

# Understanding Mental Health in Children with Rare Genetic Causes of Intellectual Disability



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This thesis is submitted for the degree of  
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# Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text. It is not substantially the same as any work that has already been submitted, or is being concurrently submitted, for any degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee.

# Abstract

Intellectual disability (ID) is a heterogeneous neurodevelopmental disorder (NDD) characterised by significant cognitive and adaptive impairments. Individuals with ID experience mental health difficulties at rates at least twice those observed in the general population, with even greater risk among those with rare genetic causes of ID (termed ‘rare ID-associated genetic conditions’). Anxiety and behaviours that challenge (BtC, including self-injury, aggression and property destruction) are particularly prevalent. Accurate assessment and identification of high-risk groups is important to improve proactive identification of symptoms. Moreover, understanding the multi-level factors associated with anxiety and BtC may also provide insight into mechanisms driving the emergence and maintenance of symptoms, ultimately leading to better interventions and improving mental health in this population.

This thesis focuses on anxiety and BtC in children with *DDX3X*-related disorder and *CASK*-related disorder, two exemplar rare ID-associated genetic conditions. We used mixed methods to characterise these difficulties. Contrary to previous literature, anxiety and self-injury were not elevated in children with *DDX3X*-related disorder when compared to children with other rare ID-associated genetic conditions, nor were there disorder specific associations between behavioural characteristics in these groups. Instead, we found a robust association between autism-related characteristics and anxiety across rare ID-associated genetic conditions, and that anxiety-related behaviours, triggers and coping strategies were comparable to those reported in idiopathic ID and autistic populations.

We also explored temperament-based self-regulation (e.g., effortful control) as a possible early-emerging trait contributing to anxiety during childhood in this population. A review of existing literature revealed inconsistent evidence for atypical self-regulation in rare genetic syndromes. Empirical testing found negative affect (another temperament dimension), but not effortful control, was consistently associated with anxiety across rare ID-associated genetic conditions. However, given the limitations of questionnaire measures, we also evaluated the feasibility of using play-based assessments and wearable devices to study self-regulation as an ongoing, dynamic ability in young children with rare ID-associated genetic conditions.

In conclusion, this thesis advances our knowledge of anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder, contributes to a mechanistic understanding of anxiety in children with rare ID-associated genetic conditions, and explores methodological approaches for future research.

*To the DDX3X-related disorder and CASK-related disorder  
communities – you have profoundly shaped both this work and who  
I am today.*

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# List of Abbreviations and Acronyms

|                |                                                                                    |
|----------------|------------------------------------------------------------------------------------|
| ABC            | Adaptive Behaviour Composite                                                       |
| ABC            | Antecedent-Behaviour-Consequence                                                   |
| ADHD           | Attention deficit/hyperactivity disorder                                           |
| ADIS-P         | Anxiety Disorders Interview Schedule for DSM-IV – Parent Version                   |
| APA            | American Psychological Association                                                 |
| ASC-ASD        | Anxiety Scale for Children – Autism Spectrum Disorder                              |
| ASC-ASD-P      | Parent version of the Anxiety Scale for Children – Autism Spectrum Disorder        |
| ASD            | Autism spectrum disorder                                                           |
| BF             | Bayes Factor                                                                       |
| BINGO          | Brain and Behaviour in Neurodevelopmental Disorders of Genetic Origin              |
| BPM            | Beats per minute                                                                   |
| BPS            | British Psychological Society                                                      |
| BtC            | Behaviours that Challenge                                                          |
| CA             | Content analysis                                                                   |
| CBCL           | Child Behavior Checklist                                                           |
| CBQ            | Challenging Behaviour Questionnaire                                                |
| CBQ            | Children's Behavior Questionnaire                                                  |
| CBQ-VSF        | Children's Behavior Questionnaire – Very Short Form                                |
| CBT            | Cognitive Behavioural Therapy                                                      |
| CBT-IU         | Cognitive Behavioural Therapy targeting Intolerance of Uncertainty                 |
| CC-ARI         | Coping Cat Accommodation Reduction Intervention                                    |
| CD             | Conduct disorder                                                                   |
| CdLS           | Cornelia de Lange syndrome                                                         |
| CIASP-ID       | Clinical Anxiety Screen for people with Severe to Profound Intellectual Disability |
| CNS            | Central nervous system                                                             |
| CNV            | Copy Number Variant                                                                |
| CS             | Cross-sectional                                                                    |
| CS-Coefficient | Correlation-Stability Coefficients                                                 |
| CUES           | Coping with Uncertainty in Everyday Situations                                     |
| DAWBA          | Development and Wellbeing Assessment                                               |
| DBC2           | Developmental Behaviour Checklist 2                                                |
| DD             | Developmental delay                                                                |
| DOB            | Date of Birth                                                                      |
| DS             | Down syndrome                                                                      |
| DSM            | Diagnostic and Statistical Manual of Mental Disorders                              |
| DSM–5          | Diagnostic and Statistical Manual of Mental Disorders (5th Edition)                |
| EBIC           | Extended Bayesian Information Criterion                                            |
| ECBQ           | Early Childhood Behavior Questionnaire                                             |
| ECG            | Electrocardiogram                                                                  |
| FA             | Family accommodation                                                               |
| FDR            | False Discovery Rate                                                               |

|            |                                                                                             |
|------------|---------------------------------------------------------------------------------------------|
| FXpm       | Fragile X pre-mutation                                                                      |
| FXS        | Fragile X syndrome                                                                          |
| HR         | Heart rate                                                                                  |
| HRV        | Heart rate variability                                                                      |
| IBQ        | Infant Behavior Questionnaire                                                               |
| IBQ-R      | Infant Behavior Questionnaire - Revised                                                     |
| IC         | Inhibitory control                                                                          |
| ID         | Intellectual disability                                                                     |
| IMAGINE-ID | Intellectual Disability and Mental Health: Assessing the Genomic Impact on Neurodevelopment |
| IQ         | Intelligence quotient                                                                       |
| IQR        | Interquartile range                                                                         |
| IU         | Intolerance of Uncertainty                                                                  |
| KMO        | Kaiser-Meyer-Olkin                                                                          |
| L          | Longitudinal                                                                                |
| Lab-TAB    | Laboratory Temperament Assessment Battery                                                   |
| LASSO      | Least Absolute Shrinkage Selection Operator                                                 |
| MHCYP      | Mental Health of Children and Young People                                                  |
| MHQ        | Medical History Questionnaire                                                               |
| MICPCH     | Microcephaly with pontine and cerebellar hypoplasia                                         |
| NIMH       | National Institute of Mental Health                                                         |
| ND-CNVs    | Copy number variants associated with neurodevelopmental disorders                           |
| NDD        | Neurodevelopmental disorder                                                                 |
| NGS        | Next-generation sequencing                                                                  |
| NHS        | National Health Service                                                                     |
| nsDD       | Non-specified developmental delay                                                           |
| ODD        | Oppositional defiant disorder                                                               |
| OR         | Odds Ratio                                                                                  |
| OSF        | Open Science Framework                                                                      |
| PCA        | Principal Components Analysis                                                               |
| PCH        | Pontocerebellar hypoplasia                                                                  |
| PMRF       | pairwise Markov random fields                                                               |
| PNS        | Parasympathetic nervous system                                                              |
| POST       | Parliamentary Office of Science and Technology                                              |
| RBQ        | Repetitive Behaviour Questionnaire                                                          |
| RCPsych    | Royal College of Psychiatrists                                                              |
| RCSLT      | Royal College of Speech and Language Therapists                                             |
| RCT        | Randomised control trial                                                                    |
| RDoC       | Research Domain Criteria                                                                    |
| RMSSD      | Root mean square of successive differences between normal heartbeats                        |
| RSA        | Respiratory sinus arrhythmia                                                                |
| RSA-R      | RSA reactivity                                                                              |
| SDNN       | Standard Deviation of Normal-to-Normal interbeat intervals                                  |
| SEN        | Special Educational Needs                                                                   |

|        |                                                        |
|--------|--------------------------------------------------------|
| SNV    | Single Nucleotide Variant                              |
| SPACE  | Supportive Parenting for Anxious Childhood Emotions    |
| SR     | Self-Regulation                                        |
| SRS-2  | Social Responsiveness Scale – Second Edition           |
| SSP-2  | Short Sensory Profile 2                                |
| TBAQ-R | Toddler Behavior Assessment Questionnaire- Revised     |
| TBPS   | Total Behaviour Problem Score                          |
| TD     | Typically Developing                                   |
| UK     | United Kingdom                                         |
| UNICEF | United Nations International Children's Emergency Fund |
| VABS   | Vineland Adaptive Behaviour Scales                     |
| VIF    | Variation Inflation Factor                             |
| VUS    | Variant of Uncertain Significance                      |
| WHO    | World Health Organisation                              |
| WS     | Williams syndrome                                      |
| XLID   | X-linked intellectual disability                       |

# Table of Contents

|                                                                                                                                                                              |            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>Declaration.....</b>                                                                                                                                                      | <b>ii</b>  |
| <b>Abstract .....</b>                                                                                                                                                        | <b>iii</b> |
| <b>Acknowledgements .....</b>                                                                                                                                                | <b>v</b>   |
| <b>List of Abbreviations and Acronyms.....</b>                                                                                                                               | <b>vi</b>  |
| <b>Chapter 1   General Introduction .....</b>                                                                                                                                | <b>1</b>   |
| <b>1.1 Neurodevelopmental Disorders and Mental Health .....</b>                                                                                                              | <b>1</b>   |
| <b>1.2 Intellectual Disability and the Advent of Genomic Medicine .....</b>                                                                                                  | <b>3</b>   |
| <b>1.3 Mental Health in Rare ID-associated Genetic Conditions.....</b>                                                                                                       | <b>4</b>   |
| 1.3.1 Common Mental Health Concerns in Rare ID-associated Genetic Conditions .....                                                                                           | 6          |
| 1.3.2 Challenges of Conducting Mental Health Research in Rare ID-associated Genetic Conditions .                                                                             | 12         |
| <b>1.4 Thesis Aims and Structure .....</b>                                                                                                                                   | <b>15</b>  |
| <b>Chapter 2   Anxiety and Behaviours that Challenge in DDX3X-related disorder and CASK-related disorder.....</b>                                                            | <b>17</b>  |
| <b>2.1 Introduction .....</b>                                                                                                                                                | <b>17</b>  |
| 2.1.1 Anxiety and BtC in DDX3X-related disorder .....                                                                                                                        | 18         |
| 2.1.2 Anxiety and BtC in CASK-related disorder .....                                                                                                                         | 19         |
| 2.1.3 Methodological Advances.....                                                                                                                                           | 20         |
| 2.1.4 Aims of the Study.....                                                                                                                                                 | 22         |
| <b>2.2 Methods .....</b>                                                                                                                                                     | <b>22</b>  |
| 2.2.1 Participants .....                                                                                                                                                     | 22         |
| 2.2.2 Procedure.....                                                                                                                                                         | 24         |
| 2.2.3 Data Analysis.....                                                                                                                                                     | 30         |
| <b>2.3 Results .....</b>                                                                                                                                                     | <b>34</b>  |
| 2.3.1 Aim 1: Medical and Developmental Characteristics of Children with DDX3X-related disorder, CASK-related disorder, and other Rare ID-associated genetic Conditions. .... | 34         |
| 2.3.2 Aim 2: Group Differences in Anxiety and BtC among Children with DDX3X-related disorder, CASK-related disorder, and other Rare ID-associated Genetic Conditions. ....   | 36         |
| 2.3.3 Aim 3: Correlates of Anxiety and BtC among Children with DDX3X-related disorder, CASK-related disorder, and other Rare ID-associated Genetic Conditions.....           | 42         |
| <b>2.4 Discussion .....</b>                                                                                                                                                  | <b>45</b>  |
| 2.4.1 Aim 2: Comparative Findings .....                                                                                                                                      | 45         |
| 2.4.2 Aim 3: Correlates of Anxiety and BtC.....                                                                                                                              | 46         |
| 2.4.4 Conclusions and Future Directions .....                                                                                                                                | 47         |
| <b>Chapter 3   Utilising Interview Methodology to Understand Anxiety Characteristics in Rare ID-associated Genetic Conditions .....</b>                                      | <b>49</b>  |
| <b>3.1 Introduction.....</b>                                                                                                                                                 | <b>49</b>  |
| <b>3.2 Method.....</b>                                                                                                                                                       | <b>51</b>  |
| 3.2.1 Participants .....                                                                                                                                                     | 51         |
| 3.2.2 Semi-structured Interview .....                                                                                                                                        | 52         |
| 3.2.3 Procedure.....                                                                                                                                                         | 54         |
| 3.2.4 Data Analysis.....                                                                                                                                                     | 54         |
| 3.2.5 Coding .....                                                                                                                                                           | 55         |
| <b>3.3 Results .....</b>                                                                                                                                                     | <b>58</b>  |

|                                                                                                                                                                              |                                                                                                                                    |            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|------------|
| 3.3.1                                                                                                                                                                        | Participants .....                                                                                                                 | 58         |
| 3.3.2                                                                                                                                                                        | Validity .....                                                                                                                     | 62         |
| 3.3.3                                                                                                                                                                        | Presenting Issue.....                                                                                                              | 62         |
| 3.3.4                                                                                                                                                                        | Predisposing Factors .....                                                                                                         | 65         |
| 3.3.5                                                                                                                                                                        | Precipitating Factors .....                                                                                                        | 65         |
| 3.3.6                                                                                                                                                                        | Perpetuating and Protective Factors .....                                                                                          | 67         |
| 3.3.7                                                                                                                                                                        | Thoughts and Feelings .....                                                                                                        | 69         |
| <b>3.4</b>                                                                                                                                                                   | <b>Discussion .....</b>                                                                                                            | <b>73</b>  |
| 3.4.1                                                                                                                                                                        | Comments on Interview Methodology.....                                                                                             | 73         |
| 3.4.2                                                                                                                                                                        | Antecedents of Anxiety.....                                                                                                        | 75         |
| 3.4.3                                                                                                                                                                        | Behaviours Associated with Anxiety .....                                                                                           | 76         |
| 3.4.4                                                                                                                                                                        | Consequences – Parent Responses to Anxiety .....                                                                                   | 77         |
| 3.4.5                                                                                                                                                                        | Conclusions .....                                                                                                                  | 78         |
| <b>Chapter 4   Temperament-based Self-Regulation and Anxiety in Rare ID-associated Genetic Conditions .....</b>                                                              |                                                                                                                                    | <b>79</b>  |
| <b>4.1</b>                                                                                                                                                                   | <b>Introduction .....</b>                                                                                                          | <b>79</b>  |
| <b>4.2</b>                                                                                                                                                                   | <b>Part A – Theoretical Review and Evidence Synthesis .....</b>                                                                    | <b>81</b>  |
| 4.2.1                                                                                                                                                                        | Temperament – A Framework for Studying Self-regulation.....                                                                        | 81         |
| 4.2.2                                                                                                                                                                        | Is Temperament-based Self-regulation Atypical in Rare ID-associated Genetic Conditions?.....                                       | 86         |
| 4.2.3                                                                                                                                                                        | Does Temperament-based Self-regulation Predict Anxiety in Rare ID-associated Genetic Conditions?.....                              | 92         |
| 4.2.4                                                                                                                                                                        | Part A Discussion.....                                                                                                             | 95         |
| <b>4.3</b>                                                                                                                                                                   | <b>Part B – New Data Examining the Links between Temperament Traits and Anxiety in Rare ID-associated Genetic Conditions .....</b> | <b>96</b>  |
| 4.3.1                                                                                                                                                                        | Method .....                                                                                                                       | 97         |
| 4.3.3                                                                                                                                                                        | Results.....                                                                                                                       | 101        |
| 4.3.4                                                                                                                                                                        | Part B Discussion.....                                                                                                             | 103        |
| <b>4.4</b>                                                                                                                                                                   | <b>General Discussion .....</b>                                                                                                    | <b>105</b> |
| <b>Chapter 5   The Feasibility of Play-based Assessments and Wearable Devices to Study Self-Regulation in Young Children with Rare ID-associated Genetic Conditions.....</b> |                                                                                                                                    | <b>107</b> |
| <b>5.1</b>                                                                                                                                                                   | <b>Introduction .....</b>                                                                                                          | <b>107</b> |
| 5.1.1                                                                                                                                                                        | Traditional Inhibitory Control Measures and Micro-analytic Coding Approaches .....                                                 | 107        |
| 5.1.2                                                                                                                                                                        | Wearable Physiological Measures and Naturalistic Settings .....                                                                    | 108        |
| 5.1.3                                                                                                                                                                        | Current Research in Rare ID-associated Genetic Conditions.....                                                                     | 109        |
| 5.1.4                                                                                                                                                                        | Study Aims .....                                                                                                                   | 110        |
| <b>5.2</b>                                                                                                                                                                   | <b>Method.....</b>                                                                                                                 | <b>110</b> |
| 5.2.1                                                                                                                                                                        | Participants .....                                                                                                                 | 110        |
| 5.2.2                                                                                                                                                                        | Procedure.....                                                                                                                     | 110        |
| 5.2.3                                                                                                                                                                        | Tasks, Equipment and Measures .....                                                                                                | 112        |
| 5.2.4                                                                                                                                                                        | Data Processing.....                                                                                                               | 116        |
| 5.2.5                                                                                                                                                                        | Data Analyses.....                                                                                                                 | 118        |
| <b>5.3</b>                                                                                                                                                                   | <b>Results .....</b>                                                                                                               | <b>122</b> |
| 5.3.1                                                                                                                                                                        | Participant Characteristics .....                                                                                                  | 122        |
| 5.3.2                                                                                                                                                                        | Aim 1: Feasibility and Performance on Frustration Tolerance and Inhibitory Control Tasks....                                       | 122        |
| 5.3.3                                                                                                                                                                        | Aim 2: Feasibility of Micro-analytic Coding of Self-Regulation Strategies.....                                                     | 123        |
| 5.3.4                                                                                                                                                                        | Aim 3: Wearable Devices – Feasibility, ECG Data Quality and Preliminary Analysis .....                                             | 124        |
| <b>5.4</b>                                                                                                                                                                   | <b>Discussion .....</b>                                                                                                            | <b>131</b> |
| 5.4.1                                                                                                                                                                        | Feasibility and Performance on Inhibitory Control Tasks .....                                                                      | 131        |
| 5.4.2                                                                                                                                                                        | Micro-analytic Coding of Self-regulatory Behaviours .....                                                                          | 132        |

|                                                                  |                                                                                   |            |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------|
| 5.4.3                                                            | Wearable Devices .....                                                            | 133        |
| 5.4.5                                                            | Future Directions .....                                                           | 134        |
| 5.4.6                                                            | Conclusions .....                                                                 | 136        |
| <b>Chapter 6   General Discussion .....</b>                      |                                                                                   | <b>138</b> |
| <b>6.1</b>                                                       | <b>Summary of Key Observations .....</b>                                          | <b>138</b> |
| 6.1.1                                                            | Chapter 2.....                                                                    | 138        |
| 6.1.2                                                            | Chapter 3.....                                                                    | 138        |
| 6.1.3                                                            | Chapter 4.....                                                                    | 139        |
| 6.1.4                                                            | Chapter 5.....                                                                    | 139        |
| 6.1.5                                                            | Summary .....                                                                     | 139        |
| <b>6.2</b>                                                       | <b>The Value and Challenges of Comparative Research .....</b>                     | <b>140</b> |
| 6.2.1                                                            | Methodological Challenges in Conducting and Interpreting Comparative Studies..... | 140        |
| 6.2.2                                                            | Questioning the Limits of Comparative Studies .....                               | 142        |
| 6.2.3                                                            | The Future of Comparative Studies: To Lump or Split? .....                        | 143        |
| 6.2.4                                                            | Summary .....                                                                     | 144        |
| <b>6.3</b>                                                       | <b>Insights from Deep Phenotyping .....</b>                                       | <b>145</b> |
| <b>6.4</b>                                                       | <b>Shared Developmental Mechanisms – The Role of Autism-Related Traits .....</b>  | <b>147</b> |
| <b>6.5</b>                                                       | <b>Conclusions.....</b>                                                           | <b>149</b> |
| <b>References.....</b>                                           |                                                                                   | <b>151</b> |
| <b>Appendices.....</b>                                           |                                                                                   | <b>175</b> |
| <b>Appendix A: Supplementary Information for Chapter 2 .....</b> |                                                                                   | <b>175</b> |
| A1.                                                              | Reliability and Validity of the CIASP-ID.....                                     | 175        |
| A2.                                                              | Network analysis edge and node stability estimates .....                          | 177        |
| <b>Appendix B: Supplementary Information for Chapter 3.....</b>  |                                                                                   | <b>179</b> |
| B1.                                                              | Anxiety Profiles.....                                                             | 179        |
| B2.                                                              | Categorising and cleaning coded items.....                                        | 189        |
| B3.                                                              | Interview item level agreement for coded items.....                               | 190        |



# Chapter 1 | General Introduction

Intellectual disability (ID) is a common category of neurodevelopmental disorder (NDD), affecting around 1.5 million people in the UK (<https://www.mencap.org.uk/learning-disability-explained/research-and-statistics/how-common-learning-disability>). Individuals with ID are at elevated risk of mental health and behavioural problems compared to the general population (Hughes-McCormack et al., 2017). This vulnerability is particularly pronounced in individuals for whom a rare genetic cause of ID has been identified (termed ‘rare ID-associated genetic conditions’) (Cunningham et al., 2020; Glasson et al., 2020; Wolstencroft et al., 2022). Understanding this elevated risk is complicated by the heterogeneous and multifaceted aetiology of ID. However, the identification of a rare genetic cause offers a biological starting point, and the opportunity to explore possible developmental mechanisms underlying risk and resilience to mental health both within and across certain rare ID-associated genetic conditions.

Anxiety and behaviours that challenge (BtC) are among the most prevalent and impairing difficulties identified in individuals with rare ID-associated genetic conditions. Emerging evidence suggests that the risk profiles, symptom presentation, and correlates of these difficulties might differ between specific genetic conditions. This highlights the need for systematic behavioural phenotyping to identify which groups might be at elevated risk, how this risk compares across conditions, and how within-condition characteristics might relate to mental health and behavioural problems (Waite et al., 2014). Moreover, moving beyond symptom-level relationships to examine developmental processes and early emerging abilities that might contribute to vulnerability, both within and across rare ID-associated genetic conditions, is key to furthering our understanding of mental health and behavioural problems within this population.

## 1.1 Neurodevelopmental Disorders and Mental Health

Neurodevelopmental disorders (NDDs, see **Figure 1.1**) are a group of complex and heterogeneous conditions that emerge early in childhood and typically persist into adulthood (Thapar et al., 2017). NDDs have their origins in atypical central nervous system (CNS) development, and encompass a range of neurological, psychiatric and cognitive differences. According to the Diagnostic and Statistical Manual of Mental Disorders (5th Ed., DSM-5), NDDs include intellectual disabilities, communication disorders, autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), specific learning disorders, motor disorders and other neurodevelopmental disorders (APA, 2013). Broader or

alternative definitions may also include disorders such as cerebral palsy, epilepsy and schizophrenia (Thapar et al., 2017).

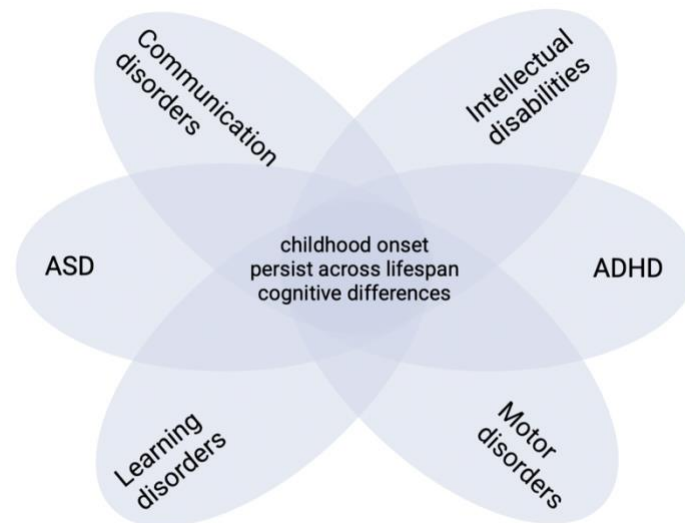


**Figure 1.1** Neurodevelopmental disorders and their shared characteristics (adapted from Thapar et al., 2017). Figure created in BioRender (<https://BioRender.com>).

Current estimates of NDD prevalence vary widely, partly due to shifting diagnostic boundaries and definitions that reflect the evolving understanding of these conditions and their diverse presentations (Vo & Webb, 2024). Comorbidity is also common and presents an additional complicating factor: ADHD affects 28-38.5% of individuals with ASD (Lai et al., 2019; Rong et al., 2021), and ASD is present in 21% of children and adolescents with ADHD (Hollingdale et al., 2020). However, these comorbidities are often not fully captured in prevalence estimates, which are typically based on singular presentations (e.g., ASD only). These limitations are beginning to be addressed; for example, the diagnostic criteria for ASD have expanded over time to better capture variability, including the formal recognition of sensory processing differences and common comorbidities, such as ID (Rosen et al., 2021).

Compared to their typically developing peers, individuals with NDDs are more likely to experience poorer physical health, lower educational attainment, reduced occupational outcomes, and increased contact with the criminal justice system (POST, 2024; WHO and UNICEF, 2023). Mental health is a significant concern, with approximately 50% of children with NDDs experiencing a mental health difficulty, including emotional disorders, such as anxiety and depression, and behavioural disorders, such as oppositional defiant disorder (ODD) and conduct disorder (CD) (Hansen et al., 2018; van Steensel et al., 2011). Clinical and population-based studies in children and adolescents with ASD, for example, have shown that approximately 70-90% meet criteria for at least one psychiatric condition, and around 40-50% meet criteria for three or more diagnoses (Salazar et al., 2015; Simonoff et al., 2008). Moreover, mental health symptoms often persist across development, exacerbate impairment

associated with NDDs, contribute to exclusion and reduced participation, impact intervention and treatment plans, and ultimately lead to a poorer quality of life for individuals and their families (e.g., Baraskewich & McMorris, 2019; Hallett et al., 2010; Hollocks et al., 2023; Simonoff et al., 2013). Consequently, mental health difficulties represent a major concern for individuals with NDDs, highlighting the critical need to identify and understand the underlying contributors.

## **1.2 Intellectual Disability and the Advent of Genomic Medicine**

ID is a common diagnostic category within NDDs, affecting approximately 1% of the global population (Maulik et al., 2011; McKenzie et al., 2016). ID is characterised by deficits in both intellectual ability (commonly defined as an intelligence quotient (IQ) < 70) and adaptive functioning across conceptual, social and practical domains (APA, 2013). ID is typically diagnosed in childhood, and often co-occurs with other NDDs, including ASD (approximately 18% of children with ID have autism, while the prevalence of ID in children with autism is around 30%, Baio et al., 2018; Tonnsen et al., 2016). Individuals with ID exhibit marked heterogeneity in cognitive, behavioural and functional domains, with severity ranging from mild to profound, based on the level of cognitive impairment and the degree of support required (Burack et al., 2021).

The reduced cost and increased accessibility of next-generation sequencing (NGS) technologies have led to a rapid expansion in the applications of genomic medicine, and a corresponding increase in the identification of rare genetic causes of ID (Jansen et al., 2023; Maia et al., 2021; C. F. Wright et al., 2023). Genetic conditions associated with ID can arise from a wide range of genetic variants, including chromosomal abnormalities, copy number variants (CNVs), and single nucleotide variants (SNVs). Recent estimates suggest that genetic causes account for approximately 30% of all cases of ID, rising to up to 60% in individuals with severe-to-profound ID (Gilissen et al., 2014; Jansen et al., 2023; Maia et al., 2021). Whilst some of these conditions are inherited, *de novo* variants (a genetic difference that arises spontaneously rather than inherited from either parent) are a frequent cause of NDDs, occurring in approximately 1 in every 300 individuals in the general population, with over 1,000 genes currently implicated (Deciphering Developmental Disorders Study, 2017).

Genetic testing is now used routinely in paediatric diagnostic settings, enabling earlier detection of rare ID-associated genetic conditions. These diagnoses are often made within the first months and years of life, sometimes before overt cognitive or behavioural symptoms emerge. As a result, there has been a shift towards a genotype-first model of diagnosis, where genetic variants are identified through genomic testing based on initial presenting difficulties, even before a full clinical profile is known. This

contrasts with the traditional phenotype-first approach, in which genetic testing followed the recognition of clinical features suggestive of a particular syndrome.

This shift towards genotype-first identification has altered the phenotypic spectrum of many rare ID-associated genetic conditions (for examples, see Section 6.2.2). However, as initial discovery cases often emphasised medical comorbidities, such as congenital abnormalities or epilepsy, existing literature likely represents individuals with more severe presentations. Moreover, early case series describing mental health and behavioural problems typically lacked standardised measures or comparison samples, making it unclear what the true profile of difficulties is. Therefore, although widespread adoption of NGS technologies has enabled the diagnosis of a growing number of individuals and rare and ultra-rare causes of ID, in the absence of systematic phenotyping, there is limited information about the range of expected clinical characteristics, thereby reducing the utility of a genetic diagnosis for both clinicians and families.

### **1.3 Mental Health in Rare ID-associated Genetic Conditions**

ID confers risk for several negative outcomes, including poor physical and mental health (Emerson & Hatton, 2013). Mental health difficulties represent the most prevalent and persistent problems associated with ID across the lifespan, and individuals with ID face a substantially elevated lifetime risk of mental health difficulties compared to the general population (S.-A. Cooper, 2020; G. Lewin et al., 2025; Mazza et al., 2020). In children and adolescents with ID, prevalence estimates of mental health difficulties range from 30-50% (Buckley et al., 2020; Einfeld et al., 2011), compared to 17.4% in their non-ID peers (NHS Digital, 2021). As such, mental health difficulties are at least twice as common in children with ID (Totsika et al., 2022) .

Several factors have been associated with increased mental health risk in individuals with ID, such as socioeconomic disadvantage, severity of ID, and physical comorbidities (S.-A. Cooper, 2020; S.-A. Cooper et al., 2007). However, the extent to which these factors explain mental health risk remains unclear. The growing identification of rare ID-associated genetic conditions presents new opportunities to explore individual differences in mental health risk within ID.

A growing body of evidence indicates that mental health and behavioural problems are highly prevalent in individuals with rare ID-associated genetic conditions. Two large-scale cohort studies and a recent meta-analysis using standardised diagnostic tools and dimensional measures consistently show high rates of emotional and behavioural problems that are significantly higher than those

observed in the general population (Cunningham et al., 2020; Glasson et al., 2020; Wolstencroft et al., 2022). Analysis of data from the UK-based IMAGINE-ID study (Intellectual Disability and Mental Health: Assessing the Genomic Impact on Neurodevelopment, a cohort study of children with ID and a diagnosed pathogenic SNV or CNV) found that 53.1% of children with a rare ID-associated genetic condition met criteria for clinically significant neuropsychiatric difficulties on the Development and Well-Being Assessment (DAWBA, a validated diagnostic interview, Goodman et al., 2000), compared to 12.8% in a nationally representative sample of typically developing children (Wolstencroft et al., 2022). Similarly, a meta-analysis by Glasson et al. (2020) found 32-74% of children and young people with rare genetic syndromes met thresholds for clinically significant emotional and behavioural problems, compared to 14% in a representative sample of children from the Australian general population.

Currently, there is limited evidence exploring whether mental health difficulties are more common in individuals with rare ID-associated genetic conditions compared to those with idiopathic ID, or other NDDs without a known genetic cause. While studies on specific rare genetic syndromes have reported increased rates of mental health issues relative to individuals with idiopathic ID and ASD (Cordeiro et al., 2011; Fiksinski et al., 2018; Royston et al., 2017; Thurman et al., 2014), it is unclear whether this trend holds at a population level. To address this, we compared published prevalence estimates of DAWBA diagnoses in 2,186 children from the IMAGINE-ID study (Wolstencroft et al., 2022) with 7,090 children with Special Educational Needs (SEN) data from the 2017 UK Mental Health of Children and Young People (MHCYP) Survey (<https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/2017/2017>). This comparison suggests that neuropsychiatric difficulties may be more prevalent in children with rare ID-associated genetic conditions (53.2%) compared to children with SEN (47.0%) and children without SEN (9.0%) from the general population<sup>1</sup>. While these rates differ significantly between groups, it is important to note that a large proportion of children with SEN

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<sup>1</sup> A significantly higher proportion of children in the IMAGINE-ID cohort received a neuropsychiatric diagnosis on the DAWBA compared to children with SEN ( $\chi^2(1) = 7.03$ , adj.  $p = .02$ ) and children without SEN in the general population ( $\chi^2(1) = 1978.1$ , adj.  $p < .001$ ). A Bonferroni correction for multiple comparisons was applied (see **Table 1.1** for group proportions).

**Table 1.1** Prevalence of any disorder on the DAWBA in IMAGINE-ID and MHCYP 2017 Survey.

| Group        | Any Disorder | No Disorder  |
|--------------|--------------|--------------|
| IMAGINE-ID   | 1161 (53.2%) | 1025 (46.8%) |
| MHCYP SEN    | 285 (47.0%)  | 321 (53.0%)  |
| MHCYP No SEN | 584 (9.0%)   | 5900 (91.0%) |

experience neuropsychiatric difficulties, and that ascertainment methods differed between these two cohort studies.

### **1.3.1 Common Mental Health Concerns in Rare ID-associated Genetic Conditions**

When considering broad domains of mental health, both population-level and condition-specific studies converge on anxiety and BtC as particular concerns in individuals with rare ID-associated genetic conditions. Wolstencroft et al. (2022) found significantly higher rates of anxiety and ODD, but not depression or CD, in children with rare ID-associated genetic conditions when compared to children in the general population (Anxiety: 10.6% [rare genetic condition] vs. 7.2% [general population], ODD: 12.1% vs. 2.9%, Depression: 0.4% vs. 2.1%, CD: 1.6% vs. 1.7%). Similarly, a review by Glasson et al. (2020) found that studies assessing psychiatric diagnoses within specific rare genetic syndromes most frequently reported anxiety and ODD, with comparatively lower rates of diagnoses such as depression and schizophrenia. These patterns are consistent with findings from cross-condition comparative studies, which report high overall rates of anxiety and BtC, as well as variation in the specific type of anxiety disorder and form of BtC between rare genetic conditions (e.g., Arron et al., 2011; Groves et al., 2022).

These common mental health concerns are also frequently observed in autistic individuals: for example, in autistic children the prevalence of anxiety ranges from 40-79% (Kent & Simonoff, 2017; van Steensel et al., 2011), and ODD from 4–37% (Kaat & Lecavalier, 2013). Autism is also highly prevalent in rare ID-associated genetic conditions (Richards et al., 2015; Ziats et al., 2020). This overlap raises the possibility that elevated rates of anxiety and ODD may, in part, reflect the high co-occurrence of ID and ASD within rare ID-associated genetic conditions. In support of this, Wolstencroft et al. (2024) found that children with rare ID-associated genetic conditions and co-occurring ASD had both a higher risk of neuropsychiatric difficulties and more severe symptoms than those without co-occurring ASD (Emotional Disorders: 15% [rare genetic condition with ASD] vs. 7.7% [rare genetic condition without ASD], Behavioural Disorders: 20.4% vs. 10%). However, autism alone is unlikely to account for the increased risk of these mental health difficulties in children with rare ID-associated genetic conditions (Edwards, 2022). For example, individuals with Williams syndrome often show high rates of anxiety despite relatively low rates of autism (Royston et al., 2017; Willfors et al., 2024), whilst those with Down syndrome exhibit elevated rates of ODD alongside lower autism prevalence (Glasson et al., 2020; Moss et al., 2013). Additionally, it may not be autism per se, but rather specific autism-related traits, such as sensory processing differences or repetitive behaviour, that contribute to heightened

vulnerability to anxiety and BtC in both individuals with idiopathic autism and rare ID-associated genetic conditions.

#### *1.3.1.1 Anxiety in Rare ID-associated Genetic Conditions*

Anxiety is a normal emotional response to stress or danger. However, anxiety can become problematic and interfere with an individual's daily life (i.e., become a disorder) when it occurs in the absence of danger, or is disproportionate to the threat posed (APA, 2021). Although certain types of anxiety disorders, such as specific phobia, social anxiety disorder and generalised anxiety disorder, have unique diagnostic criteria, according to the DSM-5 they are collectively characterised by excessive fear or worry (APA, 2013).

In the general population, anxiety disorders are among the most common mental health disorders, with an estimated lifetime prevalence of around 30% (Bandelow & Michaelis, 2015; Kessler et al., 2005; Merikangas et al., 2010). Typically, anxiety disorders have their onset in early life, with the period from early childhood to mid-adolescence representing a particularly vulnerable period (Kieling et al., 2024; Solmi et al., 2022). Moreover, if left untreated, anxiety disorders persist and have significant impacts on social, occupational and academic functioning (Copeland et al., 2014; Dickson et al., 2024; Pollard et al., 2023).

Several studies have shown that anxiety is significantly elevated in individuals with idiopathic ID compared to the general population, with prevalence estimates reaching up to 22% in children and adolescents with ID, compared to approximately 6.5% in the general population (Einfeld et al., 2011; Emerson & Hatton, 2007; Mazza et al., 2020; Polanczyk et al., 2015; Reardon et al., 2015; Reid et al., 2011). Like in the general population, anxiety in individuals with ID is also associated with a range of poor outcomes, such as increased risk of co-occurring mental health difficulties, poorer physical health, reduced social opportunities, loneliness and unemployment (El Mrayyan et al., 2019; Powers et al., 2022). However, despite this increased risk, individuals with ID are less likely to access mental health interventions (Vereenoghe et al., 2018; Whittle et al., 2018).

Anxiety is also frequently reported as a prominent feature of rare ID-associated genetic conditions (see **Table 1.2**), with significantly elevated prevalence rates compared to the general population (Edwards et al., 2022; Glasson et al., 2020; Wolstencroft et al., 2022). However, estimates of prevalence vary significantly depending on the specific genetic aetiology; for example, a recent meta-analysis found

the rate of anxiety varied across different rare conditions from 9% in Down syndrome to 73% in Rett syndrome (Edwards et al., 2022).

**Table 1.2** Reported Prevalence of Anxiety in Exemplar Rare Genetic Syndromes.

| Rare Genetic Syndrome | Prevalence estimates  |
|-----------------------|-----------------------|
| CHARGE                | 37% <sup>a</sup>      |
| Cornelia de Lange     | 54-92% <sup>b,c</sup> |
| Down                  | 9% <sup>a</sup>       |
| Fragile X             | 48% <sup>a</sup>      |
| Prader-Willi          | 10% <sup>d</sup>      |
| Rett                  | 73% <sup>a</sup>      |
| Rubenstein-Tabi       | 19% <sup>e</sup>      |
| Tuberous sclerosis    | 14% <sup>a</sup>      |
| Williams              | 48% <sup>f</sup>      |
| 3q29 deletion         | 19% <sup>a</sup>      |
| 7q11.23 duplication   | 70% <sup>a</sup>      |
| 22q11.2 deletion      | 40% <sup>a</sup>      |

<sup>a</sup> Edwards et al. (2022)<sup>†</sup>

<sup>b</sup> Crawford et al. (2017)

<sup>c</sup> Groves et al. (2022)

<sup>d</sup> Lo et al. (2015)

<sup>e</sup> Crawford et al. (2017)

<sup>f</sup> Royston et al. (2017)<sup>†</sup>

<sup>†</sup> Indicates meta-analysis

Emerging evidence suggests that, in addition to differences in overall prevalence, the type and symptom profile of anxiety disorders also varies across rare genetic syndromes. For example, individuals with Williams syndrome (WS) are more likely to experience specific phobias or generalised anxiety than social anxiety (Royston et al., 2017). In contrast, social anxiety is the most common anxiety disorder type in Fragile X syndrome (FXS, Cordeiro et al., 2011). Although these syndromes have not been directly compared, these observations are supported by cross-syndrome comparative studies, which have found divergent anxiety profiles between individuals with FXS and Cornelia de Lange syndrome (CdLS). Specifically, individuals with CdLS display higher separation anxiety and generalised anxiety compared to individuals with FXS (Crawford et al., 2017), whereas the prevalence of social anxiety, but not other anxiety disorder types (e.g., panic disorder and specific phobia) is significantly higher in FXS compared to CdLS (Groves et al., 2022). Identifying the anxiety risk profiles of different groups is likely to be of clinical importance, since different anxiety disorders are associated with distinct theoretical models and interventions when treated in the general population (for example cognitive models of social phobia and panic, Clark, 1986; Clark & Wells, 1995).

In addition to the clinical importance of identifying syndrome-specific anxiety profiles, this information can also shed light on the pathways which may contribute to emergent anxiety profiles and how these differ across conditions. For example, the mechanisms underpinning anxiety might be closely linked to the cognitive, social and sensory characteristics of a specific syndrome. This has been proposed in WS, where specific phobias, particularly those related to loud or unexpected noises, are relatively common. This may be explained by the increased sensitivity to everyday noises (termed hyperacusis) frequently reported in individuals with WS (Royston et al., 2017, 2021), although this link has yet to be formally tested.

