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Structural Integrity of the Limbic-Prefrontal Connection: Neuropathological Correlates of Anxiety in Williams Syndrome

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Abstract

Williams syndrome (WS) is a genetic condition characterized by a hypersocial personality and desire to form close relationships, juxtaposed with significant anxieties of non-social events. The neural underpinnings of anxiety in individuals with WS are currently unknown. Aberrations in the anatomical and microstructural integrity of the uncinate fasciculus (UF) have been recently implicated in social and generalized anxiety disorders. Based on these findings, we tested the hypothesis that the reported anxieties in individuals with WS share similar neuropathological correlates. Towards this end, diffusion tensor imaging (DTI) methods were employed to examine the microstructural integrity (fractional anisotropy, mean diffusivity, longitudinal diffusivity) of the UF in 18 WS and 15 typically developing adults (TD). Anxiety and sociability questionnaires were administered to determine associations with DTI indices of UF across groups. Results revealed comparable white matter integrity of the UF across groups, yet elevated subjective experience of anxiety in those with WS. Additionally, sociability and UF microstructural properties were dissociated across both groups. Whereas no relationships were found between DTI indices and anxiety in TD participants, strong negative associations were observed between these constructs in individuals with WS. Findings indicated that increased anxiety manifested by

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individuals with WS was associated with DTI measures of the UF and may signal structural or possibly physiological aberration involving this tract within the prefrontal-temporal network.

Keywords

Williams syndrome; anxiety; sociability; DTI; uncinate fasciculus

Introduction

Williams syndrome (WS) is a neurodevelopmental disorder determined by a microdeletion on chromosome 7q11.23 (Korenberg et al., 2000). The social phenotype associated with WS is characterized by a gregarious personality, exaggerated empathetic gestures, and robust drive to interact with others (Järvinen et al., 2013). Despite their motivation to develop close relationships with others (Ng et al., 2014b), individuals with WS tend to demonstrate greater anxiety relative to peers with mental retardation, mixed etiology, as well as typical development (TD)(Dykens, 2003; Ng et al., 2014a). Importantly, behavioral and neuroimaging research with individuals with WS seemingly indicate that their anxiety is largely nonsocial in nature (Meyer-Lindenberg et al., 2005; Ng et al., 2014a; Rodgers et al., 2012). However, to date, no investigation has been conducted to directly explore neural correlates of anxiety in WS.

Clinical research of individuals with anxiety diagnoses has begun to employ imaging methods to identify neural underpinnings of internalizing symptomatology. Largely, the amygdala-prefrontal connectivity has been implicated in emotion regulation (for a review see Kim et al., 2011). In particular, the uncinate fasciculus (UF) interconnects the anterior regions of the temporal lobe including the amygdala with the orbital and medial areas of the prefrontal cortex, allowing cross-communication between limbic and paralimbic substrates that process emotions as well as viscero-somatic states and the prefrontal/orbitofrontal area involved in emotion representation, learning and decision-making. Therefore, it is likely that the UF is part of the circuitry involved in the modulation of anxiety (Kim et al., 2011). Importantly, reduced fractional anisotropy of the UF has been observed in individuals with social anxiety (Phan et al., 2009) and generalized anxiety disorder (Tromp et al., 2012). Further, within those with subclinical anxiety symptoms, lower volume of the UF has been linked to increased trait anxiety (Baur et al., 2012). Altogether, recent insight from neuroimaging findings supports the hypothesis that this connecting pathway may have a vital role as part of a circuit implicated in anxiety disorders. Notably, the associations between the structural brain connectivity of the UF with level of anxiety appear specific to those with anxiety disorders, as no relationship has been found in healthy individuals (Baur et al., 2011). Consequently, investigators have proposed that this association reflects a neuropathological mechanism that may vary with symptom severity (Baur et al., 2011).

Currently, limbic-frontal pathways remain a relatively uncharted territory in WS research. Given the implications of the UF in anxiety symptomatology, an investigation examining the structural integrity of this white matter tract is warranted to more clearly determine whether those with WS share the pathological associations between UF and anxiety measures shown

in patients with anxiety disorders. The present study employed diffusion tension imaging (DTI) methods to examine the fractional anisotropy (FA), mean diffusivity (MD), and longitudinal diffusivity (LD) of the UF in adults with WS and TD counterparts. Participants were also administered inventories indexing their anxiety and sociability. Considering the consistent research implicating anxiety in WS (Dykens, 2003; Ng et al., 2014a), aberrations in the structural integrity of the UF were expected in adults with WS as compared to TD peers. Moreover, an inverse statistical association between the integrity of the UF and anxiety symptoms was expected, in line with prior research with patients with anxiety disorders (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012). However, given our recent findings indicating the dissociation between sociability and anxiety (Ng et al., 2014a), we hypothesized that measures of social behavior will be unrelated to the DTI and anxiety indices.

