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Williams syndrome-specific neuroanatomical profile and its associations with behavioral features

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ABSTRACT

Williams Syndrome (WS) is a rare genetic disorder with unique behavioral features. Yet the rareness of WS has limited the number and type of studies that can be conducted in which inferences are made about how neuroanatomical abnormalities mediate behaviors. In this study, we extracted a WS-specific neuroanatomical profile from structural magnetic resonance imaging (MRI) measurements and tested its association with behavioral features of WS. Using a WS adult cohort (22 WS, 16 healthy controls), we modeled a sparse representation of a WS-specific neuroanatomical profile. The predictive performances are robust within the training cohort (10-fold cross-validation, AUC = 1.0) and accurately identify all WS individuals in an independent child WS cohort (seven WS, 59 children with diverse developmental status, AUC = 1.0). The WS-specific neuroanatomical profile includes measurements in the orbitofrontal cortex, superior parietal cortex, Sylvian fissures, and basal ganglia, and variability within these areas related to the underlying size of hemizygous deletion in patients with partial deletions. The profile intensity mediated the overall cognitive impairment as well as personality features related to hypersociability. Our results imply that the unique behaviors in WS were mediated through the constellation of abnormalities in cortical-subcortical circuitry consistent in child WS and adult WS. The robustness of the derived WS-specific neuroanatomical profile also demonstrates the potential utility of our approach in both clinical and research applications.

1. Introduction

Williams Syndrome (WS) is a rare multi-system disorder caused by hemideletion of ~26 genes on chromosome 7. Although the cognitive impact of WS is evident in general intelligence and visuospatial capabilities, the cardinal feature of WS cognition is overly social behavior (Pober, 2010). WS individuals express heightened social approach behavior and social emotional behavior very early on, distinguishing them from others with disorders that include intellectual impairment (Doyle et al., 2004). This had led to extensive research using magnetic resonance imaging (MRI), in the hope of identifying the mediating neural processes from genetic deletions to social behavioral impact (Martens et al., 2008). Previous MRI studies had found that what distinguishes WS from other genetic disorders with intellectual impairment — e.g., Down syndrome — is not the reduced total brain volume per se, but the aberrant regionalization of the brain (Jernigan and Bellugi, 1990). The most consistent findings are the gyral patterns in the superior parietal regions and orbital frontal cortex, which were found to be different between WS patients and healthy individuals (Gaser et al., 2006; Kippenhan et al., 2005; Meda et al., 2012; Meyer-Lindenberg et al., 2004).

Yet the specificity of these findings to WS and relevance to its distinct behavioral features were left unanswered. Differences in regional cortical surface area, such as in lingual gyrus, post-central

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gyrus, and temporal poles, were also reported (Thompson et al., 2005; Wang et al., 2013). Abnormalities in the Sylvian fissures (Eckert et al., 2006) and disproportional volumetric changes of subcortical structures were also reported, but not consistent (Meyer-Lindenberg et al., 2004; Martens et al., 2009; Capitao et al., 2011; Meda et al., 2012). Furthermore, the diagnostic process for WS requires that clinicians identify individuals with WS features and use fluorescent in situ hybridization (FISH) to confirm. This precludes identification of individuals who have different deletions in the WS chromosome region (WSCR), resulting in slightly altered profiles of WS features. A recent analysis focused on cases of individuals with atypical deletions in the WSCR suggested that the varying size of the deletion would result in different behavioral profiles (Hoeft et al., 2014), which conceivably would make it difficult to identify those individuals in clinical settings. The rarity of both typical and atypical WS individuals makes the quantitative comparisons across MRI measures and groups impractical.

Here, we re-examined the WS-specific neuroanatomical profile using a novel analytic approach with the aim of developing a scoring system to quantify WS neuroanatomical variations. First, we extracted the WS-specific neuroanatomical profile from an adult WS cohort, using multiple measures derived from structural MRI of cerebrum, including subcortical volumes, cortical surface area (Dale et al., 1999; Fischl et al., 1999), sulcal depth (Kippenhan et al., 2005), and cortical surface geometry (Fan et al., 2015). To deal with the large number of MRI measures and limited sample size, we used an elastic-net model to achieve balance between the robust prediction and sparseness for easy interpretation. The resulting model provides the basis for calculating WS neuroanatomical scores that represent the similarity of an individual's brain to the WS given his/her multimodal MRI features. The generalizability of the WS-specific neuroanatomical profile was then tested in an independent child WS cohort. After establishing the generalizability of the model, we examined whether the WS neuroanatomical scores could reflect the reduced size of genetic deletions in WSCR and whether the scores were associated with the behavioral features of WS.