Several other factors have been proposed as predictors of anxiety in individuals with rare genetic syndromes, including demographic characteristics (such as age, gender, ID severity and verbal ability), autism-related characteristics, repetitive behaviour, and comorbid physical health difficulties (for discussion, see Edwards, 2022). As described above, the role of autism has received particular attention, given the high co-occurrence of autism and anxiety in rare ID-associated genetic conditions. However, it may not be autism per se that contributes to anxiety, but specific autism-related traits. For example, Crawford et al. (2023) found that repetitive speech predicted anxiety in FXS, whereas overall autism symptom severity was not associated with anxiety in CdLS. Not only do these findings suggest the role of specific autism-related traits in the emergence of anxiety, but also that the correlates of anxiety may differ across genetic syndromes, potentially reflecting underlying differences in cognitive and social characteristics. This reinforces the importance of identifying factors that contribute to within-syndrome variability in mental health difficulties, as well as exploring the extent to which such factors are shared across conditions.

#### *1.3.1.2 Behaviours that Challenge in Rare ID-associated Genetic Conditions*

Behaviours that Challenge (BtC; also called 'Challenging Behaviour') is a broad umbrella term that refers to behaviours that occur with a frequency, duration and intensity such that they can negatively affect a person's quality of life, physical safety, and emotional well-being, as well as that of those around them (Emerson, 1995; RCPsych, BPS and RCSLT, 2007). It includes behaviours that harm the person themselves (e.g., head banging, self-biting, skin picking), and behaviours that are directed at others (e.g., punching, pushing, kicking), or objects (e.g., tearing books, slamming doors, throwing objects). These behaviours are broadly categorised as self-injury, aggression, and property destruction, respectively (for a detailed description of categories of BtC see Oliver et al., 2022). BtC can result in direct physical harm, such as permanent sensory loss sustained by self-injury (Huisman et al., 2018), and can contribute to wider negative consequences, including social exclusion, reduced participation

(Emerson & Einfeld, 2011b), placement breakdown (Phillips & Rose, 2010), and increased use of psychotropic medication and other restrictive practices (O'Dwyer et al., 2018, 2019; Sheehan et al., 2015; Younan et al., 2024). They are also associated with poorer quality of life and elevated caregiver stress (Beadle-Brown et al., 2009; Griffith & Hastings, 2014). Given these wide-ranging impacts, understanding the nature (i.e., the phenomenology of the behaviour), drivers (i.e., factors associated with the likelihood of the behaviour), and functions (i.e., the different purposes the behaviour may serve) of BtC in rare ID-associated genetic conditions is essential for effective support and intervention.

Across ID populations, approximately 10-20% of individuals display BtC (Bowring et al., 2017; S. -A. Cooper et al., 2009; Emerson et al., 2001), occurring at even higher rates among individuals with co-occurring ASD (e.g., Richards et al. 2012). BtC are particularly common among individuals with rare ID-associated genetic conditions, and individuals with specific diagnoses might be more at risk (see **Table 1.3**). For example, Arron et al. (2011) found the rate of self-injury varied from 45.1% in Angelman syndrome to 92.9% in Smith-Magenis syndrome. They also found that the likelihood of displaying self-injury was significantly greater in each of the rare genetic syndromes (except Angelman syndrome) when compared to a group of individuals with idiopathic ID. Furthermore, individuals often exhibit multiple categories of BtC (e.g., both self-injury and aggression), as well as varied topographies within each category (i.e., the specific form or physical presentation of a behaviour). For example, in the wider ID population around 55% of individuals display two or more types of BtC (O'Dwyer et al., 2018). Consistently, recent studies on *SATB2*-associated syndrome found that 56% of individuals displayed two or more categories of BtC, with self-biting being the most common form of self-injury (Bissell et al., 2022; Shelley et al., 2024).

BtC typically emerge in childhood, and while there is some evidence to suggest that prevalence may increase into middle adulthood, this remains limited to studies of individuals with idiopathic ID (Davies & Oliver, 2016; Oliver & Richards, 2015). Research on the persistence of BtC in individuals with ID, both with and without a known genetic cause, is also limited and tends to focus on specific categories of BtC, particularly self-injury. Available data suggests that self-injurious behaviours, aggression and property destruction are maintained over time (Crawford et al., 2019; Dimian & Symons, 2022; Wilde et al., 2018). For example, a prospective longitudinal study conducted over a 10-year period found that self-injury persisted in 44% of autistic individuals (Lavery et al., 2020). In this study, persistence was predicted by greater impulsivity, stereotyped behaviour, social communication difficulties, as well as poorer adaptive functioning. These findings highlight that BtC emerge early in life and, without effective intervention and support, are maintained.

**Table 1.3** Reported Prevalence of Behaviours that Challenge in Exemplar Rare Genetic Syndromes.

| Rare genetic syndrome | Prevalence estimates |                     |                      |
|-----------------------|----------------------|---------------------|----------------------|
|                       | Self-injury          | Aggression          | Property destruction |
| Angelman              | 42-45 <sup>a,b</sup> | 10-73 <sup>c</sup>  | 54 <sup>b</sup>      |
| CHARGE                | 44 <sup>d</sup>      | 48 <sup>d</sup>     | -                    |
| Cornelia de Lange     | 36-88 <sup>e</sup>   | 7-75 <sup>c</sup>   | 54 <sup>b</sup>      |
| Cri du Chat           | 70-92 <sup>e</sup>   | 19-88 <sup>c</sup>  | -                    |
| Down                  | 3-45 <sup>e</sup>    | 4-41 <sup>c,f</sup> | 11 <sup>g</sup>      |
| Fragile X             | 48 <sup>h</sup>      | 36 <sup>h</sup>     | 25 <sup>h</sup>      |
| Lowe                  | 64 <sup>a</sup>      | 65 <sup>a</sup>     | -                    |
| Pitt Hopkins          | 71 <sup>b</sup>      | 54 <sup>b</sup>     | 38 <sup>b</sup>      |
| Potocki-Lupski        | 29 <sup>i</sup>      | 50 <sup>i</sup>     | 24 <sup>i</sup>      |
| Prader-Willi          | 52-96 <sup>e</sup>   | 10-73 <sup>c</sup>  | 47 <sup>g</sup>      |
| SATB2-associated      | 43 <sup>j</sup>      | 77 <sup>j</sup>     | 47 <sup>j</sup>      |
| Smith Magenis         | 44-100 <sup>e</sup>  | 57-88 <sup>c</sup>  | 77-81 <sup>i,k</sup> |
| Sotos                 | 42 <sup>g</sup>      | 43 <sup>g</sup>     | 43 <sup>g</sup>      |
| Tuberous Sclerosis    | 10-27 <sup>e</sup>   | 50 <sup>f</sup>     | -                    |
| Williams              | -                    | 6.7-15 <sup>c</sup> | -                    |

<sup>a</sup> Arron et al. (2011)<sup>b</sup> Watkins et al., 2019)<sup>c</sup> Powis & Oliver (2014)<sup>d</sup> Thomas et al. (2022)<sup>†</sup><sup>e</sup> Huisman et al. (2018)<sup>f</sup> Eden et al. (2014)<sup>g</sup> Sheth et al. (2015)<sup>h</sup> Hardiman & McGill (2018)<sup>†</sup><sup>i</sup> Bissell et al. (2018)<sup>j</sup> Shelley et al. (2024)<sup>k</sup> Sloneem et al. (2011)<sup>†</sup> Indicates meta-analysis.

Several traits have been linked with the presence of BtC in the wider NDD and rare genetic syndrome literature (Emerson & Einfeld, 2011a; Oliver et al., 2022). Individuals with moderate to profound ID are at greater risk of BtC than those with mild ID (Cooper et al., 2009; McClintock et al., 2003), and communication impairments have been associated with greater likelihood of BtC (Emerson et al., 2001; McClintock et al., 2003; Oliver et al., 2012). Moreover, neurodevelopmental traits, such as restricted and repetitive behaviours, hyperactivity and impulsivity have been associated with BtC in several rare genetic syndromes (Crawford et al., 2019; Eden et al., 2014; Oliver & Richards, 2015; Shelley et al., 2024; Wilde et al., 2018). Furthermore, recent research in *SATB2*-associated syndrome found that individuals who exhibit BtC show higher general anxiety than those who do not (Shelley et al., 2024).

In addition to these associations, BtC are thought to serve several functions. Traditional functions, as assessed via the short form version of the Questions About Behavioural Function scale (QABF-SF, Singh

et al., 2009), include access to attention or tangibles, self-stimulation, demand escape or a response to physical discomfort/pain. Other proposed functions involve communicating needs or expressing distress. For example, BtC have been described as anxiety-related behaviours in individuals with ID, with and without a rare genetic cause (Edwards et al., 2022; Royston et al., 2021, also see Chapter 3). Understanding these different associations and functions is crucial for informing early intervention, personalised support and prevention strategies for BtC in rare ID-associated genetic conditions.

### **1.3.2 Challenges of Conducting Mental Health Research in Rare ID-associated Genetic Conditions**

As outlined above, mental health difficulties, specifically anxiety and BtC, are a significant concern in individuals with rare ID-associated genetic conditions. However, despite substantial literature highlighting increased prevalence, persistence and impacts, our current understanding is limited by our methods and approaches.

One major challenge is that common mental health measures are often grounded in diagnostic criteria that were developed in typically developing populations, and as such, may not adequately capture mental health symptoms in rare ID-associated genetic conditions (Flynn et al., 2017). These measures often rely on an individual's ability to recognise internal states, such as excessive worry or low mood, and verbally communicate their needs. However, for individuals with rare ID-associated genetic conditions, particularly for those with severe-to-profound ID and who speak few or no words, these skills might not be accessible to them or their communication partners (Adams & Oliver, 2011; Mellor & Dagnan, 2005). Mental health difficulties may also present atypically within this population (Edwards et al., 2023; Lozano et al., 2022). For example, anxiety may be expressed via non-verbal vocalisations (e.g., shouting, crying, screaming) or through behaviours such as avoidance, agitation or BtC, rather than via the verbal expression of thoughts and worries that are traditionally assessed by diagnostic-based measures. Physical symptoms, such as nausea and sleeping difficulties, may also be more prominent. As such, it may be challenging to disentangle anxiety, fear and distress within these groups (for discussion of the distinction between fear and anxiety see Chapter 3, Section 3.2.5.3).

The reliance on measures grounded in diagnostic criteria may lead to inaccurate prevalence estimates and misdiagnoses in individuals with rare ID-associated genetic conditions. On one hand, mental health symptoms may be under-recognised due to atypical presentations, or as a result of diagnostic overshadowing, where mental health symptoms are attributed to ID, rather than being recognised as distinct concerns. On the other hand, characteristics of ID may be misinterpreted as signs of mental health difficulties (e.g., repetitive behaviours could be attributed to obsessive compulsive disorder).

Therefore, while the use of these measures may facilitate direct comparisons with the general population, they may not accurately assess the true prevalence of mental health symptoms in individuals with rare ID-associated genetic conditions. Hence, it is important that adopted measures are sensitive to unique patterns of symptoms in this population.

Another challenge is that mental health difficulties are often characterised using broad diagnostic categories. Terms such as anxiety or self-injury may lack the specificity to accurately describe and capture meaningful variation both within and between rare ID-associated genetic conditions, potentially leading to overgeneralisation, where important syndrome-specific differences may be overlooked (Oliver, 2017). In support of this, a substantial body of literature demonstrates that when behaviours, such as autism-related traits, repetitive behaviours and anxiety, are examined at a more granular level, syndrome-specific differences emerge (Ali et al., 2025; Bozhilova et al., 2023; Crawford et al., 2017; Edwards et al., 2022; Moss et al., 2009; Oliver et al., 2010). These differences may have important implications for selecting appropriate clinical interventions and for understanding underlying mechanisms.

Research on BtC, for example, often focuses on the overall prevalence of broad categories (e.g., aggression) without examining specific topographies (e.g., how aggression is expressed – hitting, biting, hair-pulling). This limits our ability to identify patterns that might be condition-specific, functionally distinct, or linked to different underlying mechanisms. In evidence of this, while self-injury is reported across a wide range of rare ID-associated genetic conditions, the specific topographies of self-injury, such as head banging, skin picking, or self-biting, can vary between syndromes (Huisman et al., 2018). For example, Bissell et al. (2022) found no differences in the overall prevalence of self-injury between individuals with *SATB2*-associated syndrome, Angelman syndrome, and idiopathic autism. However, they found that the number of individuals hitting themselves with their own body part (e.g., slapping their own head or face) significantly differed between groups, although this difference did not survive correction for multiple comparisons. These findings highlight the potential for phenotypic specificity to emerge when behaviours are precisely defined, even when broad categories show no group differences.

Studies of mental health in rare ID-associated genetic conditions also tend to focus on single conditions. As a result, there is a lack of comparative, cross-syndrome research. This creates several challenges. First, it limits our ability to determine whether certain difficulties are truly elevated in specific conditions (i.e., beyond what would be expected given the severity of ID). Second, it makes it

difficult to disentangle whether observed difficulties stem from general ID-related mechanisms (e.g., severity of ID or adaptive function impairments) or from condition-specific pathways.

Even when comparative studies are conducted, they face significant methodological challenges (Farran & Scerif, 2022). Recruiting adequate sample sizes for a single rare condition is inherently difficult; doing so for multiple groups presents an even greater challenge. As a result, comparative research in rare ID-associated genetic conditions is frequently limited by small sample sizes which reduces statistical power, hindering the ability to detect reliable group differences and increasing the risk of false negatives (i.e., Type II errors). This raises concerns about the generalisability and replicability of reported findings. Replication is particularly important in this field, given that behavioural phenotypes may inform clinical decision-making and guide future mechanistic research. However, in practice, very few studies are replicated.

Beyond these methodological challenges, there are also several conceptual issues with mental health studies in rare-ID associated conditions. First, there is a tendency to conflate prevalence with specificity (Waite et al., 2014). However, even if a behaviour is more common or more likely in a given rare ID-associated genetic condition, it does not mean that it is specific or causally linked to that condition. Similarly, many studies also equate descriptive behavioural profiles with mechanistic explanations, attributing behaviours directly to genetic difference or ID without considering developmental factors (Oliver et al., 2022).

Understanding the influence of early-emerging traits on mental health is especially important given that childhood and adolescence represent a particularly vulnerable period for the onset of these difficulties. For example, in the general population, the median age of onset for any mental disorder is approximately 14.5 years old (Solmi et al., 2022). Therefore, beyond characterising mental health difficulties in rare ID-associated genetic conditions, it is crucial to examine how early cognitive, emotional, and social processes contribute to risk or resilience for later mental health outcomes in this population.

Taken together, these challenges highlight the importance moving beyond traditional diagnostic-based measures and broad symptom categories in order to advance our understanding of mental health in rare ID-associated genetic conditions. By adopting sensitive, NDD-informed measures and conducting rigorous cross-syndrome comparisons, we can better strike a balance between condition-specificity, within-condition variability, and cross-condition similarity. Furthermore, integrating developmental

perspectives to examine early emerging traits will further our understanding of factors contributing to risk and resilience for mental health difficulties in this population. This comprehensive approach is essential for improving both the precision of mental health characterisation and the development of targeted interventions for individuals with rare ID-associated genetic conditions.

#### **1.4 Thesis Aims and Structure**

This thesis presents a multi-method programme of work focusing on anxiety and BtC in two exemplar rare ID-associated genetic conditions: *DDX3X*-related disorder and *CASK*-related disorder. The programme addresses key priorities in the field by combining detailed phenotypic characterisation with cross-condition comparisons, while extending existing work through the integration of developmental perspectives and methodological advances. Specifically, the thesis aims to:

1. characterise the presentation of anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder;
2. explore condition-specific differences and correlates of these emotional and behavioural difficulties within and across these disorders;
3. adopt a developmental perspective to explore self-regulation and its relationship to anxiety in young children with rare ID-associated genetic conditions; and
4. evaluate the feasibility of methods for assessing self-regulation and its relevance to anxiety in this population.

The first half of this thesis (Chapters 2 and 3) provides a detailed characterisation of anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder and directly compares these conditions to a mixed group of other rare ID-associated genetic conditions. These chapters provide converging evidence, drawing on complementary quantitative and qualitative methodologies.

Chapter 2 examines the enrichment and correlates of anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder using questionnaire measures suitable for individuals with NDDs. It replicates and extends previous findings in *DDX3X*-related disorder and provides the first systematic examination of these characteristics in *CASK*-related disorder. Within- and cross-condition associations between adaptive ability, autism-related characteristics, anxiety and BtC are also explored using pairwise correlations and a network analysis.

Chapter 3 builds on these findings by providing a more nuanced understanding of anxiety from a parent perspective. Using interview methodology grounded in a clinical framework it examines anxiety-related behaviours, antecedents and consequences.

The second half of the thesis (Chapters 4 and 5) adopts a developmental perspective to examine self-regulation as a potential predictor of anxiety and evaluates the feasibility of experimental methods for assessing this construct in young children with rare ID-associated genetic conditions.

Chapter 4 explores the relationship between temperament-based self-regulation (e.g., effortful control) and anxiety in rare ID-associated genetic conditions. The chapter begins with a review of existing literature and then uses informant report measures to examine associations between temperament-based traits (effortful control and negative affect) and anxiety in a new sample of children with rare ID-associated genetic conditions.

Chapter 5 then builds on these findings by presenting a feasibility study exploring whether play-based assessments and wearable physiological measures can be used to examine self-regulation in young children with these conditions. This chapter evaluates the practicality of these methods for capturing self-regulation as a potential early contributor to anxiety.

## Chapter 2 | Anxiety and Behaviours that Challenge in *DDX3X*-related disorder and *CASK*-related disorder

### 2.1 Introduction

Anxiety and BtC, namely self-injury, aggression and property destruction, are common in rare ID-associated genetic conditions. Reported prevalence estimates range from 9-73% for anxiety (Edwards et al., 2022), 15-95.5% for self-injurious behaviour (SIB; Huisman et al., 2018), and 3.7%-88% for aggression (Powis & Oliver, 2014). However, these estimates are highly influenced by study methodology, including definition, measurement, recruitment, and sample characteristics (e.g., prevalence and severity of autism-related characteristics). Cross-condition studies have shown that individuals with specific genetic conditions might be more at risk of anxiety and BtC, and that both anxiety disorder symptomology and BtC topology might differ between genetic conditions (e.g. Arron et al., 2011; Crawford et al., 2017; Eden et al., 2014; Edwards et al., 2022; Groves et al., 2022; Huisman et al., 2018). Therefore, accurate assessment and identification of groups at high-risk of anxiety and BtC is important to improve proactive identification of symptoms, as well as explore whether genetic aetiology or within-condition characteristics, such as experience of pain or poor sleep, influence the emergence of symptoms.

Identifying neurodevelopmental correlates – and whether these differ across genetic diagnosis groups – is also key to understanding factors contributing to anxiety and BtC in rare ID-associated genetic conditions. There is growing evidence of an overlap between anxiety and autism, with 40–80% of autistic children and adolescents meeting criteria for at least one DSM-5 anxiety disorder (Hollocks et al., 2023; van Steensel et al., 2011). In autistic individuals, anxiety may be driven by ‘core’ characteristics (e.g., communication difficulties, and restricted and repetitive behaviours, including special interests and sensory processing differences), with consistent correlational evidence linking sensory processing differences to increased anxiety (Pelluru, 2025; Powell et al., 2025). This raises the importance of considering whether autism-related characteristics contribute to anxiety in rare ID-associated genetic conditions that often exhibit high rates of autism (Richards et al., 2015; Ziats et al., 2020).

In the context of ID, however, the relationship between anxiety and autism-related traits is complicated by cognitive ability. For example, a recent meta-analysis found that anxiety was greater in autistic children with higher IQ (Mingins et al., 2020), but that few studies used anxiety measures valid for

both autistic children and those with ID. This highlights the need for research that accounts for both social development and cognitive ability when examining potential mechanisms underlying anxiety (and BtC) in rare ID-associated genetic conditions.

### **2.1.1 Anxiety and BtC in *DDX3X*-related disorder**

*DDX3X*-related disorder is an exemplar X-linked, rare ID-associated genetic condition which is thought to account for approximately 1-3% of unexplained ID in females (Snijders Blok et al., 2015). Most females with *DDX3X*-related disorder have ID of variable severity, and approximately 50% of affected individuals are minimally verbal (E. J. Forbes et al., 2024; Johnson-Kerner et al., 2020; Levy et al., 2023). *DDX3X*-related disorder has been associated with a range of neurodevelopmental and emotion-behavioural problems (Johnson-Kerner et al., 2020). In particular, high rates of autism (17-60%, Levy et al., 2023), anxiety (7-50%, Forbes et al., 2024; Ng-Cordell et al., 2023; Parra et al., 2024), self-injury (>50%, Ng-Cordell et al., 2023) and aggression (53%, Snijders Blok et al., 2015).

In a recent comparative study, Ng-Cordell et al. (2023) found that individuals with *DDX3X*-related disorder exhibited significantly higher levels of anxiety and self-injury relative to those with other rare ID-associated genetic conditions when matched at a group-level for sex, age and adaptive ability. This finding indicates that these emotional-behavioural problems may reflect condition-specific vulnerabilities in *DDX3X*-related disorder beyond what is expected for the severity of ID. In addition, they found group-specific associations between (1) higher anxiety and lower adaptive ability; and (2) higher self-injurious behaviours and lower adaptive ability, higher anxiety, and elevated autism-related characteristics. This study provides preliminary evidence that complex relationships between neurodevelopmental correlates and emotional-behavioural problems in *DDX3X*-related disorder may vary from associations observed in other rare ID-associated genetic conditions.

An important next step is to fully establish if there are unique condition-specific risks and neurodevelopmental correlates of anxiety and self-injury and *DDX3X*-related disorder is to examine whether these initial comparative findings replicate. This is particularly important given the following methodological limitations of Ng-Cordell et al. (2023). Firstly, their findings are based on a relatively small sample size, such that it is challenging to ascertain whether the available data are representative of the broader population, and therefore able to inform definitive conclusions about group differences. Secondly, in small samples, *P* values are particularly sensitive to small deviations in outcomes, thereby increasing the importance of corrections for multiple testing. In their study, Ng-Cordell et al. (2023)

did not correct for multiple testing, such that there is an increased risk of Type I error and the likelihood of falsely identifying a significant effect of group where there is none.

Finally, the questionnaire-based measures used to examine anxiety and self-injury were limited in scope. For example, their self-injury measure consisted of only three items. This limited how comprehensively these emotional-behavioural problems were assessed and the reliability of the results. Given the association between anxiety and autism-related characteristics in *DDX3X*-related disorder (Ng-Cordell et al., 2023) and high levels of aggression (Snijders Blok et al., 2015), another category of BtC, it is critical that future studies fully capture the range of possible anxiety presentations and different categories of BtC in individuals with *DDX3X*-related disorder.

Further investigation in an independent sample is needed to understand whether anxiety and self-injury differ in *DDX3X*-related disorder relative to other rare ID-associated genetic conditions, and whether there are condition-specific relationships between anxiety, BtC, adaptive ability and autism-related characteristics in this population.

### **2.1.2 Anxiety and BtC in *CASK*-related disorder**

*CASK*-related disorder is another X-linked cause of ID, which predominately affects females (Najm et al., 2008). The current prevalence of *CASK*-related disorder is unknown. Two distinct phenotypes – (1) microcephaly with pontine and cerebellar hypoplasia (MICPCH) and (2) X-linked intellectual disability (XLID) with or without nystagmus – have been associated with *CASK*-related disorder (Mori et al., 2023). These phenotypes likely represent a continuum, also involving feeding difficulties, hypotonia, epilepsy, sensorineural hearing loss and ophthalmologic problems (Dubbs et al., 2022; Hayashi et al., 2012, 2017; Moog et al., 2011; Najm et al., 2008). Most females with *CASK*-related disorder have severe motor and communication developmental delay (Dubbs et al., 2022; Hayashi et al., 2012; Moog et al., 2011; Najm et al., 2008), and a small number of cases have been reported to have an autism diagnosis (Becker et al., 2020; Deciphering Developmental Disorders Study, 2015, 2017; Dubbs et al., 2022; Seto et al., 2017).

However, until recently, the neurodevelopmental and mental health characteristics associated with *CASK*-related disorder were undocumented. Previous studies were mainly based on retrospective medical reports of individuals identified phenotype-first, with few involving concurrent assessments of developmental abilities or mental health after genetic diagnosis. In our recent review (Martin et al., 2024), we identified only one paper which described self-injurious behaviour in five female patients

with *CASK* variants ascertained for their diagnosis of pontocerebellar hypoplasia (PCH) (Burglen et al., 2012). We did not identify any published reports of anxiety in this population.

One possibility is that *CASK*-related disorder is not associated with anxiety and BtC. However, we believe that this is unlikely due to the reported prevalence in other, similar X-linked rare ID-associated genetic conditions (e.g., Rett syndrome, see Buchanan et al., 2022; Cianfaglione et al., 2015; and *DDX3X*-related disorder, see above). Instead, we suggest that these symptoms may be under-reported and under-recognised in the literature because published studies have focused on neurological and medical findings, or that they are under-diagnosed in *CASK*-related disorder because of the difficulty of reliably assessing these symptoms in individuals with severe-profound ID and limited verbal abilities.

To address this, we conducted an initial descriptive study of individuals with *CASK*-related disorder who were ascertained genotype-first and assessed concurrently using dimensional measures of neurodevelopmental and mental health characteristics designed for individuals with ID (Martin et al., 2024). We showed that most individuals with *CASK*-related disorder score in the moderate-to-serious problem range on a measure of anxiety behaviours, and that almost half of individuals were reported to have shown self-injurious behaviour or aggression within the last month. We also observed high levels of autism-related traits, but on average relatively preserved social motivation. These patterns are similar to those observed in other rare ID-associated genetic conditions.

Nevertheless, the previous study was not comparative, and therefore it is unclear whether these characteristics are more commonly observed in *CASK*-related disorder than is expected for severity of ID. Here, we explored anxiety and BtC in this same sample of individuals with *CASK*-related disorder relative to individuals with other rare ID-associated genetic conditions.

### **2.1.3 Methodological Advances**

Beyond addressing questions of replicability in *DDX3X*-related disorder and examining anxiety and BtC in *CASK*-related disorder relative to other rare ID-associated genetic conditions for the first time, we applied two methodological advances in this study.

Assessing anxiety in rare ID-associated conditions is challenging due to the complex interplay between anxiety, autism and ID (see Mingins et al., 2020). Traditional questionnaire-based measures of anxiety, which are grounded in DSM-5 symptomology, might not be appropriate for individuals with ID as these assessments often rely on verbal communication of symptoms. Instead, tools specifically developed

for individuals with ID – and not constrained by diagnostic criteria – may be a more suitable alternative better equipped to capture the unique ways anxiety presents in this population (e.g., behaviours or physical symptoms rather than verbal expression of fears and worries). Moreover, due to the high prevalence of autism in rare ID-associated genetic conditions (Richards et al., 2015; Ziats et al., 2020), it is possible that anxiety in this population might manifest more similarly to anxiety in autistic individuals, wherein specific fears, social phobia and ritualistic behaviour are commonly observed (Kerns et al., 2014). Hence, adopting measures of anxiety which are sensitive to these potential variations in anxiety presentation is important. In the current study, we included three complementary questionnaire measures of anxiety – one to replicate Ng-Cordell et al. (2023); and two to capture variations anxiety-related behaviours relevant to ID and autism.

Additionally, research examining relationships between psychological variables in individuals with rare ID-associated genetic conditions has typically relied on traditional statistical methods, such as correlation analyses or latent variable approaches (e.g., principal component analysis) (e.g., Bissell et al., 2022; Eck et al., 2024; Ng-Cordell et al., 2023). Correlation analyses are quick and easily interpretable, but only capture bivariate relationships. Latent variable approaches, while useful for identifying clusters of related variables, assume that associations arise from a single underlying cause, providing limited insight into the direct interplay among individual variables.

Network analysis addresses these limitations by modelling unique, direct and indirect associations among multiple variables simultaneously. In this model, psychological variables (e.g., symptoms or traits) are represented as nodes, and the statistical relationships or conditional dependencies between them are represented as edges (Borsboom, 2017). Edges typically reflect partial correlations, which estimate the association between two nodes while controlling for all others in the network. This structure allows researchers to visualise complex patterns of interaction, identify central or bridging nodes, and examine how changes in one variable may influence others directly or indirectly. Therefore, network analysis represents a powerful tool for disentangling complex relationships between neurodevelopmental and mental health difficulties, and for generating testable hypotheses about potential causal pathways and mechanisms.

This approach has been successfully used to explore the co-occurrence of anxiety in autistic individuals. For example, several studies have found that, while anxiety symptoms are often peripherally related to and distinct from autistic traits, certain traits such as social communication difficulties, preference for sameness, and sensory hypersensitivity may act as bridging nodes, linking

anxiety and autism-related characteristics in autistic children and adolescents (Bitsika et al., 2025; Montazeri et al., 2019; Zaidmanzait et al., In Press).

In this study, we extend our analyses beyond simple correlations and used network analysis to explore the relationships between developmental ability, autism-related traits (including repetitive and sensory behaviours), anxiety symptoms and BtC in rare ID-associated genetic conditions.

#### **2.1.4 Aims of the Study**

This study had three aims:

1. To describe the medical and developmental characteristics of children with *DDX3X*-related disorder, *CASK*-related disorder, and other rare ID-associated genetic conditions.
2. To examine differences in anxiety and BtC among children with *DDX3X*-related disorder, *CASK*-related disorder, and other rare ID-associated genetic conditions.
3. To explore the relationships between adaptive ability, autism-related traits, anxiety, and BtC in the same three genetic diagnosis groups.

Replication was a key goal of Aims 2 and 3. Specifically, we sought to replicate findings from Ng-Cordell et al. (2023). We also built on this previous study by incorporating more comprehensive measures of anxiety and BtC, adding a third comparison group (children with *CASK*-related disorder, another X-linked, female-predominant, rare ID-associated genetic condition) and adopting new analytical approaches.

## **2.2 Methods**

### **2.2.1 Participants**

This study was conducted as part of a larger project – Brain and Behaviour in Neurodevelopmental Disorders of Genetic Origin (BINGO) (Cambridge Central Research Ethics Committee IRAS reference: 11/EE/0330, ‘Phenotypes in Intellectual Disability’). Families of children and adolescents (henceforth ‘children’) with rare genetic conditions were recruited via the existing study database, and new participants were recruited via rare condition support groups and charities as well as regional genetic services in the UK. Children were invited to participate if they were aged 3-18 years old, experienced neurodevelopmental difficulties, and had a diagnosed genetic condition resulting from a variant affecting a single gene (i.e., not including multi-genic CNVs or chromosomal rearrangements). Participants were recruited to one of three groups: (1) *DDX3X*-related disorder, (2) *CASK*-related disorder, and (3) any other rare ID-associated genetic condition (henceforth ‘ID-other’). To be included in the former two groups, participants were required to have a variant of uncertain significance (VUS)

or a (likely) pathogenic variant in either the *DDX3X* or *CASK* gene. Participants in the latter group were included if they had a variant in any single gene other than the *DDX3X* or *CASK* gene. Information regarding participant's date of birth (DOB) and genetic condition were obtained when they registered to participate in the BINGO project. Medical documentation confirming parent-reported genetic diagnoses was requested from caregivers and/or medical professionals, with consent.

Participant characteristics are presented in **Table 2.1**. The three genetic diagnosis groups were comparable for chronological age ( $H(2) = 0.95, p = .62$ , False Discovery Rate (FDR) adj.  $p = .62, \eta^2 = 0.01$ ) and autism-related characteristics ( $F(2, 80) = 0.57, p = .57$ , FDR adj.  $p = .62, \eta^2 = 0.01$ ). However, the groups significantly differed in sex ( $p < .01$ , FDR adj.  $p < .01, V = 0.39$ ), whereby the number of males was higher in the ID-other group. Adaptive ability also significantly differed between groups ( $F(2, 78) = 11.51, p < .001$ , FDR adj.  $p < .001, \eta^2 = 0.23$ ), and post-hoc tests revealed adaptive ability was significantly poorer in *CASK*-related disorder versus *DDX3X*-related disorder ( $p < .001$ , 95% CI [-26.47, -7.42]), and the ID-other group ( $p < .001$ , 95% CI [7.09, 27.01]). There was no significant difference adaptive ability between the *DDX3X*-related disorder and ID-other genetic diagnosis groups ( $p = 1.00$ , 95% CI [-9.52, 9.73]).

Characteristics of participants included in the replication analyses are presented in **Table 2.2**. Participants who had previously taken part in the BINGO project or participants with *CASK*-related disorder were not included in the replication sample. This was to ensure the replication sample was independent from Ng-Cordell et al. (2023), and to prevent biasing the ID-other group towards one genetic condition. Our inclusion/exclusion criteria also slightly differed from Ng-Cordell et al. (2023) – we included male participants, and our age range was capped at 18 years old to focus on children and adolescents. Despite documented sex differences in *DDX3X*-related disorder, we did not exclude male participants due to the practical challenges of recruiting sufficient sample sizes in rare ID-associated genetic condition research. This meant that participants included in either genetic diagnosis group in the replication sample (i.e., *DDX3X*-related disorder or ID-other) could be male, whereas male participants were excluded from Ng-Cordell et al. (2023). Consequently, the groups were not matched on sex ( $p < .01$ , Odds Ratio (OR) 11.27, 95% CI [2.04, 119.17]). However, consistent with Ng-Cordell et al. (2023), genetic diagnosis groups included in the replication sample were comparable for chronological age ( $W = 303.00, p = 0.33, r = -0.14$ , 95% CI [-0.42, 0.14]), adaptive ability ( $t(42.24) = -0.02, p = .98, d = 0.01$ , 95% CI [-0.57, 0.59]) and autism-related characteristics ( $t(40.2) = 1.00, p = .33, d = -0.29$ , 95% CI [-3.37, 9.92]).

### **2.2.2 Procedure**

After providing consent, parents completed a battery of questionnaires online, by post, or via Zoom or telephone interview according to parent preference. Questionnaire details, procedures for scoring and analysis are described in **Table 2.3**.

**Table 2.1** Participant characteristics and comparison statistics for the whole sample.

| DDX3X-related disorder |          |          |           | CASK-related disorder |          |          |           | ID-other   |          |          | p value for comparison |           |          |                          |
|------------------------|----------|----------|-----------|-----------------------|----------|----------|-----------|------------|----------|----------|------------------------|-----------|----------|--------------------------|
|                        | <i>n</i> | <i>M</i> | <i>SD</i> | Range                 | <i>n</i> | <i>M</i> | <i>SD</i> | Range      | <i>n</i> | <i>M</i> | <i>SD</i>              | Range     | <i>p</i> | <i>p.adj<sup>d</sup></i> |
| Age                    | 36       | 8.8      | 3.91      | 2.95-17.06            | 28       | 8.27     | 4.38      | 3.04-16.24 | 26       | 8.23     | 5.24                   | 3.1-18.77 | .62      | .62                      |
| Sex <sup>a</sup>       | 34F:2M   |          |           |                       | 24F:4M   |          |           |            | 15F:11M  |          |                        |           | < .01    | < .01                    |
| VABS ABC <sup>b</sup>  | 30       | 63.13    | 12.85     | 34-98                 | 26       | 46.19    | 15.65     | 21-75      | 25       | 63.24    | 16.28                  | 22-94     | < .001   | < .001                   |
| SRS Total <sup>c</sup> | 33       | 72.61    | 9.66      | 57-91                 | 25       | 75.04    | 7.74      | 62-87      | 25       | 75.20    | 13.58                  | 44-95     | .57      | .62                      |

<sup>a</sup> Ratio of female to male participants.<sup>b</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).<sup>c</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).<sup>d</sup> Benjamini-Hochberg FDR correction for multiple testing.**Table 2.2** Participant characteristics and comparison statistics for the replication sample.

| DDX3X-related disorder |          |           |       | ID-other   |          |           |       | p value for comparison |                          |       |  |
|------------------------|----------|-----------|-------|------------|----------|-----------|-------|------------------------|--------------------------|-------|--|
| <i>n</i>               | <i>M</i> | <i>SD</i> | Range | <i>n</i>   | <i>M</i> | <i>SD</i> | Range | <i>p</i>               | <i>p.adj<sup>d</sup></i> |       |  |
| Age                    | 30       | 7.82      | 3.21  | 2.95-13.53 | 24       | 7.54      | 4.79  | 3.1-17.34              | .33                      | .43   |  |
| Sex <sup>a</sup>       | 28F:2M   |           |       |            | 13F:11M  |           |       |                        | < .01                    | < .01 |  |
| VABS ABC <sup>b</sup>  | 25       | 63.28     | 13.30 | 34-98      | 23       | 63.17     | 16.54 | 22-94                  | .98                      | .98   |  |
| SRS Total <sup>c</sup> | 28       | 72.07     | 9.82  | 57-91      | 23       | 75.35     | 13.03 | 44-95                  | .33                      | .43   |  |

<sup>a</sup> Ratio of female to male participants.<sup>b</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).<sup>c</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).<sup>d</sup> Benjamini-Hochberg FDR correction for multiple testing.

