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Cerebral and cerebellar MRI volumes in Williams syndrome

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ABSTRACT

Individuals with Williams syndrome (WS) present a set of cognitive, affective and motor symptoms that resemble those of patients with lesions to the cerebellum. Although there is some evidence for overall structural alterations in this brain region in WS, explorations on cerebellar white matter and cerebellar cortex volumes remain rather neglected. We aimed to compare absolute and relative cerebellar volumes, as well as patterns of white matter to cortex volumes in this brain region, between a group of individuals with WS and a group of healthy controls. T1-weighted magnetic resonance images were acquired in 17 individuals with WS and in 15 typically developing individuals. Our results showed that even though individuals from the clinical group had significantly smaller cerebrums (and cerebellums), cerebellar volumes relative to intracranial volumes were significantly enlarged. In addition, while gray matter was relatively spared and white matter disproportionately reduced in the cerebrum in WS, relative cerebellar cortex and white matter volumes were preserved. These findings support the hypothesis that volume alterations in the cerebellum are associated with the cognitive, affective and motor profiles in WS.

1. Introduction

The traditional role of motor coordination attributed to the cerebellum has been challenged by a more complex view, one that encompasses its involvement in cognitive and emotional processing (Stoodley & Schmahmann, 2010). There is ample evidence that sensorimotor functions rely on the interconnections between the cerebellum and the spinal motor systems (Grodd, Hülsmann, Lotze, Wildgruber, & Erb, 2001; Nitschke, Kleinschmidt, Wessel, & Frahm, 1996; Oscarsson, 1965; Schmahmann, 2004). However, fronto-cortico-cerebellar connections are believed to be involved in higher cognitive functions such as language and executive functions (Makris et al., 2005; Schmahmann, 2001), while cerebro-cerebellar-limbic loops are thought to be implicated in emotional regulation and processing (Stoodley & Schmahmann, 2010).

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Indeed, there is mounting functional evidence showing cerebellar activations in language, executive, visual-spatial and affective tasks (Desmond, Gabrieli, & Glover, 1998; Fink et al., 2000; Harrington et al., 2004; Hofer et al., 2007; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005; Vingerhoets, De Lange, Vandemaele, Deblaere, & Achten, 2002; Xiang et al., 2003). Clinical findings also support the notion of a multifold role of the cerebellum, as lesions in different areas of this brain structure lead to distinctive motor, cognitive and affective impairments. In this line, executive, visual spatial and linguistic impairments, along with affect dysregulation (including exacerbated anxiety and hyperspontaneous, disinhibited behavior) have been reported in patients with cerebellar lesions (for a review, see Stoodley & Schmahmann, 2010). This cluster of symptoms was termed *cerebellar cognitive affective syndrome* (Schmahmann & Sherman, 1998) and, depending on the affected cerebellar lobe, has been found to occur independently but also concomitantly with the cerebellar motor syndrome (Schmahmann, MacMore, & Vangel, 2009).

The overlap and similarities between most of the aforementioned cognitive, affective and motor symptoms of cerebellar damage and the features displayed by individuals with Williams syndrome (WS) is quite striking. WS is a neurodevelopmental disorder with an estimated prevalence of 1 in 7500 live births (Strømme, Bjømstad, & Ramstad, 2002). It is caused by a submicroscopic deletion on chromosome 7 (region 7 q11.23), including the elastin gene (ELN) (Korenberg et al., 2000). Individuals with this syndrome present distinctive features such as elfin-like face, small stature, hyperacusis, as well as cardiovascular, endocrine and connective tissue abnormalities (Udwin, 2002). Impairments in the cognitive domain include moderate intellectual disability (Howlin, Davies, & Udwin, 1998; Sampaio et al., 2009), language alterations (e.g., in syntax, morphology, phonology, pragmatics and narrative (Brock, 2007; Gonçalves et al., 2010; Karmiloff-Smith, Brown, Grice, & Paterson, 2003)), compromised executive functioning (Osório et al., 2012; Porter, Coltheart, & Langdon, 2007; Rhodes, Riby, Park, Fraser, & Campbell, 2010) and deep visual-spatial difficulties (Atkinson et al., 2003; Bellugi, Korenberg, & Klima, 2001). Individuals with WS are also well-known for their hypersociability, which manifests itself in the form of uninhibited and indiscriminate social approach behaviors (Capitão et al., 2011; Jones et al., 2000). Concomitantly, various reports underline the high incidence of anxiety disorders, particularly specific phobias and generalized anxiety disorder (Dykens, 2003; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006). In addition, WS is characterized by poor motor coordination, odd gait and hypotonia (Chapman, du Plessis, & Pober, 1996; Trauner, Bellugi, & Chase, 1989)

Recently, some researchers began to explore structural changes in the cerebellum in WS. Indeed, the cerebellum appears macroscopically enlarged in WS, relative to a small cerebrum (Jones, Hesselink, Duncan, Matsuda, & Bellugi, 2002; Schmitt, Eliez, Bellugi, & Reiss, 2001). Reports of overall brain volume reductions in comparison to healthy controls range from around 13% to 18% (Reiss et al., 2000; Sampaio et al., 2008), while cerebellar volumes appear to be reduced to a lesser extent (e.g., 7%, Reiss et al., 2000). However, data so far appear inconsistent—while some authors found evidence for a relative increase in cerebellar volume (Jones et al., 2002; Reiss et al., 2000), others reported volume preservations in this structure using either manual (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993) or semi-automated segmentation methods (Chiang et al., 2007). Furthermore, patterns of white matter to cortical volumes in the cerebellum seem to be distinct from those observed in the rest of the brain. Reiss et al. (2000) reported a relative sparing of cerebral gray matter along with a disproportionate reduction in white matter in individuals with WS, when compared with a healthy control group. Conversely, no such disproportionate reduction was found in the cerebellum, where white matter volumes were relatively preserved. Apart from this important investigation, no further studies explored white matter-cortex proportions in the cerebellum, so replication is greatly needed.

Our main goal is to compare absolute and relative cerebellar volumes, as well as patterns of white matter to cortex volumes in this brain region, between a group of individuals with WS and a group of healthy controls. By doing so, we aim to provide further insight on how such changes may be involved in their motor, cognitive and affective phenotypes. In accordance with previous findings our hypotheses are as follows: (a) the clinical group will present significantly smaller cerebral volumes than their typically developing counterparts; (b) the clinical group will present a disproportionate reduction in cerebral white matter, but not in gray matter; (c) cerebellar volumes will be preserved in the WS group (no a priori expectations regarding absolute or relative preservation); and (d) such regional volume preservation may be due to a more balanced ratio of cortical to white matter (i.e., a lesser reduction in white matter in the cerebellum than what is observed in the cerebrum).

2. Materials and methods

2.1. Participants

Participants were distributed in two groups: a group of 17 individuals with WS (10 females; aged 11–32; *M*, *SD* = 19.24, 6.04 years) and a control group of 15 individuals (8 females; aged 11–28; *M*, *SD* = 19.20, 5.55 years). Participants in the WS group tested positive in fluorescence in situ hybridization (FISH) for deletion of the elastin gene in chromosome 7 (Ewart et al., 1993), and the presence of any sensorial or speech disorder, as well as comorbidity with severe psychopathology not associated with the syndrome were defined as exclusion criteria. The control group was composed of typically developing individuals without a history of sensorial, psychiatric, or neurological disorder or cognitive impairment. Table 1 displays the main socio-demographic characteristics of the sample. The groups did not differ significantly in terms of age, $t(30) = 0.02$,