Methods

A total of 18 adults with WS and 15 TD individuals completed the study (see Table 1 for participant characteristics). Chronological age and gender distribution were statistically similar across groups. Those with WS underwent the fluorescent in situ hybridization test to confirm the genetic diagnosis (Korenberg et al., 2000). TD counterparts were recruited and screened for a history of neurological trauma, psychiatric illness, substance use, and native English speaking background. WS and TD individuals completed the Wechsler Adult Intelligence Scale 3rd Edition (Wechsler, 1997) and the briefer alternative, Wechsler Abbreviated Scale of Intelligence, respectively (Wechsler, 1999). As expected, those with WS demonstrated deficits in verbal, performance, and full scale IQ relative to TD peers ($ts >$ 5.57; $ps < .001$). The study procedures were approved by the Institution Review Board at the Salk Institute for Biological Studies and the University of California, San Diego.

Materials

The Beck Anxiety Inventory (BAI)(Beck & Steer, 1993) was administered to all participants. This inventory consisted of 21 items that yield four subscales: autonomic symptoms (BAI-A), neurophysiological symptoms (BAI-N), panic symptoms (BAI-P), and subjective symptoms (BAI-S). The total raw score (BAI-total) also describes the severity of the anxiety: 0 to 7 denotes minimal anxiety, 8 to 15 represents mild anxiety, 16 to 25 refers to moderate anxiety, and 26 to the maximum of 63 equates to severe anxiety. Consistent with the current literature in WS (Järvinen-Pasley et al., 2010; Ng et al., 2014a), caregivers of individuals with WS completed the BAI based on their observations of their child's behaviors. The TD participants were asked to complete the inventory consulting with a close family member or spouse to also include other's perception in their evaluations.

The Salk Institute Sociability Questionnaire (SISQ) was employed to examine the social approach and emotional behaviors manifested by our participants. The same administration procedures from the BAI were applied for the SISQ. The SISQ contains 16 items that yield three main quantitative subscales: Approach Strangers (SISQ-AS), Approach Familiars (SISQ-AF), and Social Emotionality (SISQ-SE). SISQ-AS and SISQ-AF evaluate the degree that participants initiate social interactions with unknown individuals or familiar peers and

family. In contrast, SISQ-SE examines the participant's emotional and empathetic responsivity towards others. The statistical properties of the SISQ have been extensively outlined in Doyle et al. (2004) and Zitzer-Comfort et al. (2007).

Imaging Collection and Processing

MRI scans were obtained with a 1.5 Tesla GE Signa HDx 0M5 TwinSpeed scanner (GE Healthcare, Wukesha, WI) (TE = 3.0 msec, TR = 8.7 msec, TI = 270 msec, flip angle = 8°, delay = 750 msec, bandwidth = ± 15.63 kHz, field of view = 24 cm, matrix = 192 × 192, voxel size = 1.25 × 1.25 × 1.2 mm). Real-time, prospective motion tracking and correction (PROMO) was used to correct for motion artifacts (Brown et al., 2010). Extensive information regarding the spiral navigator pulse sequences and an extended Kalman filter algorithm used is found in White et al. (2010). AtlasTrack automated DTI was used to produce the white matter streamlines (Hagler et al., 2009). Of note, UF in the current study involves the bundle of fibers connecting the orbitofrontal region to the anterior temporal lobe, inclusive of the amygdala.

Statistical Analysis

Analysis of covariance (ANCOVAs) was employed to determine group differences (WS/TD) in the FA, MD, and LD of the UF, with the total fiber of the respective DTI index as a covariate. Descriptive analyses were completed by applying Welch's t-tests to examine group differences across BAI and SISQ measures. Spearman's rank-order coefficient correlations were conducted to determine the associations between the FA, MD, and LD of UF with BAI and SISQ. Of note, two participants (i.e., one of each group) did not complete the inventory. Therefore, their imaging data were solely used to examine group effects across DTI measures.