**Table 2.3** Questionnaire measures: descriptions, scoring information, and study-specific considerations.

| Measure                                                                                                          | Description and scoring                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Study-specific considerations                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bespoke Medical History Questionnaire (MHQ)                                                                      | The MHQ is a study-specific assessment of parent/carer reported health conditions (in infancy, childhood, and the previous 6-months), developmental milestones, and lifetime presence of movement disorders. It also assesses current educational/occupational placement, current treatment/intervention, and family details (e.g., number of siblings).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | In this study, we only report information regarding the lifetime presence (yes/no) of health characteristics (tone abnormality, feeding difficulty, sleeping difficulty, sensory impairment, movement disorder and epilepsy), and whether major developmental milestones (sitting, walking, speech) were achieved.                                                                                                        |
| The Vineland Adaptive Behaviour Scales – Third Edition, Parent/Caregiver Form (Vineland-3; Sparrow et al., 2016) | The Vineland Adaptive Behaviour Scales (VABS) is a standardised assessment of adaptive ability that is commonly used to evaluate the level of impairment in individuals with ID and rare genetic conditions. Items are rated on a 3-point scale – <i>never</i> (0), <i>sometimes</i> (1), or <i>usually</i> (2, without help or prompting) – to indicate whether an individual performs a given behaviour. Scores are calculated across four subdomains: communication, daily living skills, socialisation, and motor skills, as well as an overall adaptive behaviour composite (ABC) score (excluding the motor skills subdomain). Raw scores for each subdomain and the composite are converted into standardised scores. The ABC score can also be categorised to indicate the level of impairment as normal (ABC $\geq 70$ ), mild (ABC = 55-69), moderate (ABC = 40-54), or severe (ABC = 25-39), profound (ABC < 25). | Level of impairment was used as a proxy measure of ID severity. Participants scoring within the normal range were categorised as mild for the purpose of standardising scores on the DBC2 (see below). Additionally, the motor skills section of the VABS is not typically administered to children above 9 years old, but in this study, we examined motor skills in all participants irrespective of chronological age. |
| Developmental Behaviour Checklist 2 (DBC2; Einfeld & Tonge, 1995; Gray et al., 2018)                             | The Developmental Behaviour Checklist 2 (DBC2) is a standardised measure of emotional and behavioural difficulties in individuals with ID. 95 items are rated on a 3-point Likert scale from 1 ( <i>not true</i> ) to 3 ( <i>certainly true</i> ) to evaluate current and recent (past 6 months) behaviours, plus one item assessing whether the individual's difficulties are in excess of developmental expectation ( <i>No</i> , <i>Yes</i> –                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | We generated standardised scores based on ID severity using the Australian norms. We also chose to focus on the anxiety subscale of the DBC2, as other characteristics                                                                                                                                                                                                                                                    |

|                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                | <p><i>Minor, Yes – Major</i>). The DBC2 can be used to generate a Total Behaviour Problem Score (TBPS) and five subscale scores: Disruptive/Antisocial (capturing challenging behaviours such as aggression and impulsivity), Self-Absorbed (reflecting behaviours common in ID and autism, including pica, mouthing objects, non-speech noises, self-injury, unusual interests, stereotypic movements, and repetitive behaviours), Social Relating (addressing social disengagement and mood-related issues), Communication Disturbance (assessing atypical speech and communication difficulties – e.g., echolalia and not interacting with own age others), and Anxiety (indicating behaviours relevant to separation anxiety and specific fears). There is some item overlap between subscales.</p>                                                                                                                                                | <p>measured by the DBC2 subscales (e.g., communication abilities and social development) are better assessed via alternative measures, such as the socialisation subscale of the VABS and the four social subscales of the SRS-2.</p>                                                                                                                      |
| <p>Social Responsiveness Scale (SRS-2; Constantino &amp; Gruber, 2012)</p>                                                                     | <p>The Social Responsiveness Scale – Second Edition (SRS-2) is an informant report assessment of autistic traits. 65 items are rated from 1 (<i>not true</i>) to 4 (<i>almost always true</i>), yielding a total score, five subscale scores (social awareness, social cognition, social communication, social motivation, and restricted interests/repetitive behaviour), and two DSM-aligned subscales (social communication and interaction, and restricted interests/repetitive behaviours).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p>Parents/carers completed either the preschool (for children aged 2.5-4.5 years old) or school-aged (for children aged 4-18 years old) form based on their child's chronological age. For children aged 4-4.5 years old (eligible for both forms) the school-aged form was used. Scores on the DSM-related subscales are not reported in this study.</p> |
| <p>Clinical Anxiety Screen for people with Severe to Profound Intellectual Disability (CIASP-ID; Mingins et al., 2024; Waite et al., 2022)</p> | <p>The Clinical Anxiety Screen for people with Severe to Profound Intellectual Disability (CIASP-ID) is an informant report screening tool for anxiety in individuals with ID who have limited communication. Behavioural indicators of anxiety are rated on a 7-point scale from 1 (<i>almost never</i>) to 7 (<i>all of the time or more than once a day</i>) to examine the frequency of each behaviour over the past month. If respondents are unsure whether a behaviour had occurred, they are instructed to score the item 1 (<i>almost never</i>). Additional items are included to explore how typical specific behaviours are (e.g., appearing withdrawn/vacant, spending time alone and asleep), using a 5-point scale from 1 (<i>a lot more than typical</i>) to 5 (<i>a lot less than typical</i>). In addition to a scale score for anxiety, the CIASP-ID generates scale scores for pain, low energy/withdrawal, and consolability.</p> | <p>Emerging evidence suggests the CIASP-ID is a reliable and valid measure of anxiety symptoms in individuals with moderate-severe ID and a range of communication abilities (Mingins et al., 2024). For further evidence see <b>Appendix A1</b>.</p>                                                                                                      |

|                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anxiety Scale for Children – Autism Spectrum Disorder (ASC-ASD-P; Rodgers et al., 2016) | The Anxiety Scale for Children – Autism Spectrum Disorder (ASC-ASD-P) is a parent report measure of anxiety traits in young people aged 8-16 years old with autism spectrum disorder. 24 items are rated on a 4-point Likert scale from 0 ( <i>never</i> ) to 3 ( <i>always</i> ). A total score and four subscale scores – Separation Anxiety (5 items), Uncertainty (8 items), Performance Anxiety (5 items), and Anxious Arousal (6 items) – were calculated. A score of 20 or more on the total score might be indicative of significant levels of anxiety, but there are currently no indicative cut-offs for the subscales. | Although the ASC-ASD-P was designed for autistic children aged 8-16 years old, it has been used in studies of autistic children as young as 5 years old (Adams et al., 2019; Simpson et al., 2020), children with co-occurring ASD and ID (communication with Jacqui Rodgers), and individuals with rare genetic syndromes (see Groves et al., 2022). It is therefore appropriate to use this measure in this study. |
| Challenging Behaviour Questionnaire (CBQ; BEOND, 2022; Hyman et al., 2002)              | The Challenging Behaviour Questionnaire (CBQ) is an informant report measure of the presence and severity of BtC – self-injury, aggression, property destruction and stereotypic behaviour. The presence of each well-defined BtC category within the past month is rated yes/no. If the behaviour has occurred, subsequent questions regarding the severity of behaviour were asked and a severity score (a number from 1-14) based on the frequency, duration, and severity of behaviour was generated.                                                                                                                         | Consistent with Bissell et al. (2022) we do not report stereotypic behaviour measured by the CBQ, as the RBQ stereotyped behaviours scale (see details below) provides a more detailed description.                                                                                                                                                                                                                  |
| Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009)                             | The Repetitive Behaviour Questionnaire (RBQ) is an informant report measure of the frequency of repetitive behaviours (e.g., body rocking, hand flapping, repetitive questioning) in individuals with rare genetic syndromes, that is suitable for both verbal and non-verbal individuals. 19 operationally defined, observable behaviours are rated on a 5-point Likert scale from 1 ( <i>never</i> ) to 5 ( <i>more than once a day</i> ). The RBQ can be used to generate a total score and five subscale scores: stereotyped behaviour (3                                                                                     | Typically, restricted preferences and repetitive speech subscales are not calculated for individuals with limited verbal ability. We did not have a consistent measure of verbal ability in this study, so to ensure scores were                                                                                                                                                                                     |

|                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                          | <p>items), compulsive behaviour (8 items), insistence on sameness (2 items), restricted preferences (3 items), and repetitive use of language (3 items). Clinical cut-offs can also be obtained. If an individual scores 'once a day' or 'more than once a day' on one or more items within a subscale they are considered to be above the clinical threshold for that subscale. Individuals are also considered to be above the clinical threshold for the total score if they score 'once a day' or 'more than once a day' on one or more items.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>comparable between participants and to prevent the possibility of losing potentially informative information about verbal repetitive behaviour, we choose to use the verbal scoring approach across all participants. We scored missing items as 1 (never).</p> |
| <p>Short Sensory Profile 2 (SSP-2, Dunn et al. 2014)</p> | <p>The Short Sensory Profile 2 (SSP-2) is a parent report measure of the frequency of sensory behaviours in children aged 3-14 years old. 34 items are rated on a 5-point Likert scale from 1 (<i>almost never</i>) to 5 (<i>almost always</i>). Items are rated 0, if the corresponding behaviour has never been observed or if it is not applicable. Sensory differences are assessed across four subscales – Seeking/Seeker (7 items), Avoiding/Avoider (9 items), Sensitivity/Sensor (10 items), and Registration/Bystander (8 items) – which represent the sensory patterns from Dunn's Sensory Processing Framework (Dunn, 1997). There are also summary scores for sensory and behavioural items, respectively. The seeking subscale refers to the degree to which the child obtains sensory input (e.g., whether they rock in a chair, on the floor, or while standing). The avoiding subscale refers to the degree to which a child is bothered by sensory input (e.g., how stubborn and uncooperative they can be). The sensitivity subscale refers to the degree to which a child detects sensory input (e.g., how distracted they are when there is a lot of noise around). The registration subscale refers to the degree to which a child misses sensory input (e.g., whether they bump into things, failing to notice objects or people in the way).</p> | <p>No relevant study considerations.</p>                                                                                                                                                                                                                           |

### 2.2.3 Data Analysis

Data were analysed using RStudio, version 2024.04.2+764. The study analysis plan was pre-registered on the Open Science Framework (OSF) and can be accessed online (see [https://osf.io/b74eu/?view\\_only=772571c0c45f436dbd74e48796f5613c](https://osf.io/b74eu/?view_only=772571c0c45f436dbd74e48796f5613c)). The analyses and subsequent results are described in three parts, reflecting the study aims.

#### 2.2.3.1 Aim 1: Describing the Medical and Developmental Characteristics of Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated genetic Conditions.

Data from the bespoke study medical history questionnaire (MHQ) was synthesised to estimate the proportion of participants with specific medical characteristics. The data were collapsed across infancy and childhood and, therefore, represent ‘lifetime ever’ prevalence, irrespective of whether the medical difficulty had persisted or resolved. The number of participants who had achieved specific developmental milestones, namely sitting, walking and speech (e.g., first words, complete sentences) was also calculated.

#### 2.2.3.2 Aim 2: Examining Group Differences in Anxiety and BtC among Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated Genetic Conditions.

##### 2.2.3.2.1 Step 1: Replication

Consistent with Ng-Cordell et al. (2023), we used Chi-square tests to compare categorical data between *DDX3X*-related disorder and ID-other, and parametric independent sample t-tests, or nonparametric Mann-Whitney U tests to compare continuous data between genetic diagnosis groups. Differences between genetic diagnosis groups were examined for the same variables reported in Ng-Cordell et al. (2023). As previously, self-injurious behaviour (SIB) scores were calculated by summing raw scores on three items from the Developmental Behaviour Checklist 2 (DBC2, Einfeld & Tonge, 1995; Gray et al., 2018), which capture behaviours relevant to self-injury (head banging, self-biting/picking, and skin picking/scratching).

##### 2.2.3.2.2 Step 2: Novel Analyses

Chi-square tests were used to compare categorical data between the *DDX3X*-related disorder, *CASK*-related disorder and ID-other, and parametric one-way ANOVAs, or nonparametric Kruskal-Wallis tests were used to compare continuous data between genetic diagnosis groups. Appropriate post-hoc analyses were selected to follow-up any significant group differences (e.g., Tukey’s HSD, Dunn’s test). To account for multiple testing and minimise the likelihood of type I errors, a Benjamini-Hochberg FDR correction was applied.

Additionally, to prevent overemphasis of statistical significance when interpreting the data and to supplement frequentist hypothesis testing, we also conducted Bayesian analyses. Beyond examining whether data supports the alternative hypothesis over the null hypothesis in frequentist analyses, generation of Bayes Factors also facilitates exploration of whether data support the null hypothesis (i.e., evidence of ‘commonality’ between groups) over the alternative hypothesis (i.e., evidence of differences between groups) (Bissell et al., 2022; Surtees et al., 2019). Considering both degrees of difference and commonality is clinically important when evaluating phenotypic specificity of mental health and behaviour in rare ID-associated genetic conditions. Group differences in categorical data were explored using the contingency table Bayes factor test from the R package *BayesFactor* (Morey & Rouder, 2024) and Bayesian ANOVAs were used to compare continuous data between groups. Currently, there is no Bayesian alternative of a nonparametric Kruskal-Wallis test. As such, Bayesian ANOVAs were run even in instances where data violated the assumptions of normality and/or homogeneity of variances, which were examined prior to both frequentist and Bayesian analyses using Shapiro-Wilks test of normality (Shapiro & Wilk, 1965) and Levene’s test (Levene, 1960), respectively. Since Bayesian hypothesis testing allows for flexible modelling and the incorporation of priors, it might be more robust to violations of normality and/or homogeneity of variance than conventional frequentist approaches. However, caution should still be taken when interpreting the results of Bayesian ANOVAs on non-normal and/or heteroscedastic data. Bayes Factors (BFs) were interpreted in line with Jefferys (1961), whereby a  $BF \geq 3$  is indicative of ‘substantial’ evidence for the alternative hypothesis, whereas  $BF \leq 1/3$  provides ‘substantial’ evidence for the null hypothesis.

#### 2.2.3.3. Aim 3: Exploring Correlates of Anxiety and BtC among Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated Genetic Conditions.

##### 2.2.3.3.1 Step 1. Replication

Consistent with Ng-Cordell et al. (2023), we used pairwise Pearson correlations to examine relationships between age, adaptive ability, anxiety and self-injury in *DDX3X*-related disorder and ID-other, separately. We then applied z-score transformations and Fisher’s exact test to examine whether the strength of correlations differed between *DDX3X*-related disorder and ID-other.

##### 2.2.3.3.2 Step 2: Novel Analyses

We conducted network analysis to examine the complex relationships between neurodevelopmental and mental health characteristics in rare ID-associated genetic conditions. This approach is favourable over conventional correlational analyses as it allows you to model the relationships between two variables, whilst controlling for all other possible relationships within the network. We estimated a

pairwise Markov random fields (PMRF) model, also referred to as a partial correlation network, for the combined sample using the *estimateNetwork* package in R (Epskamp et al., 2018).

A description of variables included as nodes in the model can be found in **Table 2.4**. In our pre-registration, we did not specify which of the three anxiety measures would be included in the network model. However, since each of these three measures might capture unique aspects of anxiety relevant to individuals with rare ID-associated genetic conditions, we reduced these measures into a single composite score using Principal Components Analysis (PCA). PCA without rotation was conducted using the R package *psych* (Revelle, 2024), and the number of factors retained was fixed as one. Data were standardised and outliers were removed to meet the assumptions of PCA. The Kaiser-Meyer-Olkin (KMO) test of sampling adequacy and Bartlett's test of sphericity were also applied to determine the suitability of data for PCA analysis. The Kaiser-Meyer-Olkin measure confirmed sampling adequacy for PCA (KMO = .71), and KMO values for each individual measures were  $\geq .69$ , which is above the acceptable limit (KMO > .5). We found linear associations between the anxiety measures (see **Figure 2.1**), and that the results of Bartlett's test of sphericity ( $\chi^2(3) = 86.17, p < .001$ ) indicated that correlations were sufficiently large for PCA. A summary of the PCA is displayed in **Table 2.5**. The principal component had an eigenvalue of 2.17. All three anxiety measures loaded strongly onto the principal component ( $\geq 0.84$ ) and accounted for 73% of variance. Subsequently, factors scores were used as the anxiety measure in the network analysis reported below.

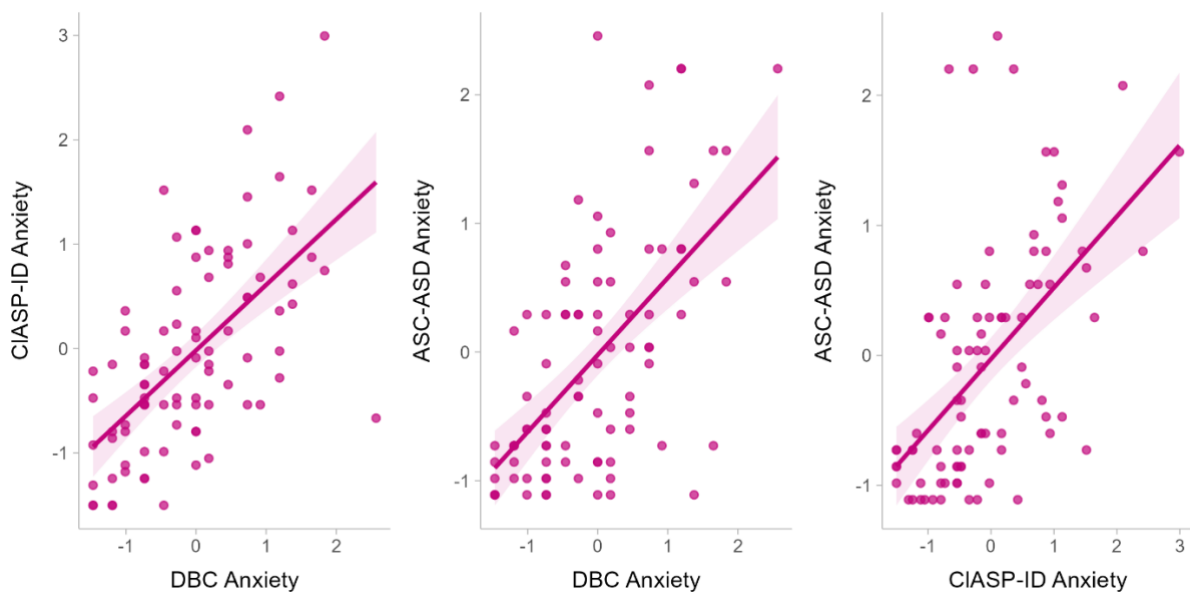


**Figure 2.1** Scatterplots showing the association between standardised scores on anxiety measures that were included in the composite anxiety score.

**Table 2.4** Description of nodes included in the network analysis.

| Node | Description            | Measure                                                                                                            |
|------|------------------------|--------------------------------------------------------------------------------------------------------------------|
| 1    | Adaptive Ability       | VABS ABC                                                                                                           |
| 2    | Anxiety                | Anxiety composite score generated from DBC2 Anxiety T-scores, ASC-ASD total score, CIASP-ID Anxiety subscale score |
| 3    | Social Awareness       | SRS-2 subscale                                                                                                     |
| 4    | Social Cognition       | SRS-2 subscale                                                                                                     |
| 5    | Social Communication   | SRS-2 subscale                                                                                                     |
| 6    | Social Motivation      | SRS-2 subscale                                                                                                     |
| 7    | Self-injury            | CBQ subscale severity score, scored as 0 for individuals who do not display behaviour                              |
| 8    | Aggression             | CBQ subscale severity score, scored as 0 for individuals who do not display behaviour                              |
| 9    | Property Destruction   | CBQ subscale severity score, scored as 0 for individuals who do not display behaviour                              |
| 10   | Stereotyped Behaviour  | RBQ subscale                                                                                                       |
| 11   | Compulsive Behaviour   | RBQ subscale                                                                                                       |
| 12   | Restricted Behaviour   | RBQ subscale                                                                                                       |
| 13   | Insistence on Sameness | RBQ subscale                                                                                                       |
| 14   | Repetitive Behaviour   | RBQ subscale                                                                                                       |
| 14   | Sensory Seeking        | SSP-2 subscale                                                                                                     |
| 16   | Sensory Avoiding       | SSP-2 subscale                                                                                                     |
| 17   | Sensory Sensitivity    | SSP-2 subscale                                                                                                     |
| 18   | Sensory Registration   | SSP-2 subscale                                                                                                     |

**Table 2.5.** Summary of the principal components analysis to generate the anxiety composite score.

| Measure              | Anxiety Composite |
|----------------------|-------------------|
| DBC2 Anxiety T-score | 0.87              |
| CIASP-ID Anxiety     | 0.85              |
| ASC-ASD Total        | 0.84              |
| Eigenvalues          | 2.18              |
| % of variance        | 72.68             |

To estimate the network, we used graphical Least Absolute Shrinkage Selection Operator (LASSO) in combination with Extended Bayesian Information Criterion (EBIC). LASSO is a regularisation technique that controls for small partial correlations between variable pairs by shrinking and setting negligible coefficients to zero. This results in a sparse network. The degree of regularisation is set by the EBIC hyperparameter. We set our EBIC parameter to 0.5, which is the default for the EBICglasso function from the *qgraph* package in R (Epskamp et al., 2012).

The network was visualised using the *qgraph* package in R (Epskamp et al., 2012), and node layout was determined by the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991), whereby the most highly connected nodes are placed more centrally within the network. Edges represent the correlation strength between nodes, whereby thicker and more saturated edges reflect stronger

connections. Blue edges represent positive associations, while red edges represent negative associations.

We also computed two centrality measures for each node within the network – strength and betweenness – which indicate the relative importance of each node within the network structure. Node strength was calculated as the sum of absolute value of edges connected to any one node. Betweenness was the number of times any one node in the network lies on the shortest path between two other nodes in the network.

Additionally, before drawing inferences from our resultant network structure, we examined whether network parameters (i.e., network edge and centrality estimates) were accurate (Briganti et al., 2024; Epskamp et al., 2018). To determine edge weight accuracy, we ran a non-parametric bootstrap using the *bootnet* package (Epskamp et al., 2018), specifying 1000 permutations to generate 95% confidence intervals for each edge in the network. Further, to examine the stability of centrality measures, we estimated network models based on subsets of the data. This was quantified using Correlation-Stability Coefficients (CS-Coefficient) (Epskamp et al., 2018). CS-Coefficients estimate the maximum percentage of your sample which can be dropped to maintain a correlation of at least  $r = 0.7$  between your case-dropped sample, and the original centrality index. In other words, if you can drop a significant proportion of cases and maintain high correlation, it suggests that the relationships between nodes at a network level are not being influenced by sample characteristics. CS-Coefficients should preferably be above 0.5 and not below 0.25 (Epskamp et al., 2018).

## 2.3 Results

### 2.3.1 Aim 1: Medical and Developmental Characteristics of Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated genetic Conditions.

Medical and developmental milestone information is presented in **Table 2.6**. Feeding difficulties were the most frequently reported health characteristics in *DDX3X*-related disorder and ID-other (*DDX3X*-related disorder: 88.6%, ID-other: 73.1%), whereas tone abnormalities were the most frequently reported health characteristics in *CASK*-related disorder (85.7%). Sleeping difficulties were common across all three genetic diagnosis groups (*DDX3X*-related disorder: 74.3%, *CASK*-related disorder: 78.6%, ID-other: 73.1%), whereas sensory impairments were markedly more frequent in *CASK*-related disorder compared to the other two groups (*CASK*-related disorder: 82.1%, *DDX3X*-related disorder: 65.7%, ID-other: 53.8%). Epilepsy was more commonly reported in *CASK*-related disorder and the ID-other groups compared to *DDX3X*-related disorder (*CASK*-related disorder: 32.1%, ID-other: 38.5%,

*DDX3X*-related disorder: 22.9%). Movement disorders were more common in *DDX3X*-related disorder and *CASK*-related disorder, than in the ID-other group (*DDX3X*-related disorder: 53.8%, *CASK*-related disorder: 56.0%, ID-other: 33.3%).

Most participants in each genetic diagnosis group had achieved the ability to sit independently (*DDX3X*-related disorder: 97.1%, *CASK*-related disorder: 85.7%, ID-other: 100%). The proportion of participants achieving the ability to walk independently was high in the *DDX3X*-related disorder and ID-other groups (*DDX3X*-related disorder: 90.9%, ID-other: 80.0%) but was lower in *CASK*-related disorder (57.1%). The proportion of participants achieving the ability to speak their first words was also lower in the *CASK*-related disorder group (*CASK*-related disorder: 50.0%, *DDX3X*-related disorder: 77.1%, ID-other: 84.6%), but of those children who had started speaking a similar proportion had achieved complete sentences across genetic diagnosis groups (*DDX3X*-related disorder: 66.7%, *CASK*-related disorder: 50.0%, ID-other: 63.6%).

**Table 2.6** Medical and developmental characteristics for each genetic diagnosis group.

|                                                           | <i>DDX3X</i> -related disorder | <i>CASK</i> -related disorder | ID-other             |
|-----------------------------------------------------------|--------------------------------|-------------------------------|----------------------|
| Medical Health characteristics                            |                                |                               |                      |
| Tone abnormalities <sup>a</sup> ; n (ever present %)      | 27 (77.1)                      | 24 (85.7)                     | 17 (65.4)            |
| Feeding difficulties <sup>a</sup> ; n (ever present %)    | 31 (88.6)                      | 23 (82.1)                     | 19 (73.1)            |
| Sleeping difficulties <sup>a</sup> ; n (ever present %)   | 26 (74.3)                      | 22 (78.6)                     | 19 (73.1)            |
| Sensory impairments <sup>a</sup> ; n (ever present %)     | 23 (65.7)                      | 2 (82.1)                      | 14 (53.8)            |
| Epilepsy <sup>a</sup> ; n (ever present %)                | 8 (22.9)                       | 9 (32.1)                      | 10 (38.5)            |
| Movement disorder <sup>b</sup> ; n (ever present %)       | 14/26 (53.8)                   | 14/25 (56)                    | 7/21 (33.3)          |
| Developmental milestones                                  |                                |                               |                      |
| Sitting <sup>c</sup> ; n (achieved %)                     | 34/35 (97.1)                   | 24/28 (85.7)                  | 26/26 (100)          |
| Sitting; age of acquisition range                         | 6 months – 4 years             | 7 months – 3 years            | 4 months – 4 years   |
| Walking <sup>c</sup> ; n (achieved %)                     | 30/33 (90.9)                   | 16/28 (57.1)                  | 20/25 (80)           |
| Walking; age of acquisition range                         | 12 months – 3 years            | 13 months – 9 years           | 1.5 – 3.5 years      |
| Speech <sup>c</sup> ; n (achieved %)                      | 27/35 (77.1)                   | 14/28 (50)                    | 22/26 (84.6)         |
| Speech – first words <sup>c</sup> ; n (achieved %)        | 27/27 (100)                    | 14/14 (100)                   | 22/22 (100)          |
| Speech – first words; age of acquisition range            | 9 months to 4 years            | 9 months to 8 years           | 12 months to 8 years |
| Speech – complete sentences <sup>c</sup> ; n (achieved %) | 18/27 (66.7)                   | 7/14 (50)                     | 14/22 (63.6)         |

<sup>a</sup> Data derived from Medical History Questionnaire; presence of difficulty in infancy, childhood, or past 6-months (y/n).

<sup>b</sup> Data derived from Medical History Questionnaire; presence of involuntary movement disorder or diagnosis of a movement disorder ever (y/n).

<sup>c</sup> Data derived from Medical History Questionnaire; reached milestone (yes/not yet).

### 2.3.2 Aim 2: Group Differences in Anxiety and BtC among Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated Genetic Conditions.

#### 2.3.2.1 Step 1 Results: Replication

The second aim of the study was to examine group differences in anxiety and self-injury, and test specific predictions arising from Ng-Cordell et al. (2023). As shown in **Figure 2.2**, anxiety does not significantly differ between genetic diagnosis groups in the replication sample ( $W = 320.50$ ,  $p = .50$ ,  $r = 0.09$ , 95% CI [-0.18, 0.37]). However, self-injury significantly differed between groups ( $W = 481.00$ ,  $p = .03$ ,  $r = 0.30$ , 95% CI [0.02, 0.56]), with greater self-injury observed in the ID-other group ( $mdn = 2$ ) compared to the *DDX3X*-related disorder group ( $mdn = 1$ ).

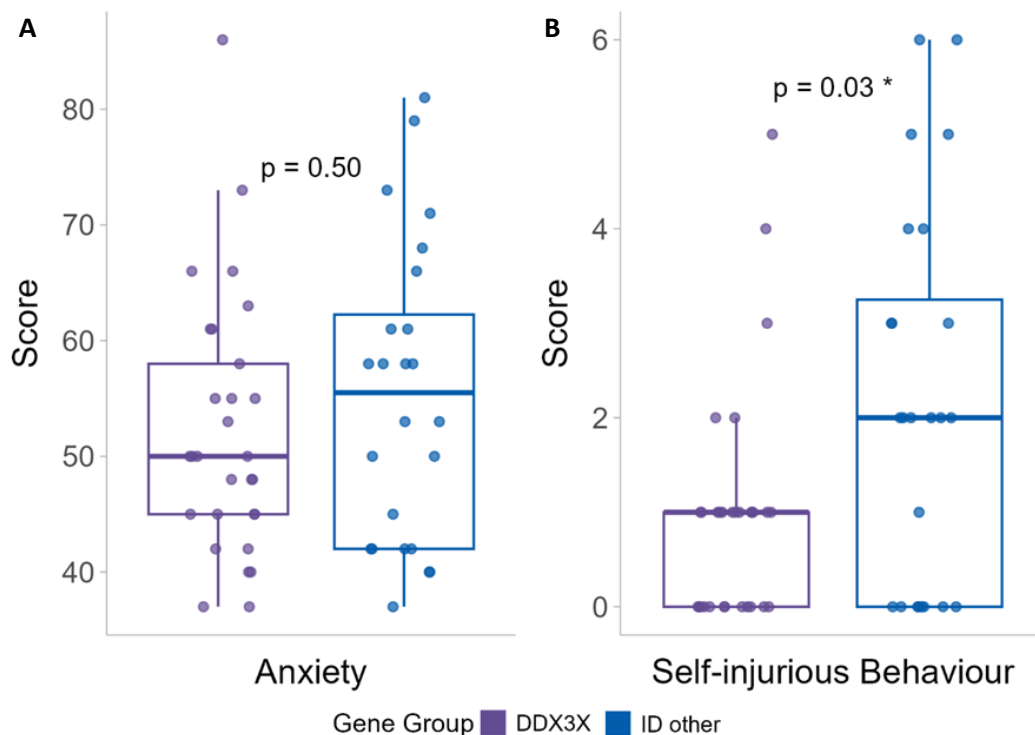


**Figure 2.2** Boxplots used to represent non-normally distributed data based on the median and interquartile range (IQR). **A** Wilcoxon rank-sum test comparing DBC2 anxiety subscale T-scores between groups. **B** Wilcoxon rank-sum test comparing DBC2 self-injury scores (a composite score of items on the DBC2 associated with self-injury) between groups (\* $p < .05$ ).

To examine whether sex was driving the difference in self-injurious behaviour between groups, we ran multiple regression analyses including gene group, sex and their interaction as predictors of self-injury. We performed bootstrapping with 2000 resamples to obtain robust estimates of the regression coefficients and their confidence intervals as the assumptions of linear regression were violated. The regression model was not significant ( $F(3, 50) = 2.43$ ,  $p = .08$ ) and only explained a small proportion of variance in self-injury ( $R^2 = .13$ ). However, despite the overall non-significance of the model, the bootstrapped confidence interval for genetic diagnosis group did not overlap with zero, suggesting genetic diagnosis group is a significant predictor of self-injury ( $B = 1.15$ , 95% BCa CI [0.38, 3.06]). The

bootstrapped confidence interval for all other predictors overlapped with zero (see **Table 2.7**). These findings suggest that genetic diagnosis group, but not sex or the interaction between genetic diagnosis group and sex, had significant effect on self-injury.

**Table 2.7** Coefficients and confidence intervals for bootstrapped regression examining genetic diagnosis group (*DDX3X*-related disorder, ID-other), sex and their interaction on self-injurious behaviour.

| Predictor                     | Coefficient | 95% BCa CI    |
|-------------------------------|-------------|---------------|
| Intercept                     | 0.54        | [-0.61, 1.00] |
| Gene Group                    | 1.59        | [0.04, 3.09]  |
| Sex                           | 0.46        | [-0.39, 1.53] |
| Gene Group by Sex interaction | -0.38       | [-2.22, 1.42] |

### 2.3.2.2 Step 2 Results: Novel Analyses

We aimed to further refine the description of anxiety and BtC in *DDX3X*-related disorder, and explore these difficulties in *CASK*-related disorder for the first time, by comparing scores on comprehensive measures of anxiety and BtC between these genetic diagnosis groups and to a group of individuals with other rare ID-associated conditions (ID-other). As shown in **Figures 2.3 and 2.4**, we found no significant differences in anxiety symptoms on any of the three measures between genetic diagnosis groups, or in the prevalence of each BtC category. Examination of severity of BtC responses indicated no significant differences in the self-injury subscale between groups. However, severity scores on the aggression and property destruction subscales were significantly greater in ID-other compared to *DDX3X*-related disorder and *CASK*-related disorder (Aggression severity:  $F(2, 39) = 5.52$ ,  $p = .01$ , FDR adj.  $p = .04$ , BF = 7.16; Property destruction severity:  $H(2) = 12.34$ ,  $p < .01$ , FDR adj.  $p = .02$ , BF = 233.09). Additionally, although significant group differences in the prevalence of aggression ( $\chi^2(2) = 5.38$ ,  $p = .07$ , FDR adj.  $p = .16$ , BF = 1.22) and severity of self-injury ( $F(2, 33) = 3.63$ ,  $p = .04$ , FDR adj.  $p = .13$ , BF = 1.98) did not survive the FDR correction for multiple testing, inspection of the Bayes Factors suggests there is anecdotal evidence for a group difference on these subscales of the CBQ (Aggression prevalence: BF = 7.16; Self-injury severity: BF = 1.98), whereby severity is greater in the ID-other group.

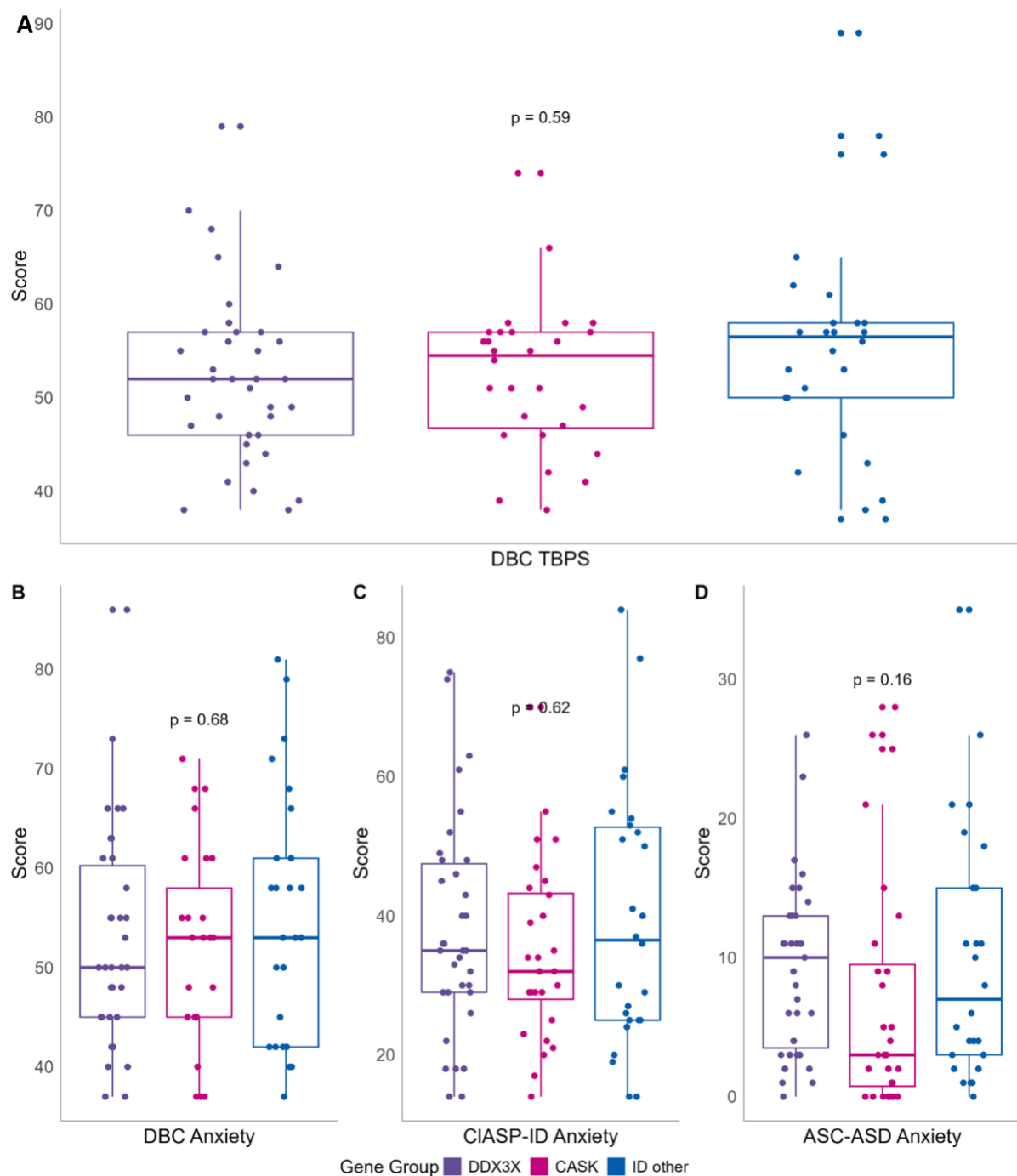


**Figure 2.3.** Emotional and behavioural difficulties and anxiety across genetic diagnosis. Boxplots are used to represent continuous data. **A** ANOVA analysis comparing DBC2 total problem behaviour scores (TBPS) between genetic diagnosis groups. **B** ANOVA analysis comparing DBC2 anxiety t-scores between genetic diagnosis groups. **C** ANOVA analysis comparing CIASP-ID anxiety subscale scores between genetic diagnosis groups. **D** Kruskal-Wallis analysis comparing ASC-ASD total scores between genetic diagnosis groups. Adjusted p-values (significant group differences  $p < 0.05$ , FDR correction) are presented.

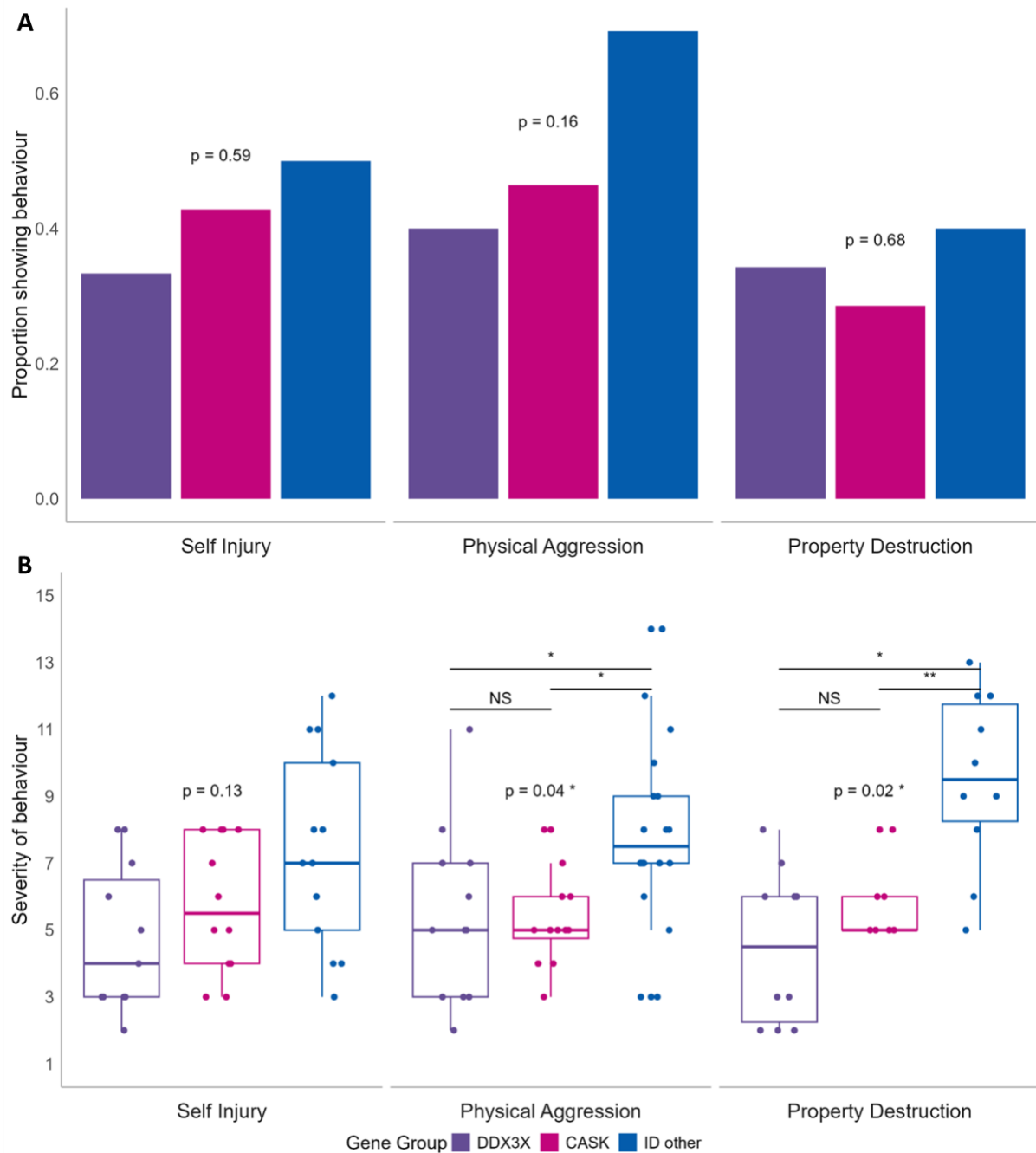


**Figure 2.4** Behaviours that challenge across genetic diagnosis groups, whereby bar graphs are used to represent categorical data (**A**) and boxplots are used to represent continuous data (**B**). **A** Chi-square analyses comparing frequencies of self-injury, aggression and property destruction between genetic diagnosis groups. **B** ANOVA analyses comparing self-injury and aggression severity between genetic diagnosis groups, and Kruskal-Wallis analysis comparing property destruction severity between genetic diagnosis groups. Adjusted p-values (significant group differences  $p < 0.05$ , FDR correction) are presented.

In our pre-registration, we proposed that we would run the same analyses described above whilst also controlling for age, sex and adaptive ability as possible covariates. Prior to running these analyses, we examined the relationship between these possible covariates and our dependent variables. We found no significant relationships between age, sex or adaptive ability and our dependent variables, except for adaptive ability and anxiety measured via the parent version of the Anxiety Scale for Children – Autism Spectrum Disorder (ASC-ASD-P; Rodgers et al., 2016) (Kendall Tau = 0.21,  $p = .007$ ). Due to the fact we identified minimal group differences and few significant relationships between possible covariates and our dependent variables, we elected to not run these additional analyses but to focus on an integrated network analysis across the full cohort (see Section 2.3.3.2).

In addition to examining the prevalence and severity of each category of BtC between genetic diagnosis groups, we used a modified version of the CBQ (BEOND, 2022) to explore the specific topographies of each category of BtC (i.e., what self-injurious behaviours did children and adolescents within each genetic diagnosis group engage in?) (see **Figure 2.5**). We found that children with *CASK*-related disorder who recently engaged in aggressive behaviour did not ‘hit others with objects’ or ‘spits at others’, unlike children in the *DDX3X*-related disorder or ID-other groups (see **Figure 2.5B**). The former behaviour requires fine-motor control to hold an object, a developmental skill which is poorer in children with *CASK*-related disorder. Similarly, the latter behaviour requires opportunity (i.e., someone getting close enough – many children with *CASK*-related disorder do not have gross motor skills to enable walking/running) and facial/mucus production.

