Morphology and Morphometry of the cerebellum in Williams syndrome: A T1-weighted MRI study

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Background. Williams Syndrome (WS) is a rare genetic disorder, with an estimated incidence of 1 in 25000 births, caused by the deletion of one copy of about 20 contiguous genes on the long arm of the chromosome 7 (Korenberg et al., 2000). Most individuals with WS show cognitive areas of strength and weakness in different cognitive domains. Previous neuroimaging studies have been performed to identify anatomical correlates accounting for the cognitive profile observed in individuals with WS. The most consistent findings indicate the presence of occipital and parietal cortex abnormalities which may account for the visuo-spatial deficits occurring in WS (Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Eckert et al., 2005). In the face of overall reduction in brain volume, the preservation of the cerebellar volume in individuals with WS seems to be a consistent result across studies (Chang et al., 2007; Schmitt et al., 2001, Reiss et al., 2000; Jerningan and Bellugi, 1990). Previous neuroimaging investigations in WS cerebellum have mainly identified cerebellar abnormalities and indirectly interpreting these abnormalities with clinical and behavioural characteristics. An approach providing additional information is to correlate the cerebellar volume with behavioural measures, in order to identify cerebellar characteristics potentially accounting for specific clinical features. In the present study we first identify cerebellar volume abnormalities in WS by comparing three vermian subregions of interest (one for the anterior and two for the posterior vermis) for patients and controls. To directly associate the cerebellar vermis volume to neuropsychological investigations we correlate the three cerebellar subregion measures to behavioural measures of an extensive cognitive battery. Finally, to find a geometric model that could account for the anomalous cerebellar shape of individuals with WS, we apply a geometric form that better approximates the shape of the cerebellum of patients and controls.

Methods. Twelve subjects with WS and 13 typically developing control subjects were recruited for this study. In all WS subjects, the clinical diagnosis was confirmed by genetic investigation (FISH), which showed the characteristic deletion on chromosome band 7q11.23. Behavioural assessment. An extensive neuropsychological battery was administered to each WS subject. The following cognitive domains were explored: a) global cognitive functioning b) linguistic abilities; c) visuo-motor and visuo-spatial abilities; d) verbal and visuo-spatial short-term memory. Images acquisition. Brain MRI scans were performed at 1.5T (Siemens, Magnetom Vision, Erlangen, Germany). Image preprocessing. To obtain measurements in WS cerebellum native space, each image was processed according to previous published protocol (Mostofsky et al., 1998; Schmitt et al., 2001). To adjust cerebral measurements for individual and group differences in brain size, a second set of data was created by linearly registering each brain volume to the Montreal Neurological Institute 305-template (Collins et al., 1994), hereafter referred to as data in scaled space. Cerebellum Volume. The cerebellum was manually outlined in native and also in scaled space delineating the boundaries. Briefly, after selecting the most medial sagittal MRI section and following major fissures, the cerebellum was subdivided into three subregions of interest (ROIs) by circumscribing lobules I–V, VI–VII, and VIII–X separately (see Figure 1, upper panel). In order to investigate difference in the cerebellum shape we approximated the cerebellum midsagittal slice to an ellipse. Approximating ellipse was found according to the following criteria: the ellipse of minimal area among all those that enclose the whole cerebellum slice. Ellipses were centred at the barycentre of the cerebellum slice. Features of the ellipses scrutinized for statistical differences were: the semi-axes length A, B and the ratio A/B (see Figure 1, lower panel for an exemplification). Results. Neuropsychological assessment. As expected, the scores of WS group were lower than controls on tests assessing visuo-motor and visuo-spatial abilities. Moreover, WS subjects performed poorly on tasks exploring sentence repetition and sentence comprehension. Cerebellum Volume. We found that controls have a larger anterior cerebellum portion (lobules I–V) in absolute value (t(23)= 3.15; p = 0.004). After normalization (scaled space) WS group showed a larger posterior cerebellum portion (lobules VI–X) compared with controls (t(23) = -2.701; p = 0.015). Specifically, lobules VI–VII contributed to determine the significant difference between WS subjects and controls in the posterior cerebellum (t(23)= -2.506; p = 0.03). No differences were found neither in all the other subregions neither in the total cerebellum volume, both in the absolute and scalar space. Cerebellum Shape. We found that cerebellum in WS group show a significant different A/B ratio compared with control subjects in scaled space (t(23) = -2.903; p = 0.03) suggesting for a atypical relation between the width and the height (see Figure 1). Correlation between neuropsychological measures and cerebellum volumes. The analysis of Pearson's correlation were performed among neuropsychological scores adjusted for individual and group differences in brain size. We found that anterior cerebellar lobule measures significantly correlated with linguistic ability scores (Sentence Comprehension Test r = -0.79, p = 0.02; and Sentence Repetition r = -0.85, p = 0.007) and with short-term memory ability scores, such as verbal short term memory (DIGIT Span Task r = -0.9; p = 0.002), and visuo-spatial short-term memory (Corsi Blocks Task r = -0.82; p = 0.013). Posterior cerebellum lobule measures were significantly correlated with linguistic ability scores (Sentence Comprehension Test r = -0.79, p < 0.001; and Peabody Picture Vocabulary Test r = -0.79; p = 0.02), with phonological word fluency (Phonological Fluency Test r = -0.88; p = 0.004), and with visuo-motor abilities (Developmental Test of Visual-Motor Integration r = -0.72; p = 0.043).

Discussion. Our results showed behavioural and brain gross-anatomy abnormalities in individuals with WS. The direct correlation between volumes of cerebellar subregions and measures of cognitive abilities has provided interesting results on the comprehension of some patho-physiological aspects underlying the clinical features of WS.

Figure 1. Volume and shape measurements in WS group and Control Subjects

Upper Panel: Circumscription of the cerebellar vermis on the midsagittal image. The vermis was divided into three portions: the anterior vermis lobules I–V- in red, the posterior lobules lobules VI–VII in green, and lobules VIII–X in blue. Lower Panel: Cerebellar Shape approximation. The figure simplifies how shape measurement was performed. In green the ellipse; in pink the vertical semi-axis; in orange the horizontal semi-axis. W_m_15= subject with William syndrome, male, 15 years hold; C_m_13=...