Results

ANCOVAs revealed no significant group differences across FA, MD, and LD of the right and left UF. Table 1 outlines BAI, SISQ, and DTI averages across groups. In line with previous findings (Ng et al., 2014a), group differences were found in BAI total, Welch's F(1, 26.40)=4.20, p =.05, and more robustly BAI-S, Welch's F(1, 28.10)=6.61, p = .02. Participants with WS were rated higher in SISQ Global Sociability relative to the TD comparisons, Welch's F(1, 30.33)=7.56, p =.01. Compared to the TD group, those with WS scored higher across all SISQ subscales, Welch's Fs > 5.24, ps < .029.

Spearman rho correlations yielded no significant associations between BAI and SISQ measures across both groups. As shown in Table 2, significant associations were found between BAI and DTI indices in the WS sample; however, no relationship was found in the TD group. In the participants with WS, the FA of the right UF was inversely related to BAI-A, $r_s(17)=−0.61$, $p=.01$, and MD of the left UF was similarly negatively correlated to BAI-N, $r_s(17)=−0.56$, $p=.02$. Notably, LD of the UF was found to have strongest associations with all BAI subindices: BAI-N (right: $r_s(17)=−0.59$, $p=0.01$; left: $r_s(17)=−0.64$, $p=.006$), BAI-S (right: $r_s(17)=−0.61$, $p=0.01$; left: $r_s(17)=−0.69$, $p=.002$), BAI-P (right: $r_s(17)=−0.57$, $p=0.02$; left: $r_s(17)=−0.50$, $p=.04$), and BAI-A (right: $r_s(17)=−0.73$, $p=0.001$; left: $r_s(17)=$

−0.68, p=.003). When examining global anxiety, MD of the left UF was found to show a moderate relationship ($r_s(17)$=−0.55, p=0.02), whereas, LD of bilateral UF resulted in strong associations (right: $r_s(17)$=−0.77, p<0.001; left: $r_s(17)$=−0.76, p<.001). In contrast, no associations were observed between SISQ and UF DTI indices in both groups.

Discussion

The present study yielded three important findings. First, in line with prior evidence (Dykens, 2003; Järvinen et al., 2013; Ng et al., 2014a), those with WS were rated higher in subjective anxiety and social behaviors than TD counterparts; however, no differences were observed between groups in white matter microstructural properties. Second, LD of the UF was inversely associated with panic, neurophysiological, autonomic and subjective experiences of anxiety in individuals with WS but not in those with normative development. Finally, measures of sociability (i.e., approach strangers/familiars, social emotionality) were unrelated to either the white matter structural characteristics of the UF or anxiety ratings. Altogether, the unique association between microstructural features of the UF and anxiety in the WS group underscores their anxiety profile (Ng et al., 2014a, 2014b).

Importantly, research to date has raised questions regarding the anxiety features in WS, and whether these symptom patterns are similar between those with and without the genetic condition. As indicated, anxiety in WS particularly comprises significant phobic fears (Dykens, 2003) paired with unusual physiological reactivity (Ng et al., 2014a), which may stem from cardiovascular abnormalities associated with the syndrome (e.g., supravalvular aortic and pulmonary stenosis) (Pober, 2010). As such, whether the anxiety manifested in WS is driven by similar neurobiological underpinnings as the anxiety in individuals without the genetic deletion is unclear. However, our results indicated that those with WS may share similar neurobiological correlates as patients diagnosed with anxiety disorders yet lacking the genetic condition (see Phan et al., 2009; Tromp et al., 2012), suggesting that the internalizing symptoms in WS and TD may have similar pathologic origins in the brain. Moreover, our study did not yield significant relationships between social behaviors in individuals with WS with their anxiety and UF fiber properties, suggesting that these internalizing symptoms were not associated with their social functioning.

Notably, individuals with WS did not differ in microstructural properties of the UF tract relative to TD, yet showed robust correlations between UF measures and multiple aspects of anxiety, raising the possibility that their anxiety may be subserved by some form of alteration in cross-communicative functions of this tract. For example, reduced connections or variations in axonal propagation between these limbic and prefrontal regions may allow either abnormal function of the anterior temporal region including the fusiform gyrus, middle temporal gyrus, amygdala and/or the orbitofrontal regions, both implicated in social disinhibition in WS (Meyer-Lindenberg et al., 2005; Mimura et al., 2010; Mobbs et al., 2004; Mobbs et al., 2007), to augment threat perception. In a fMRI study with individuals with WS (Meyer-Lindenberg et al., 2005), the orbitofrontal cortex was found to atypically interact with the amygdala, leading the authors to hypothesize that affect dysregulation in WS may stem from disrupted regulatory interactions of the frontal and limbic regions. Consistent with these observations, our results suggest that the cross-communication