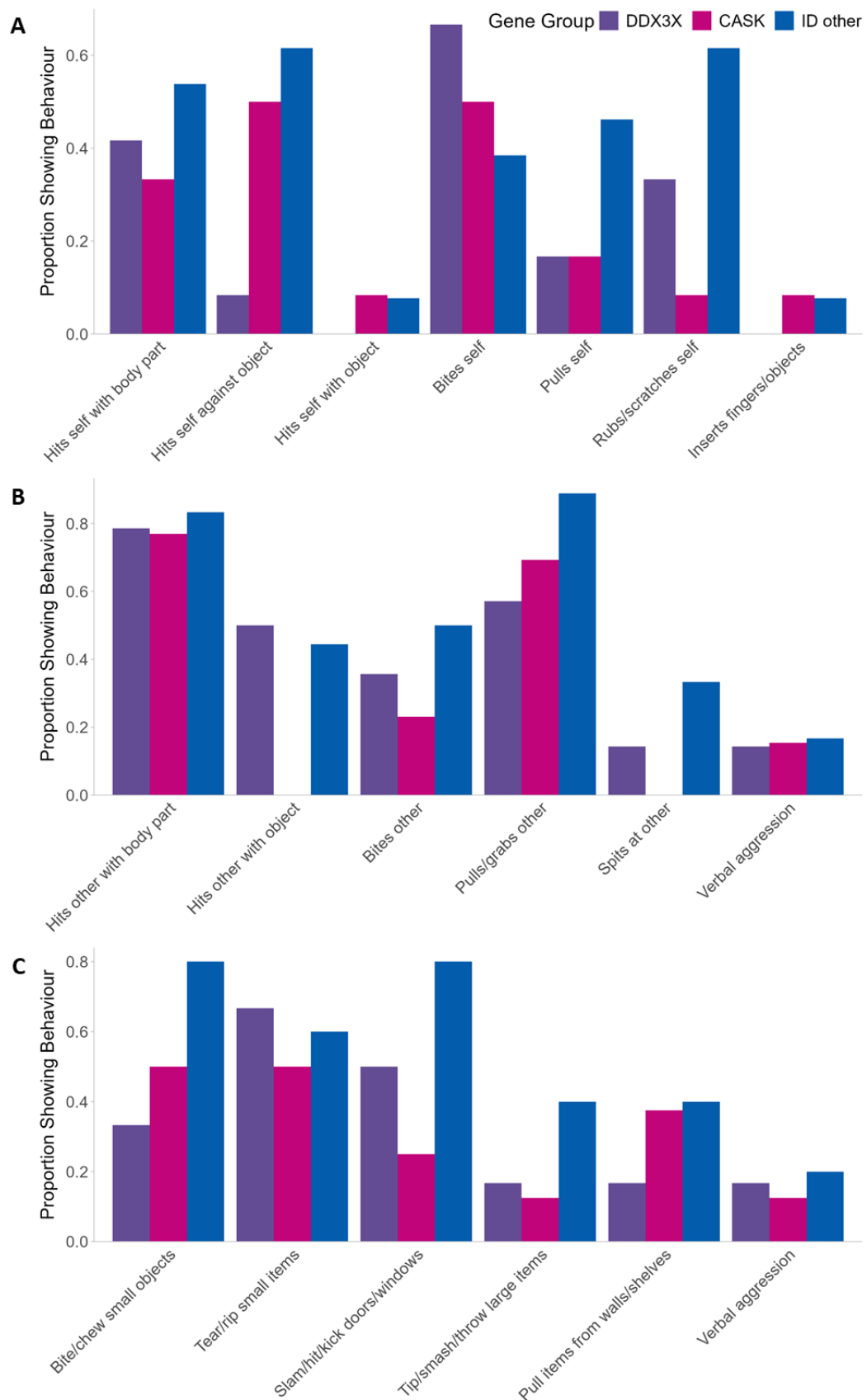


**Figure 2.5** Bar graphs representing the proportion of individuals displaying each topography of self-injury (A), aggression (B), and property destruction (C). Data is missing for one topography of aggression ('Rubs/pinches/scratches others') and property destruction ('Throwing/kicking/smashing small items') as they were omitted from the online questionnaire in error.

### 2.3.3 Aim 3: Correlates of Anxiety and BtC among Children with *DDX3X*-related disorder, *CASK*-related disorder, and other Rare ID-associated Genetic Conditions.

#### 2.3.3.1 Step 1 Results: Replication

The third aim of this study was to examine the relationships between adaptive ability, autism characteristics, anxiety and self-injury. For each genetic diagnosis group in the replication sample (*DDX3X*-related disorder and ID-other), Pearson correlations for pairwise complete data are presented in **Figure 2.6**. Consistent with Ng-Cordell et al. (2023), we found higher anxiety was associated with elevated autism characteristics in both genetic diagnosis groups (*DDX3X*-related disorder:  $r = 0.55$ ,  $p < .01$ ; ID-other:  $r = 0.59$ ,  $p < .01$ ), and that the strength of these correlations did not significantly differ between groups ( $Z = -0.21$ ,  $p = 0.83$ ). We also found a significant association between higher self-injury and higher anxiety but, unlike in Ng-Cordell et al. (2023), this relationship was not specific to the *DDX3X*-related disorder group (*DDX3X*-related disorder:  $r = 0.53$ ,  $p < .01$ ; ID-other:  $r = 0.58$ ,  $p < .01$ ), and the strength of association did not differ between genetic diagnosis groups ( $Z = -0.26$ ,  $p = .79$ ). Additionally, within the ID-other group we found a significant association between higher self-injury and (1) lower adaptive ability ( $r = -0.44$ ,  $p = .03$ ) and (2) greater autism characteristics ( $r = 0.45$ ,  $p = .03$ ), as well as a significant relationship between lower adaptive ability and greater autism characteristics ( $r = -0.47$ ,  $p = .03$ ).

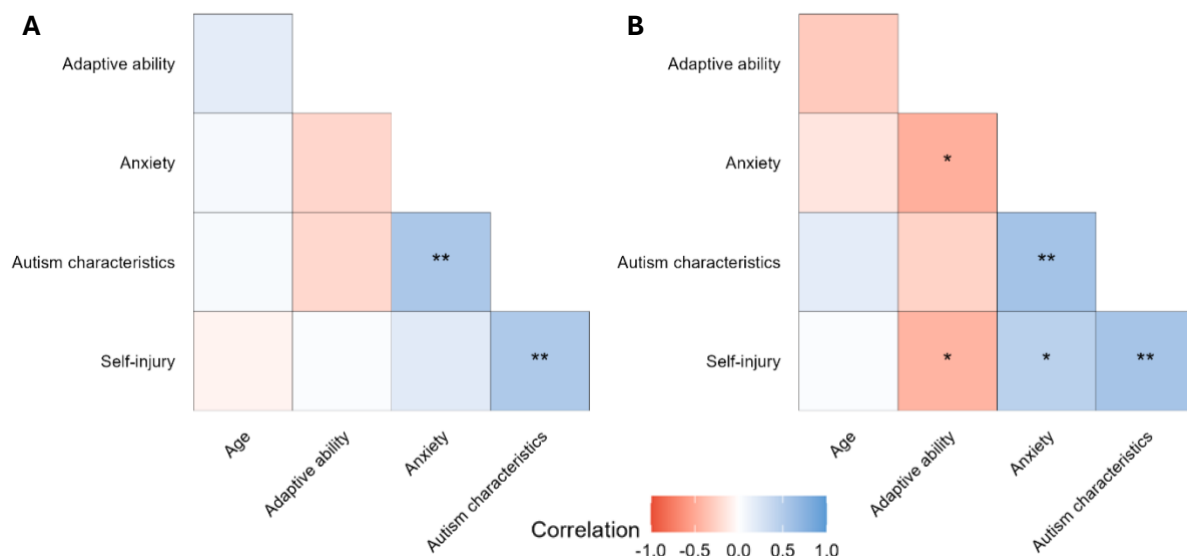


**Figure 2.6** Correlation plots showing the relationships between age, neurodevelopmental and mental health characteristics in *DDX3X*-related disorder (**A**) and ID-other (**B**) groups. Asterisks represent significant within-group correlations (\* $p < .05$ , \*\*  $p < .01$ ). Fisher's exact tests revealed no group differences in correlation strengths between groups ( $p < 0.05$ ).

### 2.3.3.2 Step 2 Results: Novel Analyses

Finally, to build on the analysis above, we adopted a network approach to understand the relationships between neurodevelopmental and mental health dimensions across the combined cohort. The estimated network comprising all 18 variables is shown in **Figure 2.7**. The anxiety composite score showed the largest unique relationship with Sensory Avoiding. In addition to Sensory Avoiding, the anxiety composite score also shared a direct edge with Social Communication. Both Aggression Severity and Property Destruction Severity only share a unique edge with Self-injury Severity. Self-injury Severity, on the other hand, also shared a direct edge with Sensory Avoiding, Sensory Sensitivity, and Social Awareness. The bootstrapped 95% confidence intervals for the edges are presented in **Appendix A2, Figure A2.1**. The large CIs around the estimated edge-weights means we cannot reliably interpret the order of the edges. In terms of network centrality measures, Social Communication had the highest node strength, followed by Sensory Avoiding and Sensory Sensitivity (see **Figure 2.8A**). Social Communication had the highest betweenness centrality, followed by Sensory Sensitivity, and Self-injury Severity (see **Figure 2.8B**). Results of the centrality measure stability analysis are shown in **Appendix A2, Figure A2.2**, and the CS-coefficients indicated that both the strength ( $CS(\text{cor} = 0.7) = 0.04$ ) and betweenness ( $CS(\text{cor} = 0.7) = 0.00$ ) centrality estimates are unstable under sub-setting cases. This suggests that our node-level estimates are not readily interpretable.

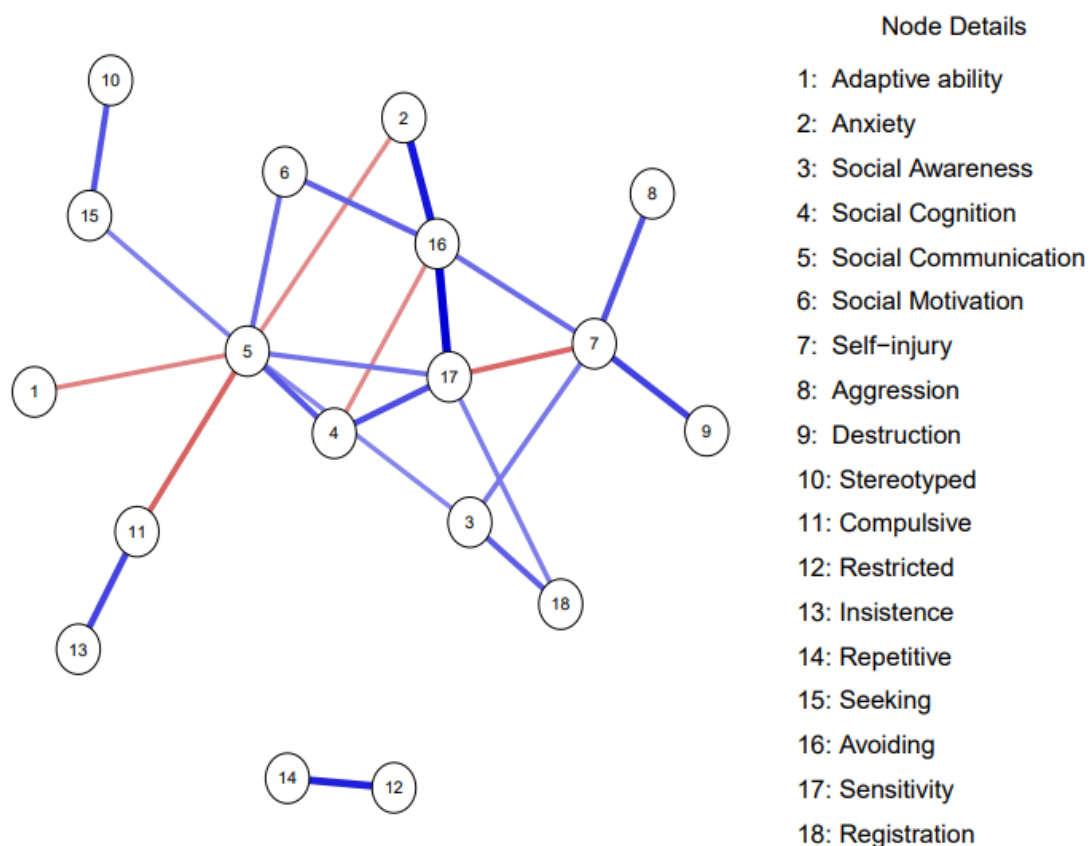


**Figure 2.7** Estimated network structure for the combined sample. Positive associations between nodes are represented in blue, while negative associations are represented in red. Thicker and more saturated edges reflect stronger relationships between nodes.

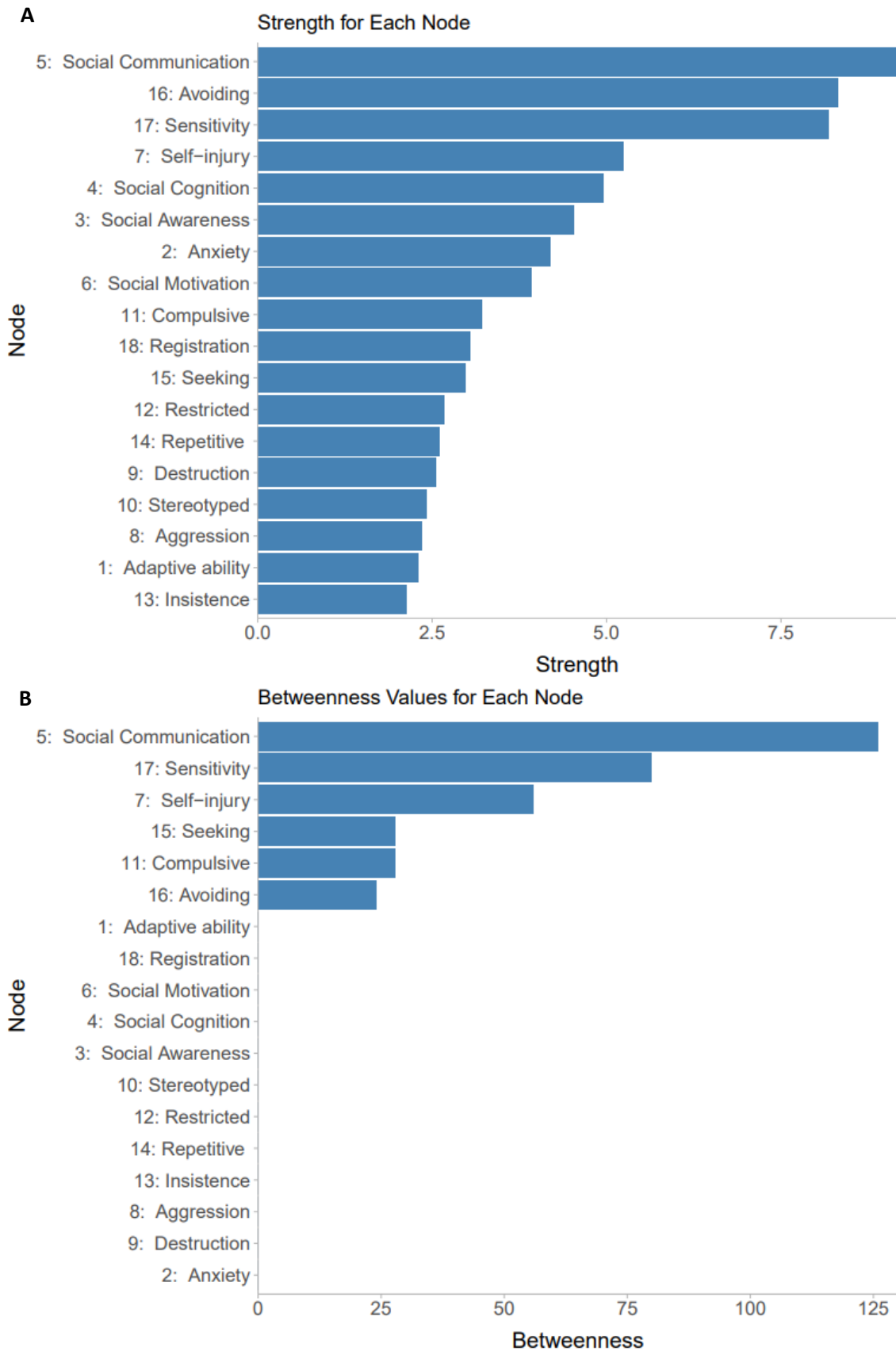


**Figure 2.8** Node centrality measures for the combined sample. **A** Node strength. **B** Node betweenness.

## 2.4 Discussion

In this study, we investigated anxiety and BtC in children with *DDX3X*-related disorder, *CASK*-related disorder and other rare ID-associated genetic conditions, using questionnaire measures designed for populations with NDDs. We first described the medical and developmental characteristics of each group (Aim 1), then examined group differences in anxiety and BtC (Aim 2), and finally explored within- and cross-condition correlates of these mental health difficulties (Aim 3). While the descriptive findings (Aim 1) are reported in full, the discussion primarily focuses on the results of Aims 2 and 3, which sought to replicate and then extended previous work.

### 2.4.1 Aim 2: Comparative Findings

A key objective of this study was to replicate group differences reported by Ng-Cordell et al. (2023), who found higher anxiety and self-injurious behaviour in young women with *DDX3X*-related disorder, relative to individuals with other rare ID-associated genetic conditions (termed ‘ID-other’). Surprisingly, findings from the present study do not support this pattern. We found no significant group differences using the same measure of anxiety and, contrary to our prediction, we found self-injury was significantly lower in the *DDX3X*-related disorder group compared to the ID-other group.

A lack of replication may be explained by differences in sample characteristics. Participants in the current study (i.e., replication sample) were, on average, younger and had higher adaptive ability than those included in Ng-Cordell et al. (2023). It is possible that anxiety and BtC may increase with age, or be associated with poorer adaptive ability in *DDX3X*-related disorder: for example, Ng-Cordell et al. (2023) found poorer adaptive ability was associated with higher anxiety in individuals with *DDX3X*-related disorder but not in individuals with other rare ID-associated genetic conditions. However, it is notable that, we did not replicate this relationship in the present study. Therefore, it remains unclear whether discrepant findings reflect differences in sample characteristics between Ng-Cordell et al. and the current study, or true effects of genetic diagnoses on behaviour.

Another possible explanation is that the measures of anxiety and self-injury that were used in Ng-Cordell et al. (2023) and in the present replication may not have been sensitive enough to detect group differences. As discussed in Section 1.3.2, a lack of precision may lead to overgeneralisation (Oliver, 2017). However, we did not find any group differences on more comprehensive measures of anxiety and self-injury when compared between these two groups and to children with *CASK*-related disorder. In addition, the results of Bayesian analyses provided evidence in support of the null hypothesis – that is, evidence in favour of no meaningful group differences in anxiety and self-injury.

These findings underscore the importance of caution when interpreting comparative research in the context of rare ID-associated genetic conditions, and the need for replication in order to establish robust findings.

#### **2.4.2 Aim 3: Correlates of Anxiety and BtC**

Despite the absence of hypothesised group differences, consistent with Ng-Cordell et al. (2023), we found an association between greater autism characteristics and anxiety behaviours. We also found that the strength of this relationship did not differ between genetic diagnosis groups (i.e., *DDX3X*-related disorder and ID-other). This finding suggests that autism-related characteristics might be a shared neurodevelopmental correlate of anxiety across rare ID-associated genetic conditions. Therefore, understanding the link between autism-related characteristics and anxiety behaviours might be critical to identifying developmental pathways to anxiety in these conditions.

We also observed associations between anxiety and autism-related characteristics in our network analysis. Specifically, we found that the anxiety composite measure shared a direct edge with social communication and sensory avoiding. This suggests that greater communication difficulties and increased efforts to actively avoid overwhelming sensory input (e.g., loud noises, intense touch sensations) may be linked to anxiety in children with rare ID-associated genetic conditions. This is consistent with findings from two recent network analyses in autistic children (Bitsika et al., 2025; Zaidmanzait et al., in press). These studies found that sensory hypersensitivity and social communication difficulties acted as key bridge nodes linking autism and anxiety symptoms.

Sensory processing difficulties may be particularly relevant to the emergence of anxiety across neurodevelopmental populations. There is consistent correlational evidence showing an association between sensory hypersensitivity and anxiety in autistic individuals (MacLennan et al., 2021; Wigham et al., 2015), as well longitudinal studies indicating a unidirectional relationship between sensory hyperreactivity and anxiety in both autistic and typically developing children (Carpenter et al., 2019; Green et al., 2012). In the context of rare ID-associated genetic conditions, there is also emerging evidence of a relationship between sensory processing and anxiety in Williams syndrome (Glod et al., 2019; Royston et al., 2021), and sensory processing differences have been proposed as a factor influencing social anxiety in Fragile X syndrome (Crawford, 2023). Taken together, this work suggests that sensory processing differences warrant further investigation as a possible developmental risk factor for the emergence of anxiety in neurodevelopmental populations, including individuals with a rare genetic diagnosis.

In addition to anxiety, we found that greater autism-related traits were correlated with increased self-injury across groups in the present replication analyses. Our network analysis also revealed a direct link between sensory processing difficulties and self-injury. Taken together, these findings suggest that sensory processing differences may contribute to the high co-occurrence of anxiety and BtC in rare ID-associated genetic conditions. However, the directionality of these relationships remains unclear and could be considered in future longitudinal studies.

It was surprising that nodes corresponding to subscales on the Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009) were peripheral in our network. This was unexpected given the established, albeit weak, association between repetitive behaviours and anxiety in autistic children (Vasa et al., 2020), as well as the link between repetitive behaviours and BtC in rare genetic syndromes (see Section 1.3.1.2). Adaptive ability was also a peripheral node in our network, but this is somewhat less surprising given inconsistent findings regarding the overlap between anxiety, autism and cognitive ability (Mingins et al., 2020). Finally, it is important to note that whilst we focused on nodes corresponding to anxiety and BtC when interpreting our psychological network, it is possible that associations between other nodes could also be informative (Bringmann & Eronen, 2018).

Findings from the network analysis should also be interpreted with caution as edge and node level estimates exhibited instability. This instability is likely attributable to the small sample size, which made it difficult to accurately estimate correlations between variables included in the network. To account for this, we utilised subscale scores rather than individual questionnaire items. This allowed us to generate a network examining factor-factor associations, rather than symptom-symptom associations, and reduce the number of estimated correlations, but this may not have been sufficient to generate a stable network.

#### **2.4.4 Conclusions and Future Directions**

This study advances our understanding of anxiety and self-injury children with *DDX3X*-related disorder and *CASK*-related disorder. Contrary to previous findings from Ng-Cordell et al. (2023), we found that anxiety and self-injury were not elevated in *DDX3X*-related disorder compared to individuals with other rare ID-associated conditions. Additionally, children with *CASK*-related disorder did not differ from either the *DDX3X*-related disorder group, or the ID-other comparison group on any measure of anxiety or self-injury, suggesting that these difficulties are not more common in this population than would be expected given the severity of ID. Instead, we found substantial within-condition variability in these

mental health difficulties. Findings from this study also indicate that autism-related traits may be a cross-condition correlate of anxiety and self-injury in children with rare ID-associated genetic conditions.

In addition, our use of Bayesian analyses highlights the value of this approach, particularly for interpreting non-significant results. For example, when examining group differences in anxiety and self-injury in this study, we found that Bayesian evidence supported the null hypothesis, strengthening the conclusion that previously reported group differences in anxiety and BtC may not be meaningful. We also applied a data-driven network approach to examine the relationships between neurodevelopmental and mental health characteristics in rare ID-associated genetic conditions. Our findings illustrate the value of this approach in generating novel hypotheses regarding the mechanisms linking the co-occurrence between mental health difficulties. Such methods are informative and should be incorporated into future, larger studies to further our understanding of mental health in rare ID-associated genetic conditions.

The findings from this study also have broader implications for research in this field. Currently, few comparative studies are conducted in the context of mental health research in rare ID-associated genetic conditions, and even fewer are replicated. Despite this, strong claims are often made about condition-specific difficulties and associations based on limited data. Without robust replication, there is a risk of over-interpreting findings that may reflect sample-specific factors rather than true differences between genetic conditions. The present study highlights the limitations of small, comparative studies, and supports a shift towards investigating shared mechanisms. Research grouping rare ID-associated genetic conditions together may offer more generalizable insights, rather than focusing on condition-specific comparisons which remain difficult to replicate and interpret.

# Chapter 3 | Utilising Interview Methodology to Understand Anxiety Characteristics in Rare ID-associated Genetic Conditions

## 3.1 Introduction

Our understanding of anxiety within rare ID-associated genetic conditions is largely derived from studies utilising questionnaire measures. These measures are typically designed for populations without ID and utilise DSM diagnostic criteria for anxiety, which may be inappropriate for individuals with rare ID-associated genetic conditions, who can have challenges verbally communicating or having their symptoms of anxiety recognised. Additionally, autism-related characteristics are common in rare ID-associated genetic conditions (Richards et al., 2015; Ziats et al., 2020), and there is evidence that anxiety-associated triggers and behaviours may differ in autistic individuals (Kerns et al., 2014). For example, unusual phobias (e.g., babies and balloons) and excessive worry about changes in routine or novelty have been associated with anxiety in autistic individuals (Kerns et al., 2014; Lau et al., 2020; Rodgers et al., 2016). Anxious feelings may also manifest differently in autistic individuals, such as increased avoidance or escape behaviours, and BtC (Adams et al., 2019; Ozsivadjian et al., 2012).

One approach to address these challenges is to use questionnaire measures specifically designed for autistic individuals and individuals with ID (see Chapter 2 for examples). These measures resemble conventional diagnostic-based measures, as they include a checklist of behaviours and yield scores on a scale from more-to-less anxiety symptoms. When used comparatively, they can provide useful insights into which rare ID-associated genetic conditions have a relatively increased risk of anxiety. However, even these adapted questionnaire-based measures do not provide any information about the broader context in which anxiety emerges or how it is maintained in individuals with rare ID-associated genetic conditions – information that is important for understanding individual needs and developing effective interventions.

A complementary approach to assess anxiety in rare ID-associated genetic conditions is through interview methodology and qualitative analysis. Qualitative data can provide rich and detailed insights into complex and poorly understood behaviours and emotions. Additionally, interview methodology can be applied flexibly, such that questions can be adapted to participants' communication style and clarifications can be sought, enabling a deeper and more representative understanding of behaviour. Semi-structured interviews informed by models from clinical psychology (e.g., the ABC model from

functional analysis (Yoman, 2008) and the 5Ps formulation model (Dudley & Kuyken, 2014)) have previously been used to explore problem behaviour in several rare ID-associated genetic conditions, including repetitive behaviours in Prader Willi and Fragile X syndromes (Woodcock et al., 2009), temper outbursts in Prader Willi and Lowe syndromes (Cressey et al., 2019; Tunnicliffe et al., 2014), skin picking in Prader Willi syndrome (Bull et al., 2021) and, more recently, anxiety in Williams syndrome (Royston et al., 2021).

These studies have demonstrated utility in mapping behavioural characteristics, as well as possible antecedents and consequences of behaviour in rare genetic syndromes. For example, in the aforementioned study using interview methodology to explore anxiety in Williams syndrome, Royston et al. (2021) found that anxiety was frequently triggered by 'negative emotions in others', despite low rates of social anxiety reported in the literature (Royston et al., 2017). Their findings suggest that social-related fears in Williams syndrome might be linked to challenges understanding or responding to negative emotions in others, which is distinct from cognitive models that posit social phobia typically arises from a fear of negative evaluation by others (Clark, 2001; Clark & Wells, 1995).

The manifestation of unusual social fears in Williams syndrome is also distinct from that reported in autistic individuals, wherein social fears are not associated with worries of social rejection (Kerns et al., 2014), but are often accompanied by attempts to avoid or escape situations in which others are present. In contrast, Williams syndrome is associated with hyper-sociability (Jones et al., 2000; Mervis & Klein-Tasman, 2000) and in this context 'negative emotions in others' might be challenging not because they are social, but rather because they are unpredictable. Such links between social-related fears in Williams syndrome, and challenges understanding or responding to negative emotions, would be difficult to capture using diagnostic-based questionnaire measures of anxiety. This highlights the value of interview methodology to deepen our understanding of behaviour in rare ID-associated genetic conditions.

In summary, interview methodology and formulation frameworks from clinical psychology can help to build models of behaviour. These models can then be empirically tested to improve our understanding of mental health in rare ID-associated genetic conditions, where there might be complex relationships between cognitive development, social characteristics, and mental health symptoms.

Here, we used interview methodology and a formulation framework with a combination of qualitative approaches to: (1) explore manifestations and antecedents of anxiety in children and adolescents with

rare ID-associated genetic conditions from a parent/carer perspective; and (2) explore child and parent/carer responses to anxiety that might maintain anxiety and serve as possible targets for intervention. Overall, this study aimed to improve our understanding of anxiety in children and adolescents with rare ID-associated genetic conditions with implications for clinical research and practice.

## **3.2 Method**

### **3.2.1 Participants**

Parents/carers (henceforth referred to as 'parents' for brevity) who had consented to take part in the study outlined in Chapter 2 were invited to take part in an online interview. Parents were informed that they would be asked about their child's current abilities and whether their child experiences any emotional difficulties, such as worries or low mood. Of 89 families invited, seven did not respond and two declined to participate. The interview was also deemed inappropriate for four families lacking proficiency in spoken English, and one family was unable to complete the anxiety interview due to time constraints. See **Table 3.1** for demographic information of parents who took part in the interview.

We did not specify that interviews should take place without the child present. As such, there were several cases where children were present during sections or throughout the whole interview, for example because of childcare arrangements or the interview taking place at home in the evening. Occasionally children interrupted the interview and were captured on the audio recording, for example if they were requesting something from their parent. For one interview, the child wanted to be involved but only parent responses were included in the subsequent analysis.

**Table 3.1** Demographic information for interviewed parents

|                                                      | Interviewed parents<br>( <i>n</i> = 85 parents; <i>n</i> = 75 child participants) | Interviewed parents who reported participant anxiety ( <i>n</i> = 45 parents; <i>n</i> = 39 child participants) |
|------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <i>Relationship to child participant<sup>a</sup></i> |                                                                                   |                                                                                                                 |
| Mother, <i>n</i> (%)                                 | 73 (85.88)                                                                        | 37 (82.22)                                                                                                      |
| Father, <i>n</i> (%)                                 | 10 (11.76)                                                                        | 6 (13.33)                                                                                                       |
| Caregiver, <i>n</i> (%)                              | 2 (2.35)                                                                          | 2 (4.44)                                                                                                        |
| <i>Country</i>                                       |                                                                                   |                                                                                                                 |
| UK, <i>n</i> (%)                                     | 36 (48.00)                                                                        | 20 (51.28)                                                                                                      |
| USA, <i>n</i> (%)                                    | 21 (28.00)                                                                        | 9 (23.08)                                                                                                       |
| Canada, <i>n</i> (%)                                 | 4 (5.33)                                                                          | 3 (7.69)                                                                                                        |
| Ireland, <i>n</i> (%)                                | 3 (4.00)                                                                          | 2 (5.13)                                                                                                        |
| Australia, <i>n</i> (%)                              | 3 (4.00)                                                                          | 1 (2.56)                                                                                                        |
| Germany, <i>n</i> (%)                                | 2 (2.67)                                                                          | 1 (2.56)                                                                                                        |
| Netherlands, <i>n</i> (%)                            | 2 (2.67)                                                                          | 1 (2.56)                                                                                                        |
| Spain, <i>n</i> (%)                                  | 2 (2.67)                                                                          | 1 (2.56)                                                                                                        |
| Mexico, <i>n</i> (%)                                 | 1 (1.33)                                                                          | 1 (2.56)                                                                                                        |
| Poland, <i>n</i> (%)                                 | 1 (1.33)                                                                          | 0 (0.00)                                                                                                        |
| Sweden, <i>n</i> (%)                                 | 1 (1.33)                                                                          | 0 (0.00)                                                                                                        |

<sup>a</sup> 9 mother-father and 1 mother-caregiver dyads were interviewed together, and their responses were combined in the subsequent analyses.

### 3.2.2 Semi-structured Interview

We adopted the semi-structured interview schedule used by Royston et al. (2021), which was initially applied to examine anxiety in Williams syndrome, a rare genetic syndrome characterised by high prevalence of anxiety (~48%, Royston et al., 2017). Although the interview schedule was designed primarily for use in individuals with Williams syndrome, the questions cover aspects relevant to broader neurodevelopmental disorders and has been successfully employed to examine the presentation and triggers of anxiety, as well as the parental experience and management of anxiety, in autistic individuals who speak few or no words (Edwards et al., 2023; Tarver et al., 2021).

The interview schedule is comprised of four sections (see **Figure 3.1**) and was designed to elicit a description of anxiety symptoms within a 5Ps formulation framework from a parent perspective. The 5Ps formulation framework is an atheoretical model which can be used to describe an individual's current difficulties with respect to five Ps – presenting, predisposing, precipitating, perpetuating and protective factors (Dudley & Kuyken, 2014).

Interview questions covered the behaviours, thoughts, frequency, severity and impact of anxiety (presenting issue); comorbid depression and family history of anxiety (predisposing factors); common antecedents (precipitating factors); and strategies used to manage and/or cope with the anxiety (perpetuating and protective factors). The interview schedule consisted of open and fixed response

questions; examples are provided in **Table 3.2**. Prompts were included to obtain further information. For example, Royston et al. (2021) reported that parents found it challenging to discuss what their child might be thinking or feeling when they were anxious. Therefore, to ensure we would obtain sufficient analysable responses to this question, we informed parents that this was a difficult question and encouraged a response even if they were unsure.

In this study, Section A was used as a screener to identify children who had potentially experienced anxiety, whether their anxiety was triggered by specific events or occurred more generally, and if they experienced comorbid low mood. This enabled the interviewer (J.M)<sup>1</sup> to determine which sections of the interview were most relevant to each child's experience of negative emotion. At the end of Section A, parents who did not report anxiety were asked if there was anything else they'd like to tell the researchers about their child and were encouraged to share both positive and negative experiences.

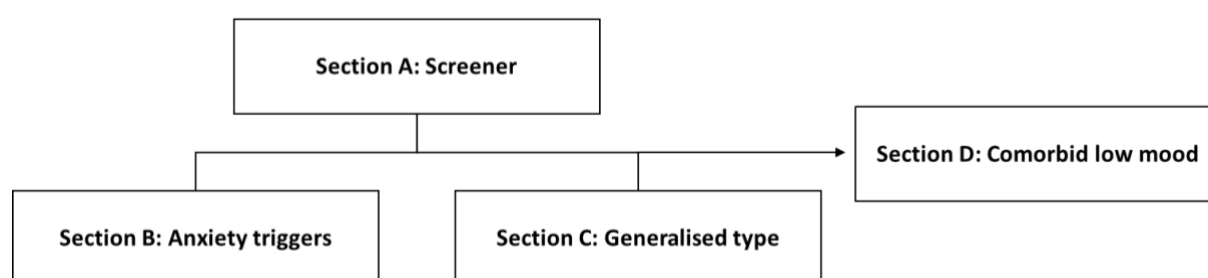


**Figure 3.1** Structure of Anxiety Interview. Adapted from Royston et al. 2021.

**Table 3.2** Example question structures and recording instructions from interview schedule

| Question                                                                                                     | Information recorded on coding sheet                                           | Question type |
|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------|
| I am interested in any difficult or negative emotions that (X) might experience. Can you tell me about them? | Listen to account and record negative emotions.                                | Open          |
| Does (X) ever get anxious, worried or apprehensive?                                                          | State yes or no                                                                | Fixed         |
| How severe would you say the anxiety shown during these events is?                                           | Report the severity of behaviour (0 = N/A, 1 = Mild, 2 = Moderate, 3 = Severe) | Fixed         |
| What do you think (X) is thinking when they are feeling anxious? Why do you think that?                      | Listen to account and record thoughts and feelings                             | Open          |
| How much control do you feel you have over X's anxiety and the impact it has on you?                         | Report control out of 10 (0 = no control, 10 = extreme control)                | Fixed         |

<sup>1</sup> Jessica Martin

### 3.2.3 Procedure

Each parent was interviewed between June 2023 and May 2024. Interviews were conducted online via Zoom Video Communications (<https://zoom.us/>) or by telephone, according to parent preference. Prior to starting the anxiety interview, parents were reminded that they did not have to answer any of the interview questions, and that they could withdraw at any point without having to give a reason why. They were also informed that they could take breaks. All interviews were conducted by the researcher J.M. With parental consent, interviews were audio-recorded and transcribed verbatim. Interviews were transcribed using Zoom's inbuilt automated transcription. The researcher A.M.F<sup>2</sup> then checked the transcripts for accuracy against each audio file and replaced any identifying information with descriptors (e.g., [child name]). One parent of twins recruited into the study did not consent to audio-recording, so only interview coding data and researcher notes are available for two participants. For participants without parent-reported anxiety, interviews lasted 4 to 26 minutes with a mean of 11 minutes ( $SD = 4.75$ ). For participants with parent-reported anxiety, interviews lasted 24 to 64 minutes with a mean of 42 minutes ( $SD = 10.97$ ). Parents had previously completed the questionnaires described in Chapter 2 (see **Table 2.3**), and scores from these measures were analysed to describe the sample characteristics and examine the internal validity of the interview.

### 3.2.4 Data Analysis

Findings are presented for the combined sample, and for each genetic diagnosis group (i.e., *DDX3X*-related disorder, *CASK*-related disorder and ID-other), in a descriptive format within the 5Ps formulation model. Consistent with Royston et al. (2021), perpetuating and protective factors are presented together as they were examined in the interview via questions about child and parent coping strategies. 'Thoughts and Feelings' are also presented separately, rather than within the presenting issue subsection of the results, consistent with how the data were analysed in a subsequent coding phase (see Section 3.2.5). Unless otherwise specified, 'participants' refers to children with a diagnosed rare ID-associated genetic condition, not their parents who were interviewed, and  $n$  refers to the number of child participants.

For each participant, an anxiety profile capturing 'what happens when they are anxious' was also plotted by the researcher L.A.M<sup>3</sup> and reviewed by J.M (see **Appendix B1**). These profiles show the antecedents, anxiety-related behaviours and parent coping strategies, for each participant, as well as information about the duration and severity of anxiety.

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<sup>2</sup> Alkistis Mavroglou-Foti

<sup>3</sup> Leanne Al-Mrayat

### 3.2.5 Coding

#### 3.2.5.1 Coding Phases

Anxiety characteristics in rare ID-associated genetic conditions were examined in relation to the 5Ps formulation framework (i.e., presenting, predisposing, precipitating, perpetuating and protective factors) using two phases of coding. In the first phase, fixed-response questions were analysed using the coding scheme developed by Royston et al. (2021). In a secondary analysis phase, mixed-methods content analysis was applied to understand what parents' thought their child might be thinking or feeling when they were anxious. This was an open-ended question for which no pre-existing coding procedure had been outlined by Royston et al. (2021), but is an essential component of the presenting issue within the 5Ps framework which has yet to be explored in rare ID-associated genetic conditions.

#### 3.2.5.2 Coding Procedure for Fixed-response Questions

We adopted the coding scheme used by Royston et al. (2021), which was developed from expert opinion and pre-existing coding schemes generated from validated questionnaire and interview measures of anxiety and behaviour. The coding scheme was applied during the interviews to quantify parent responses in real time. A second researcher (J.E<sup>4</sup> or A.M.F), was present in 84.62% of the interviews, and completed a coding sheet for each participant. They also summarised any other relevant information in note form. Codes and notes were manually entered into an Excel spreadsheet and combined with demographic data for analyses using R Studio (Version: 2024.04.2+764). Before calculating inter-rater reliability and summarising the codes for each genetic group, an additional step of further categorising coded information (e.g., assigning age of onset categories), and cleaning uncertain codes and notes was completed (for documentation of this process see **Appendix B2, Table B2**). To assess inter-rater reliability, the percentage agreement at an item level was calculated. The mean agreement was 94.83% (range 72.73%-100%), and 67 of the items had 90% agreement or above (see **Appendix B3, Table B3.1-B3.5**). Parents' responses were divided into 'DDX3X-related disorder', 'CASK-related disorder' and 'ID-other' and the number of participants and frequencies (where appropriate) were calculated for these groups, as well as the combined sample.

