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The Relationship between Anxiety and Executive Functioning in Children with Williams Syndrome

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Abstract

Objective: Anxiety has a major impact on children with William syndrome and their families, as does executive dysfunction. Poor executive functioning may play a role in causing or maintaining anxiety. However, little research has investigated this relationship in individuals with WS. The primary aim of this study was to investigate whether impairments in executive functioning are associated with greater anxiety in pre-schoolers and school-aged children with WS (N = 28; age range = 3 - 9 years).

Method: Parents completed the Spence Children's Anxiety Scale or Spence Preschool Anxiety Scale and the Behaviour Rating Inventory of Executive Functioning (preschool or school-age version).

Results: Correlations revealed several significant, positive and moderate relationships between generalised anxiety and the executive functions of interest (inhibition, shifting, working memory, and emotional control), controlling for age and IQ.

Conclusions: This study provides some support for theoretical models that suggest a role of executive functioning in anxiety. Findings have important clinical implications in relation to the management of anxiety and executive dysfunction in WS.

Keywords: Williams syndrome; Executive functioning; Anxiety; Children

Abbreviations: WS: Williams Syndrome; ADHD: Attention Deficit Hyperactivity Disorder; GAD: Generalised Anxiety Disorder; PAS: Preschool Anxiety Scale; BRIEF: Behaviour Rating Inventory of Executive Functioning; SCALE-P: Spence Children's Anxiety Scale - Parent Form; GEC: Global Executive Composite; ELC: Early Learning Composite; ODQ: Overall Developmental Quotient; DQ: Developmental Quotients; ASD: Autism Spectrum Disorder; GCA: General Conceptual Ability: DAS-II: Differential Ability Scale (2nd Edition); CBT: Cognitive Behaviour Therapy

Introduction

Williams Syndrome (WS) is a neurodevelopmental condition with anxiety as a hallmark feature [1]. While our knowledge of anxiety in WS has grown substantially in terms of its prevalence and trajectory from childhood to adulthood, less is known about the mechanisms that cause and maintain anxiety in WS. A clearer understanding of such mechanisms in WS will aid in developing targeted interventions in order to reduce the impact of anxiety in this disorder. This study explored the relationship between anxiety and executive functioning in a paediatric WS sample.

WS is caused by a deletion of approximately 26 to 28 genes on chromosome 7 at the location 7q11.23 [2] and has a reported prevalence of somewhere between 1:7,500 [3] and 1:20,000 [4]. The condition is characterised by a distinct physical, cognitive, psychological and behavioural phenotype. Physical characteristics include dysmorphic facial features; short stature, cardiovascular and renal abnormalities, and hyperacusis. Behaviourally, WS is characterised by hyper-sociability and a high incidence of co-morbid Attention Deficit Hyperactivity Disorder (ADHD). Cognitively, individuals with WS typically display a mild to moderate intellectual disability, with a relative weakness in spatial construction abilities [5,6]. In addition to their intellectual impairment, deficits have been found in shifting or cognitive flexibility [7-9], working memory [8-10], and inhibition [7,10].

Anxiety is frequently present in individuals with WS [1]. Royston et al. [1] conducted a meta-analysis and reported that specific phobias and generalised anxiety disorder (GAD) were the most prevalent anxiety subtypes in WS, with a 39% and 10% quality effects pooled prevalence, respectively [1]. However, Dykens [11] noted that 51% of their WS sample endorsed the

item of being a "worrier", and 96% indicated having "marked, persistent, anxiety-producing fears" on the Child Behaviour Checklist for ages 4 to 18 [12]. Hence, the majority of individuals with WS suffer from symptoms of anxiety, with a smaller, but still high proportion, meeting criteria for an anxiety disorder diagnosis.

The Relationship between Executive Dysfunction and Anxiety

Attempts to understand the aetiology and maintenance of anxiety in the general population have generated considerable research interest and have led to the development of anxiety models. Of particular note, the Attentional Control Theory postulates that anxiety is associated with deficits in inhibiting task-irrelevant information, shifting attention, and updating working memory [13]. Eysenk et al.'s [13] model has been supported by numerous studies in the general population [14,15], which often utilise Stroop tasks. In one version of the Stroop task, anxious individuals (those with worries of a social or physical nature) were slower at naming the colour of the text, if the written word was threatening (e.g., 'cancer' representing physical threats, and 'failure' for social threats) compared to neutral (e.g., 'holiday') [15]. Derryberry and Reed [16] asserted that the negative attention bias in anxious individuals makes inhibiting the task-irrelevant information difficult. As the attention of the anxious individual is drawn to the negative/threatening word, they are slower at shifting their attention away from the threatening stimulus to the colour-naming task. Hence, anxious individuals experience difficulties in inhibiting and shifting away from negative/threatening information/stimuli. As anxious individuals are unable to filter out distractors (i.e., threatening stimuli) and focus on task-relevant information, their ability to update and manipulate information in the working memory system is impaired [17].

