement of the vermis was based on a previously existing protocol (Mostofsky et al., 1998a). This protocol consists of first determining the best midsagittal slice (derived by rotating the imaging dataset in three dimensions) based on clarity of the cerebellar vermis, cerebral aqueduct, corpus callosum, spinal cord, and fourth ventricle. The vermis was then divided into three regions of interest (ROIs) by circumscribing lobules I–V, VI–VII, and VIII–X separately, following major fissures (Fig. 1). Interrater reliability for circumscribing these vermal sub-regions was calculated using the intraclass correlation coefficient on 10 datasets. These values were 0.98 for lobules I–V, 0.95 for lobules VI–VII, and 0.84 for lobules VIII–X.

Because brain size is generally correlated with cerebellar volume, an ROI encompassing the intracranial space was drawn and measured on the same midsagittal image for each subject to use as a covariate. The intracranial area was circumscribed by following the interior of the cranial bone (following the marrow of the basiocciput), including optic chiasma and the pituitary stalk, but excluding the sella turcica (Scnitzlein, 1985). The inferior border was defined by a line drawn between the tip of the foramen magnum to the dens. Intrarater reliability for 10 datasets was 0.98.

2.3. Data analysis

Since the data were not normally distributed, non-parametric statistics were employed. Mann–Whitney *U* tests were used with a two-tailed *P* value of 0.05 set as

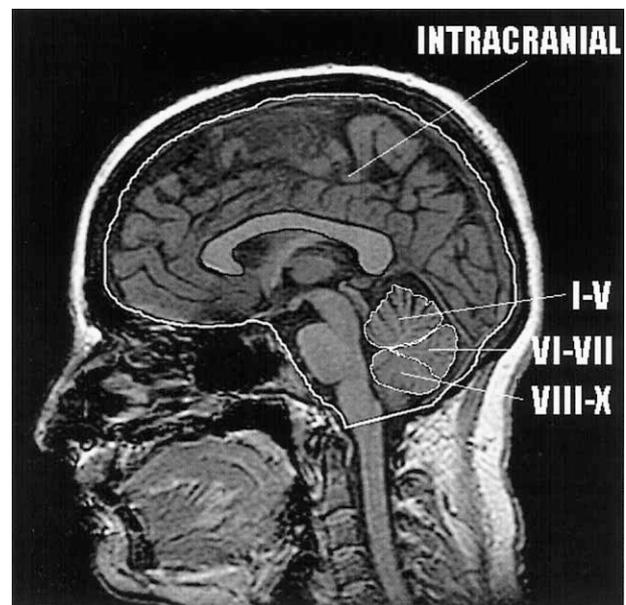


Fig. 1. Circumscription of the cerebellar vermis on the midsagittal image. The vermis was divided into three portions, the anterior vermis (lobules I–V), lobules VI–VII, and lobules VIII–X. An region of interest (ROI) encompassing the intracranial space also was drawn in order to account for total brain size.

Table 1

Descriptive statistics comparing the areas (in cm²) of the cerebellar vermal lobules of a group with WMS and an individually age-and gender-matched typically developing control group^a

Structure	WMS	Control	<i>P</i>	<i>z</i>	WMS (adjusted) ^b	Control (adjusted) ^b	<i>P</i> ^c	<i>z</i> ^c
Lobules I–V	4.76 (0.64)	5.41 (0.44)	<i>P</i> <0.001	3.41	0.0336 (0.0039)	0.0342 (0.0024)	NS	0.49
Lobules VI–VII	3.51 (0.50)	3.72 (0.67)	NS	0.87	0.0263 (0.0048)	0.0222 (0.0029)	<i>P</i> =0.008	2.65
Lobules VIII–X	3.77 (0.44)	3.72 (0.42)	NS	0.45	0.0267 (0.0037)	0.0236 (0.0022)	<i>P</i> =0.006	2.73
Posterior Vermis	7.49 (0.99)	7.24 (0.74)	NS	1.16	0.0531 (0.0062)	0.0458 (0.0037)	<i>P</i> <0.001	4.27
Total Vermis	12.25 (0.99)	12.64 (1.02)	NS	1.18	0.0867 (0.0071)	0.0806 (0.0050)	<i>P</i> <0.001	4.25
Intracranial area	141.63 (9.33)	158.30 (13.46)						

^a Posterior vermis is the sum of lobules VI–X.

^b The ratio of structure over intracranial area.

^c Adjusted for intracranial area.

the significance threshold. In order to account for the effects of brain size, measurements were co-varied by dividing them by the total intracranial area.