#### 3.2.5.3 Coding Procedure for Open-ended Questions

To gain a better understanding of what children might be thinking or feeling when they were anxious (a component of the presenting issue), we conducted mixed-methods content analysis on parents' open-ended responses. Content analysis is a mixed-methods research approach that systematically

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<sup>4</sup> Josefine Eck

reduces textual data into categories. These categories can then be quantified through frequency counts (quantitative content analysis) or interpreted to identify patterns and meaning (qualitative/inductive content analysis). The process of content analysis is rule-guided, and can be applied to various textual sources, such as interviews, group discussions, and (social) media content. Content analysis involves three key phases: immersion/familiarisation, reduction and interpretation. Coding is central to content analysis and involves systematically categorising data into meaningful units which can represent concepts and themes. Coding can be approached in two ways: deductive coding, where text is searched for pre-determined codes that are developed from pre-existing theories, frameworks or the research question; or inductive coding, where codes are developed from the text itself via a process of familiarisation and iterative analysis. The process of coding exists on a spectrum from manifest coding, which focuses on the explicit, surface-level content of the text, with minimal inference (i.e., 'what has been said'); to latent coding, which explores implicit meanings within the text, requiring larger inferential steps and contextual interpretation (i.e., 'what has intended to be said') (Bengtsson, 2016; Vears & Gillam, 2022). Ongoing debates within the literature concern whether content analysis should incorporate quantification or be used solely qualitatively.

Here, the aim was to explore commonalities and differences in parents' responses, in order to provide an insight into what children with rare ID-associated genetic conditions might be thinking or feeling when they are anxious. As described by Vears and Gillam (2022), first round coding in qualitative/inductive content analysis involves identifying 'meaning units' – segments of text relating to the research question – which are then organised into codes and categories. Typically, meaning units are identified across full transcripts, as this allows researchers to preserve context and capture nuanced meanings (Graneheim & Lundman, 2004). Whole transcripts are also deemed the most suitable unit of analysis, as they provide a comprehensive understanding of participant responses and reduce the risk of fragmentation – a loss of context by breaking text into smaller chunks that might affect interpretation.

However, in this study, due to time constraints and our specific research question, only sections of transcript whereby parents responded to the key question – '*What do you think (X) is thinking when they are feeling anxious?*' – were extracted as the material to be analysed (see **Table 3.3** for detailed prompts). While this approach may have led to the omission of unprompted discussion of thoughts and feelings, it was consistent with the approach used for fixed-response questions whereby parents' responses were coded for individual questions, as well as being proportionate given the number of participants ( $n = 39$ ) and the goal of our analysis. Furthermore, smaller units of text, such as responses

to key questions, can be appropriate depending on the research objective (Elo & Kyngäs, 2008; Graneheim & Lundman, 2004).

**Table 3.3** Thoughts and Feelings – Key Question and Prompts

| Question                                                                                | Prompts                                                                                                                          |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| What do you think (X) is thinking when they are feeling anxious? Why do you think that? | What behaviours does (X) show?<br>What does (X) say to make you think this?<br>Do you think they are feeling any other emotions? |

Within the extracted sections, the unit of analysis was defined as segments of the text which conveyed parent’s distinct perceptions and ideas about their child’s thoughts and feelings. These could vary in length from a phrase to several sentences. Additionally, to minimise researcher interpretation and to stay close to the words used by parents, a manifest analysis was chosen (Bengtsson, 2016).

All available transcript sections ( $n = 38$ ) were checked for accuracy by the researcher (J.M) and uploaded into NVivo (Version 14, Release 14.23.4 [49], Lumivero, 2023) a qualitative data management software. The analysis process followed the stages described in (Bengtsson, 2016). Transcript sections were re-read line by line, and key concepts were highlighted to obtain meaning units, which were then condensed and annotated with descriptive labels, codes (e.g., fear), or paraphrased (e.g., thoughts about trigger). Related codes were then grouped together to form subcategories of thoughts and feelings. For example, fear was coded as a feeling and escape was coded as a thought. To increase validity and reduce bias, codes and their categories were discussed and reflected on with members of the research team (L.A.M and K.B<sup>5</sup>) until consensus was reached.

One challenge which emerged whilst conducting the content analysis was whether to split fear and anxiety into separate subcategories of feeling or to lump them together. Among emotion researchers it is currently debated whether fear and anxiety are distinct (see Daniel-Watanabe & Fletcher, 2022). Fear and anxiety are both defensive and triggered by threat of harm. As such, models separating emotions in terms of their valence and arousal struggle to make distinctions between fear and anxiety as both emotions are characterised by negative valence and high arousal. Definitions from DSM-5 and Research Domain Criteria (RDoC) imply that fear and anxiety differ in terms of the immediacy, proximity and certainty of threat, whereby fear is an emotional response to real/perceived acute threat and anxiety is emotional response to the anticipation of threat that is ambiguous or uncertain (

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<sup>5</sup> Kate Baker

APA, 2013; NIMH, n.d.-a, n.d.-b). However, the DSM-5 also defines anxiety disorders as conditions that share features of excessive fear and worry, such that anxiety is synonymous with fear and worry (APA, 2013). There are anxiety disorders that are characterised by fear (e.g., specific phobia), those that are characterised by worry (e.g., generalised anxiety disorder), as well as those that contain elements of both (e.g., social phobia). Moreover, within everyday language fear and anxiety are used interchangeably, and people often use fear-related language to describe anxiety (e.g., “I am afraid that I won’t get an interview”). Therefore, there is rationale for considering fear and anxiety as both distinct, and related constructs. In the subsequent content analysis, we selected to treat anxiety and fear as distinct subcategories of feelings. Whilst it is possible that parent’s conceptual understanding of the difference between anxiety and fear may not accurately reflect the precise definitions we use within research or clinical practice, when reflecting on their child’s experience some parents used both terms to convey unique ideas about their child’s emotions, implying that they are distinct feelings.

### 3.3 Results

#### 3.3.1 Participants

We found 39/75 children who were screened had parent-reported anxiety (see **Figure 3.2**). We first examined whether there were any demographic differences between participants who were screened as having parent-reported anxiety compared to participants who did not have parent-reported anxiety. Appropriate statistical tests were selected and non-parametric methods were used if data violated the assumption of normality and/or homogeneity of variance, which were examined via Shapiro-Wilks test of normality (Shapiro & Wilk, 1965) and Levene’s test (Levene, 1960), respectively. We found no statistical differences in age, sex or adaptive ability between participants with and without parent-reported anxiety (see **Table 3.4**).

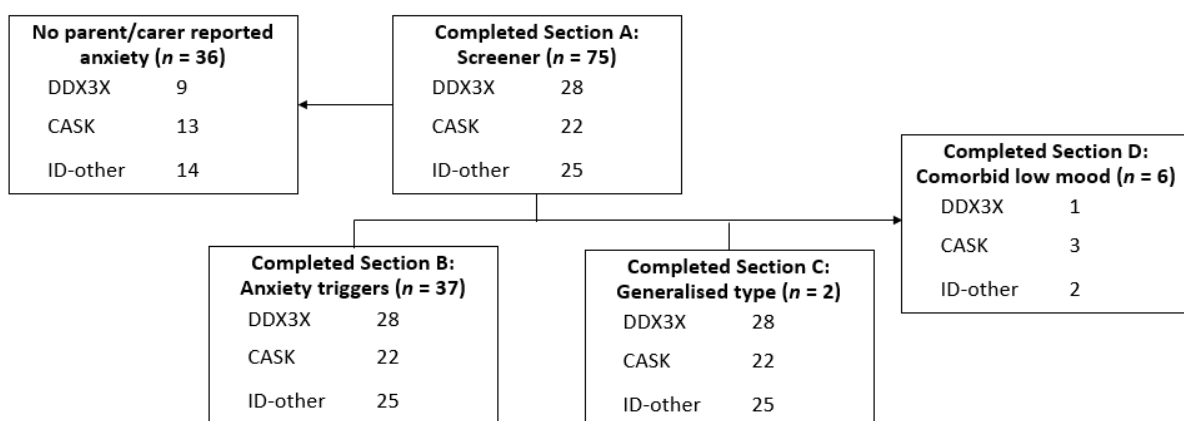


**Figure 3.2** Flow Chart. Adapted from Royston et al. (2021).

**Table 3.4** Demographic information for participants with and without parent-reported anxiety.

|                          | Parent-reported anxiety on interview Section A |            |                        |            |          |                           |
|--------------------------|------------------------------------------------|------------|------------------------|------------|----------|---------------------------|
|                          | Yes ( <i>n</i> = 39)                           |            | No ( <i>n</i> = 36)    |            | <i>p</i> | <i>p.adj</i> <sup>e</sup> |
|                          | <i>M</i> ( <i>SD</i> )                         | Range      | <i>M</i> ( <i>SD</i> ) | Range      |          |                           |
| Age                      | 8.78 (4.29)                                    | 2.95-17.34 | 8.08 (4.82)            | 3.04-18.77 | .29      | .49                       |
| Sex <sup>a</sup>         | 9M:30F                                         |            | 6M:30F                 |            | .69      | .69                       |
| VABS ABC <sup>b</sup>    | 59.56 (17.92)                                  | 22-98      | 57.03 (14.23)          | 22-84      | .50      | .62                       |
| DBC2 TBPS <sup>c</sup>   | 55.69 (10.11)                                  | 41-89      | 50.53 (8.40)           | 37-76      | .04      | .21                       |
| SRS-2 Total <sup>d</sup> | 76.08 (9.30)                                   | 59-95      | 73.11 (11.82)          | 44-95      | .24      | .49                       |

<sup>a</sup> Ratio of male to female participants.

<sup>b</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).

<sup>c</sup> Total Behaviour Problem Scores (TBPS) from the Developmental Behaviour Checklist 2 (DBC2).

<sup>d</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).

<sup>e</sup> Benjamini-Hochberg FDR correction for multiple testing.

We also examined whether there were any demographic differences between genetic diagnosis groups, within participants with parent-reported anxiety (**Table 3.5**). We observed a significant association between sex and genetic group ( $p < .001$ ), whereby the *DDX3X*-related disorder and *CASK*-related disorder groups had a higher proportion of females compared to the ID-other group. This was to be expected given *DDX3X*-related disorder and *CASK*-related disorders predominately affect females (Najm et al., 2008; Snijders Blok et al., 2015). Adaptive ability also significantly differed between groups ( $F(2, 36) = 5.06$ ,  $p = .01$ ,  $\eta^2 = 0.22$ ), and post-hoc comparisons using Tukey's HSD revealed significant group differences in VABS ABC scores between the *CASK*-related disorder group and both the *DDX3X*-related disorder (mean difference = 19.82, 95% CI [3.73, 35.91],  $p = .01$ ) and the ID-other group (mean difference = 19.37, 95% CI [1.50, 37.25],  $p = .03$ ). There was no significant difference in VABS ABC scores between the ID-other group and the *DDX3X*-related disorder group (mean difference = -0.44, 95% CI [-15.51, 14.62],  $p = 1.00$ ).

Finally, we reviewed the developmental characteristics of all participants with parent-reported anxiety (**Table 3.6**) in order to capture any frequent patterns of co-occurrence with anxiety. We did not observe any clear patterns (e.g., participants who were severely affected across domains). Overall, participants spanned a wide range of adaptive and communication abilities, and the majority of participants experienced moderate-serious emotional-behavioural problems and high levels of autism characteristics.

**Table 3.5** Demographic information for participants with parent-reported anxiety by genetic diagnosis group.

|                       | DDX3X-related disorder<br>( <i>n</i> = 19) |            | CASK-related disorder<br>( <i>n</i> = 9) |            | ID-other ( <i>n</i> = 11) |            | <i>p</i> value for<br>comparison |
|-----------------------|--------------------------------------------|------------|------------------------------------------|------------|---------------------------|------------|----------------------------------|
|                       | <i>M</i> ( <i>SD</i> )                     | Range      | <i>M</i> ( <i>SD</i> )                   | Range      | <i>M</i> ( <i>SD</i> )    | Range      |                                  |
| Age                   | 8.68 (4.51)                                | 2.95-17.06 | 9.45 (3.31)                              | 4.10-13.26 | 8.41 (4.89)               | 3.32-17.34 | .64                              |
| Sex <sup>a</sup>      | 1M:18F                                     |            | 2M:7F                                    |            | 6M:5F                     |            | < .01                            |
| VABS ABC <sup>b</sup> | 64.26 (14.32)                              | 34-98      | 44.44 (14.94)                            | 29-74      | 63.82 (12.12)             | 46-89      | .01                              |
|                       |                                            |            |                                          |            |                           |            | .02                              |

<sup>a</sup> Ratio of female to male participants.<sup>b</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).<sup>c</sup> Benjamini-Hochberg FDR correction for multiple testing.

**Table 3.6** Participant-level characteristics for participants with parent-reported anxiety.

| ID | Group | Age (years) | Adaptive Ability <sup>a</sup> | Communication <sup>b</sup> | Emotional-behavioural problems <sup>c</sup> | Autism Characteristics <sup>d</sup> |
|----|-------|-------------|-------------------------------|----------------------------|---------------------------------------------|-------------------------------------|
| 1  | DDX3X | 17.03       | Mild                          | Normal                     | Serious                                     | Severe                              |
| 2  | DDX3X | 11.27       | Normal                        | Normal                     | Serious                                     | Moderate                            |
| 3  | DDX3X | 12.86       | Moderate                      | Moderate                   | Serious                                     | Severe                              |
| 4  | DDX3X | 17.06       | Mild                          | Normal                     | Serious                                     | Moderate                            |
| 5  | DDX3X | 13.25       | Normal                        | Normal                     | Moderate                                    | Moderate                            |
| 6  | DDX3X | 9.1         | Mild                          | Moderate                   | Moderate                                    | Mild                                |
| 7  | DDX3X | 5.18        | Mild                          | Mild                       | Moderate                                    | Severe                              |
| 8  | DDX3X | 4.9         | Moderate                      | Severe                     | Moderate                                    | NA                                  |
| 9  | DDX3X | 4.68        | Moderate                      | Severe                     | Serious                                     | Severe                              |
| 10 | DDX3X | 4.08        | Mild                          | Mild                       | Serious                                     | Severe                              |
| 11 | DDX3X | 8.8         | Mild                          | Moderate                   | Serious                                     | Severe                              |
| 12 | DDX3X | 3.27        | Mild                          | Mild                       | Serious                                     | Moderate                            |
| 13 | DDX3X | 8.39        | Normal                        | Normal                     | Moderate                                    | Mild                                |
| 14 | DDX3X | 7.13        | Severe                        | Profound                   | Moderate                                    | Mild                                |
| 15 | DDX3X | 11.07       | Mild                          | Moderate                   | Moderate                                    | Moderate                            |
| 16 | DDX3X | 7.94        | Mild                          | Mild                       | Serious                                     | Severe                              |
| 17 | DDX3X | 2.95        | Normal                        | Normal                     | Serious                                     | Mild                                |
| 18 | DDX3X | 3.24        | Normal                        | Normal                     | Serious                                     | Moderate                            |
| 19 | DDX3X | 12.69       | Normal                        | Normal                     | Moderate                                    | Normal                              |
| 20 | CASK  | 7.03        | Severe                        | Profound                   | Serious                                     | Severe                              |
| 21 | CASK  | 7.46        | Moderate                      | Severe                     | Serious                                     | Severe                              |
| 22 | CASK  | 4.1         | Moderate                      | Severe                     | Moderate                                    | Moderate                            |
| 23 | CASK  | 9.9         | Severe                        | Profound                   | Serious                                     | Severe                              |
| 24 | CASK  | 12.76       | Normal                        | Normal                     | Serious                                     | Severe                              |
| 25 | CASK  | 11.12       | Severe                        | Profound                   | Moderate                                    | Moderate                            |
| 26 | CASK  | 13.26       | Severe                        | Profound                   | Moderate                                    | Severe                              |
| 27 | CASK  | 12.9        | Moderate                      | Profound                   | Serious                                     | Moderate                            |
| 28 | CASK  | 6.52        | Mild                          | Moderate                   | Serious                                     | Severe                              |
| 29 | Other | 16.67       | Moderate                      | Moderate                   | Moderate                                    | Mild                                |
| 30 | Other | 4.18        | Mild                          | Moderate                   | Serious                                     | Moderate                            |
| 31 | Other | 6.33        | Normal                        | Normal                     | Serious                                     | Moderate                            |
| 32 | Other | 7.38        | Mild                          | Mild                       | Serious                                     | Severe                              |
| 33 | Other | 3.32        | Mild                          | Mild                       | Serious                                     | Moderate                            |
| 34 | Other | 7.83        | Normal                        | Normal                     | Serious                                     | NA                                  |
| 35 | Other | 4.8         | Moderate                      | Severe                     | Serious                                     | Severe                              |
| 36 | Other | 5.89        | Normal                        | Normal                     | Serious                                     | Severe                              |
| 37 | Other | 12.57       | Moderate                      | Mild                       | Serious                                     | Severe                              |
| 38 | Other | 17.34       | Profound                      | Profound                   | Serious                                     | Severe                              |
| 39 | Other | 6.16        | Normal                        | Normal                     | Serious                                     | Severe                              |

<sup>a</sup> Adaptive behaviour severity was determined using Adaptive Behaviour Composite (ABC) scores from the Vineland Adaptive Behaviour Scale (VABS).

<sup>b</sup> Communication severity was determined using communication domain scores from the VABS.

<sup>c</sup> Clinically significant emotional and behavioural problems were identified using established cut-off scores from the Developmental Behavior Checklist 2 (DBC2).

<sup>d</sup> Severity of autism characteristics was determined using standard clinical cut-off scores from the Social Responsiveness Scale, Second Edition (SRS-2).

### 3.3.2 Validity

To examine the internal consistency of the anxiety interview, we examined whether there were differences on three questionnaire-based measures of anxiety between participants with and without parent-reported anxiety. We ran Mann-Whitney U tests comparing scores on the DBC2 Anxiety subscale, the CIASP-ID Anxiety subscale and total scores on the ASC-ASD between groups (**Table 3.7**). We found scores were significantly higher on all three measures in the parent-reported anxiety group (DBC2 Anxiety:  $W = 335.50$ ,  $p < .001$ ,  $p.adj < .001$ ,  $r = 0.51$ ; CIASP-ID Anxiety:  $W = 315.00$ ,  $p < .001$ ,  $p.adj < .001$ ,  $r = 0.53$ ; ASC-ASD Anxiety:  $W = 239.50$ ,  $p < .001$ ,  $p.adj < .001$ ,  $r = 0.65$ ). To further support the internal validity and specificity of the anxiety interview, we examined whether there were differences in the pain and low energy/withdrawal subscales of the CIASP-ID between participants with and without parent-reported anxiety. We found no differences in scores on these subscales between groups (CIASP-ID Pain:  $W = 641.50$ ,  $p = .79$ ,  $p.adj = .79$ ,  $r = 0.06$ ; CIASP-ID Low energy/withdrawal:  $W = 677.00$ ,  $p = .79$ ,  $p.adj = .79$ ,  $r = 0.04$ ), suggesting that the interview is able to distinguish participants with anxiety from participants with other potential causes of distress that exhibit symptom-symptom overlap with anxiety in individuals with ID (Mingins et al., 2024).

**Table 3.7** Scores on questionnaire-based measures of anxiety for participants with and without parent-reported anxiety.

|                                    | Parent-reported anxiety on interview Section A |       |  |                 |       |            |
|------------------------------------|------------------------------------------------|-------|--|-----------------|-------|------------|
|                                    | Yes ( $n = 39$ )                               |       |  | No ( $n = 36$ ) |       |            |
|                                    | $M (SD)$                                       | Range |  | $M (SD)$        | Range |            |
| DBC2 Anxiety                       | 57.47 (11.28)                                  | 37-86 |  | 47.86 (8.44)    | 37-71 | $p < .001$ |
| CIASP-ID Anxiety                   | 43.92 (15.81)                                  | 17-84 |  | 30.09 (11.37)   | 14-61 | $p < .001$ |
| ASC-ASD Anxiety                    | 12.33 (8.43)                                   | 0-35  |  | 4.03 (3.93)     | 0-15  | $p < .001$ |
| CIASP-ID Pain                      | 17.23 (7.35)                                   | 9-45  |  | 16.94 (7.91)    | 9-43  | $p = .66$  |
| CIASP-ID Low energy/<br>withdrawal | 11.49 (6.04)                                   | 6-33  |  | 11.06 (4.74)    | 6-21  | $p = .79$  |

<sup>a</sup> Benjamini-Hochberg FDR correction for multiple comparisons.

### 3.3.3 Presenting Issue

#### 3.3.3.1 General Characteristics of Anxiety and Negative Emotions

When exploring anxiety in participants with parent-reported anxiety, we found that the majority had anxiety triggered by specific events ( $n = 37$ ), whilst the remaining two participants were reported to have a more generalised type of anxiety. For these two cases, symptoms occurred at a constant level, rather than in bursts. Amongst participants with parent-reported anxiety, anxiety was reported to be the most problematic negative emotion for only 18 participants. Parents also reported anger/frustration, BtC, low self-esteem, and hyperactivity/impulsivity to be the most problematic negative emotion.

### 3.3.3.2 Anxiety-related Behaviours

We found parents reported a wide range of anxiety-linked behaviours (see **Figure 3.3**). Across the combined sample (i.e., all genetic diagnosis groups), we found changes in movements were the most commonly reported signs of anxiety (38 participants were reported to have at least one change in movement), whereas fewer participants had at least one reported communication ( $n = 36$ ), facial ( $n = 28$ ), or physiological change ( $n = 21$ ). Of the 36 pre-specified codes, crying ( $n = 22$ ) and muscle tension ( $n = 19$ ) were the most commonly reported anxiety-linked behaviours. Other examples given by parents not captured by the 36 pre-specified codes included looking worried or scared, clinging to parent, bruxism (teeth grinding), repetitive questioning, and whining/complaining sounds.

Commonly reported signs within each genetic diagnosis group were repetitive speech and talking to others in *DDX3X*-related disorder, palpitations and difficulty breathing in *CASK*-related disorder, and aggression and blushing in the ID-other group.

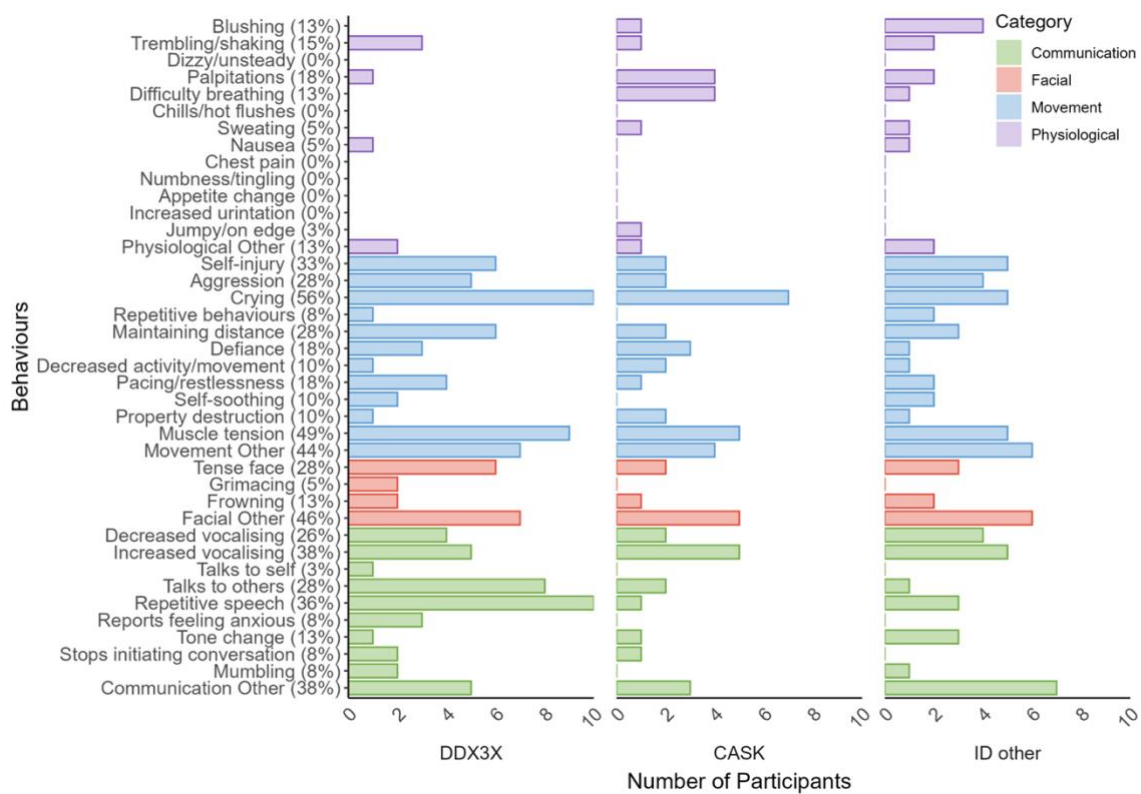


**Figure 3.3** Anxiety-related behaviours for each genetic diagnosis group. Percentages represent the proportion of the combined sample that were reported to display each anxiety-linked behaviour.

### 3.3.3.3 Frequency, Severity and Impact

Parents of children with anxiety triggered by specific events (i.e., parents who completed section B) were asked to describe a recent example of when their child was anxious, and rate how frequently this sort of event occurred. Across genetic diagnosis groups, we found anxiety was reported to be

somewhat frequent and typically occurred at least once a week (see **Table 3.8**). All parents were asked to rate the severity of anxiety, as well as the impact on both the individual and their family (see **Table 3.8**). Overall, we found anxiety was reported to be of moderate severity, with symptoms being noticeable to others, distressing and taking time to overcome. When asked about the impact of anxiety on wellbeing, we found most parents believed anxiety had a mild-moderate impact on their child and a mild impact on the family. However, for 11 participants (28.21%) parents rated anxiety to severely impact their family.

The frequency of anxious episodes did not seem to differ between genetic diagnosis groups. However, in children with *DDX3X*-related disorder, anxiety was more likely to be rated as mild, whereas severe symptoms were more commonly reported in the ID-other group. Moreover, for participants in the *CASK*-related disorder and ID-other groups, we found parents were more likely to rate the impact of anxiety on their family as severe, compared to the impact on their child.

**Table 3.8** Frequency, Severity and Impact of Anxiety

|                              | Number of Participants, <i>n</i> (%) |             |            |             |
|------------------------------|--------------------------------------|-------------|------------|-------------|
|                              | <i>DDX3X</i>                         | <i>CASK</i> | ID-other   | All         |
| <i>Frequency<sup>a</sup></i> |                                      |             |            |             |
| Never/less than once a month | -                                    | -           | 1 (10.00%) | 1 (2.7%)    |
| At least once a month        | 6 (31.58%)                           | 3 (37.50%)  | -          | 9 (24.32%)  |
| At least once a week         | 8 (42.11%)                           | 4 (50.00%)  | 7 (70.00%) | 19 (51.35%) |
| At least once a day          | 4 (21.05%)                           | 1 (12.50%)  | 1 (10.00%) | 6 (16.22%)  |
| Unclear                      | 1 (5.26%)                            | -           | 1 (10.00%) | 2 (5.41%)   |
| <i>Severity</i>              |                                      |             |            |             |
| Mild                         | 10 (52.63%)                          | 2 (22.22%)  | 1 (9.09%)  | 13 (33.33%) |
| Moderate                     | 8 (42.11%)                           | 5 (55.56%)  | 3 (27.27%) | 16 (41.03%) |
| Severe                       | 1 (5.26%)                            | 2 (22.22%)  | 6 (54.60%) | 9 (23.10%)  |
| Unclear                      | -                                    | -           | 1 (9.09%)  | 1 (2.56%)   |
| <i>Impact on Child</i>       |                                      |             |            |             |
| No Impact                    | 6 (31.58%)                           | 1 (11.11%)  | 1 (9.09%)  | 8 (20.51%)  |
| Mild                         | 8 (42.11%)                           | 2 (22.22%)  | 3 (27.27%) | 13 (33.33%) |
| Moderate                     | 4 (21.05%)                           | 5 (55.56%)  | 4 (36.36%) | 13 (33.33%) |
| Severe                       | 1 (5.26%)                            | 1 (11.11%)  | 2 (18.18%) | 4 (10.26%)  |
| Unclear                      | -                                    | -           | 1 (9.09%)  | 1 (2.56%)   |
| <i>Impact on Family</i>      |                                      |             |            |             |
| No Impact                    | 2 (10.53%)                           | 1 (11.11%)  | 1 (9.09%)  | 4 (10.26%)  |
| Mild                         | 11 (57.99%)                          | 3 (33.33%)  | 2 (18.18%) | 16 (41.03%) |
| Moderate                     | 3 (15.79%)                           | 2 (22.22%)  | 3 (27.27%) | 8 (20.51%)  |
| Severe                       | 3 (15.79%)                           | 3 (33.33%)  | 5 (45.45%) | 11 (28.21%) |

<sup>a</sup> Data is not available for 2 participants (*CASK*-related disorder, *n* = 1; ID-other, *n* = 1) who were reported to have a more generalised type of anxiety and whose parents were not asked about frequency of anxiety provoking events (i.e., parents who completed section C of the interview).

### 3.3.4 Predisposing Factors

We also explored possible factors predisposing anxiety in children with rare ID-associated conditions, such as a mood disorder or family history of anxiety. Co-occurring depressive symptomology and low mood was reported by six parents (*DDX3X*-related disorder,  $n = 1$ ; *CASK*-related disorder,  $n = 3$ ; ID-other,  $n = 2$ ). Anxiety characteristics and depressive symptomology were linked for some children ( $n = 3$ ). For example, one parent described how their child's low mood made their anxiety worse, whereas another explained how experiencing lots of anxiety-provoking situations can cause their child to experience low mood. In terms of developmental onset, depressive symptomology and low mood was reported to emerge after anxiety characteristics in the majority of children ( $n = 4$ ), but one parent described low mood emerging at an early age, whilst another noticed these behaviours emerging at around the same time.

To explore whether children have a family history of anxiety, parents were asked '*Does anyone else close to (X) share the same or similar emotions?*'. Due to inconsistent reporting of relatives (i.e., parent vs. mother/father, sibling vs. brother/sister), we calculated the number of participants who had at least one first degree relative (i.e., parent or sibling) with anxiety versus no relatives with anxiety. We found approximately half ( $n = 19$ ) were reported to have at least one first degree relative with anxiety (see **Table 3.9**), and parents were the most commonly reported relative across genetic diagnosis groups (13 participants were reported to have at least one parent with anxiety). However, these results should be interpreted with caution as parents also reported relatives with social-emotional-behavioural problems other than anxiety, such as autism and ADHD, sensory sensitivities, and difficulties with anger/frustration. Hence, it was challenging to distinguish whether there was a family history of anxiety.

**Table 3.9** Number of participants with a relative with anxiety per genetic diagnosis group.

|                                              | Number of Participants, $n$ |             |                       |     |
|----------------------------------------------|-----------------------------|-------------|-----------------------|-----|
|                                              | <i>DDX3X</i> <sup>a</sup>   | <i>CASK</i> | ID-other <sup>a</sup> | All |
| At least one 1 <sup>st</sup> degree relative | 8                           | 6           | 5                     | 19  |
| No relatives                                 | 9                           | 3           | 4                     | 16  |

<sup>a</sup> Four participants were reported to have more distant relatives (e.g., a grandparent) with a history of anxiety (*DDX3X*-related disorder,  $n = 2$ ; ID-other,  $n = 2$ ).

### 3.3.5 Precipitating Factors

#### 3.3.5.1 Age of Onset

Anxiety onset was plotted as a bar chart for the combined sample with participants in each genetic diagnosis group indicated by colour (**Figure 3.4**). A general pattern was observed whereby anxiety

onset peaked at 2-years old and 5-years old. Additionally, we found 5 participants were reported as having ‘always’ been anxious by their parent.

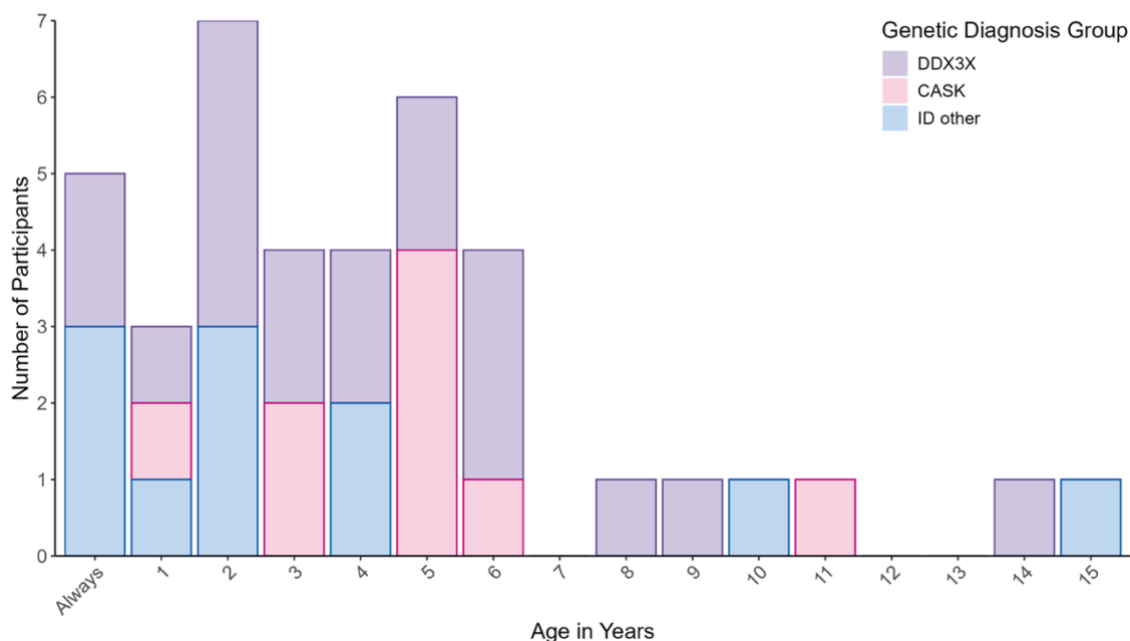


**Figure 3.4** Bar chart of parent-reported age of onset of anxiety for the combined sample.

### 3.3.5.2 Events/triggers at Onset of Anxiety

We found it was challenging for parents to answer whether anything in particular had happened around the onset of their child’s anxiety (i.e., if there were any specific events or triggers). For 18 participants, parents did not report anything specific (*DDX3X*-related disorder,  $n = 9$ ; *CASK*-related disorder,  $n = 2$ ; ID-other,  $n = 7$ ). Of the 12 pre-specified codes, difficulties with school routines ( $n = 1$ ), difficulties with school routines and transitions ( $n = 4$ ), friendships/social isolation ( $n = 2$ ), chronic ill health ( $n = 2$ ), any other chronic adversity ( $n = 1$ ) were reported as potential trigger events. Other examples of events preceding anxiety included developments in cognition/communication abilities, the COVID-19 pandemic, increased opportunities for socialisation with age, birth of a younger sibling, and an event linked with a specific phobia or antecedent (e.g., building work at home and medical appointments).

### 3.3.5.3 Antecedents for Anxious Episodes

Except for health worries, we found all of the predefined triggers of anxiety were reported for at least one participant in this study (see **Figure 3.5**). New situations were the most frequently reported antecedent of anxiety across genetic diagnosis groups. Other common triggers included sensory overload in *DDX3X*-related disorder, routine changes in *CASK*-related disorder, and everyday events in the ID-other group.

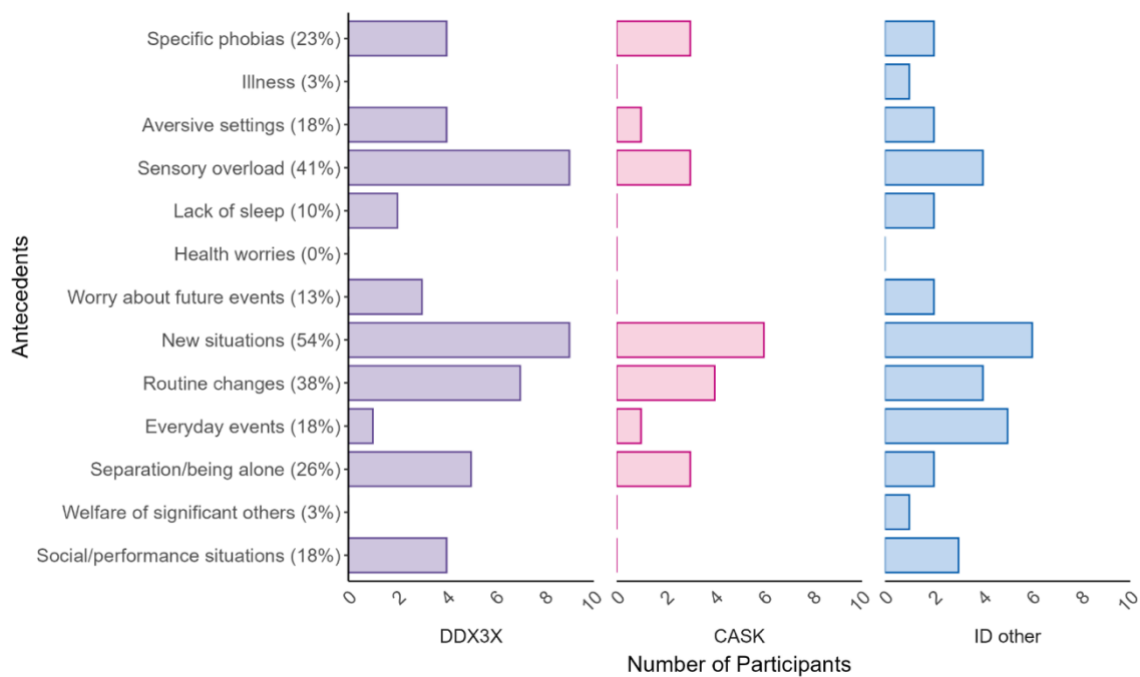


**Figure 3.5** Antecedents of anxious episodes for each genetic diagnosis group. Percentages represent the proportion of the combined sample that were reported to be triggered by each antecedent.

### 3.3.6 Perpetuating and Protective Factors

#### 3.3.6.1 Child Coping Strategies

Approximately half of all participants were reported to engage in some type of behaviour which might reduce their anxiety ( $n = 21$ ). Examples included self-soothing behaviours, such as sucking fingers and rocking body, seeking reassurance or comfort from a parent, and distractions, such as playing with toys or singing. No coping strategy/strategies stood out as being especially common in one genetic diagnosis group.

It was, however, challenging for some parents to distinguish between what might be a behavioural presentation of anxiety versus a coping strategy. Some parents also reported that the coping strategies their child enlisted could make things worse or even become problematic. For example, parents whose child was reported to regulate their emotions with their hands described how their child could be rough when playing with their hands, or even bite them if they were in their mouth.

#### 3.3.6.2 Parent Coping Strategies

Parents also employed several coping strategies to reduce their child's anxiety (**Table 3.10**). The most commonly reported strategy for the combined sample was distraction/redirection ( $n = 26$ ), including humour and/or changing the content of conversation. Other commonly used strategies were giving physical contact ( $n = 23$ , e.g., hugs/cuddles, stroking hair and holding hands) and reassurance ( $n = 17$ , e.g., soothing words, telling child that it's okay, that everything is good, or that they won't encounter

the anxiety trigger). Some of the strategies described could be categorised as preventative, to avoid anxiety occurring (e.g., avoidance and preparation), or reactive, used once an outburst had begun (e.g., distraction/redirection and removal of the stimulus or the child from the situation).

**Table 3.10** Parent coping strategies for management of their child's anxiety

|                                      | Number of Participants, <i>n</i> |             |          |     |
|--------------------------------------|----------------------------------|-------------|----------|-----|
|                                      | <i>DDX3X</i>                     | <i>CASK</i> | ID-other | All |
| Distraction/redirection              | 14                               | 8           | 4        | 26  |
| Physical contact                     | 10                               | 7           | 6        | 23  |
| Reassurance                          | 8                                | 3           | 6        | 17  |
| Communication                        | 7                                | 1           | 3        | 11  |
| Removal of stimulus/from situation   | 5                                | 3           | 3        | 11  |
| Avoidance                            | 5                                | 4           | 1        | 10  |
| Preparation                          | 4                                | 1           | 1        | 6   |
| Approach activities at child's pace  | 1                                | 1           | 2        | 4   |
| Time and space                       | -                                | 1           | 2        | 3   |
| Breathing/mindfulness techniques     | 1                                | -           | 1        | 2   |
| Calming presence                     | 1                                | 1           | -        | 2   |
| No/late disclosure of upcoming event | -                                | -           | 1        | 1   |
| Keep routine                         | -                                | -           | 1        | 1   |
| Positive reinforcement               | -                                | -           | 1        | 1   |

### 3.3.6.3 Control

Overall, we found parents perceived themselves as having a reasonable level of control over the impact of their child's anxiety (*mdn* = 6, *range* = 0-10), but this was highly variable (see **Figure 3.6**).