Few studies have investigated this relationship between executive functioning and anxiety in WS. Ng-Cordell, Hanley, Kelly & Riby [18] studied 26 individuals with WS aged 5 to 37 years and found that greater anxiety symptomology was associated with more severe executive dysfunction in shifting, inhibition and emotional control. A regression model found that shifting was the only significant predictor of anxiety severity, when controlling for the other executive functions.

Woodruff-Borden, Kistler, Henderson, Crawford & Mervis' [19] study was the first longitudinal examination into anxiety and its relationship to executive functioning in WS. Multilevel logistic regression models showed that those with an anxiety diagnosis had significantly higher Behavioural Regulation Index scores (measured on the Behaviour Rating Inventory of Executive Functioning [BRIEF], an index comprised of Inhibit, Shift, and Emotional Control; Gioia, Isquith, Guy, Kenworthy & Baron [20].

The above studies [18,19] explored the anxiety as a single construct, and this has precluded investigations into the relationship between the different subtypes of anxiety and executive functioning. To the author's knowledge, there is only one study to date that has examined the relationship between an anxiety subtype and executive functioning in WS. Pitts, Klein-Tasman, Osborne and Mervis [21] investigated specific phobias and found that more severe behavioural and emotional self-regulation difficulties predicted a greater likelihood of specific phobia diagnosis in participants with WS aged 6 to 17 years. Investigations into other anxiety subtypes are necessary in order to identify differences between anxiety subtypes.

The present study

The aim of the present study was to investigate the relationship between various executive functioning sub-domains and the severity of symptoms in various anxiety subtypes in children with WS. Anxiety subtypes included: physical injury fears, separation anxiety, social anxiety, obsessive-compulsive disorder and generalised anxiety disorder. In line with previous findings, the executive functions investigated were shifting, inhibition, working memory, and emotional regulation. It was predicted that all the executive functioning subdomains would be significantly and positively correlated with increased anxiety symptoms for all anxiety subtypes, with the exception of inhibition, which would be negatively correlated with social anxiety in WS.

Method

Participants

Participants were recruited through the Williams Syndrome Australia Limited and the Williams Syndrome Association of New Zealand. Twenty-eight participants with WS (14 males) aged from 3 to 9 years (M = 5.21 years, SD = 1.47 years) were included. Diagnosis of WS was confirmed through genetic testing, which showed a microdeletion at 7q.11.23. During recruitment, all WS participants were interviewed for a history of other neurological anomalies unrelated to the syndrome. Any such anomalies, which may impact executive functioning or anxiety, served as exclusion criteria from the study. No participants were excluded based on this criterion. All participants underwent cognitive/developmental assessment. Sixteen participants were administered the Mullen's Scale of Early Learning [22]. Twelve participants were administered the Differential Ability Scale, Second Edition [23]. Parents of the participants completed either the Preschool Anxiety Scale-Parent Version [24] or the Spence Children's Anxiety Scale - Parent Form [25], as well as either the preschool or child version of the Behaviour Rating Inventory of Executive Function [20,26]. Measures were chosen according to the child's chronological age. Sample characteristics are reported in Table 1.

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Table 1: Characteristics of the sample.

	Mean	Range	Standard Deviation
Age (years)	5.21	3.30 - 9.46	1.47
IQ (standard scores *M*=100, *SD*=15)	**55.70**	28.62 - 73.36	11.72
Executive Functioning - BRIEF-P & BRIEF			
Inhibit	**67.79**	43 - 91	10.85
Shift	60.48	42 - 77	9.53
Emotional Control	**65.28**	38 - 86	12.21
Working Memory	**76.41**	60 - 93	9.91
Anxiety - PAS & SCAS-P			
GAD	**1.07**	-1.38 - 6.46	1.67
Social Anxiety	-0.85	-1.50 - 1.57	.64
OCD	0.41	-.74 - 7.32	1.80
Physical Injury Fears	0.18	-1.42 - 1.96	.81
Separation Anxiety	0.35	-1.28 - 2.77	1.02

Note: IQ scores <70 indicate intellectual disability. Scores from the BRIEF-P and BRIEF are T-scores, where T-scores ≥ 65 are clinically elevated. Scores from the PAS and SCAS-P are z-scores, where z-scores > 1 are clinically elevated. Mean scores in the elevated range are in **boldface**.

