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Characterizing associations and dissociations between anxiety, social, and cognitive phenotypes of Williams syndrome

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ABSTRACT

Williams syndrome (WS) is a neurogenetic disorder known for its "hypersocial" phenotype and a complex profile of anxieties. The anxieties are poorly understood specifically in relation to the social-emotional and cognitive profiles. To address this gap, we employed a Wechsler intelligence test, the Brief Symptom Inventory, Beck Anxiety Inventory, and Salk Institute Sociability Questionnaire, to (1) examine how anxiety symptoms distinguish individuals with WS from typically developing (TD) individuals; and (2) assess the associations between three key phenotypic features of WS: intellectual impairment, social-emotional functioning, and anxiety. The results highlighted intensified neurophysiological symptoms and subjective experiences of anxiety in WS. Moreover, whereas higher cognitive ability was positively associated with anxiety in WS, the opposite pattern characterized the TD individuals. This study provides novel insight into how the three core phenotypic features associate/dissociate in WS, specifically in terms of the contribution of cognitive and emotional functioning to anxiety symptoms.

1. Introduction

Williams syndrome (WS) is a genetic disorder that stems from a microdeletion on chromosome 7q.11.23 (Korenberg et al., 2000), with prevalence ratings ranging from 1 in 7000–20,000 individuals (Jones & Smith, 1975; Stromme, Bjomstad, & Ramstad, 2002). WS is typified by a multitude of medical and physical abnormalities, e.g., supravalvular aortic and pulmonary stenoses, hypercalcemia, hypotonia, and distinct elfin-like facial features (Pober, 2010). Furthermore, WS is typically associated with mild to moderate cognitive impairment; however, upon meeting a person with WS, these disabilities may not at first be apparent. Specifically, the intellectual impairment of WS is characterized by drastic deficits in visuospatial construction contrasted with markedly higher verbal abilities (Mervis & John, 2010; Searcy et al., 2004). Thus, the non-verbal cognitive deficits are masked by relatively strong expressive language capabilities (Mervis & Velleman, 2011), and engaging social-interactive, verbal and non-verbal communicative behaviors (Järvinen-Pasley et al., 2008; Reilly, Bernicot, Vicari, Lacroix, & Bellugi, 2005; Reilly, Klima, & Bellugi, 1990; Reilly, Losh, Bellugi, & Wulfeck, 2004).

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Individuals with WS exhibit a range of unique social attributes including diminished fear to approach strangers (Doyle, Bellugi, Korenberg, & Graham, 2004; Haas et al., 2009; Järvinen-Pasley et al., 2008), an intensified attraction to faces (Jones et al., 2000), and an exaggerated use of affective and linguistic devices to socially engage others (Losh, Bellugi, & Anderson, 2001). We have pioneered in the development of measures attempting to capture the nature of the unusual social behavior of WS in real-life, e.g., the Salk Institute Sociability Questionnaire (SISQ) (Doyle et al., 2004; Järvinen-Pasley et al., 2010; Jones et al., 2000; Zitzer-Comfort, Doyle, Masataka, Korenberg, & Bellugi, 2007). Our studies and those of others have consistently indicated that individuals with WS demonstrate higher global sociability and approachability toward strangers as compared to any other group tested (Autism, Down syndrome, language impairment, unilateral focal lesions, typical development (TD)). The prosocial nature characterizing WS is well defined by both neuroimaging and behavioral research (Golarai et al., 2010; Gothelf et al., 2008; Haas et al., 2012, 2010, 2009; Haas & Reiss, 2012; Järvinen-Pasley et al., 2008; Meyer-Lindenberg et al., 2005) with some hints from genetic studies (Dai et al., 2009; Jabbi et al., 2012; Karmiloff-Smith et al., 2012; Mervis et al., 2012). Yet these distinctive social traits typically coexist with a multitude of general anxieties and other maladaptive behaviors, as well as intellectual impairment, and it is currently poorly understood how the major phenotypic characteristics of WS may relate to each other.