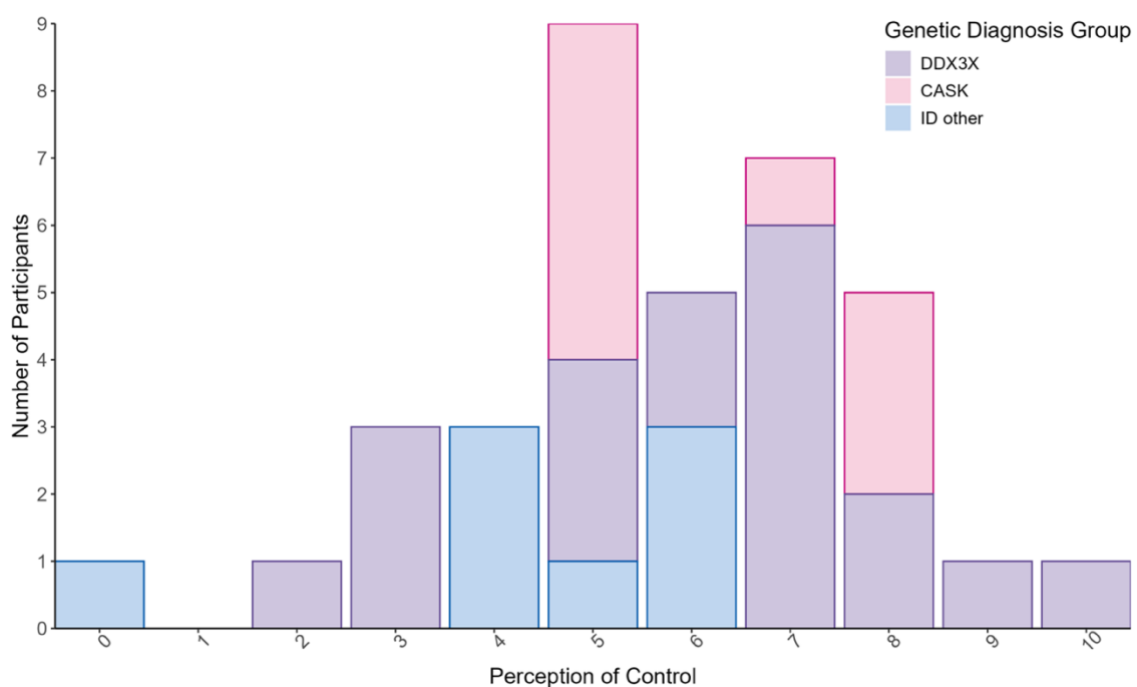


**Figure 3.6** Parent perception of control for the combined sample.

### 3.3.7 Thoughts and Feelings

To examine parents' reflections on their child's thoughts and feelings when anxious, we conducted mixed-methods content analysis on subsections of the interview transcripts. Meaning units, sections of the text that reflected parents' unique understanding of their child's thoughts and feelings, were identified and then coded within two overarching categories – thoughts and feelings. Subcategories of each overarching category were then formed by grouping related codes.

Under the overarching category of feelings, seven subcategories were identified, including fear, anxiety, panic, unravelled, unhappy, anger and excitement (example codes and quotes are provided in **Table 3.11**). The most commonly reported feelings were fear ( $n$  participants = 15) and anxiety ( $n$  participants = 13). These emotions were often mentioned in relation to their child's difficulty managing uncertain/unpredictable events or their level of understanding, as well as specific triggers (e.g., being separated from a parent). We identified notably fewer codes within the overarching category of thoughts (thoughts:  $n$  codes = 19, feelings:  $n$  codes = 47), and these were organised into four subcategories: escape, no thought, negative thoughts about self/ability, and thoughts related to anxious triggers (example codes and quotes are provided in **Table 3.12**).

Although we found most parents were able to reflect on their child's thoughts and feelings, many found this challenging and often framed their responses as a "*guess*" or "*just speculation*". For some parents, this may reflect the inherent difficulty of interpreting their child's internal experiences, particularly if their child is unable to express themselves verbally. Despite these challenges, parents consistently expressed a strong desire to understand their child's thoughts, feelings, and behaviours. See example quotes in **Table 3.13**.

**Table 3.11** Parent reflections on children's feelings when they are anxious.

| Feeling     | n <sup>a</sup> | Example codes                              | Example quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------|----------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anxiety     | 13             | anxious, worry, worried, anxiety           | <p>'No, just anxious, I think.' – (Participant 37)</p> <p>'I think generally it's just a kind of worry.' – (Participant 6)</p> <p>'Yeah. She's feeling anxious about the unknown. Again, it's things that will be out of control, isn't it? She's feeling anxious about what might happen? So...' – (Participant 1)</p> <p>'Or I think she worries, she's going to go do something that is unknown.' – (Participant 13)</p>                                                                                                                                                                                                                                                                                      |
| Fear        | 15             | fear, petrified, scared, terrified         | <p>'Obviously, there's fear there. You know, so he's feeling some kind of fear, you know, but it doesn't have to be anything that's irrational fear or, you know. So, it's not necessarily explainable, but it's obviously something in his head that he finds difficult.' – (Participant 29)</p> <p>'Oh, she's absolutely terrified and she doesn't know what's happening, and she like feels that there's like danger and danger, like something is going to happen to her, I think. Absolutely cannot like, yeah, get – escape it and she feels like trapped and terrified and, yeah, doesn't know what's happening.' – (Participant 28)</p> <p>'I think she's scared of the unknown.' – (Participant 13)</p> |
| Panic       | 3              | panic                                      | <p>'Now, I'm sure his heart rate and everything must - is probably going up. I'm not feeling his heart or whatever, but he's - like it is a bit of a panic thing but... I'm not su - he can't really describe his thoughts or his fears. So, I don't know, I find it hard to answer that question.' – (Participant 29)</p> <p>'Even for things that he- we know he can do. When he's anxious he cannot decide to do it right? If that makes sense. So it becomes really... Yeah, he becomes panicky basically.' – (Participant 34)</p> <p>'there's just this pure panic and terror of not knowing what's coming' – (Participant 26)</p>                                                                          |
| Unravelling | 5              | ungrounded, stress, uneasiness, unravelled | <p>'Unsettled. Uhm... Very ungrounded, it's like she is completely discombobulated. I think it's distress rather than anger. It's, it's just that she's sort of in a little mini crisis.' – (Participant 2)</p> <p>'Well, I guess a bit of stress and you know, like... Uhm... Uneasiness and... Yeah.' – (Participant 11)</p> <p>'It's like the rug has been whipped out from under her feet. You know like, if this hasn't happened, like nearly, like everything is brought into question [laughter]. You know it's like well if this one thing isn't the way you said it was going to be, what can I [laughter], what can I trust in?' – (Participant 36)</p>                                                |

|            |   |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------|---|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Unhappy    | 5 | upset, sad, unhappy | <p>'And it's... that's horrible because she's really upset about something, but she's laughing to try and cover it up. And it was- Oh god that's terrible. Cause I could see the state that she was in.' – (Participant 4)</p> <p>'I don't know. I think maybe a bit sadness [JM]. As when you look at somebody's face and you think oh like I don't- Maybe she's just, I don't know, I don't know what's going on with her.' – (Participant 31)</p> <p>'Yes, yeah, yeah, we know she's not happy [laughter]'. – (Participant 9)</p> |
| Anger      | 2 | anger, angry        | <p>'I mean, certainly, as like - it could be, there's definitely a huge anger or rage or sadness and just like complete overwhelm.' – (Participant 36)</p> <p>'Angry or anger [laughter]? That we're not doing what she wants to do, you know the - or that we took, took her to that place.' – (Participant 17)</p>                                                                                                                                                                                                                 |
| Excitement | 1 | excitement          | <p>'Or excitement. Because sometimes it's a bit, you know like, the, the difference... The limit is very thin between the excitement and the anxiety.' – (Participant 11)</p>                                                                                                                                                                                                                                                                                                                                                        |

<sup>a</sup> Number of participants with at least one code in the subcategory.

**Table 3.12** Parent reflections on children's thoughts when they are anxious.

| Thought                              | <i>n</i> <sup>a</sup> | Example codes                                                              | Example quotes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------|-----------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Escape                               | 5                     | escape, home                                                               | <p>'Yeah. No, she's probably just thinking. Go away, go away, get me out of here [laughter].' – (Participant 6)</p> <p>'I think she's thinking that she just wants to go home probably [laughter].' – (Participant 33)</p> <p>'I think she's not probably thinking much beyond, get that away or get me out of here.' – (Participant 7)</p>                                                                                                                                                                               |
| No thought                           | 6                     | no thought, cannot think, not thinking, blank                              | <p>'I think it's a total chaos in his mind. So, he cannot think of anything at that moment.' – (Participant 34)</p> <p>'I don't know if there's a lot of thought going on. I think it, it feels like a really instinctive, like physical reaction. I don't think there is an awful lot of deep thought or worry about a particular thing happening.' – (Participant 20)</p> <p>'I think everything kind of goes a little bit blank, that like things just don't make sense anymore.' – (Participant 36)</p>               |
| Negative thoughts about self/ability | 3                     | not able, negative self-thoughts, ability to cope                          | <p>'That he cannot, that he's not capable of doing what he's supposed to do. [...] Low self-esteem. I would say.' – (Participant 34)</p> <p>'Negative thoughts. [...] Like why do I have to, why do I have to have all these things wrong with me?' – (Participant 24)</p> <p>'I guess she will think that it's too scary for her, it's - that she will not be able to cope with it, that she will have bad feelings about it, something like that.' – (Participant 19)</p>                                               |
| Thoughts related to anxious trigger  | 4                     | thoughts about separation, questioning uncertainty, thoughts about trigger | <p>'I kind of think that she thinks that we are not coming back, or whoever is gone is not coming back. I'm not really sure why, because she understands other concepts. Why she would not understand that concept, you know.' – (Participant 15)</p> <p>'Why are you doing this? Why can't I be at home? Why can't I be in school? What's going to happen?' – (Participant 25)</p> <p>'Oh... I, yeah, it is tricky, but... I don't know. Probably why is there a hole in the ceiling [laughter]?' – (Participant 25)</p> |

<sup>a</sup> Number of participants with at least one code in the subcategory.

**Table 3.13** Example quotes.

| Quotes expressing difficulty identifying child's thoughts and feelings.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Quotes expressing desire to understand child's thoughts and feelings.                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>'I'm not su- he can't really describe his thoughts or his fear. So, I don't know, I find it hard to answer that question' – (Participant 29)</p> <p>'it's so hard because she can't tell us, I think.' – (Participant 31)</p> <p>'I think. Just maybe, I don't know, I don't know what's going on in his head really, what he's thinking about, and he doesn't tell me much, so he's not a very conversation boy.' – (Participant 37)</p> <p>'Uhm... It's hard cause obviously she can't communicate. [...] I'm guessing there but that's the type of thinking it. Thoughts I think she's having.' – (Participant 9)</p> | <p>'I think it's... I don't know what she's thinking, but I wish I did.' – (Participant 33)</p> <p>'I mean I'd love to know what's going on.' – (Participant 27)</p> <p>'Can I look in your head [referring to her child, laughter]? I'm sometimes wondering myself what she's thinking, if she's thinking, what she's thinking.' – (Participant 22)</p> |

### 3.4 Discussion

Anxiety is highly prevalent in rare ID-associated genetic conditions, including *DDX3X*-related disorder and *CASK*-related disorder, but beyond this our understanding of factors contributing to the emergence and maintenance of anxiety in these conditions is limited. Studying anxiety in rare ID-associated genetic conditions is challenging, both due to differences in symptom presentations and the poor suitability of questionnaire-based measures grounded in diagnostic criteria. Whilst questionnaire-based measures designed to be appropriate for individuals with NDDs capture variability in anxiety-related behaviours, they do not provide information about the antecedents or maintenance of anxiety. Here, the utilisation of interview methodology and a formulation framework provided an information-rich approach to examine factors important for generating models of anxiety in rare ID-associated genetic conditions. Modifications to the prompts outlined in the original interview schedule, also allowed us to obtain sufficient analysable responses to examine children's anxiety-related thoughts and feelings from a parent perspective for the first time. The discussion examines the utility and limitations of the present approach and considers the relevance of the emergent findings for clinical practice and future research.

#### 3.4.1 Comments on Interview Methodology

Using the interview schedule designed by Royston et al. (2021) we obtained information about anxiety in children with rare ID-associated genetic conditions from a parent perspective. This approach was particularly useful for generating data that could be organised within an ABC model from functional

analysis (Yoman, 2008) (see **Figure 3.7**), enabling the formulation of antecedents, anxiety-related behaviours and maintenance factors – a key aim of this study.



**Figure 3.7** Summary of key anxiety characteristics identified across rare ID-associated genetic disorder groups in this study presented within an ABC model.

#### 3.4.1.1 Limitations

However, reliance on parental report introduced several limitations. First, recall bias may have affected the accuracy of data synthesised within the precipitating factor, as parents were required to retrospectively report age-of-onset and possible antecedents. Second, limits in parental knowledge of family mental health history, may have constrained the completeness of data presented in the predisposing factor. Third, consistent with previous research (Simpson et al., 2020; Tarver et al., 2021), some parents struggled to differentiate anxiety-related behaviours from coping strategies or other problem behaviours, such as repetitive movements (e.g., finger twisting or mouthing). Fourth, the majority of parents reported mild impact of anxiety, which may, in part, reflect family avoidance of anxiety inducing situations or adaption over time.

Additionally, it is possible that some of the information collected in the interview may reflect general experiences of negative emotions, rather than be anxiety-specific. In support of this, we found difficulties other than anxiety, such as frustration, anger and BtC, were reported to be the most problematic negative emotion. This aligns with observations that externalising problems are more commonly reported in clinical settings (correspondence with Jane Waite). Nevertheless, some externalising difficulties might occur as downstream manifestations of anxiety. For example, we found that self-injury was reported as an anxiety-related behaviour for one third of participants, and that several parents reported that their child might feel angry or frustrated when they are anxious. These patterns highlight the need for good functional assessments of problem behaviours in children with rare ID-associated genetic conditions.

Despite these limitations, tentative developmental patterns were observed, with reported antecedent events partially aligning with peaks in the overall age-of-onset pattern. For example, several parents

reported symptom onset at around 5-years-old and difficulties with school transitions as a possible antecedent events. Although reported separately, considered together these findings may suggest possible links between developmental changes and the emergence of anxiety. However, these interpretations remain speculative and require further exploration in prospective longitudinal studies.

#### *3.4.1.2 Strengths*

The interview demonstrated several methodological strengths. We found the interview had good internal validity, distinguishing participants with and without parent-reported anxiety on questionnaire-based anxiety scales, but not on measures of depression and pain. This indicates specificity for anxiety, as opposed to overlapping problem behaviours that have been reported in ID populations (see Mingins et al., 2024). We also found that the interview had good inter-rater reliability, suggesting this method can be used to consistently characterise anxiety in rare ID-associated genetic conditions, irrespective of assessor. However, coding relied on researcher interpretation because the coding scheme lacked operationalised definitions of anxiety-related behaviours, which may limit comparisons across studies. Future researchers should develop a comprehensive codebook and consider adding additional codes for anxiety-related behaviours, such as ‘looking worried/scared’, that were consistently reported in this and other studies (e.g., Edwards et al., 2023; Royston et al., 2021).

Overall, this study demonstrates both the strengths and limitations of parent-report interviews for exploring anxiety in rare ID-associated genetic conditions. While valuable for generating rich, structured information about antecedents, behaviours, and anxiety maintenance, parent-report data are affected by recall bias, knowledge constraints, difficulty distinguishing behaviours, and potential underreporting of impact. These considerations underscore the need for multi-informant approaches, functional assessments, and prospective longitudinal studies to more accurately characterise anxiety in children with rare ID-associated genetic conditions.

#### **3.4.2 Antecedents of Anxiety**

Unpredictability and uncertainty are inherent features of the most common anxiety triggers reported in the current study (i.e., new situations, sensory overload and routine changes), consistent with findings from previous interview-based studies of individuals with rare genetic syndromes and autistic individuals who speak few or no words (Edwards et al., 2023; Mingins et al., 2024; Royston et al., 2021), as well as research identifying ‘atypical’ anxiety in autistic individuals without ID (Kerns et al., 2014). Challenges coping with or responding negatively to unpredictable and uncertain situations at a cognitive, emotional or behavioural level (known as intolerance of uncertainty, IU, Dugas et al., 1998) has been identified as a key transdiagnostic mechanism implicated in psychopathology (Carleton et al.,

2012; McEvoy et al., 2019) that is particularly relevant to the emergence and maintenance of generalised anxiety disorder (Dugas & Robichaud, 2007).

IU has also been proposed as a mechanism underlying anxiety in autistic individuals (e.g., Boulter et al., 2014; Rodgers et al., 2017). In support of this, several meta-analyses have found a strong positive association between IU and anxiety in typically developing and autistic individuals (Bird et al., 2024; Jenkinson et al., 2020; Osmanağaoğlu et al., 2018), and interventions targeting IU are also successful at reducing anxiety in these populations (e.g., Cognitive Behavioural Therapy targeting Intolerance of Uncertainty (CBT-IU, Hebert & Dugas, 2019; Wahlund et al., 2020) and Coping with uncertainty in everyday situations (CUES, Rodgers et al., 2023)). Moreover, recent studies have found that IU is a direct predictor of anxiety in several rare genetic syndromes, as well as a mediator of the relationship between autism-related characteristics and anxiety in this population (Edwards, 2022; V. Perry, 2019; K. Smith et al., 2025; South et al., 2021; Uljarević et al., 2018). Hence, IU might be a possible mechanism underlying anxiety in rare ID-associated genetic conditions. Future studies are required to further examine IU as a predictor of anxiety in rare ID-associated genetic conditions, whilst also considering how cognitive and communication abilities might interact with IU by impacting an individual's understanding of their changing environment.

### **3.4.3 Behaviours Associated with Anxiety**

Similar anxiety-related behaviours were observed across genetic diagnosis groups, including increases in vocalisations, such as crying and shouting, and BtC, particularly self-injury. This is consistent with interview-based studies in individuals with rare genetic syndromes and autistic individuals who speak few or no words (Edwards et al., 2023; Miggins et al., 2024), who have a similar profile of verbal communication abilities to participants in the current study. However, this is somewhat different to the pattern of anxiety-related behaviours identified in individuals with Williams syndrome who, on average, have relatively preserved communication abilities (e.g., Mervis & John, 2008). In line with this, Royston et al. (2021) found the majority of individuals with Williams syndrome were able to self-report feelings of anxiety. This raises the importance of considering whether verbal communication abilities contribute to the types of anxiety-related behaviours observed in different rare ID-associated genetic conditions.

To date, there is limited empirical literature examining the relationship between verbal communication ability and anxiety in rare ID-associated genetic conditions. However, preliminary evidence suggests that greater verbal communication is associated with increased identification of DSM-5 anxiety

presentations in autistic individuals, and a greater number of reported anxiety triggers in individuals with moderate-profound ID (Edwards, 2022; Kerns et al., 2014). It is therefore possible that verbal communication abilities might bias the recognition of anxiety in rare ID-associated genetic conditions. Clinically, it is important that the presence of anxiety disorders is not undermined by verbal communication abilities. This study provides examples of unusual non-verbal anxiety presentations that are common across several rare ID-associated genetic conditions, and should be considered in clinical practice.

#### **3.4.4 Consequences – Parent Responses to Anxiety**

Parents in our study used a wide range of coping strategies, such as providing distraction, physical contact and reassurance, that are consistent with previously reported parental responses to anxiety in autistic children and young people with or without ID and a rare genetic syndrome (Fynn et al., 2023; Tarver et al., 2021). Although some coping strategies might be useful in alleviating or preventing anxiety in the short-term, they can also contribute to the maintenance of anxiety. Avoidance and reassurance, for example, have been implicated in several anxiety disorders (Halldorsson & Salkovskis, 2023; Kobori & Salkovskis, 2013). These coping strategies inadvertently maintain anxiety by removing opportunities for exposure to anxiety and distress, thereby preventing an individual from learning they can cope and increasing reliance on others for regulation.

Additionally, the process of parents modifying their behaviour with the goal of alleviating or avoiding distress associated with their child's anxiety is known as family accommodation (FA). FA has been widely documented in paediatric anxiety disorders, specifically obsessive-compulsive disorder, in both typically developing and autistic children. FA has also been associated with more severe anxiety symptoms, poorer treatment outcomes, and greater impact on family wellbeing and quality of life (e.g., Frank et al., 2022; Lebowitz et al., 2013, 2016; Brennan et al., 2025; E. R. Kagan et al., 2017).

There is preliminary evidence that interventions focused on reducing FA can lead to reductions in anxiety disorder symptoms in typically developing and autistic children (e.g., Supportive Parenting for Anxious Childhood Emotions (SPACE, Lebowitz et al., 2020; Rozenblat et al., 2025) and Coping Cat Accommodation Reduction Intervention (CC-ARI, E. R. Kagan et al., 2023)). In particular, interventions that focus on parents, such as SPACE, might be more desirable for anxiety in children with rare ID-associated genetic conditions, given that Cognitive Behavioural Therapy (CBT) or modified-CBT might be inappropriate due to the dependence on metacognitive abilities and abstract thinking, skills that maybe more difficult for children with rare ID-associated genetic conditions.

### **3.4.5 Conclusions**

In summary, adopting interview methodology and a formulation framework is a utile approach to generate reliable and valid information about anxiety in children with rare ID-associated genetic conditions. The descriptions of anxiety-related triggers and behaviours synthesised in this study could be used in clinical practice to recognise the different ways anxiety can manifest in children with rare ID-associated genetic conditions. This would be particularly useful for individuals with limited verbal communication abilities, where previously these difficulties may have been a barrier to anxiety diagnoses. Alongside this, similarities in the patterns of antecedents and coping strategies can provide insights into the possible mechanisms involved in the emergence and maintenance of anxiety in rare ID-associated conditions that can be investigated in future research, as well as used as a guide for possible intervention and management strategies.

# Chapter 4 | Temperament-based Self-Regulation and Anxiety in Rare ID-associated Genetic Conditions

## 4.1 Introduction

Anxiety is the most prevalent mental health disorder in children and adolescents, affecting approximately 6.5% of youth worldwide (Polanczyk et al., 2015). It is associated with impaired functioning, lower quality of life and increased risk for other mental health difficulties, if untreated (Essau et al., 2014; Pine et al., 1998; Woodward & Fergusson, 2001). Anxiety is even more common among individuals with intellectual disability (ID), particularly those with rare genetic conditions (Edwards et al., 2022; Groves et al., 2022).

Despite this increased risk, little is known about the mechanisms that contribute to anxiety in individuals with rare ID-associated genetic conditions. Most research in this area has focused on the genetic and clinical characteristics of these populations. However, the psychological or developmental processes that occur in these conditions are rarely investigated, with the exception of a few particularly well-studied genetic syndromes, such as Williams syndrome, Down syndrome and Fragile X syndrome (Burack et al., 2021, 2024; Cicchetti & Beeghly, 1990; Johnson et al., 2024; Karmiloff-Smith, 1998). As a result, investigating and utilising frameworks from developmental psychology and psychopathology may represent a unique opportunity to understand the heightened prevalence of anxiety in individuals with rare ID-associated genetic conditions.

Self-regulation is a construct from developmental psychopathology that is considered to play a critical role in the emergence of mental health disorders such as anxiety (Kostyrka-Allchorne et al., 2020; Nigg, 2017; Robson et al., 2020; Rothbart, 2011). It is broadly defined as the ability to dynamically modulate emotion, cognition and behaviour in a flexible, goal-oriented manner (Nigg, 2017). Anxiety disorders are known to be associated with difficulties in physiological regulation, such as heightened autonomic arousal (Chalmers et al., 2014; Cheng et al., 2022; B. H. Friedman, 2007) and attentional control, including threat-related attentional bias (Bar-Haim et al., 2007; Dudeney et al., 2015). Importantly, deficits in early self-regulation consistently predict anxiety symptoms in later childhood and adolescence (e.g., Eisenberg et al., 2009; Muris et al., 2008). Therefore, self-regulation serves not only as a concurrent marker but also as a developmental risk factor for the emergence of anxiety disorders in the general population, warranting investigation in individuals with rare ID-associated genetic conditions.

However, studying self-regulation and its links to anxiety is challenging because self-regulation is a complex, internal process that cannot be directly observed (Nigg, 2017). Consequently, multiple fields have attempted to operationalise self-regulation, each with its own terminology and measurement tools. Prominent frameworks include executive function (EF)-based models from cognitive neuroscience, which focus on higher-order cognitive processes, and temperament-based models from developmental psychology, which emphasise emotional and behavioural responses (Gagne, 2017; Zhou et al., 2012). Although integrative accounts have been proposed (e.g., Bailey & Jones, 2019; Gagne, 2017; Gagne et al., 2021; Nigg, 2017; Zhou et al., 2012), a unified framework is still lacking. As a result, researchers must select an approach appropriate to their research question(s) and study population.

EF-based models describe a set of higher-order cognitive processes that enable deliberate, goal-directed control of thoughts and actions (Carlson, 2005; Carlson et al., 2013). Core EF skills include inhibition, updating/working memory, and shifting/cognitive flexibility (Miyake et al., 2000; Miyake & Friedman, 2012). EF is typically assessed via structured, often computerised tasks. While these tasks can provide precise information about specific cognitive difficulties and their underlying neural systems, they have important limitations. First, they are highly demanding, requiring language comprehension and sustained attention, which may constrain performance in young children with rare ID-associated genetic conditions and underestimate their self-regulatory capacity. Second, EF tasks are conducted in artificial settings and may not capture regulation as it occurs in emotionally salient, everyday contexts, limiting their ecological validity for understanding real-world self-regulation.

In contrast, temperament-based models describe early-emerging individual differences in reactivity and regulation of emotion, affect and attention (Rothbart & Bates, 1998; Rothbart & Derryberry, 1981). These regulatory tendencies can be measured in infancy, before the onset of language, and remain relatively stable across development (Bornstein et al., 2015; Kopala-Sibley et al., 2018), making them accessible even for children who are developmentally delayed. Temperament is also typically assessed using parent-report questionnaires or structured observations, capturing how children manage attention and behaviour in everyday, emotionally meaningful contexts, rather than relying on structured cognitive tasks. Importantly, temperament traits have been linked to anxiety in children with and without neurodevelopmental disorders (Kostyrka-Allchorne et al., 2020). Therefore, temperament-based models offer a practical and valid framework for examining self-regulation and its links to anxiety in children with rare ID-associated genetic conditions.

In this chapter, we will discuss the opportunities and challenges of using a temperament framework to examine the links between early self-regulation and anxiety in rare ID-associated genetic conditions. In Part A, we review the theoretical and methodological background on this topic and then synthesise existing literature in rare genetic syndromes to address two specific questions: (1) is temperament-based self-regulation atypical in rare ID-associated genetic conditions? and (2) does temperament-based self-regulation predict anxiety in rare ID-associated genetic conditions? In Part B, we present new data examining the links between temperament-based self-regulation (effortful control), reactive temperament traits (negative affect) and anxiety in children with rare ID-associated genetic conditions. This data is used to test two specific predictions: (1) poorer self-regulation predicts greater anxiety symptoms, and (2) higher reactivity predicts greater anxiety symptoms. The chapter concludes with a short, integrated summary and discussion of future directions.

## **4.2 Part A – Theoretical Review and Evidence Synthesis**

### **4.2.1 Temperament – A Framework for Studying Self-regulation in Early Development**

Temperament has a long-standing history in developmental psychology. Though its conception and measurement have varied overtime, it is commonly understood to mean biologically-based individual differences in emotion, attention and behaviour (Rothbart & Bates, 1998, 2006; Rothbart & Derryberry, 1981). While several models of temperament exist (reviewed in Fu & Pérez-Edgar, 2015; Goldsmith et al., 1987; Shiner et al., 2012), the most comprehensive and influential theory of temperament is Rothbart and colleagues' psychobiological model (Rothbart & Bates, 1998; Rothbart & Derryberry, 1981).

In Rothbart's model, temperament is defined along two broad dimensions of reactivity and regulation, which are themselves composed three high order domains – negative affect, surgency and effortful control – that reflect more specific affective, motor and cognitive processes (see **Figure 4.1**).

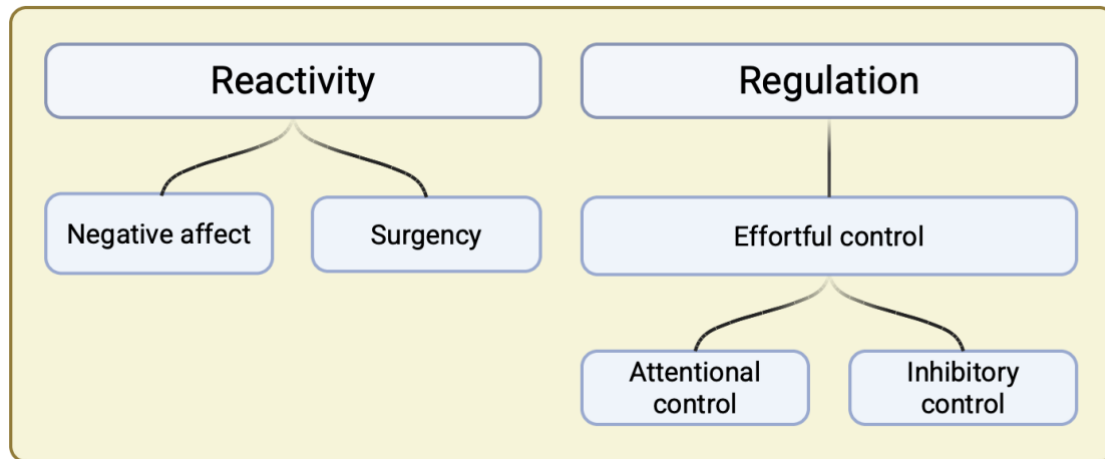


**Figure 4.1** The hierarchical organisation of temperament according to Rothbart and colleagues. In this model, temperament is composed of two broad dimensions: reactivity and regulation. Reactive traits (i.e., negative affect and surgency) reflect the intensity and quality of responses to internal and external stimuli. Negative affect refers to an individual's tendency to experience negative emotions, such as fear, sadness and discomfort; surgency encompasses high activity levels, sociability and pleasure. Regulatory traits refer to the modulation of reactive tendencies through effortful control, a construct involving executive processes, such as attentional control and inhibitory control. Figure created in BioRender (<https://BioRender.com>).

#### 4.2.1.1 Temperament-based Self-regulation (Effortful Control) and Anxiety

Here, we focus on effortful control, the primary temperament domain relevant to self-regulation (Rueda et al. 2004). Effortful control is defined as "the ability to inhibit a dominant response to perform a subdominant response" (Rothbart & Bates, 1998, p. 137) and "the efficiency of executive attention – including the ability to inhibit a dominant response and/or to activate a subdominant response, to plan, and to detect errors" (Rothbart & Bates, 2006, p. 129). It encompasses the ability to voluntarily control attention (i.e., attentional control via focusing and shifting) and to flexibly inhibit dominant behaviours (i.e., inhibitory control), allowing us to 'inhibit actions we desire, and activate activities we would prefer not to engage in' (Rothbart, 2004, p. 497).

Effortful control develops over time through the maturation of executive processes and frontal brain regions (e.g., anterior cingulate cortex, anterior insula, basal ganglia and the dorsolateral prefrontal cortex, Rothbart et al., 2007). The ability to orient attention to alternative sensory input is observable in infancy (Rothbart, 1981) and continues to develop throughout early childhood, becoming stable in adolescence (Bornstein et al., 2015; Kopala-Sibley et al., 2018).

Temperament-based self-regulation is hypothesised to have a direct role in the emergence of psychopathology, whereby children high in effortful control are thought to be better able to regulate emotion, cognition and behaviour, making them less vulnerable to psychopathology (e.g., Eisenberg

et al., 2009). In support of this, several cross-sectional studies have shown low effortful control is associated with high internalising symptoms (e.g., mood disorders and anxiety) across diverse populations (e.g., Burrows et al., 2016; De Pauw et al., 2011; Vervoort et al., 2011). Moreover, a recent meta-analysis of longitudinal studies found that poorer temperament-based self-regulation in infancy predicts internalising symptoms in later childhood and adolescence (Kostyrka-Allchorne et al., 2020).

In addition to broad domains of psychology (i.e., internalising symptoms), effortful control may also play a direct role in the development of anxiety, whereby high levels of effortful control mitigate against anxiety by preventing or reducing the distress experienced in aversive or challenging situations. For example, attentional control may reduce biases toward negative or threatening stimuli, while inhibitory control may decrease susceptibility to repetitive negative thinking (e.g., rumination). Cross-sectional studies in diverse populations consistently report that effortful control is negatively associated with anxiety symptoms (e.g., Ersoy et al., 2021; Niditch & Varela, 2018; Raines et al., 2019; Uljarević et al., 2017; Vervoort et al., 2011), and that certain subcomponents of effortful control may exert stronger influences than others (White et al., 2011).

Alongside directly predicting internalising symptoms, effortful control may also moderate the relationship between anxiety and reactive temperament traits, particularly those characterised by heightened negative emotionality (e.g., negative affect and behavioural inhibition) (Lonigan & Phillips, 2001; Muris & Ollendick, 2005). For example, in children with high negative affect, high levels of effortful control might buffer against the emergence of anxiety. Conversely, in children with low levels of negative affect, the association between effortful control and internalising symptoms may be attenuated or non-significant. In support of this, high negative affect in combination with low effortful control has consistently been shown to predict increased risk for internalising difficulties (Gulley et al., 2016; Muris et al., 2007; Oldehinkel et al., 2007). For example, Raines et al. (2023) found a statistically significant interaction between negative emotionality and effortful control in children with diagnosed anxiety, whereby the relationship between negative emotionality and anxiety was weaker in children with higher levels of effortful control. This interaction highlights the critical role of effortful control in shaping how early reactivity influences anxiety risk, in addition to directly predicting vulnerability.

In sum, there is considerable evidence establishing links between effortful control and anxiety in diverse populations (see **Figure 4.2** for schematic). This suggests that effortful control may be an important developmental risk factor for anxiety disorders. However, these associations have not been studied extensively for children with ID-associated genetic conditions, so it remains unclear whether

the same relationships hold in this population, or whether they differ in strength, form or specificity. It is therefore critical to establish whether effortful control develops atypically in children with rare ID-associated genetic, and whether effortful control is linked to anxiety in this population. This work represents important next steps towards understanding mechanisms underlying anxiety in young children with rare ID-associated genetic conditions.

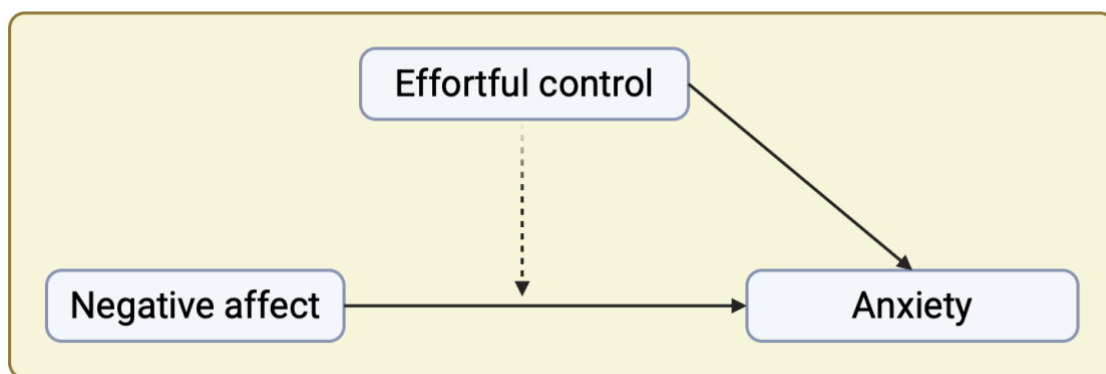


**Figure 4.2** The relationship between temperament-based self-regulation (e.g., effortful control), reactive temperament traits (e.g., negative affect) and anxiety. Solid lines represent direct relationships, while dashed lines represent a moderator. Figure created in BioRender (<https://BioRender.com>).

#### 4.2.1.2 Measuring Temperament-based Self-regulation (Effortful Control)

Research examining temperament-based self-regulation (e.g., effortful control) has employed a range of measurement tools across different levels of analysis (i.e., behaviour, cognition and physiology). Among these, informant-report measures such as Rothbart's temperament questionnaires (see <https://research.bowdoin.edu/rothbart-temperament-questionnaires/>) are most commonly used, particularly in studies investigating the links between effortful control and psychopathology. This widespread use is largely due to their ease of implementation, cost-effectiveness and ability to capture children's typical behaviours across diverse everyday contexts.

However, despite their practicality, these measures have several limitations. Informant-report data can be influenced by social desirability bias, informant characteristics (e.g., personality, mental health) and differences in how items are interpreted. Moreover, Rothbart's questionnaires often include specific items (e.g., 'Is afraid of burglars or the "boogie man."' from the Child Behavior Questionnaire – Very Short Form (CBQ-VSF, Putnam & Rothbart, 2006)) that may not be equally relevant or observable across children of different genders, cultural backgrounds, or socio-economic statuses, raising concerns about validity (Putnam et al., 2024). These measures are also age-specific (e.g., the Infant Behavior Questionnaire (IBQ, Rothbart, 1981) for infants, the Early Childhood Behavior Questionnaire (ECBQ, Putnam et al., 2006) for toddlers, and the Children's Behavior Questionnaire (CBQ, Rothbart et

al., 2001) for children aged 3–7 years old) and although theoretically aligned, differences in item content and structure limits comparability across versions and complicates longitudinal research.

Observational measures, including episodes from the Laboratory Temperament Assessment Battery (Lab-TAB, Gagne et al., 2011; Goldsmith & Rothbart, 1991, 1996; Planalp et al., 2017), have also been used to assess components of effortful control, particularly inhibitory control. Examples include temptation-based delay of gratification tasks, in which children are asked to refrain from touching a visible reward (e.g., the snack and gift delay tasks, Kochanska et al., 1996, 2000). These tasks are conceptually similar to, and overlap with, those developed from an executive function perspective on self-regulation from cognitive neuroscience. For example, in the toy prohibition task, children are instructed not to touch an attractive object, such as a glitter wand (Friedman et al., 2011). Other overlapping examples include the Shapes Task (Kochanska et al., 2000) and the Day-Night Task (Gerstadt et al., 1994), both of which assess inhibitory and attentional control under conflicting stimulus-response conditions. While these methods may offer greater ecological and behavioural specificity than informant-report measures, they are often based on a single trial, increasing vulnerability to measurement noise and limiting variability in individual differences (e.g., in a prohibition task a child can either wait to touch an attractive object or not, Holmboe et al., 2021), which are particularly relevant when examining associations with psychopathology.

Rothbart's psychobiological model emphasises a biological basis of temperament traits and temperament researchers increasingly highlight the importance of including biological markers alongside traditional behavioural measures (J. Kagan, 1994; Rothbart et al., 1994). Respiratory sinus arrhythmia (RSA), the natural fluctuation in heart rate that occurs with breathing, is widely used as a non-invasive index of parasympathetic nervous system (PNS) functioning, specifically reflecting vagal (vagus nerve) influence on the heart. In research, RSA is often examined at rest (baseline RSA) and during tasks that elicit emotional or cognitive challenge (RSA reactivity, i.e., the change in RSA from a baseline state in response to task demands). RSA is thought to support engagement with the environment by facilitating regulation of emotions and behaviour (Porges, 2007).

Typically, high baseline RSA and greater RSA reactivity are associated with greater regulatory control. For example, a recent meta-analysis showed higher baseline RSA was associated with fewer anxiety symptoms in autistic individuals (Yarger et al., 2024). Conversely, there is evidence that low baseline RSA and lower RSA reactivity is associated with increased internalising and externalising behaviours (Beauchaine et al., 2007; Hastings et al., 2008). As such, baseline RSA and RSA reactivity may serve as

important biological markers of self-regulation that complement traditional observational and questionnaire-based measures.

In sum, there are multiple, complementary methods that can be used to examine temperament-based self-regulation (e.g., effortful control). While this review focuses primarily on Rothbart's questionnaire measures due to their widespread use in mental health research in other diverse populations, observational and physiological methods may capture additional information about self-regulation that is highly relevant to understanding its links with anxiety in rare ID-associated genetic conditions.

#### **4.2.2 Is Temperament-based Self-regulation Atypical in Rare ID-associated Genetic Conditions?**

Several studies have examined whether temperament-based self-regulation is atypical in a few relatively well-characterised rare genetic syndromes (e.g., Fragile X syndrome, Williams syndrome and Down syndrome).

Studies that have compared temperament-based self-regulation in these syndromes to other groups using Rothbart's temperament questionnaires have reported mixed results (see **Table 4.1**). For example, in Fragile X syndrome (FXS), two initial studies found effortful control to be significantly lower in preschool and primary school aged males with FXS compared to typically developing males (Low Kapalu & Gartstein, 2016; Robinson et al., 2018). In contrast, a more recent study found no difference in regulatory capacity between infants with FXS, the FXS pre-mutation (FXSpm) and typically developing infants (Tonnsen et al., 2019). A similarly mixed pattern of findings has been reported in individuals with Down syndrome (DS), with two studies documenting elevated regulatory abilities in infancy (Gartstein et al., 2006; Rothbart & Hanson, 1983), two studies finding no significant differences in regulatory ability/effortful control in infancy and childhood (Nygaard et al., 2002; Ohr & Fagen, 1993), and one study identifying poorer effortful control in childhood relative to typically developing peers (Lukowski & Milojevich, 2017).

