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Cerebellar vermis abnormalities and cognitive functions in individuals with Williams syndrome

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ABSTRACT

In Williams syndrome (WS) cerebellar measures were only indirectly related to behavioral outcomes. T1-weighted magnetic resonance images and neuropsychological data were acquired to investigate whether cerebellar vermis differences were present in 12 WS individuals compared with 13 chronological age-matched controls and whether WS cerebellar vermis measures were related to cognitive scores. In WS participants, we observed a significant increase in the volume of the posterior superior cerebellar vermis (lobules VI–VII) and an atypical ratio between width and height of the cerebellar vermis. Furthermore, we found an inverse correlation between cerebellar posterior vermis volume and scores on implicit learning, phonological fluency and the verbal short-term memory tasks. The present study supported a role for the posterior cerebellar vermis in higher cognitive processes and indicated that the cerebellar vermis abnormalities (enlargement) in WS individuals have an effect in worsening the cognitive performance in specific domains.

1. Introduction

Traditionally, the cerebellum has been related to the control of motor coordination, balance and motor speech. During recent decades, however, results from neuroanatomical, neuroimaging, experimental and clinical studies have substantially extended the cerebellar role to cognitive and affective regulation (Stoodley & Schmahmann, 2010). Specifically, neuroanatomical studies have shown cerebellar connectivity with associative areas of the cerebral cortex involved in higher cognitive functions, and functional neuroimaging has provided evidence of cerebellar activation during a variety of cognitive tasks such as problem-solving, working memory, verb generation and attention (Pope & Miall, 2012; Tian et al., 2011; Villanueva, 2012). Moreover, neuropsychological research developed sensitive tests allowing identifying specific cognitive and affective disturbances following cerebellar damage (Tedesco et al., 2011).

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Although most researches focus on the contribution of cerebellar hemispheres in cognition (Roldan Gerschcovich, Cerquetti, Tenca, & Leiguarda, 2011; Stoodley & Schmahmann, 2010), it has also pointed out that even the vermis is involved in cognitive operations, as abstract reasoning, verbal and visual memory, language, classical conditioning and sequence learning (Bolduc et al., 2011, 2012; Desmond & Fiez, 1998; Hodge et al., 2010; Middleton & Strick, 1994; Okugawa, Nobuhara, Takase, & Kinoshita, 2007; Paul et al., 2009).

Cerebellar vermis abnormalities have been described in several neurodevelopmental disorders. For example, alterations in cerebellar vermis size have been documented in Attention Deficit Hyperactivity Disorder (ADHD) (Bledsoe, Semrud-Clikeman, & Pliszka, 2011), fragile X syndrome (Mostofsky et al., 1998), 22 deletion syndrome (Eliez, Schmitt, White, Wellis, & Reiss, 2001), and Williams syndrome (WS) (Schmitt, Eliez, Warsofsky, et al., 2001).

WS is a neurogenetic disorder with an estimated incidence of up to 1 in 7500 live births (Strømme, 2002) and with documented physical, cognitive, behavioral and neuroanatomical expressions. It is caused by a hemideletion on chromosome 7q11.23, which includes about 17–25 genes (Korenberg et al., 2000). The medical abnormalities of WS individuals include facial dysmorphology, hyperacusia, cardiovascular, renal, musculoskeletal and endocrine malfunctions (American Academy of Pediatrics, 2001; Pober & Dykens, 1996). Although a high variability in cognitive and behavioral performance has been described in the WS population (Porter & Coltheart, 2005, 2006), studies on cognitive and psychopathological functioning have documented specific features in WS. Mild to severe intellectual disability co-occurs with relatively spared language, exceptional facial recognition, and severe deficits in visuo-spatial processing, exploration, executive functions and implicit learning (Atkinson et al., 2001; Bellugi, Lichtenberger, Jones, Lai, & St George, 2000; Foti et al., 2011; Mandolesi et al., 2009; Menghini, Addona, Costanzo, & Vicari, 2010; Vicari, Verucci, & Carlesimo, 2007). As for psychiatric disorders, anxiety is the most prevalent disorder in WS individuals (Dodd & Porter, 2009). Hyperactivity and attention/concentration problems are also described and the presence of ADHD has been reported in 43% of WS individuals (Bedeschi et al., 2011; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Leyfer, Woodruff-Borden, & Mervis, 2009; Stinton, Elison, & Howlin, 2010). Mood disorders (depression, dysthymia, manic-depressive disorder) have been found in 13–15% of WS individuals (Dodd & Porter, 2009).

Despite the overall reduction of brain volume in WS individuals, neuroimaging studies have described a preserved (Chiang et al., 2007; Reiss et al., 2000) or even enlarged (Jernigan & Bellugi, 1990; Schmitt, Eliez, Warsofsky, et al., 2001) cerebellar vermis when manually traced volume measurements (region of interest technique – ROI) were applied. When automated measures were employed (Campbell et al., 2009; Menghini et al., 2011; Meyer-Lindenberg et al., 2004; Reiss et al., 2004), however, results did not confirm the manually obtained data. In fact, some studies found increased regional gray matter volume in the posterior right cerebellum (Campbell et al., 2009; Menghini et al., 2011), whereas others reported left cerebellar superior intermediate and inferior hemispherical zone reduction (Eckert et al., 2006; Reiss et al., 2004). These controversial findings are likely related to the abnormalities in WS brain shape and size, which introduce a bias during the image pre-processing phase of automated analyses.

The purpose of the present study was twofold. First, we sought to determine whether cerebellar vermis volume measured by the ROI technique differed between a WS sample and a sample of typically developing controls. Although operator-dependent and time-consuming, the ROI is a well-validated approach, limits bias of automated measures and it is strongly suggested especially when interested in brain regions with a high regional specificity (Di Paola et al., 2010). Based on a previous study of the cerebellum in WS (Schmitt, Eliez, Warsofsky, et al., 2001), we hypothesized significantly larger posterior cerebellar vermis volume and atypical relation between width and height in the cerebellar vermis in WS participants. Furthermore, we correlated the vermian volumes with the scores obtained on an extensive neuropsychological battery to identify whether and how cerebellar vermis characteristics are related to specific cognitive features of individuals with WS. Indeed, although the cognitive phenotype of WS individuals has often been linked to their cerebellar abnormalities, to date no study has directly correlated cerebellar vermis structural data with cognitive measures in the same WS individuals.

2. Methods

2.1. Participants

WS participants were recruited at the Bambino Gesù Children's Hospital in Rome, one of the main national landmark hospitals for WS patients and their parents. Bambino Gesù Children's Hospital follows these patients for medical and neuropsychiatric conditions from birth across the lifespan with periodic follow-ups. Twelve WS individuals (5 women; age $M = 18.6$, $SD = 6.0$ years, range 13–30 years) and 13 age-matched controls (6 women; age $M = 18.5$, $SD = 5.6$ years, range 12–29 years), all right-handed, participated in this study. MRI images of participants have already been reported in previous studies on gray matter cerebral changes (Menghini et al., 2011) and the corpus callosum (Luders et al., 2007; Tomaiuolo et al., 2002).

In all WS individuals, the clinical diagnosis was confirmed by genetic investigation (FISH). Exclusion criteria were the presence of neurosensory deficits, such as hypoacusia or severe visual impairments, and epilepsy.

Participants in the control group were matched by mean chronological age to participants with WS. All participants came from upper-middle-class families, as assessed by a short questionnaire addressed to participants or their caregivers. Observations were carried out after informed consent had been obtained from all participants and their families.