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MRI amygdala volume in Williams Syndrome

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ABSTRACT

One of the most intriguing characteristics of Williams Syndrome individuals is their hypersociability. The amygdala has been consistently implicated in the etiology of this social profile, particularly given its role in emotional and social behavior. This study examined amygdala volume and symmetry in WS individuals and in age and sex matched controls. Magnetic resonance imaging scans were obtained on a GE 1.5-T magnet with 1.5-mm contiguous slices and were used to measure whole gray matter, white matter and cerebrospinal fluid volumes, as well as amygdala volume (right and left). Results revealed significantly reduced intracranial volume in individuals with WS, compared with controls. There were no differences between groups in absolute amygdalae volume, although there was a relative increase in amygdalae volumes, when adjusted for total intracranial content. There were no inter-hemispheric differences in amygdalae volumes in both groups. These results suggest a relative increase in amygdala volume in WS compared with healthy controls that likely reflects abnormal neurodevelopmental processes of midline brain structures.

1. Introduction

Williams Syndrome (henceforth WS) is a rare genetically determined neurodevelopmental disorder with an estimated incidence of 1 in 7500 to 20 in 30,000 births (Strømme, Bjømstad, & Ramstad, 2002) and is caused by a hemideletion on chromosome 7q11.23 (Ewart et al., 1993; Peoples et al., 2000). Individuals with WS display an unusual phenotype, which includes a distinctive profile of physical, medical, neurocognitive, behavioral, and neuroanatomical characteristics. One of the most striking features of individuals with WS is a distinctive social-affective profile, characterized by high sociability, disinhibition, over-friendliness (Bellugi, Adolphs, Cassady, & Chiles, 1999; Klein-Tasman & Mervis, 2003), and strong empathy (Klein-Tasman & Mervis, 2003). Indeed, individuals with this syndrome reveal a facility for making social contacts as well as being particularly sensitive to others' feelings. Many aspects of this social profile (in particular the attraction to social interaction) are evident in early childhood, suggesting that this aspect of the WS phenotype may be independent of other cognitive impairments and pervasive across age spans (Jones et al., 2000).

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The etiology of this social phenotype is still unknown. However, the role of the amygdala has consistently been hypothesized as being implicated in the WS social phenotype (Bellugi et al., 1999; Capitao et al., 2011; Meyer-Lindenberg, Hariri, et al., 2005). In general, the amygdala modulates a large variety of psychological functions, such as emotional expression and processing, including emotional facial expression recognition (e.g., Adolphs, Tranel, Damasio, & Damasio, 1994, 1995), emotional memory (e.g., Cahill, Babinsky, Markowitsch, & McGaugh, 1995), emotional auditory recognition (e.g., Scott et al., 1997) and fear conditioning (e.g., LeDoux, 1998). It is thus an important component of the neural network that underlies social cognition (Adolphs, 1999, 2003), playing a key role in processing social-related stimuli (Adolphs, 1999, 2003) and monitoring environmental events such as danger (Amaral, 2002).

These findings, have led some researchers to propose that abnormal amygdala processing may be responsible for the hypersocial behavior typical of WS phenotype (Galaburda & Bellugi, 2000; Reiss et al., 2004). In fact, researchers have used neuroimaging technology in an attempt to tackle the neural substrates involved in the WS social-affective profile (Meyer-Lindenberg, Hariri, et al., 2005). However, structural magnetic neuroimaging studies have produced inconsistent results regarding volume and gray matter density of the amygdala in WS. More specifically, absolute volume of the amygdala in WS was found to be similar to comparison groups, using both manual segmentation methods [either analyzed within limbic system structures (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993) or individually (Martens, Wilson, Dudgeon, & Reutens, 2009; Reiss et al., 2004)] and automatic segmentation methods (e.g., voxel-based morphometry) (Chiang et al., 2007; Reiss et al., 2004). In parallel, disproportional enlargement of this structure, characterized by relative increases in volumes and gray matter density have also been reported in WS (Martens et al., 2009; Reiss et al., 2004). Contradictory findings, however, have also been reported by Meyer-Lindenberg and collaborators, where a relative increase of amygdala gray matter density was not observed in WS (Meyer-Lindenberg et al., 2004). Negative findings with respect to increased amygdala volume have also been reported in a post-mortem study (Galaburda & Bellugi, 2000). Such inconsistencies among studies are likely due to the use of different methods to analyze amygdala structure and volume and the use of different groups of individuals with WS (with intelectual disabilities or normal IQ), making it difficult to take definitive conclusions concerning amygdala volumetric differences in WS.

Given the inconsistent findings for amygdala involvement in WS and our previous neuropsychological study partially supporting the amygdala contribution to WS hypersociability (Capitao et al., 2011), the aim of this study was to analyze amygdala volumes in individuals with WS and in typically developing controls matched for sex and age, by employing a manual tracing method performed in realigned native space. This manual tracing methods allows for a more rigorous analysis, in comparison with surface analysis, since this method uses simultaneous images of the coronal, sagittal and axial views (Martens et al., 2009).

2. Method

2.1. Participants

Study participants included 17 individuals with WS (7 males and 10 females) (19.29 ± 6.29; age-range: 11–34 years) and 16 healthy controls individually matched for sex and age[2] (7 males and 9 females) (19.88 ± 6.67; age-range: 11–34 years). Mean Full Scale IQ was 52.27 (± 9.79) for WS and 108 (± 10.31) for controls. WS diagnoses were made by FISH confirmation of elastin gene deletion (Ewart et al., 1993). Controls were typically developing individuals without evidence of psychiatric, neurological disorder or cognitive impairment. After a complete description of the study, each participant or their guardians gave written informed consent for the participation in the study via consent forms. All participants were right-handed, determined through clinical interview.

Table 1 displays socio-demographic characteristics of the sample. There was no significant group differences in the socio-demographic characteristics, including age ($t(31) = -.257$, $p = .80$) and socio-economical status—Graffar index ($Z = -.160$, $p = .90$), although the groups did differ in education level ($Z = -2.70$, $p < .01$) and in IQ ($Z = -4.33$, $p < .001$) (data is shown in Table 1).

2.2. MRI acquisition and processing

MRI images were obtained on a 1.5 T General Electric system (GE Medical Systems). The scans acquisition protocol consisted of contiguous 1.5-mm coronal T1 slices of the whole brain and an axial PD/T2 sequence. The parameters used were echo time: 5.0 ms, repetition time: 35 ms, flip angle: 45°, acquisition matrix: 256×192, voxel dimensions: $0.9375\ \text{mm} \times 0.9374\ \text{mm} \times 1.5\ \text{mm}$). Images were aligned and resampled ($0.9375\ \text{mm}^3$, cubic interpolation) and an atlas-based expectation maximization segmentation was used (Pohl, Bouix, & Kikinis, 2004).

2.3. Region of interest definition

The amygdala was outlined manually using the 3D Slicer Software (http://www.slicer.org/) in realigned native space coronal images (Fig. 1), with guidance from sagittal and coronal views. Segmentation was performed in coronal slices from anterior to posterior. In the anterior border, the first slice of the amygdala was identified at the level where the white matter

[2] One participant was matched for two subjects with WS.