between these neural substrates, rather than abnormal structural integrity of the UF, may largely contribute to the high anxiety in those with WS. Yet, more direct investigations to examine associations between these interactions and social/emotional functioning in WS to better elucidate the nature of the anxiety linked to this neurogenetic condition. Further systematic research with integrated methodological techniques, e.g., DTI with fMRI or whole brain connectivity analyses, will be needed in order to better understand the neurologic markers of anxiety. Importantly, the genetic profile of WS is well-characterized; therefore, this syndrome serves as an excellent model to better understand interactions among genes, brain, and social behaviors.

The current study found increased subjective experiences of anxiety in adults with WS relative to TD peers, yet, comparable white matter structural properties of the UF tract. However, unique to WS, and similar to recent investigative observations in patients with anxiety disorders, the microstructural characteristics of the UF tract were associated with anxiety. Notably, no relationships were observed between the DTI indices of the UF and social behaviors. Persons with WS demonstrate similar neurobiological correlates in limbic-frontal connections as TD individuals diagnosed with anxiety.

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Table 1

Participant Characteristics

	Mean (SD)[Range]	
	Williams Syndrome (N=18)	Typical Development (N=15)
Age (years)	31.9 (11.4) [19.0–56.9]	26.2 (7.0) [17.9–43.1]
Sex	7F	9F
Handedness	14R, 4L	12R, 3L
VIQ	72.1(9.0)	94.3(13.4)
PIQ	65.8(5.3)	96.3(15.5)
FIQ	66.7(6.4)	95.2(14.1)
BAI Total Raw	**6.5(6.8)**	**2.5(4.0)**
BAI Neurophysiological Symptoms	0.2(0.4)	0.1(0.2)
BAI Subjective Symptoms	0.4(0.3)	0.1(0.2)
BAI Panic Symptoms	0.2(0.3)	0.1(0.2)
BAI Autonomic Symptoms	0.4(0.5)	0.2(0.4)
SISQ Global Sociability	**5.5(1.2)**	**4.4(1.2)**
SISQ Approach Strangers	5.0(1.8)	3.8(1.3)
SISQ Approach Familiar	6.5(1.1)	5.1(1.6)
SISQ Social Emotionality	5.5(0.9)	4.1(1.0)
Uncinate Fasciculus (R/L)		
Fractional Anisotropy	0.40(0.02)/0.41(0.02)	0.40(0.02)/0.41(0.02)
Mean Diffusivity	0.81(0.02)/0.80(0.02)	0.82(0.02)/0.80(0.02)
Longitudinal Diffusivity	1.19(0.03)/1.17(0.03)	1.20(0.03)/1.19(0.03)

Note. The Beck Anxiety Inventory (BAI) and Salk Institute Sociability Questionnaire (SISQ) were administered to caregivers of WS participants, and directly to TD participants. One caregiver of a WS participant and one TD adult did not complete the BAI; therefore, the average BAI scores above reflect data of 17 WS participants and 14 TD adults.

Table 2

Associations Between DTI measures, BAI subscales, and SISQ subscales in Williams Syndrome Controlling for Age.

DTI measures	BAI-N	BAI-S	BAI-P	BAI-A	SISQ-AS	SISQ-AF	SISQ-SE
Uncinate Fasciculus (R)							
Fractional Anisotropy	−0.31	−0.33	−0.24	−0.61**	0.07	−0.12	0.04
Mean Diffusivity	−0.18	−0.15	−0.28	0.03	−0.16	−0.11	−0.17
Longitudinal Diffusivity	−0.59*	−0.61**	−0.57*	−0.73***	−0.29	−0.39	−0.21
Uncinate Fasciculus (L)							
Fractional Anisotropy	−0.03	−0.25	−0.09	−0.36	0.08	−0.09	−0.11
Mean Diffusivity	−0.56*	−0.44	−0.37	−0.38	−0.21	−0.26	−0.05
Longitudinal Diffusivity	−0.64**	−0.69**	−0.50*	−0.68**	−0.14	−0.37	−0.14

*
$p < .05$

**
$p < .01$

***
$p > .001$