There are several possible reasons for inconsistent findings using Rothbart's temperament questionnaires. Firstly, it is possible that the three-factor temperament structure identified in the general population (i.e., negative affect, surgency and effortful control, Rothbart et al., 2001) may not hold in rare genetic syndromes, raising questions about construct validity and measurement invariance. For example, Leyfer et al. (2012) found that a four-factor solution was more appropriate in children with Williams syndrome (WS). Within this syndrome group, key cognitive processes relevant to effortful control loaded onto one factor resembling Rothbart and colleagues' model, whereas items

relevant to negative affect were split across two factors. As such, questionnaire-based temperament scales developed in typically developing samples might capture dimensions relevant to self-regulation in WS, such as attention and inhibitory control, but not dimensions relevant to negative affect. Conversely, evidence from children with FXS suggests that the original three-factor structure of the CBQ is largely retained (Roberts et al., 2014), suggesting that the underlying structure of temperament traits in FXS is similar to that observed in the general population.

Secondly, differences in the granularity at which self-regulation is assessed using Rothbart's questionnaire measure might account for differences in study findings. For example, one study of children aged 4–11 years with DS found that, while children with DS did not differ significantly from typically developing children on broad temperament dimensions (e.g., effortful control), they had lower scores on the attentional focusing and inhibitory control subscales (Nygaard et al., 2002). This highlights the importance of considering the level of granularity at which traits are analysed when using standardized questionnaires to examine self-regulation in rare ID-associated genetic conditions.

Thirdly, it is possible that Rothbart's temperament questionnaires might not be sensitive to differences in self-regulation in rare genetic syndromes. A recent study using multi-level assessments of temperament-based self-regulation in FXS found no differences in parent-reported inhibitory control between 12-month-old infants with FXS and age-matched infants without neurodevelopmental or genetic disorders (Black et al., 2021). This study did, however, find infants with FXS show decreased behavioural inhibition and visual attention during an observational measure of self-regulation, as well as a blunted RSA reactivity to a social stressor compared to control infants. These findings suggest that self-regulation is atypical in infants with FXS, but that these differences are not captured by parent report measures. In support of this, several other studies have shown that infants and children with FXS show lower baseline RSA and blunted RSA reactivity to sudden stressors (Hall et al., 2009; Heilman et al., 2011; Hogan et al., 2021; Roberts et al., 2012). However, findings are not entirely consistent. For example, a recent study, which included both males and females with FXS, found no significant difference in baseline RSA between children with FXS, typically developing and autistic children (Wall & Roberts, 2023).

Inconsistent findings have also emerged across studies comparing questionnaire-based and observational measures of temperament-based self-regulation in children with WS and DS. For example, school-aged children with WS and age-matched children with and without neurodevelopmental disabilities do not significantly differ on questionnaire-based measures of

effortful control (Klein-Tasman & Mervis, 2003; Lai et al., 2022). However, Arnold (2022) found that more than 50% of children aged 6-8-years-old with WS fail the gift wrap task, an observational measure of inhibitory control that most typically developing 5-year-olds successfully complete (Kochanska et al., 1996). Similarly, there is some evidence that children with DS perform more poorly on delay of gratification tasks than typically developing children matched both on chronological and mental age (Cuskelly et al., 2003, 2016; Fontana, Usai, Pellizzoni, et al., 2021; for review see, Fontana, Usai, Toffalini, et al., 2021). Performance on these observational tasks should be interpreted with caution, as they often involve complex instructions, are one-off assessments and use simple pass/fail criteria (as discussed in Section 4.2.1.2). This makes it challenging to determine if observed effects reflect true group-based differences in children's ability to inhibit impulses, or instead reflect task demands.

Finally, mixed findings might be the result of atypical developmental trajectories. For example, the discrepancy between findings utilising questionnaire-based measures in FXS may be due to the different age ranges included in the studies – the initial two studies focused on children older than 12-months (Low Kapalu & Gartstein, 2016; Robinson et al., 2018), whereas the later study focused on infants younger than 12-months (Black et al., 2021). This raises the possibility that differences in self-regulation in FXS might only emerge (or be detectable) in childhood. In support of this, several longitudinal studies have shown that toddlers and preschool aged children with FXS do not demonstrate expected gains in effortful control with age, and that the difference in ability compared to typically developing peers magnifies overtime (Hunt et al., 2023; Robinson et al., 2018).

Cross-sectional studies in DS also point to an atypical developmental trajectory, whereby infants with DS demonstrate greater or no differences in self-regulatory abilities in infancy compared to typically developing children, but that this may not persist into early childhood (see **Table 4.1**). However, these differences might also reflect a lack of continuity between early regulatory capacity in infancy, as measured by the IBQ or the Infant Behavior Questionnaire - Revised (IBQ-R, Gartstein & Rothbart, 2003), and later effortful control, as measured by the CBQ, rather than true developmental changes. As such, longitudinal studies accounting for the limitations of questionnaire-based temperament measures are required to understand developmental changes in self-regulation in FXS and DS, as well as other rare ID-associated genetic conditions.

**Table 4.1** Details of study examining temperament-based self-regulation in rare genetic syndromes using Rothbart's temperament questionnaires.

| Study/Reference               | Sample                                                                                                                                                                                          | Design | SR Measure    | Is SR different?                                                                                                                                                                                    |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Fragile X syndrome</i>     |                                                                                                                                                                                                 |        |               |                                                                                                                                                                                                     |
| Low Kapalu & Gartstein (2016) | FXS (N = 26; Age: M = 68.69 months, SD = 17.48 months, Range = 39-93 months; Sex: male = 100%)<br>TD (N = 26; Age: M = 68.23 months, SD = 18.10 months, Range = 37-93 months; Sex: male = 100%) | CS     | CBQ           | Yes – effortful control is lower in boys with FXS than TD controls.                                                                                                                                 |
| Robinson et al. (2018)        | FXS (N = 97; Sex: male = 100%)<br>TD (N = 32; Sex: male = 100%)<br>Age range of sample across all time-points: 1.3 to 9.4 years.                                                                | L      | TBAQ-R<br>CBQ | Yes – effortful control is lower in boys with FXS than TD controls, and this gap magnifies from 1.5 to 5 years old.                                                                                 |
| Tonnsen et al. (2019)         | FXS (N = 24, Sex: male = 50%)<br>FXpm (N = 22, Sex: % male = 36%)<br>TD (N = 24, Sex: male = 60%)<br>Age range of sample across all time-points: 5.26-15.19 months                              | L      | IBQ-R         | No – effortful control does not differ between groups (FXS, FXSpm, TD).                                                                                                                             |
| Black et al. (2021)           | FXS (N = 31; Age: M = 12.41 months, SD = 1.49 months; Sex: male = 68%)<br>TD (N = 41; Age: M = 12.41 months, SD = 0.60 months; Sex: male = 68%)                                                 | CS     | IBQ-R         | Yes - infants with FXS exhibited a blunted RSA response (i.e., reduced RSA reactivity, reflecting poorer physiological regulation) to the stranger in the stranger approach episode of the Lab-TAB. |
| Hunt et al. (2023)            | FXS (N = 79, Sex: male = 100%)<br>TD (N = 49, Sex: male = 100%)<br>Age range of sample across all time-points: 16 to 71 months                                                                  | L      | ECBQ<br>CBQ   | Yes – inhibitory control is lower in boys with FXS, and this difference emerges between 24 and 36-months old.                                                                                       |

| Williams syndrome            |                                                                                                                                                                                                                                                                    |    |     |                                                                                                                                                                                                            |  |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Klein-Tasman & Mervis (2003) | WS (N = 23; Age: M = 9 years, 2 months, Range = 8 years, 1 months–10 years, 11 months; Sex: male = 52%)<br>DD (N = 20; Age: M = 9 years, 6 months, Range = 8 years, 3 months–10 years, 10 months; Sex: male = 60%)                                                 | CS | CBQ | No – there is no difference in effortful control between children with WS and children with other aetiologies of developmental delay.                                                                      |  |
| Lai et al. (2022)            | WS (N = 14; Age: M = 10.91 years, SD = 1.77 years; Sex: male = 29%)<br>ASD (N = 25; Age: M = 10.10 years, SD = 1.85 years; Sex: male = 76%)<br>TD (N = 25; Age: M = 10.14 years, SD = 1.75 years; Sex: male = 48%)                                                 | CS | CBQ | No – there is no difference in inhibitory control between children with WS and autistic children or TD controls.                                                                                           |  |
| Down syndrome                |                                                                                                                                                                                                                                                                    |    |     |                                                                                                                                                                                                            |  |
| Rothbart & Hanson (1983)     | DS (N = 15; Sex: male = 47%)                                                                                                                                                                                                                                       | CS | IBQ | Yes – infants with DS have higher scores on the duration of orienting subscales at 6- and 9-months old compared to IBQ norms.                                                                              |  |
| Ohr & Fagen (1993)           | DS (N = 18; Age: M = 112.3 days, SD = 8.61 days, Range = 94-124 days; Sex: male = 50%)<br>TD (N = 20; Age: M = 111.4 days, SD = 10.13 days, Range = 95-126 days; Sex: male = 70%)                                                                                  | CS | IBQ | No – there is no difference in IBQ subscales between groups.                                                                                                                                               |  |
| Nygaard et al. (2002)        | DS (N = 55; Age: M = 86.1 months, SD = 23.4 months, Range = 4-11 years; Sex: male = 53%)<br>Premature (N = 97; Age: M = 60.2 months, SD = 0.56 months; Sex: male = 51%)<br>TD (N = 91; Age: M = ~74 months, SD = ~6 months, Range = 5.5-7y years; Sex: male = 44%) | CS | CBQ | Mixed – there were no differences in effortful control between groups, but children with DS scored lower attentional focusing compared TD control and lower on inhibitory control compared to both groups. |  |

|                            |                                                                                                                                                                                            |    |       |                                                                                                         |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-------|---------------------------------------------------------------------------------------------------------|
| Gartstein et al.<br>(2006) | DS (N = 17; Age: M = 32.82 weeks, SD = 11.01 weeks, Sex: male = 41%)<br>TD (N = 17; Age: M = 32.71 weeks, SD = 10.77 weeks; Sex: male = 41%)                                               | CS | IBQ-R | Yes – infants with DS exhibited higher levels of orienting/regulating capacity compared to TD controls. |
|                            | DS (N = 19; Age: M = 33.29 months, SD = 1.98 months, Range = 18-53 months; Sex: male = 42%)<br>TD (N = 20; Age: M = 20.65 months, SD = 1.93 months, Range = 15-28 months; Sex: male = 50%) | CS | ECBQ  | Yes - effortful control is lower in children with DS compared to TD controls.                           |

SR – self-regulation, FXS – Fragile X syndrome, TD – Typically developing, FXpm – Fragile X premutation, WS – Williams syndrome, DD – Developmental delay, DS – Down syndrome, nsDD – non-specified developmental delay, CS – Cross-sectional, L- Longitudinal, CBQ - Children's Behavior Questionnaire (Ahadi et al., 1993; Rothbart et al., 2001), TBAQ-R - Toddler Behavior Assessment Questionnaire- Revised (Rothbart et al., 2003), ECBQ - Early Childhood Behavior Questionnaire (Putnam et al., 2006), IBQ-R - Infant Behavior Questionnaire – Revised (Gartstein & Rothbart, 2003), Lab-TAB - Laboratory Temperament Assessment Battery (Goldsmith & Rothbart, 1996), RSA – Respiratory Sinus Arrhythmia

### **4.2.3 Does Temperament-based Self-regulation Predict Anxiety in Rare ID-associated Genetic Conditions?**

Effortful control has been proposed as a key predictor of internalizing symptoms, including anxiety, in typically developing and autistic populations. However, to the best of our knowledge, only two studies have examined whether this relationship generalises to rare ID-associated genetic conditions using Rothbart's temperament questionnaires (see **Table 4.2**), representing an important gap in the literature. Moreover, although these studies have considered both between-group comparisons and within-sample associations, findings are mixed. For example, Leyfer et al., (2012) found that children with WS who had an anxiety disorder scored significantly lower on a factor reflecting effortful control compared to those without an anxiety disorder. In contrast, a more recent study reported that effortful control did not significantly predict anxiety in children with and without FXS (Robinson, 2015).

While findings from questionnaire-based studies are mixed and limited in scope, there is growing research examining the link between physiological markers of temperament-based self-regulation and anxiety in rare ID-associated genetic conditions, particularly in FXS. As described above, cardiac indices, such as RSA, may offer more nuanced insights into temperament-based self-regulation in FXS and other similar conditions. Both baseline and task-related changes in RSA have been used to explore how autonomic dysregulation in infancy might contribute to the emergence of anxiety in FXS. However, despite documented differences in RSA and RSA reactivity in FXS (see Section 4.2.2), RSA is not a significant predictor of concurrent or later anxiety symptoms in toddlers and preschool-aged children with FXS (Hogan et al., 2021; Wall & Roberts, 2023).

There is also evidence exploring the relationship between cognitive skills and anxiety in rare ID-associated genetic conditions. In WS, several studies have consistently shown that difficulties shifting attention, a key component of effortful control, are associated with increased anxiety symptoms and social phobia (Greiner De Magalhães et al., 2022; Ng-Cordell et al., 2018; Pitts et al., 2016; Woodruff-Borden et al., 2010). More specifically, difficulties shifting executive attention has been shown to independently predict anxiety symptoms, over and above other executive processes relevant to self-regulation (Ng-Cordell et al., 2018) and compared to ADHD symptoms (Greiner De Magalhães et al., 2022). Taken together with the findings of Leyfer et al., (2012), these studies provide preliminary evidence that effortful control and its component processes may underlie anxiety in individuals with WS.

Although self-regulation differences have been documented in DS, DS is not typically associated with elevated anxiety, unlike FXS and WS (see Section 1.3.1.1, **Table 1.2**). To date, no known studies have examined the link between temperament-based self-regulation and anxiety in DS. Some evidence suggests that executive functions relevant to effortful control are linked to internalising difficulties in DS (García-Villamizar et al., 2020), though more robust evidence points to associations with externalising behaviours, such as aggression and rule-breaking (Soltani et al., 2025).

**Table 4.2** Details of studies assessing the link between temperament-based self-regulation and anxiety in rare genetic syndromes using Rothbart's questionnaire measures.

| Study/Reference           | Sample                                                                                                                                                                                                                                                  | Design | SR Measure  | Anxiety Measure | Does SR predict anxiety?                                                                                                                                                            |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Fragile X syndrome</i> |                                                                                                                                                                                                                                                         |        |             |                 |                                                                                                                                                                                     |
| Robinson, 2015            | FXS ( $N = 60$ , Age: $M = 4.01$ years*, $SD = 1.07$ years, $Range = 1.5$ - $5.76$ years, Sex: male = 100%)<br>TD ( $N = 34$ , Age: $M = 3.07$ years*, $SD = 0.83$ years, $Range = 1.98$ - $4.50$ years, Sex: male = 100%)<br>*Age at first assessment. | L      | ECBQ<br>CBQ | CBCL            | No – effortful control does not predict anxiety symptoms.                                                                                                                           |
| <i>Williams syndrome</i>  |                                                                                                                                                                                                                                                         |        |             |                 |                                                                                                                                                                                     |
| Leyfer et al., 2012       | WS ( $N = 192$ , Age: $M = 7.28$ years, $SD = 1.75$ years, $Range = 5.01 - 10.94$ years; Sex: male = 45%)                                                                                                                                               | CS     | CBQ         | ADIS-P          | Yes – children with WS and anxiety disorder diagnosis scores significantly lower on a factor reflecting effortful control compared to children with WS without an anxiety disorder. |

SR – self-regulation, FXS – Fragile X syndrome, TD – Typically developing, L – Longitudinal, CS – cross-sectional, ECBQ – Early Childhood Behavior Questionnaire (Putnam et al., 2006), CBQ – Children's Behavior Questionnaire (Ahadi et al., 1993; Rothbart et al., 2001), CBCL – Child Behavior Checklist (Achenbach & Rescorla, 2001), ADIS-P – Anxiety Disorders Interview Schedule for DSM-IV – Parent Version (Silverman & Albano, 1996)

#### 4.2.4 Part A Discussion

In part A of this chapter, we aimed to provide both an overview of temperament-based self-regulation and its association with anxiety in diverse populations, and a review of existing literature in rare ID-associated genetic conditions. In the review, we addressed two specific questions: (1) whether temperament-based self-regulation is atypical in rare ID-associated genetic conditions, and (2) whether it predicts anxiety in these groups. Consulting the literature, we found research addressing these questions is limited and that findings are inconsistent, possibly reflecting methodological limitations and the challenges of adopting a developmental perspective.

Addressing question 1, studies investigating temperament-based self-regulation in rare genetic syndromes have produced conflicting findings, with some studies showing poorer effortful control when compared to controls and others finding no differences. Interpreting these mixed findings is challenging because of several methodological factors. Specifically, participants in these studies are drawn from different age groups (i.e., infant vs. preschool) or across broad age ranges (e.g., 5-10 years old in Leyfer et al., 2012), groups are not consistently matched with controls (e.g., chronological vs. mental age), and studies have utilised different methodological approaches that may not be comparable (e.g., questionnaire vs. observational measures).

Addressing question 2, it is possible that temperament-based self-regulation may not directly predict anxiety in rare ID-associated genetic conditions; rather, it may predict hyperactive and social-communication difficulties. In support of this, cross-sectional and longitudinal studies in FXS have shown that temperament-based self-regulation measured at a behavioural and physiological level predicts both autism spectrum disorder (ASD) and attention deficit hyperactive disorder (ADHD) symptoms (Hogan et al., 2021; Hunt et al., 2023; Roberts et al., 2012; Robinson et al., 2018; Wall & Roberts, 2023). Similar findings have emerged in studies of infant siblings of children with diagnosed autism (Bedford et al., 2019; Ersoy et al., 2021; Garon et al., 2016; Perry et al., 2024; Shephard et al., 2019). Taken together, these findings suggest that temperament-based self-regulation might be a developmental mechanism underlying the emergence of ASD and/or ADHD symptoms across diverse populations. Future research is needed to examine whether these findings extend to rare ID-associated genetic conditions other than FXS.

While effortful control may be associated with ASD and ADHD symptoms in FXS, other temperament traits, such as negative affect and behavioural inhibition, may predict anxiety in this population. Temperament traits marked by heightened sensitivity to negative stimuli are consistent predictors of

anxiety across diverse populations (Burrows et al., 2016; De Pauw et al., 2011; Forbes et al., 2017; Kostyrka-Allchorne et al., 2020). Several studies have found negative affect is positively associated with anxiety, but not autism symptoms in both males and females with FXS (Tonnsen et al., 2013; Wall et al., 2019; Wall & Roberts, 2023). There is some, albeit inconsistent, evidence that general arousal may also predict anxiety in FXS (Hogan et al., 2021; Klusek et al., 2013). These findings suggest that reactive temperament traits may predict anxiety in rare ID-associated conditions, although current evidence is limited to FXS and the role of regulatory capacities in shaping these relationships remains to be investigated.

It also remains unclear whether emerging findings extend across rare ID-associated conditions or are syndrome-specific. As highlighted previously, whilst some studies suggest a relationship between effortful control and anxiety in individuals with WS, this association has not been observed in FXS. Instead, in FXS there is emerging evidence that negative affect is a predictor of anxiety. This divergence highlights the possibility of syndrome-specific pathways to anxiety, whereby temperament traits might differentially contribute to anxiety depending on the genetic and neurodevelopmental context. However, these interpretations remain tentative, as current research is limited by small sample sizes, methodological variability, and a lack of longitudinal and comparative data. Whether these differences reflect true syndrome-specific mechanism or are an artefact of study design and measurement is an important avenue for future research.

#### **4.3 Part B – New Data Examining the Links between Temperament Traits and Anxiety in Rare ID-associated Genetic Conditions**

To date, there are no known studies examining both effortful control and negative affect as predictors of anxiety in rare ID-associated genetic conditions using Rothbart's temperament questionnaires, despite the widespread adoption of these measures in other populations. Here, we used the CBQ-VSF (Putnam & Rothbart, 2006), a parent-report temperament measure for children aged 3-7 years old, to examine the links between temperament traits and anxiety in rare ID-associated genetic conditions. In particular, the current study aims to:

- 1) Examine whether self-regulation and reactivity are predictors of anxiety in rare ID-associated genetic disorders.
  - a. It was hypothesised that poorer self-regulation (i.e., lower effortful control) and greater reactivity (i.e., higher negative affect) will independently predict greater anxiety symptoms.

- 2) Explore whether genetic diagnosis predicts anxiety, and if genetic diagnosis influences the relationship between temperament-based self-regulation, reactivity and anxiety.
  - a. No specific hypotheses were made.

The hypotheses, method and analysis presented in part B of this chapter were pre-registered on the OSF ([https://osf.io/b74eu/?view\\_only=772571c0c45f436dbd74e48796f5613c](https://osf.io/b74eu/?view_only=772571c0c45f436dbd74e48796f5613c)). Any deviations from the pre-registration are highlighted and explained below.

### 4.3.1 Method

#### 4.3.1.1 Participants

Participants aged 3-18 years old with developmental difficulties and a diagnosed pathogenic or likely pathogenic variant in the *DDX3X* or *CASK* gene, or any other gene associated with ID were recruited to take part in the study outlined in Chapter 2. Participants were included in the subsequent analysis if they were aged 3-7 years old and their parent/carer had completed a measure of temperament traits (see below). The final sample consisted of 46 children who are described in **Table 4.3** and **Table 4.4**.

**Table 4.3** Participant characteristics.

| Variable                       | <i>n</i> | <i>M (SD)</i> | Range        |
|--------------------------------|----------|---------------|--------------|
| Age                            | 46       | 4.96 (1.41)   | 2.95 - 7.83  |
| Sex (% female)                 | 46       | 82.61         | -            |
| VABS ABC <sup>a</sup>          | 43       | 60.93 (13.88) | 34 - 94      |
| DBC2 TBPS <sup>b</sup>         | 46       | 52.61 (8.84)  | 37 - 76      |
| SRS-2 Total <sup>c</sup>       | 43       | 73.58 (9.60)  | 55 - 95      |
| Effortful Control <sup>d</sup> | 46       | 4.16 (0.86)   | 2.5 - 6.5    |
| Negative Affect <sup>e</sup>   | 46       | 3.46 (0.9)    | 1.55 - 5.67  |
| Anxiety Composite <sup>f</sup> | 46       | -0.03 (0.98)  | -1.41 - 2.13 |

<sup>a</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).

<sup>b</sup> Total Behavioural Problem Score (TBPS) from the Developmental Behaviour Checklist 2 (DBC2).

<sup>c</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).

<sup>d</sup> Score on the effortful control subscale of the Children's Behavior Questionnaire (CBQ-VSF).

<sup>e</sup> Score on the negative affect subscale of the CBQ-VSF.

<sup>f</sup> See Chapter 2, Section 2.3.3.5 for generation of the Anxiety Composite.

**Table 4.4** Participant characteristics and comparison statistics for the whole sample.

|                        | DDX3X-related disorder |       |           | CASK-related disorder |       |           | ID-other |       |           | p value for comparison |
|------------------------|------------------------|-------|-----------|-----------------------|-------|-----------|----------|-------|-----------|------------------------|
|                        | M                      | SD    | Range     | M                     | SD    | Range     | M        | SD    | Range     |                        |
| Age                    | 4.96                   | 1.37  | 2.95-7.13 | 4.90                  | 1.42  | 3.04-7.46 | 4.99     | 1.51  | 3.10-7.83 | .99                    |
| Sex (% female)         | 100                    |       |           | 100                   |       |           | 55.56    |       |           | < .001                 |
| VABS ABC <sup>a</sup>  | 59.64                  | 13.74 | 34-75     | 54.71                 | 10.11 | 38-75     | 66.56    | 14.84 | 42-94     | .05                    |
| DBC TBPS <sup>b</sup>  | 49.57                  | 7.12  | 38-64     | 52.43                 | 9.87  | 39-74     | 55.1     | 8.90  | 37-76     | .22                    |
| SRS Total <sup>c</sup> | 70.67                  | 8.09  | 57-85     | 72.93                 | 7.86  | 61-84     | 75.88    | 10.75 | 55-93     | .32                    |

<sup>a</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).<sup>b</sup> Total Behavioural Problem Score (TBPS) from the Developmental Behaviour Checklist 2 (DBC2).<sup>c</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).<sup>d</sup> Benjamini-Hochberg FDR correction for multiple testing.

#### 4.3.1.2 Measures

Parents previously provided demographic information (DOB, sex and affected gene) and completed a series of questionnaires as outlined in Chapter 2 (see **Table 2.3**). Scores from these measures were used to generate sample characteristics (see **Table 4.3** and **Table 4.4**), as well as covariates in our planned regression analyses (see Section 4.3.2.2). Consistent with the approach taken in our network analyses in Chapter 2, anxiety composite scores were used as a measure of anxiety in the subsequent analysis.

To assess temperament-based self-regulation and reactivity, we used the effortful control and negative affect subscales from the CBQ-VSF (Putnam & Rothbart, 2006). The effortful control subscale includes items related to attentional control, inhibitory control, perceptual sensitivity and low intensity pleasure (Putnam & Rothbart, 2006), whereas the negative affect subscale includes items related to shyness, fear, anger and sadness (Rothbart et al., 2001). The three-factor structure of the CBQ is valid in children with FXS (Roberts et al., 2014), and the effortful control subscale has previously been used to examine self-regulation in children with rare genetic syndromes (see above), hence it was deemed appropriate for the current study population. The distribution of scores on this measure for each genetic diagnosis group and the combined sample is presented in **Figure 4.3**.

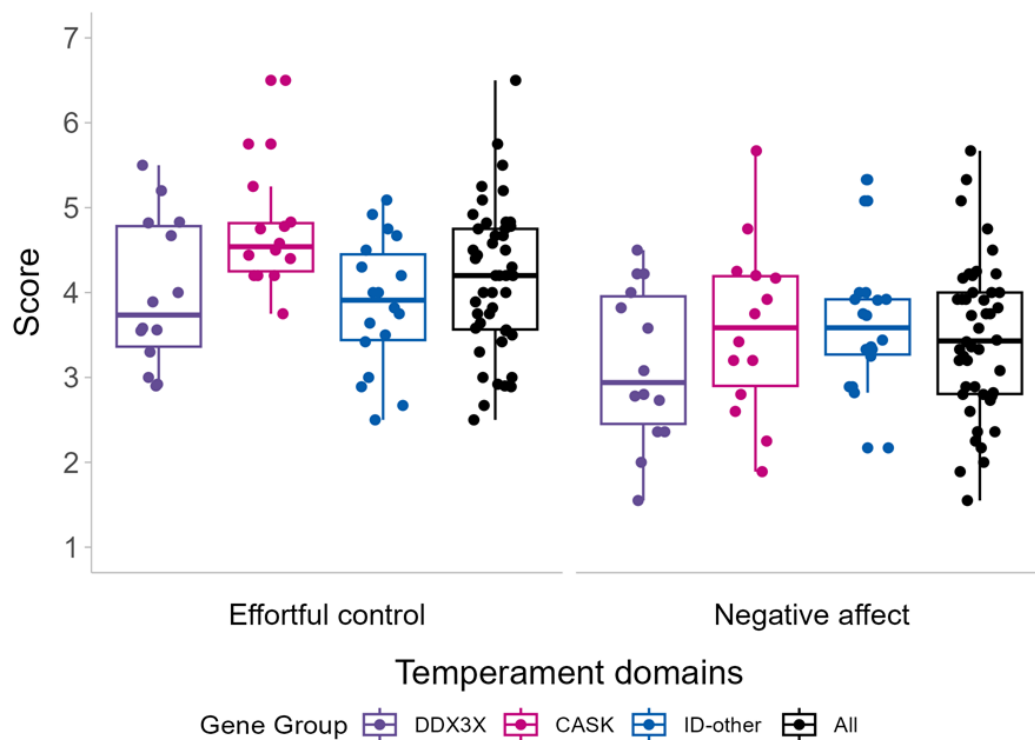


**Figure 4.3** Distribution of effortful control and negative affect scores on the CBQ-VSF for each genetic diagnosis group and the combined sample.

#### 4.3.2.2 Data Analysis

In our pre-registration we proposed a single linear model to examine whether temperament-based self-regulation, reactivity and genetic diagnosis are predictors of anxiety in rare ID-associated conditions, and whether genetic diagnosis influences the relationship between temperament-based self-regulation, reactivity and anxiety. This model also included age, sex and adaptive ability as planned covariates. An a priori power analysis (see [https://osf.io/b74eu/?view\\_only=772571c0c45f436dbd74e48796f5613c](https://osf.io/b74eu/?view_only=772571c0c45f436dbd74e48796f5613c)) revealed that the minimum sample size required to test our model was  $N = 64$ . Our final sample consisted of 46 children, meaning that the study was underpowered for the planned analysis.

To overcome the issue of statistical power, we decided to examine a simpler model. This addressed our primary research question of whether temperament-based self-regulation and reactivity predict anxiety in rare ID-associated genetic conditions. Therefore, for our new model, we regressed anxiety composite scores on CBQ-VSF effortful control and CBQ-VSF negative affect scores. Further statistical justification of only testing this simpler model was: (1) that we did not find a statistical relationship between any of our planned covariates (age, sex, and adaptive abilities) and our dependent variable (anxiety composite score) (see **Figure 4.5**); and (2) that we did not observe any differences in anxiety between genetic groups (see Chapter 2).

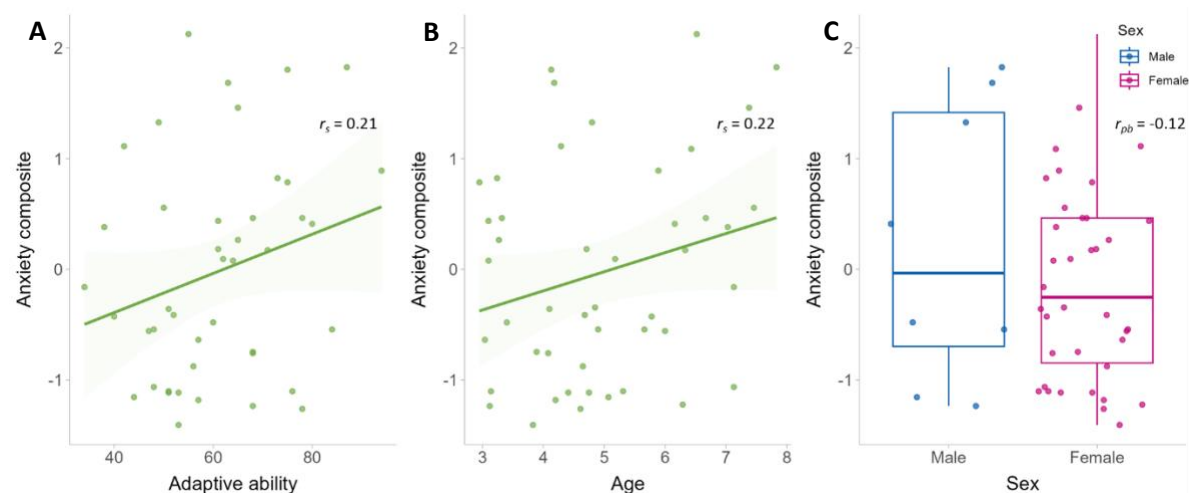


**Figure 4.5** Relationship between the anxiety composite and planned covariates: adaptive ability (A), age (B), sex (C). Green line represents line of best fit and shaded areas indicate 95% CI.

To ensure we had sufficient power to test our new model, we conducted a power analysis using G\*Power based on data from Wall and Roberts (2023). The effect size for the FXS anxiety regression model in Wall & Robert's study was 0.33 (calculated using the following formula  $f^2 = R^2 / (1 - R^2)$ ) and is considered to be large using Cohen's (1988) criteria. With a significance criterion of  $\alpha = 0.05$  and a power of  $= .80$ , the minimum sample needed to detect an effect of this size in a regression model

with two predictors is  $N = 33$ . Thus, the current sample size of 46 is adequate to test this simplified model.

#### 4.3.3 Results

**Table 4.5** displays the results of testing the assumptions of the regression model predicting anxiety composite scores from effortful control and negative affect. The Durbin-Watson test for independence of errors was non-significant, indicating minimal autocorrelation. Variation inflation factors (VIFs) were used to test the assumption of multicollinearity and demonstrated acceptable levels of correlation between the predictor variables. Homoscedasticity was examined using the Breusch-Pagan test, and the non-significant result suggests the residuals are distributed with equal variance for each level of the predictor variables (i.e., heteroscedasticity was not present). Data were normally distributed, as shown by the result of the Shapiro-Wilk test.

**Table 4.5** Assumption testing for regression analyses

| Assumption             | Test                        | Result                      |
|------------------------|-----------------------------|-----------------------------|
| Independence of Errors | Durbin-Watson               | $d = 1.57, p = .14$         |
| Homoscedasticity       | Breusch-Pagan               | $\chi^2(2) = 1.09, p = .58$ |
| Normality of Residuals | Shapiro-Wilk                | $W = .98, p = .54$          |
| Multicollinearity      | Variation Inflation Factors | All VIFs < 10               |

The regression model was first estimated using the full dataset and then rerun excluding outliers. Outliers were defined as observations exceeding two standard deviations above or below the mean. Removing outliers did not change the direction or statistical significance of the predictors but did increase the variance explained ( $R^2$ ) (see **Table 4.6**). Results presented below are based on the full sample to capture the complete range of effects.

**Table 4.6** Full model results for regression with and without outliers included.

|           | Anxiety Composite (with outliers) |           |          |          | Anxiety Composite (without outliers) |           |          |          |
|-----------|-----------------------------------|-----------|----------|----------|--------------------------------------|-----------|----------|----------|
|           | <i>Estimate</i>                   | <i>SE</i> | <i>t</i> | <i>p</i> | <i>Estimate</i>                      | <i>SE</i> | <i>t</i> | <i>p</i> |
| Intercept | -1.46                             | 0.76      | -1.91    | .06      | -1.37                                | 0.66      | -2.08    | .04      |
| EC        | -0.08                             | 0.16      | -0.51    | .62      | -0.19                                | 0.13      | -1.39    | .17      |
| NA        | 0.51                              | 0.15      | 3.39     | <.01     | 0.57                                 | 0.13      | 4.51     | <.001    |
| $R^2$     |                                   |           |          | 0.18     |                                      |           |          | 0.31     |

EC effortful control; NA negative affect

The overall regression model was significant ( $F(2, 43) = 5.76, p < .01, R^2 = 0.18$ ) and accounted for 18% of variance in the anxiety composite score. **Figure 4.6** shows the influence of temperament-based self-regulation and reactivity on anxiety in rare ID-associated genetic conditions. Notably, effortful control was not an independent predictor of anxiety composite scores ( $\beta = -0.08, p = .62$ ). However, greater

negative affect was a significant independent predictor of higher scores on the anxiety composite ( $\beta = 0.51, p < .01$ ). Whilst we were unable to statistically examine the effect of genetic diagnosis on the relationship between temperament-based self-regulation, reactivity and anxiety, visual inspection of the data suggests there is a consistent trend across genetic diagnosis groups.

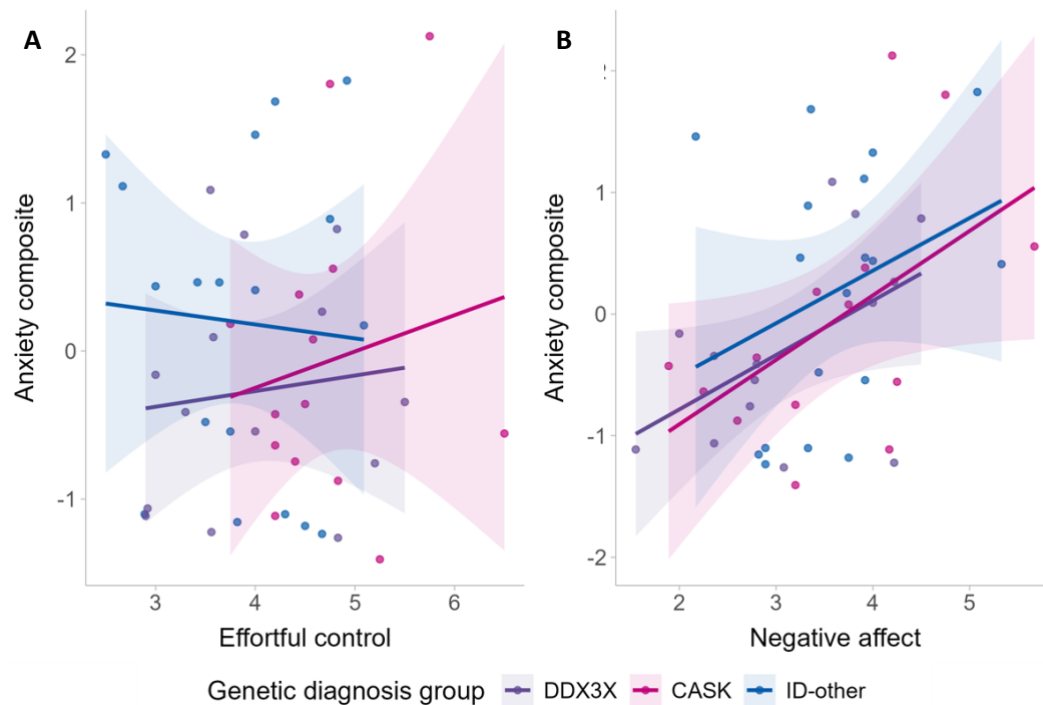


**Figure 4.6** Relationship between anxiety and effortful control (A), and negative affect (B). Data includes outliers. Coloured lines represent line of best fit for each diagnostic group and shaded areas indicate 95% CI.

We also considered that, whilst effortful control may not directly influence anxiety, it could act as an important moderator of the relationship between negative affect and anxiety symptoms. Visualisation of this data suggests that the association between negative affect and anxiety is stronger in individuals with high effortful control, relative to those with low effortful control, based on a median split of the data (Figure 4.7). However, this was not included as a planned analysis in our pre-registration, and we do not have power to statistically examine this relationship, so this finding should be interpreted with caution.

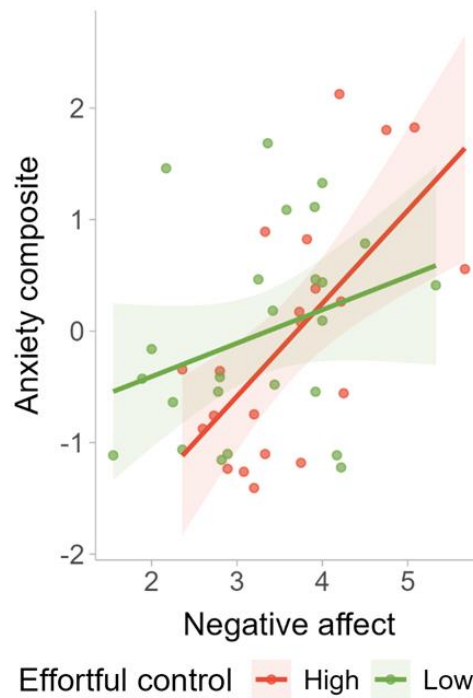


**Figure 4.7** The relationship between negative affect and anxiety composite scores at high and low effortful control based on a median split of the data. Coloured lines represent line of best fit for each level of effortful control and shaded areas indicate 95% CI.

#### 4.3.4 Part B Discussion

Temperament-based self-regulation has been studied as a predictor of anxiety in both the general population and autistic individuals, but it has not been widely considered in the context of rare ID-associated genetic conditions, despite the elevated risk of anxiety in this population. The present study provides the first known investigation of effortful control and negative affect, measured via Rothbart's temperament questionnaires, as predictors of anxiety within a single model. Partially consistent with our hypotheses, we found negative affect, but not effortful control, significantly predicted anxiety, with higher negative affect associated with greater anxiety. Due to a limited sample size and insufficient statistical power, we were unable to formally assess whether these associations were influenced by specific genetic diagnosis. However, visual inspection of the data suggests that the observed trends were broadly consistent across genetic diagnosis groups, indicating that negative affect might be an important predictor of anxiety across rare ID-associated genetic conditions.

The finding that negative affect is a significant predictor of anxiety aligns with existing literature in diverse populations, including children with FXS (Burrows et al., 2016; De Pauw et al., 2011; M. K. Forbes et al., 2017; Kostyrka-Allchorne et al., 2020; Tonnsen et al., 2013; Wall et al., 2019; Wall & Roberts, 2023). However, it is possible that the observed relationship between negative affect and anxiety symptoms is partially confounded by item-level overlap between questionnaire measures. For

example, some items used to examine negative affect might closely resemble early manifestations of anxiety, such as fearfulness, excessive worry and difficulty soothing. In addition, because both constructs are typically assessed using parent-report questionnaires, the observed association may be inflated due to shared method variance. Future research may benefit from adopting more objective measures of emotional reactivity, such as physiological indicators (e.g., heart rate, skin conductance and cortisol) to better probe the relationship between overlapping constructs and reduce potential reporter bias. However, such studies (e.g. Hogan et al., 2021) carry their own limitations and should also be interpreted with caution, as general arousal may be heightened in the context of anxiety, making it difficult to interpret whether increased emotional reactivity reflects an early risk mechanism or an emerging symptom.