3. Results

Table 1 summarizes our results. In absolute terms, there were no significant differences between total vermis size in WMS and those of normal controls despite a significantly reduced intracranial area ($z=4.07$; $P<0.001$). After controlling for intracranial area, the vermis was found to be proportionally larger in WMS ($z=4.25$; $P<0.001$). The relative increase in vermal size in WMS was most influenced by the proportional enlargement of the posterior–inferior region compared with the control group ($z=4.27$; $P<0.001$). Both lobules VI–VII and lobules VIII–X were significantly larger in the WMS group after adjusting for intracranial area ($z=2.65$; $P=0.008$ and $z=2.73$; $P=0.006$, respectively). Unlike the posterior vermis, the area of lobules I–V was significantly smaller in the WMS population before adjusting for intracranial area ($z=3.41$; $P<0.001$).

4. Discussion

Our data indicates that WMS represents an unusual case of proportional posterior vermal enlargement in a neurogenetic disorder. In light of reports of proportional enlargement of total cerebellar volume as well as the preservation of the cerebellar tonsils in WMS (Wang et al., 1992), it seems that increased posterior vermis size is part of a more general pattern of relative neocerebellar increases.

The neocerebellum, including the posterior vermis, cerebellar tonsils, and neocerebellar cortex, is developmentally, evolutionarily, and histologically distinct from anterior cerebellar regions (Loeser et al., 1972; Jernigan and Bellugi, 1990; Yachnis and Rorke, 1999). Through phylogenetic history, the neocerebellum has

grown proportionally larger in mammals and particularly in humans, suggesting that this region may be involved in novel or cognitively complex functions (Pansky, 1982). Functional imaging studies have demonstrated an association between neocerebellar activation and both language ability and verbal fluency (Ackermann et al., 1998; Desmond et al., 1998; de Zubicaray et al., 1998; Schlosser et al., 1998). These linguistic functions, which are relatively preserved in WMS (Bellugi et al., 1999, 2000), also are typically associated with activation of the frontal cortex. The neocerebellum develops in parallel with the frontal lobe, and has strong connections to frontal and prefrontal cortex (Pansky, 1982; Schmahmann, 1991). The frontal lobes, like the cerebellum, appear to be relatively preserved in WMS (Reiss et al., 2000).

Anomalies in vermal size have been reported in other neurogenetic syndromes and psychiatric disorders. Individuals with fragile X syndrome and a subgroup of individuals with autism have been observed to have decreased posterior vermis size, though the autism literature is still considered controversial (Courchesne et al., 1988; Reiss et al., 1988; Guerreiro et al., 1998; Mostofsky et al., 1998a; Saitoh and Courchesne, 1998; Levitt et al., 1999). Both persons with fragile X and autism typically display socially avoidant behaviors and problems with social intelligence, communication, and linguistic prosody (Cohen et al., 1988, 1991; Njardvik et al., 1999; Robertson et al., 1999). Similarly, individuals with velo-cardio-facial syndrome (VCFS) and Joubert syndrome, two other neurogenetic disorders in which affected individuals typically have social and communication problems, also show vermal hypoplasia (Holroyd et al., 1991; Eliez et al., 2001). The social problems associated with these conditions can be contrasted with the hypersocial behavior and proportional cerebellar increases typical of persons with WMS (Jones et al., 2000). Cumulatively, these data suggest that the cerebellum may be an essential component of the neuroanatomic substrate of socio-emotional behavior.

Our findings demonstrate a possible biological etiology for the neurological problems seen in WMS. In

addition, our data supports the growing body of information that implicates the cerebellum in higher cognitive ability and behavior. However, the mechanism of posterior vermis involvement in this broad array of functions is uncertain; nor is it clear that disorders with different genetic etiologies influence vermal morphology via similar channels, regardless of similarities in behavioral phenotype. It is probable that the true nature of the posterior vermis is more basic, such as the modulation of sensory information, which might simultaneously impact many higher cognitive and behavioral functions. One limitation of the present study is the inability to dissociate what components of the WMS behavioral phenotype truly are linked to the observed vermal increases. Though the proportional vermal increases in WMS seem to be relatively unique in the field of neurogenetics, this study does not directly compare subjects with WMS to other groups with mental retardation. Further studies, particularly utilizing functional imaging as a probe of in vivo neurocognitive network activation, could help to dissociate what components of cognition and emotion have substrates in the cerebellum. The study of Williams syndrome and other neurogenetic disorders provides a rare opportunity to examine specific genetic influences on behavior, neuroanatomy, and neurodevelopment.

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