Measures

Preschool anxiety scale - parent version (PAS): The PAS [24] is a 28-item measure of anxiety symptoms for children aged 3 to 5 years old. There are 5 subscales–physical injury fears, separation anxiety, social phobia, OCD, and GAD. Parents are asked to rate the items on a 5-point scale (0 = not true at all to 4 = very often true). Standardised scores can be calculated using the mean scores and standard deviations provided by Spence et al. [24].

Spence children's anxiety scale - parent form (SCAS-P): The SCAS-P [25] is a 38-item measure of anxiety symptoms for children aged 6 to 18 years. There are 6 subscales—panic/agoraphobia, physical injury fears, separation anxiety, social phobia, OCD, and GAD. Parents are asked to rate the items on a four-point scale (i.e., never, sometimes, often, always). Standardised scores can be calculated using the mean scores and standard deviations provided by [27].

Behaviour rating inventory of executive function - preschool (BRIEF-P): The BRIEF-P [26] is a 63-item informant-report questionnaire examining executive functioning in children aged 2 years 0 months to 5 years 11 months. Parents rate the frequency of particular behaviours over the past 6 months on a 3-point scale (1 = never, 2 = sometimes, and 3 = often). The five clinical subscales are Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organise. There are three indexes: Inhibitory Self-Control Index, Flexibility Index, and Emergent Metacognition Index. The five clinical scales sum to create a total composite score (i.e., the global executive composite [GEC]).

Behaviour rating inventory of executive function - parent form (BRIEF): The BRIEF [20] is an 86-item parent-report questionnaire examining executive functioning in children aged 5 to 18 years. Parents rate the frequency of particular behaviours over the past 6 months on a 3-point scale (1 = never, 2 = sometimes, and 3 = often). The eight clinical subscales are Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organise, Organisation of Materials, and Monitor. There are two indexes: Metacognition Index, and the Behavioural Regulation Index. All eight scales sum to create a total composite score (global executive composite [GEC]).

Mullen's scale of early learning (Mullen's): The Mullen's is a performance-based test measuring development in children, aged 0 to 68 months. It contains 124 items that cover the five domains of development: gross motor, fine motor, visual reception, receptive language, and expressive language (for further details, see Mullen [22]). Four of the domains (fine motor, visual reception, receptive language, and expressive language) are combined to create the Early Learning Composite (ELC) score, a standardised score equivalent to an IQ (*M*=100, *SD*=15).

Differential ability scale (2nd Edition) (DAS-II): The DAS-II is a performance-based test of cognitive ability for children aged 2 years 6 months to 17 years old (for further details, see Elliot [23]). A global cognitive ability score, General Conceptual Ability (GCA), can be derived from the core subtests of a battery (*M*=100, *SD*=15).

Scoring

Raw scores were converted into standard scores (T scores for the BRIEF-P and BRIEF; z-scores for the PAS and SCAS-P, cognitive ability quotients for the DAS-II), in accordance with the tests' respective manuals. For the Mullen's, an overall developmental quotient (ODQ) was calculated by averaging the developmental quotients (DQ) from the fine motor, visual reception, receptive

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language, and expressive language subscales. A DQ is calculated using the following formula: DQ = age-equivalent/chronological age x 100. The calculated ODQ was used instead of the ELC, as many participants performed at floor with a T-score of 20 [28,29]. The DAS-II GCA and Mullen's ODQ were collapsed into a single variable, henceforth called IQ. Previous studies have also collapsed the DAS-II and Mullen's as the two tests have been shown to have good convergent validity in Autism Spectrum Disorder (ASD) and non-ASD populations [30], and good concurrent validity in typically-developing individuals, and individuals with ASD or developmental delays [31].

Data analysis

Partial correlations were used to examine the relationship between anxiety and executive functioning, while controlling for age and IQ. All tests were two-tailed. Non-parametric tests were employed where appropriate. Due to the small sample size, and in order to reduce the likelihood of Type-II error, the p value was set to 0.05 for all inferential statistical tests [32].