An accumulating literature consistently indicates that psychopathologies pertaining to anxieties and abnormal fears are among the most common diagnoses within the WS population, and these symptoms also appear relatively stable across development (Dykens, 2003; Dykens, Rosner, Ly, & Sagun, 2005; Einfeld, Tonge, & Florio, 1997; Einfeld, Tonge, & Rees, 2001; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Leyfer, Woodruff-Borden, & Mervis, 2009; Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010). For example, in a large-scale study, Leyfer et al. (2009) examined the prevalence of anxiety disorders in a sample of 132 children with WS by administering the Anxiety Disorder Interview Schedule (ADIS-IV) to their caregivers. Compared to children with developmental disabilities, those with WS were more likely to meet criteria for specific phobia, general anxiety disorder, and separation anxiety, with over 60% of the participants likely to have at least one type of anxiety disorder. In another study, Cherniske et al. (2004) reported that over 60% of the 20 adults with WS tested exhibited moderate to severe anxiety and simple phobias. Notably, studies assessing anxiety in WS have predominantly focused on indexing such individuals' experiences of fear and worry across different contexts (e.g., Dykens, 2003); yet no known studies have elucidated whether anxiety in individuals with WS may actually constitute physiological symptoms (e.g., palpitations, shakiness, abdominal discomfort). This is important as such features are largely incorporated in diagnoses of anxiety and specific phobia disorders (American Psychiatric Association, 2000). Considering that those with WS experience significant cardiovascular and gastrointestinal abnormalities including hypertension, supravalvular aortic stenosis, and diverticular disease (Pober, 2010), which may contribute to their anxiety features, investigations attempting to disentangle the characteristic anxiety in WS as a function of psychological and physical characteristics is of significance. While elevated anxieties in WS have been consistently documented relative to controls with intellectual impairment of unspecified origin (Dykens, 2003; Gosch & Pankau, 1994) as well as other genetic disorders (e.g., Prader Willi Syndrome, Down Syndrome, Fragile X) (Dykens et al., 2005; Einfeld, Tonge, Turner, Parmenter, & Smith, 1999; Sarimski, 1997), comparisons with healthy controls with normal intellectual function are virtually non-existent. This is of important for being able to clarify whether the anxiety features that are typically elevated in individuals with WS may generally pertain to psychological states of worry or fear as noted in the aforementioned research, or whether they may actually closely relate to the physiological symptomatology, or both. Moreover, these comparisons are necessary to understand the potential convergences and divergences between anxiety features, cognitive ability, and social-emotional functioning in WS, as virtually all neurodevelopmental disorders are associated with some degree of social dysfunction as well as atypical cognition.

Only a handful of existing studies have directly examined the association between anxiety and cognition in WS. In one such study, Leyfer et al. (2006) documented no differences in general intellectual functioning between children and adolescents with WS who either met or did not meet the diagnosis of specific phobia. In a similar vein, Woodruff-Borden et al. (2010) reported a lack of association between composite intelligence quotient (IQ) and anxiety in children and adolescents with WS. A recent study by Riby et al. (2013) similarly reported no association between anxiety and cognitive ability in their sample of participants with WS. It is noteworthy here, however, that the study of Riby et al. (2013) did not include a comprehensive assessment of cognitive skill but only utilized single measures tapping into receptive vocabulary (British Picture Vocabulary Scale II) and non-verbal reasoning (Ravens Coloured Progressive Matrices) for a subset of the participants. Moreover, the sample was characterized by a broad age range (6–36 years). It is thus possible that the lack of significant association between anxiety and IQ reflects a developmental effect in light of evidence suggesting that subdomains of intellectual functioning may not reach stability until adolescence (Hopkins & Bracht, 1975). Interestingly, and Porter et al. (2009) tested 20 adults with WS who either met or did not meet the diagnosis of general anxiety, and the groups did not significantly differ in their performance on the Woodcock Johnson Test of Cognitive Ability-Revised. However, upon examining the descriptive trends within the WS sample, the five adults with WS who were diagnosed with general anxiety disorder achieved greater average cognitive scores as compared to those without the anxiety diagnosis. More developmental research evaluating the relationship between cognitive ability and anxiety in WS is thus needed to illuminate the potentially moderating effect of IQ on the severity of internalizing symptomatology, and the current study is aimed at addressing this gap particularly in the steady state.

Two recent studies have addressed the link between social functioning and anxiety profiles in individuals with WS. First, Riby et al. (2013) employed the Spence Children's Anxiety Scale (SCAS-P) and the Social Responsiveness Scale respectively,