2. Materials and methods

2.1. Participants

All participants were recruited as part of a multi-project program, including two cohorts in current analyses, one as child cohort and the other as adult cohort. Except time of recruitment, age differences, additional diagnostic groups, and behavior measures, the protocols for inclusion and imaging acquisition were kept the same, which were described in separate publications (Eckert et al., 2006; Mills et al., 2013). Participants were screened based on the following measures: normal or corrected vision/hearing, English native-language speaker, and no remarkable mental health history. Caregivers completed an interview and extensive demographic and family history questionnaires to assess whether participants met the screening criteria. Caregivers and child participants provided consent and assent, respective, for participation. Individuals with intellectual disabilities required a more simple, verbally delivered description for assent along with guardian informed consent. All procedures were explained in person, within the testing environment, with the caregiver present, to show the participants more concretely what to expect. They could choose at any time to withdraw from participation, even after beginning. Study protocols were approved by the Institutional Review Boards at the Salk Institute and at UCSD.

2.1.1. Adult WS cohort

The adult cohort, on which the WS-specific neuroanatomical profile was trained, consisted of 22 individuals with “typical” WS deletions (approximately 26 genes in the WSCR 7q11.23 region) as well as 16 healthy controls (HC) (Table 1). Part of this cohort has been involved in a series of MRI studies for WS that were published elsewhere (Eckert et al., 2006; Van Essen et al., 2006). The diagnosis of WS was based on clinical presentation (WS Diagnostic Score Sheet) and confirmation of meeting genetic criteria for WS using fluorescent in situ hybridization. HCs were screened for a history of neurological disorders, psychiatric illness, and substance abuse. Intellectual functioning was assessed with the age-appropriate version of the Wechsler tests to include the Wechsler Adult Intelligence Scale 3rd Edition, Wechsler Abbreviated Scale of Intelligence (WASI), and Wechsler Intelligence Scale for Children 3rd Edition WISC-III (Wechsler, 2008). Sociability was assessed with the Salk Institute Sociability Questionnaire (SISQ) (Doyle et al., 2004).

2.1.2. Child cohort

The generalizability of the WS-specific neuroanatomical profile was tested with a cohort of 60 children (age range 6 to 13 years): seven individuals with WS, 23 typical developing children (TD), and 30 individuals with heterogeneous diagnoses to include high-functioning autism (HFA), specific language impairment (SLI), and focal lesions in the brain (FL). The demographic characteristics of each cohort are shown in Table 1. Children with WS were diagnosed using the same criteria as adults with WS. Subjects in the TD group were recruited from the community, had scores on a standardized test of intellectual functioning (WASI) in the normal range and no history of developmental or language delay. Individuals with HFA, SLI, and FL were recruited from populations at a local pediatric neurology clinic and a clinic for speech and language disorders (Mills et al., 2013). Detailed recruiting procedures and diagnostic criteria can be found in previously published studies (Mills et al., 2013).

2.1.3. Individuals with atypical deletions in WSCR

We further examined if the scores from the trained model for WS-specific neuroanatomical profile can identify whose brain phenotypes lie between WS and HC, such as individuals with reduced deletion size on WSCR. We tested our model on five individuals from one family with small deletions on chromosome 7q11.23, sparing regions coding for *FZD9*, *GTF2I*, and *GTF2IRD1* (Hoeft et al., 2014).

2.1.4. Imaging acquisition and extracting multimodal MRI features

All participants were scanned on a 1.5 Tesla MRI scanner (GE HDxt, echo time (TE) = 3.0 ms, repetition time (TR) = 8.7 ms, inversion time = 270 ms, flip angle = 8°, field of view = 24 cm, voxel size = 1.25 × 1.25 × 1.2 mm). To reduce and prevent possible motion artifacts, real-time prospective motion tracking and correction (PROMO) was used for all participating subjects (White et al., 2010; Brown et al., 2010). Distortions caused by nonlinearity of the spatial encoding gradient fields were corrected with predefined nonlinear transformations (Jovicich et al., 2006). Non-uniformity of signal intensity was reduced with the nonparametric nonuniform intensity normalization method (Sled et al., 1998). After initial image data inspection and quality control, T1-weighted images underwent automated volumetric segmentation and cortical surface reconstruction using methods implemented in Freesurfer software (Dale et al., 1999; Fischl et al., 1999). This automated processing corrects variations in image intensity due to RF coil sensitivity inhomogeneities, registers to a common reference, then segments volumes into cortical and subcortical structures. For each cohort, one staff research associate performed quality control (QC) of the surfaces and segmentations for all MRI images at the same time, blind to age and group identification. Both the child cohort and the adult cohort went through the same QC processes. The segmentations and reconstructed surfaces were inspected for accuracy, manually edited using control points, and iteratively reprocessed, blind to age or group labels, to ensure consistent quality across different cohorts.

Four different morphological measures of T1-weighted images were derived, including the volumes of subcortical structures (Dale et al.,