Results

Partial correlations showed that GAD scores are significantly correlated with inhibit scores (r_s = .42; p = .031), shift scores (r_s = .43; p = .024), emotional control (r_s = .53; p = .005) and working memory (r_s = .44; p = .023), controlling for IQ and age. All significant correlations were of a moderate size and in the positive direction, such that greater executive dysfunction was associated with more severe generalised anxiety symptoms (see Table 2).

Table 2: Correlations between Anxiety Subtypes Symptom Severity and Level of Executive Dysfunction (N = 29).

Executive Functioning	Anxiety Subtype				
	GAD [a]	Social Phobia [a]	OCD [a]	Physical Injury	Separation Anxiety
Inhibit	.42 *	0.18	0.31	-0.04	0.3
Shift	.43 *	0.21	0.01	-0.08	0.15
Emotional Control	.53 **	-0.08	0.17	0.05	0.13
Working Memory	.44 *	. 11	0.12	0.1	0.27

Note: * significant at .05 level; ** significant at the .01 level; a = Spearman's rho; GAD = Generalised Anxiety Disorder; OCD = Obsessive Compulsive Disorder.

Discussion

This study expanded on findings from the existing literature on the relationship between anxiety and executive functioning in a sample of children with WS. Past research had tended to look at total executive functioning and total anxiety rather than exploring executive functioning subdomains and anxiety subtypes. In addition, anxiety and executive functioning have remained relatively unexplored in an exclusively young paediatric WS sample.

As predicted, results showed that increases in generalised anxiety symptomology were significantly associated with greater difficulties in inhibition, shifting, working memory, and emotional control. This is consistent with cognitive models of anxiety-such as Eysenk, Derakshan, Santos & Calvo's [13] Attentional Control Theory-which describe how anxiety impairs shifting, inhibiting, and working memory abilities, and propose that executive dysfunction maintains anxiety.

Clinically, the GAD–executive functioning relationship suggests that early intervention targeted at either executive functioning or anxiety may generalise to improve the other domain. Findings also suggest that a combination of anxiety management, such as cognitive behaviour therapy (CBT) and cognitive/executive functioning intervention may be particularly efficacious, however further research is needed before any firm claims can be made.

Contrary to expectations, social phobia, OCD, physical injury, and separation anxiety were not significantly correlated with executive functioning. This suggests that the executive functioning–anxiety relationship in WS may not be as consistent or robust as suggested by previous research, and that there may also be other factors at play that are confounding this relationship. However, more research in this area is warranted.

The study's limitations need to be noted. First, the use of informant-report questionnaires is limited, as they are prone to informant bias. To reduce this bias, future studies should aim to collect information from multiple informants (e.g., both parents/caregivers and teachers). Researchers may also wish to supplement these questionnaires with diagnostic interviews of anxiety and performance-based measures of executive functioning. With regards to the latter, one study, albeit in adults with WS, found a significant and strong correlation between the BRIEF and performance-based measures of executive functioning [33], so the use of performance-based measured are not as crucial as the utilisation of diagnostic measures of anxiety. Second, the anxiety questionnaires utilised in this study-the SCAS-P and PAS-are limited in that they do not investigate specific phobias, the most common anxiety in WS [1].

The final limitation is the small sample size and associated lack of statistical power. Larger samples would enable researchers to determine which executive functions are most related to anxiety. However, WS has a low prevalence rate and obtaining large samples can be difficult, especially in a short time frame and in samples of a restricted age range. Indeed, the current study recruited children nationally. Future researchers need to work

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together to build larger, multi-site datasets across countries. This will also provide an opportunity to investigate cultural differences.

In addition to improving the methodology and addressing future directions mentioned above, future studies may delineate the directionality of the executive functioning–anxiety relationship using a longitudinal study design. While several studies have found associations between executive functioning and anxiety, including the findings of the present study, the directionality of this relationship remains unclear. Some researchers claim that executive functioning deficits are risk factors for anxious psychopathology (e.g., difficulty regulating intrusive thoughts, catastrophising and ruminating; Han et al. [34]; Nelson et al. [35]), while others believe that chronic anxiety leads to the executive functioning deficits [36-38]. This necessitates further research to allow clinicians to make informed decisions regarding which deficit (i.e., executive functioning or anxiety) to prioritise during intervention, in order to enhance the therapy's efficacy.

In conclusion, the current study highlights the contribution of executive dysfunction in generalised anxiety. These findings have theoretical and clinical implications that may help lessen the burden of generalised anxiety in young children with WS and their families.

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