Interestingly, while we hypothesised effortful control would directly predict anxiety in rare ID-associated genetic conditions, effortful control was not found to be a significant predictor of anxiety in this study. There are several possible explanations for this. First, effortful control is a multidimensional construct comprised of attentional and inhibitory control processes. It is possible that certain components, rather than effortful control overall, are predictive of anxiety. In support of this, Chetcuti et al. (2023) found a significant negative association between attentional control, but not inhibitory control, and anxiety in autistic young people. Moreover, attentional shifting, but not inhibitory control, is a predictor of anxiety in children and adults with WS (Greiner De Magalhães et al., 2022; Ng-Cordell et al., 2018). Therefore, future studies should investigate the relationship between component processes of effortful control and anxiety in rare ID-associated genetic conditions. This is particularly relevant given the heterogeneity of cognitive profiles across rare genetic syndromes (e.g. Bush & Scott, 2022; Miezah et al., 2021; Pegoraro et al., 2014) and could potentially explain the variability in anxiety risk between some genetic syndrome groups.

Second, our data suggests that effortful control may moderate the relationship between negative affect and anxiety in rare-ID associated genetic conditions. However, the trend observed in this study is the opposite of what is typically reported in the literature. One possible explanation is that the component processes of effortful control may differentially moderate the relationship between negative affect and anxiety (Buzzell et al., 2021; Chetcuti et al., 2023). For example, White et al. (2011) found that among children with high behavioural inhibition (a temperament disposition characterised by heightened vigilance, withdrawal and fear in response to novelty and/or ambiguity, see Kagan et al., 1985), high attentional control was associated with decreased anxiety risk, whereas low inhibitory control increased anxiety risk. This pattern could potentially account for the unexpected trend in our

findings, but our sample included children with a range of negative affect scores, not just those high in negative affect. Going forward, future work should not only investigate whether temperament-based self-regulation moderates the relationship between negative affect and anxiety in rare ID-associated genetic conditions, but also how different subcomponents of effortful control (i.e., attention control and inhibitory control) might differentially affect this relationship.

Finally, effortful control may have a longitudinal impact on the emergence of anxiety that is not apparent in our cross-sectional analyses. In typically developing populations, there is evidence that temperament-based self-regulation in infancy predicts internalising difficulties in early childhood (Kostyrka-Allchorne et al., 2020), and that effortful control in middle childhood predicts anxiety in later life (Muris et al., 2008). However, it remains unclear whether longitudinal effects of effortful control on anxiety are present and detectable at young ages, since most research in typically developing populations has focused on broader internalising symptoms or older children. There is, however, compelling evidence from longitudinal studies of infant siblings of children with an autism diagnosis showing that effortful control measured in infancy or early toddlerhood predicts later anxiety, potentially via its impact on early-emerging negative affect or behavioural inhibition (Ersoy et al., 2021; Smith et al., 2022). These findings underscore the complex links between temperament-based self-regulation, reactivity and anxiety over developmental time and highlight the need for longitudinal studies in rare ID-associated genetic conditions.

Whilst the links between temperament and anxiety in rare-ID associated populations are complex and require further study, it is possible that traits such as effortful control may be more strongly related to other developmental outcomes in these groups. In the general population, there is some evidence that poorer effortful control is strongly linked to externalising difficulties (Eisenberg et al., 2009; Morris et al., 2014; Olson et al., 2005). Moreover, effortful control has recently been linked to autism and ADHD symptoms in infant siblings of autistic children (Ersoy et al., 2021; R. C. Perry et al., 2024) and children with FXS (Hunt et al., 2023; Robinson et al., 2018). These findings suggest that while temperament-based self-regulation might be a useful, measurable construct for understanding early development in rare genetic syndromes, it may be more relevant to neurodevelopmental, rather than mental health outcomes in this population.

#### **4.4 General Discussion**

In this chapter, we explored whether our understanding of anxiety in rare ID-associated genetic conditions could be enhanced by examining constructs from developmental psychology that have been

linked to anxiety in other diverse populations. One such construct is self-regulation, which can be operationalised as effortful control within a temperament framework. Effortful control is particularly relevant to childhood mental health research, as it can be reliably measured in early development, remains relatively stable over time, and has been shown to predict both concurrent and later anxiety in typically developing and autistic populations. Studying effortful control in children with rare ID-associated genetic conditions may therefore offer useful insights into the emergence of anxiety in this population.

However, based on the evidence reviewed in part A, we cannot draw strong conclusions as to (1) whether self-regulation is atypical in rare ID-associated genetic conditions, and (2) if the widely documented links between effortful control and anxiety generalise to this population. Moreover, in our analyses presented in part B, we found that negative affect, but not effortful control, was a significant predictor of anxiety in children with rare ID-associated genetic conditions, and that this pattern is likely consistent across rare genetic diagnosis groups.

Several methodological limitations constrain the interpretation of findings from both parts A and B of this chapter. In part A, limitations arise from the scarcity of studies, particularly those examining the links between effortful control and anxiety in rare ID-associated genetic conditions, as well as variability in study populations and measures. In part B, the empirical analyses are limited by a small sample size, a broad participant age range, and a cross-sectional design. A key concern across both parts is the reliance on questionnaire-based measures which, while cost-effective and easy to administer, may lack sensitivity to detect subtle differences in effortful control in rare ID-associated genetic conditions. There also appears to be a mismatch between how self-regulation is conceptualised and how it is measured (see Chapter 5 for further discussion).

Addressing these methodological challenges is essential for advancing our understanding of self-regulation in children with rare ID-associated genetic conditions. This will enable us to investigate key outstanding questions: for example, do components of effortful control (i.e., attentional and inhibitory control) differentially predict anxiety in this population, and how do they interact with negative affect? Building on this, Chapter 5 explores alternative measurement tools and analytical approaches for studying self-regulation in children with rare ID-associated genetic conditions.

# Chapter 5 | The Feasibility of Play-based Assessments and Wearable Devices to Study Self-Regulation in Young Children with Rare ID-associated Genetic Conditions

## 5.1 Introduction

Self-regulation is an ongoing, dynamic process that unfolds across time and context (Nigg, 2017). However, many of the common assessment tools, including parent-report measures and performance-based laboratory tasks, capture limited snapshots of this complex ability. Parent-report measures typically reflect caregivers' global impressions of a child's regulatory abilities across everyday situations, but lack sensitivity to short-term changes. Laboratory-based tasks (e.g., prohibition tasks and delay of gratification tasks; Friedman et al., 2011; Kochanska et al., 2000) often reduce self-regulation to static, binary outcomes (e.g., whether or not a child touches a prohibited object), rather than capturing how children actively exert self-regulation. As such, these methods are limited in content (i.e., what aspects of self-regulation they measure) and temporality (i.e., when and over what time span self-regulation is measured), and, therefore, may not adequately capture self-regulation in young children. Consequently, these measures may limit our ability assess the relevance of early self-regulation to mental health outcomes, such as anxiety.

### 5.1.1 Traditional Inhibitory Control Measures and Micro-analytic Coding Approaches

One way to assess the dynamic nature of children's self-regulation is through fine-grained, micro-analytic coding of behaviour during traditional play-based laboratory assessments of inhibitory control, such as delay of gratification tasks. These tasks require children to resist an immediate reward in order to receive a larger reward later, and children's performance is typically assessed using binary pass/fail measures or simple behavioural coding schemes.

Unlike these traditional outcome-focused measures, a micro-analytic coding approach may offer more nuanced insights into how children regulate their behaviours in real time. During the wait period of delay tasks, children display a rich variety of behaviours (e.g., fidgeting, self-talk, looking away) that reflect active regulatory strategies used to manage the demands of the task. To capture these moment-to-moment changes, the wait period can be divided into small epochs (e.g., 1- or 5-second intervals) and specific, observable behaviours can be coded as they occur. This approach allows researchers to

understand how self-regulatory strategies unfold over time, and whether they predict task success and other developmental outcomes.

Several studies in typically developing toddlers have demonstrated the value of this approach (Fiske, 2023; Manfra et al., 2014; Mulder et al., 2019). For example, Manfra et al. (2014) showed that the use of specific strategies, such as unintelligible verbalisations and movements that increase the physical distance from the reward, predicted delay success. Building on this, Mulder et al. (2019) found that regulatory strategies evolve across delay tasks, and that children who spent more time withholding visual attention and keeping their hands away from the reward were more likely to succeed, particularly when these behaviours occurred early in the wait period. These studies collectively illustrate the value of micro-analytic coding to enhance our understanding of not only what strategies children use to self-regulate, but how these strategies unfold over time and predict task performance. However, further research is needed to explore the links between dynamic changes in self-regulatory behaviours and longer-term outcomes such as anxiety.

While micro-analytic coding of behaviour during structured, play-based tasks provides rich detail about self-regulatory strategies, this approach has limitations. Delay tasks do not fully capture the complexity of self-regulation as it occurs in real-world contexts. In particular, these tasks are typically experimenter-initiated and highly structured, with the timing and nature of regulatory demands determined by the experimenter (i.e., what the desired object is, when it is presented, and how it is prohibited) (Wass & Jones, 2023). As a result, regulatory demands are artificially isolated into short, well-defined episodes that may not correspond to the kinds of spontaneously emerging, personally salient challenges children encounter in everyday life.

In addition, the behaviours coded during these tasks (e.g., gaze aversion, fidgeting, or self-talk) are generally assumed to reflect self-regulatory processes. However, such behaviours may serve multiple functions. As an example, fidgeting may indicate boredom or restlessness, but also sensory-seeking or self-soothing. The requirement for subjective interpretation of these behaviours may introduce ambiguity and limit the validity of conclusions drawn from these data.

### **5.1.2 Wearable Physiological Measures and Naturalistic Settings**

An alternative approach is to use physiological measures collected in naturalistic settings. This may overcome several of the limitations described above by providing continuous and objective data that capture self-regulatory processes as they unfold in everyday contexts.

Advances in wearable technology have made it possible to collect multimodal physiological (autonomic and movement) data in real time, outside of laboratory environments. This allows researchers to track physiological changes in response to naturally occurring and child-initiated events. A recent study by Wass et al. (2019) demonstrates the utility of wearable physiological measures for studying individual differences in self-regulation in naturalistic settings. In this study, they examined differences in arousal regulation during naturally occurring episodes of negative affect in infants from noisy versus quiet home environments. Day-long recordings of physiological (autonomic and movement) and audio data were collected from infants using wearable sensors in their home environments. Autonomic arousal was assessed using a composite measure that combined heart rate (HR), heart rate variability (HRV) and movement signals (see Wass et al., 2015, 2016). Periods of peak negative affect were identified by manually coding infant vocalisations on a 9-point scale, ranging from 1 ('fussy') to 9 ('happy'). Using this approach, they found that infants from noisier home environments showed a faster decrease in autonomic arousal in the 1–5 minutes following a negative vocalisation, compared to those from quieter homes, suggesting faster physiological recovery (i.e., more effective self-regulation). Consistently, the same infants also showed faster recovery following a stress-inducing laboratory task (the Still-Face Paradigm, Gagne et al., 2011). Taken together, these findings suggest that wearable sensors offer a valid approach to study self-regulation in naturalistic settings, and enables the investigation of factors that may influence early self-regulation, with potential relevance to the emergence psychopathology in later childhood.

### **5.1.3 Current Research in Rare ID-associated Genetic Conditions**

To date, there have been limited attempts to apply these methods to study self-regulation in the context of ID and/or rare genetic conditions. Play-based inhibitory control tasks have been used in several studies of children and adults with rare genetic syndromes, often finding deficits compared to typically developing comparison groups (e.g., Arnold, 2022; Fontana et al., 2021). However, no studies have applied a micro-analytic coding approach to examine self-regulatory strategies during these tasks in this population.

Additionally, whilst physiological measures have also been used to study self-regulation in rare genetic syndromes, typically these studies focus on a changes in a single autonomic measure, such as RSA in response to lab-based stressors (e.g., Black et al., 2021). Other physiological measures, such as wearable actigraph monitors, have contributed to our understanding of gait and sleep difficulties in rare genetic syndromes (Agar et al., 2023; González Barral & Servais, 2025), but have not yet been

applied to the study of self-regulation. Taken together, this suggests that these physiological measures could be informative in this population.

Despite the potential of applying micro-analytic coding to play-based assessments and using wearable physiological devices in naturalistic setting, no research has yet integrated these methods, or applied them to study self-regulation in children with rare ID-associated genetic conditions. Before these approaches can be applied at scale, it is first necessary to evaluate the feasibility of these measurement tools and analysis approaches in this population.

#### **5.1.4 Study Aims**

In this study, we aimed to examine whether we can administer play-based assessments and simultaneously collect physiological data via wearable devices to study self-regulation in young children with rare ID-associated genetic conditions, as well as whether we can apply analysis methods to capture dynamic aspects of self-regulation. To evaluate the feasibility of these methods, the following pilot steps were taken. First, we explored the proportion of children who attempted each play-based assessment, and their performance using traditional pass/fail measures (in order to determine task suitability and whether analysable data can be obtained). Second, we completed micro-analytic coding of children's behaviour during the first 60 seconds of a delay task. Finally, we assessed the practicality of collecting physiological (autonomic and movement) data via wearable devices. We also explored the quality of the autonomic data collected across both structured researcher-led play-based assessments and unstructured naturalistic settings, and whether it may be possible to generate an arousal composite combining different physiological signals.

### **5.2 Method**

#### **5.2.1 Participants**

Participants with rare genetic ID-associated conditions, aged 3-7 years old, based in the UK, and who had consented to take part in the study outlined in Chapter 2 were invited to take part in a home-based testing session. Of the 18 eligible participants, 10 took part. There were several reasons why 8 of the participants did not take part, including no response ( $n = 2$ ), parents declining audio/video recording ( $n = 2$ ), parents having concerns about their child's ability to engage in activities once these had been explained to them ( $n = 2$ ), and being unable to find a convenient day and time for the session ( $n = 2$ ).

#### **5.2.2 Procedure**

Pilot sessions were conducted in participants' homes, typically in the family living room, by two researchers (JM<sup>1</sup> and AMF<sup>2</sup>). All testing sessions were conducted in the morning, with the exception of one testing session which was conducted in the afternoon. Upon arrival, researchers informed the parent(s) about the nature of the play-based assessments and wearable device, and the research equipment was set-up as shown in **Figure 5.1A**. Then, with the assistance of the parent(s), researchers applied the wearable device to the child as depicted in **Figure 5.1B**. The home-based testing session consisted of two-parts: play-based assessments with a researcher and naturalistic recording.

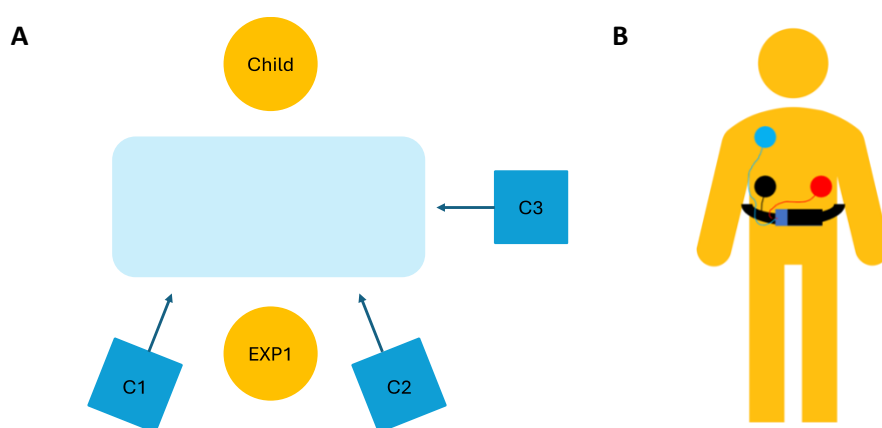


**Figure 5.1** Technical equipment (**A**) and wearable device set-up (**B**). **A** EXP1 – Experimenter 1, C1 – Camera 1, C2 – Camera 2, C3 – Camera 3.

In each pilot session, participants completed several play-based assessments (see **Table 5.1**, and Section 5.2.3) with a researcher whilst wearing a wearable device. At the beginning and end of the play-based assessments there was a 5-minute free play activity, in which the researcher encouraged the child to play with them. The purpose of this was for the child to become familiar with the researcher and to resolve the structured testing session. If a child became distressed or distracted, the activity and/or testing session was terminated at the discretion of the researcher and/or parent(s).

Behaviour during the play-based assessments was recorded with three video cameras (see **Figure 5.1A**). Two Sony ZV1 Cameras were placed either side of the researcher on the other side of the play-table from the child and focused on the child's face and body. A third wide-angle lens camera (Canon Legria Mini X) was positioned at the end of the play-table and provided full view of the child and researchers' bodies. Each of the cameras was connected to a live production switcher (ATEM Mini Extreme ISO), which enabled simultaneous recording from all three cameras. The third camera was

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primarily used for coding children’s behaviour (see Section 5.2.4.2), and the first two cameras functioned as a substitute where the third camera did not fully capture children’s behaviours.

After the structured play-based assessments, participants continued to wear the wearable device for approximately two hours whilst going about their typical activities. Parents were provided with additional electrodes in case any were removed by their child or became loose. They were also informed that they could remove the wearable device at any point if it was causing their child distress or discomfort.

A parent was present in most (7/8) testing sessions. Children were allowed to take breaks at any point during the play-based assessments, and parents were informed that they could terminate the testing session at any point without having to give a reason why. The duration of the visit, including naturalistic recording, lasted approximately 2½ - 3½ hours.

**Table 5.1** Order and timing of play-based assessments.

| Order | Activity         | Time (minutes) |
|-------|------------------|----------------|
| 1     | Free Play 1      | 5              |
| 2     | Toy Removal      | 5              |
| 3     | Toy Prohibition  | 1              |
| 4     | Marshmallow Task | 5              |
| 5     | Pen Prohibition  | 3              |
| 6     | Gift Delay       | 5              |
| 7     | Free Play 2      | 5              |
|       | Total            | 29             |

### 5.2.3 Tasks, Equipment and Measures

#### 5.2.3.1 Toy Retraction

In the Toy Retraction task (adapted from the End of the Line task from the pre-school Lab-TAB, Gagne et al., 2011; Goldsmith et al., 1999), the experimenter showed the child a sensory ball and demonstrated how it worked (e.g., whether you could squeeze, bounce or stretch the ball, see **Figure 5.2**). The experimenter then encouraged the child to play with the ball by handing it to them and saying: “Your turn”. After 60 seconds of play, the experimenter removed the ball from the child and hid it behind their back. Keeping a neutral face and firm tone, they said: “[child’s name], no more playing with this ball. I don’t like it” and looked away from the child. If the child questioned the experimenter, they said “That is the way it is”. After 30 seconds, the experimenter then looked at child and said “I’ve changed my mind. I think that is a good ball to play with”, before handing the ball back to the child and playing for 30 seconds. This procedure was then repeated twice, with two new sensory balls that were introduced to the child (see **Figure 5.2**).

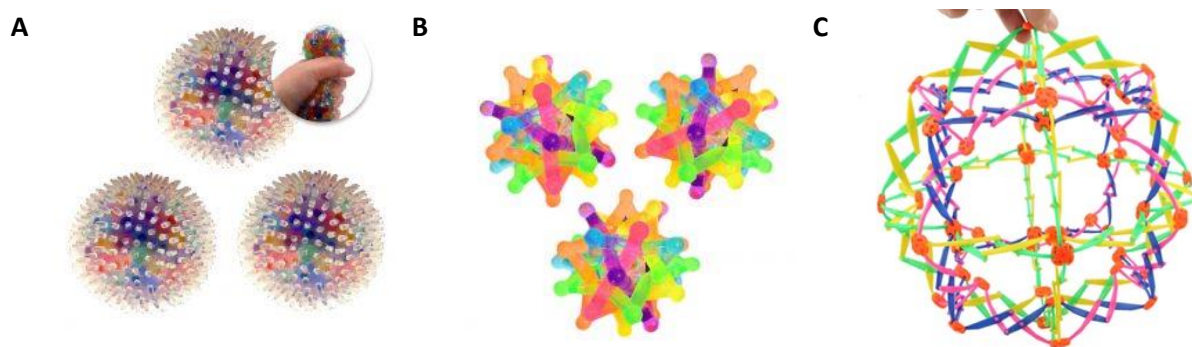


**Figure 5.2** Sensory balls used in the Toy Retraction task. **A** Spiky squeeze ball. **B** Tactile knitted light-up ball. **C** Peegsan expand ball.

### 5.2.3.2 Inhibitory Control – Prohibition Tasks

Two inhibitory control tasks were used to assess children’s ability to follow a prohibition. For both tasks, children were seated at a play-table across from the experimenter (see **Figure 5.1A** above). Another experimenter and the child’s caregiver were present in the room, but where they were positioned was dependent on the layout of the family home. For both tasks, whether or not the prohibition was broken by the child was coded (i.e., whether they passed or failed).

In the Toy Prohibition task (Friedman et al., 2011; Portugal et al., 2023), an attractive toy (a fidget slug, see **Figure 5.3A**), that had previously been out of sight of the child (in a bag next to the experimenter), was placed in front of them. In a stern voice, the experimenter immediately instructed the child not to touch the toy: “[child’s name] don’t touch”. The experimenter then turned away from the child for 30 seconds. If the child had not already touched the fidget slug within 30 seconds, the experimenter gave prompts to release the prohibition approximately five seconds apart: at 30 seconds, a verbal prompt (“[child’s name], touch it”); at 35 seconds, a second verbal prompt whilst pointing at the fidget slug (“Touch the slug”); and at 40 seconds, a demonstration of touching the fidget slug with verbal encouragement (“Look – I am touching it. You touch it too”). Once the prohibition was released, the experimenter played with the child for 30 seconds before putting the fidget slug away. If the prohibition was not released after the prompts, the task was terminated. Experimenters recorded whether the child was able to refrain from touching the fidget slug as pass/fail.

The Pen Prohibition task (Fiske et al., in prep) is similar to the Toy Prohibition task described above. However, in this task, the attractive object was a novelty pen (see **Figure 5.3B**) and children had up to four opportunities to demonstrate successful restraint. The experimenter showed the child the novelty pen, which had previously been out of sight. The experimenter then looked at the child and said, “I

need to write something before we start the next game”, before angling their body slightly away from the child and writing in a notepad on the table with the novelty pen. As soon as the child touched the pen, the experiment said “No” in a stern voice and, if applicable, removed the pen from the child. The experimenter then continued to write with the pen. The child was then given 30 seconds to restrain themselves from touching the pen. If the child touched the pen again, the “No” command was repeated, and the child was given 15 seconds to restrain themselves from touching the pen. This was repeated until successful restraint or after four “No” commands. If the child did not touch the pen within the first 30 seconds, this was recorded as successful restraint. Upon successful restraint, the prohibition was released using the same prompts as above (see Toy Prohibition task), and the experimenter played with the child for 30 seconds before putting the pen away. Experimenters recorded whether the child was able to refrain from touching the pen as pass/fail. These task instructions are slightly modified from (Fiske et al., in prep) wherein rather than continuing to write, the experimenter absentmindedly put the pen down on the table within reach of the child.



**Figure 5.3** Toys used in the prohibition tasks. **A** Fidget Slug. **B** Novelty Pen.

#### 5.2.3.3 Inhibitory Control – Delay of Gratification Tasks

Two inhibitory control tasks were used to assess children’s ability to delay gratification. Consistent with the prohibition tasks, children were sat opposite the experimenter at a play-table.

In the Marshmallow task (adapted from Mischel et al., 1972, 1989), the experimenter showed the child two marshmallows (or an equivalent desirable food reward, determined via correspondence with individual parents) and said “I have some treats”. They then instructed the child by saying “I am going to leave the room. I am going to leave one here (demonstrating by putting the marshmallow on the table). If you eat this one, then you will only get one. If you wait, you’ll get two”. Then the experimenter left the room for 3 minutes. During this period, the parent and the other experimenter remained in the room and were instructed to stay neutral, only intervening to ask the child to sit down if they got up from the play table. If the child had to be asked to sit down five times, the experimenter was called

back into the room. If the child ate the marshmallow before the 3 minutes were up, they were allowed to get up and interact with their parent and the other experimenter. After the 3 minutes had passed, the experimenter returned to the room. If the child had eaten the marshmallow, the experimenter said, “Ah, you ate it! Was it good?”. If the child had not eaten the marshmallow, the experimenter gave the child another and said, “Well done, you can eat them both now.”. Experimenters recorded whether the child was able to refrain from eating the marshmallow as pass/fail.

The Gift Delay task (adapted from the ‘Gift-in-bag’ task, Kochanska et al., 2000) is similar to the Marshmallow task, but here the reward was a present (bubbles in a gift bag, see **Figure 5.4**). In this task, the experimenter showed the child a colourful gift bag and explained it was a present for them: “You’ve done such a good job helping me today, so I have a present for you.”. The experimenter then acted confused and said: “Oh no! I have forgotten my bow!”, before pointing at where the child is sitting and instructing them to “Try not to touch it, until I come back”. The experimenter then left the room for 3 minutes. The child remained in the room with their parent and the other experimenter, who were given the same instructions as in the Marshmallow task. After the 3 minutes had passed, the experimenter returned to the room. If the child had opened the present, the experimenter said, “Oh I see you have found the bubbles – is that good?”. If the child had not already opened the present, the experimenter said “Ah, I found the bow”, before sticking it on the bag and telling the child “You’ve done such a good job today, thank you! You can have a look at your present!”. The experimenter then played with the child for 30 seconds before stopping the task. Experimenters recorded whether the child was able to refrain from touching the gift bag as pass/fail.



**Figure 5.4** Materials used in the Gift Delay task. **A** Gift Bag. **B** Foil Bow. **C** Bubbles.

#### 5.2.3.4 Wearable Device

We adopted bespoke wearable devices from Wass and colleagues (see Goldenberg et al., 2024) (**Figure 5.5**). Wearable devices were manufactured by Harkwood industries and consisted of a 3-lead electrocardiogram (ECG) monitor, actigraph, GPS and microphone, all of which were contained within

a small plastic box measuring approximately 5 x 7 cm. For children to be able to wear the device, it was inserted into a cotton pouch with a press stud close that was sewn on to an elasticated belt. This elasticated belt was then secured with a Velcro fastening around each child's middle and worn under their clothing.



**Figure 5.5** Wearable device.

#### 5.2.3.5 Questionnaire Measures

Questionnaire measures outlined in Chapter 2 were used to characterise the sample included in this pilot study.

### 5.2.4 Data Processing

This section outlines the steps taken to pre-process the ECG and actigraph data collected via the wearable device. While the device also recorded GPS and audio data, analysis of this data was beyond the scope of this thesis chapter (for examples see, Goldenberg et al., 2024; Smith et al., 2023; Wass et al., 2019, 2021, 2025). ECG and actigraphy data pre-processing were carried out using a modified, bespoke Python script (courtesy of Gio Esposito, University of East London) originally developed for ECG and actigraphy data collected from infants.

#### 5.2.4.1 ECG Data

The ECG data were first resampled to a uniform sampling rate of 250 Hz (i.e., 250 samples per second). Prior to R-peak detection, signal cleaning was performed using the *ecg\_clean* function from the NeuroKit2 package (Makowski et al., 2025). R peaks were then identified using NeuroKit2's *ecg\_peaks* function, and instantaneous heart rate (HR), in beats per minute (BPM), was calculated from inter-beat intervals using the *signal\_rate* function.

Signal quality was evaluated using the *ecg\_quality* function, which quantifies how closely each detected heartbeat matches the average heartbeat morphology. Segments with quality scores below 0.7 were masked. To account for signal dropout, periods where either one or both ECG leads were disconnected were also masked.

Epoch-level quality control was implemented by down-sampling the HR signal into non-overlapping 5-second epochs. Within each epoch, HR was smoothed using a 4th-order Butterworth low-pass filter with a 10 Hz cut-off to reduce the influence of unrealistic high-frequency fluctuations. The mean HR, mean ECG amplitude, and average signal quality were computed for each epoch. Epochs with physiologically implausible BPM values or poor signal quality (i.e.,  $< 0.7$ ) were excluded from heart rate variability (HRV) analysis.

HRV was computed using a sliding 2-minute window centred on each 5-second epoch. Only windows containing less than 50% missing or invalid data were retained. Two time-domain HRV metrics were calculated: standard deviation of the time between successive normal heartbeats (SDNN, in ms) and the root mean square of successive differences between these intervals (RMSSD, in ms). HRV estimates were restricted to the central portion of each recording, excluding the first and last 10 minutes.

Outlier removal was performed using an interquartile range (IQR)-based method. BPM, SDNN, and RMSSD values falling outside  $\pm 1.5 \times \text{IQR}$  were excluded. Finally, HR and HRV values were normalized using z-scores.

#### 5.2.4.1 Actigraphy Data

Actigraphy data were recorded using the wearable device. As metadata on the device's sampling frequency were unavailable, we estimated the sampling rate by calculating the mode of the number of samples per second over the first 140 seconds of the recording. The modal sampling frequency was 40 Hz.

To compute an overall measure of movement, we calculated the sum of the absolute values of the accelerometer's three axes (x, y, and z), producing a single scalar value that reflects total motion regardless of direction. This signal was smoothed using a low-pass Butterworth filter to reduce high-frequency noise, and the first-order absolute difference was computed to capture changes in movement over time. The resulting signal was then down sampled to 1Hz by averaging values within each one-second window.

## 5.2.5 Data Analyses

### 5.2.5.1 Aim 1: Feasibility and Performance on Frustration Tolerance and Inhibitory Control Tasks

The first aim of this pilot study was to examine the feasibility of structured observational measures of self-regulation in young children (aged 3-7 years old) with rare ID-associated genetic conditions.

Feasibility was assessed as the proportion of participants who were able to attempt the Toy Retraction task (a measure of frustration tolerance), and each of the play-based inhibitory control tasks. Drawing on approaches used in studies of young children with idiopathic ID and DS (Pinks et al., 2023; Schworer et al., 2022; Walsh et al., 2025), completion was defined as attempting the task in accordance with the protocol outlined above. No formal criteria were used, but non-attempt was typically due to behaviours such as leaving the play area, climbing on the play-table, or signs of emotional distress (e.g., crying). We adopted a post-hoc threshold of 80% completion for a task to be considered feasible, consistent with previous studies evaluating tasks assessing executive functions in children and adolescents with idiopathic ID and DS (Hessl et al., 2016; Pinks et al., 2023; Schworer et al., 2022; Walsh et al., 2025).

In addition to feasibility, we examined task performance on each of the inhibitory control measures using a binary pass/fail metric. Including performance data is important for two reasons: (1) it helps determine whether the tasks are suitable for the target population, and (2) it shows whether completed tasks yield analysable data, rather than just indicating participation (Pinks et al., 2023; Walsh et al., 2025). Taken together, this information provides a comprehensive understanding of both the feasibility of the tasks and their ability to produce meaningful data in this population.

### 5.2.5.2 Aim 2: Feasibility of Micro-analytic Coding of Self-Regulation Strategies

The second aim of this study was to explore whether it is possible to use a micro-analytic coding approach to examine self-regulation strategies employed by children with rare ID-associated genetic conditions. This approach has demonstrated utility in typically developing young children (Fiske, 2023; Manfra et al., 2014; Mulder et al., 2019).

We decided to examine behaviour on the Gift Delay task as this has been extensively analysed using similar approaches in previous studies of typically developing children (Fiske, 2023; Mulder et al., 2019). Video recordings of the first 60 seconds of the 3-minute wait period were extracted using FFmpeg, a command-line tool for processing multimedia files (FFmpeg Developers). Children's behaviour was then coded during 5-second intervals by JM. 5-seconds epochs are longer than the

intervals used in several previous studies adopting a micro-analytic approach to study self-regulation in children (1-second intervals; e.g., Cole et al., 2017, 2020; Fiske, 2023; Mulder et al., 2019), but this generated a manageable number of epochs to be coded in this pilot study (consistent with Suata, 2024). We adopted a previously developed coding scheme used in Fiske (2023) (see **Table 5.2**). Changes to the coding scheme were discussed between researchers (JM and KB<sup>3</sup>), and are highlighted in bold. Adaptations to the coding scheme were made based on both the research setting (i.e., family homes) and characteristics of the participant group. For example, we extended 'looks at door' to 'looks at door/exit' to account for situations where the door was not visible on camera. We also added behaviours that may be specific to ID. For example, 'repeated hand movement' was added to the category 'hands – distract', and '(including sounds/signs)' was added to 'making contact with others'.

To present the data, we collapsed codes across modality and type to examine the presence/absence of behaviour across the first minute of the Gift Delay task. We selected the following categories reported by Mulder et al. (2019) – 'Visual – Distract', 'Hands – Withhold', 'Hands – Distract', 'Body – Distract' – and two previously unreported categories – 'Communication – Focus' and 'Communication – Distract'. We also report the epochs in which children failed to inhibit their desire to touch, open or play with the gift.

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<sup>3</sup> Kate Baker

**Table 5.2** Coding scheme for the Gift Delay task. Text in bold indicates changes from Fiske's (2023) coding scheme.

| Modality      | Type     | Behaviour                                                                        |
|---------------|----------|----------------------------------------------------------------------------------|
| visual        | focus    | looks towards object                                                             |
| visual        | withhold | eyes are closed                                                                  |
| visual        | distract | looks at <b>door/exit</b>                                                        |
| visual        | distract | looks behind                                                                     |
| visual        | distract | looks at his/her own hands                                                       |
| visual        | distract | looks at cue in the environment                                                  |
| visual        | distract | looks at person                                                                  |
| communication | focus    | talks/asks questions about the object to someone else                            |
| communication | focus    | talks about what they are doing regarding the object to someone else             |
| communication | focus    | talks/asks questions about the object/what they are doing to him/herself         |
| communication | focus    | talks/asks about the experimenter with someone else                              |
| communication | focus    | talks/asks about the experimenter to self                                        |
| communication | withhold | repeats the rule regarding the task to someone else                              |
| communication | withhold | repeats the rule regarding the task to themselves                                |
| communication | distract | making contact with others (generally) ( <b>including sounds/signs</b> )         |
| communication | distract | talks about object un-related actions/asks general questions to someone else     |
| communication | distract | sings or hums, makes noises (not language), muttering, <b>laughing</b>           |
| communication | distract | talks in general to him/herself or talks about what they are doing to themselves |
| communication | -        | does not speak                                                                   |
| motor - hands | focus    | almost touching the object                                                       |
| motor - hands | focus    | reaching or pointing toward object                                               |
| motor - hands | relaxed  | hands are (relaxed) above the table                                              |
| motor - hands | withhold | hands are placed on top of one another                                           |
| motor - hands | withhold | holding own hands/arms                                                           |
| motor - hands | withhold | hands are underneath the table                                                   |
| motor - hands | withhold | sits on own hands                                                                |
| motor - hands | withhold | head resting on hands                                                            |
| motor - hands | distract | touches own face or mouth                                                        |
| motor - hands | distract | fine motor movements (e.g., fiddles with clothes, fingers)                       |
| motor - hands | distract | repeated hand movements (e.g., flapping/clenching/chest banging)                 |
| motor - hands | distract | points at/signals to another object in the room                                  |
| motor - hands | distract | hand gestures to parent                                                          |
| motor - hands | distract | tapping/rubbing hands/ <b>fingers</b> on table/legs                              |
| motor - hands | failure  | <del>low:</del> child touches, holds or shakes object                            |
| motor - hands | failure  | child throws/pushes bag off table                                                |
| motor - hands | failure  | child moves bag to peek/look inside                                              |
| motor - hands | failure  | medium: child unpacks/attempts to unpack the object                              |
| motor - hands | failure  | <del>high:</del> child uses/ <b>plays with</b> the object                        |
| motor - body  | distract | child is turned to face parent/wall behind them/ <b>to the side</b>              |
| motor - body  | focus    | child moves/leans toward object                                                  |
| motor - body  | withhold | child moves/leans away from object                                               |
| motor - body  | distract | rocks or dances with body                                                        |
| motor - body  | distract | child is away from table                                                         |
| motor - body  | distract | fidgiting with legs/wobbling legs                                                |
| motor - body  | distract | lay down their head on back of chair/table                                       |
| motor - body  | distract | child is under the table                                                         |
| motor - body  | distract | child climbs on chair/table                                                      |
| motor - body  | failure  | stands up in chair to peek in bag                                                |

### *5.2.5.3 Aim 3: Wearable Devices – Feasibility, ECG Data Quality, and Preliminary Analyses*

The final aim of this pilot study was to examine the feasibility of using wearable devices to obtain physiological data (ECG and actigraphy data) in young children with rare ID-associated genetic conditions. Feasibility was assessed as the proportion of participants who were able to wear the device for the duration of the play-based testing session and for a subsequent period of naturalistic recording.

We also evaluated the quality of the ECG data through visual inspection. To extract ECG data corresponding to the period during which children were engaged in play-based assessments, we used UTC (Coordinated Universal Time) timestamps. UTC timestamps were recorded by both the wearable device and the live production switcher, meaning the different data types could be aligned according to this measure. We also extracted one hour of naturalistic ECG recording, beginning 45 minutes after the identified start time of each play-based assessment. The proportion of missing ECG data within these segments was then calculated for each participant as a coarse measure of ECG quality.

Previous studies using the wearable devices piloted here (e.g., Goldenberg et al., 2024; Smith et al., 2023; Wass et al., 2019, 2021, 2025) have generated arousal composites combining HR, HRV and movement signals. This approach is grounded in research showing that these physiological measures co-vary in typically developing infants (Wass et al., 2015, 2016) and, more recently, young children (Goldenberg et al., 2024). To evaluate whether this composite approach would be appropriate for children with rare ID-associated conditions, we examined the relationships between these measures in this population. Consistent with the method described by Wass and colleagues, we calculated cross-correlations to assess temporal dependencies between these signals. We also computed zero-order (zero-lag) correlations to measure the overall strength of association without accounting for temporal shifts.

## 5.3 Results

### 5.3.1 Participant Characteristics

Data from 8/10 of the participants who took part in the home-based testing session are included in the analyses presented below (see **Table 5.3** for a summary of participant characteristics). Data from two participants were excluded: one was unable to complete the play-based assessments due to physical disability (inability to sit independently and limited motor control), and testing for the other was terminated after they became dysregulated during the first free play task and were unable to continue.

**Table 5.3** Participant characteristics ( $N = 8$ )

| Variable                       | $M (SD)$      | Range       |
|--------------------------------|---------------|-------------|
| Age                            | 5.11 (1.52)   | 3.14 – 7.38 |
| Sex (% female)                 | 62.50         |             |
| VABS ABC <sup>a</sup>          | 64.75 (14.51) | 40 – 84     |
| DBC TBPS <sup>b</sup>          | 50.25 (7.59)  | 37 – 58     |
| SRS Total <sup>c</sup>         | 73.12 (12.25) | 55 – 85     |
| Effortful Control <sup>d</sup> | 3.83 (0.39)   | 3.30 – 4.30 |

<sup>a</sup> Adaptive Behaviour Composite (ABC) from the Vineland Adaptive Behaviour Scale (VABS).

<sup>b</sup> Total Behavioural Problem Score (TBPS) from the Developmental Behaviour Checklist 2 (DBC2).

<sup>c</sup> Total score from the Social Responsiveness Scale – Second Edition (SRS-2).

<sup>d</sup> Effortful control subscale score from the Children’s Behavior Questionnaire – Very Short Form (CBQ-VSF).

### 5.3.2 Aim 1: Feasibility and Performance on Frustration Tolerance and Inhibitory Control Tasks

#### 5.3.2.1 Feasibility

We found only two of the inhibitory control tasks exceeded our post-hoc feasibility criteria ( $\geq 80\%$  completion, see Section 5.2.5.1): the Toy Prohibition and Pen Prohibition tasks (see **Table 5.4**). We also found that fewer children were able to complete the delay of gratification tasks (75.0%) compared to the simpler prohibition tasks (87.5-100%). During these tasks, we observed that younger children were less likely to complete tasks, and often appeared fatigued towards the end of the testing session. Furthermore, there was substantial variation in children’s willingness to interact with researchers and their overall interest in the tasks, with individuals either disinterested or experiencing intense excitement being less likely to complete these tasks.

#### 5.3.2.2 Performance on Inhibitory Control Tasks

Children’s ability to inhibit their desire to touch an attractive object or delay a reward varied between inhibitory control tasks (see **Table 5.4**). For the prohibition tasks, we found more children demonstrated inhibitory control on the Pen Prohibition task compared to the Toy Prohibition task (85.7% vs 37.5%). For the delay of gratification tasks, we found more children demonstrated inhibitory

control on the Marshmallow task compared to the Gift Delay task (50.0% vs. 33.3%). Overall, performance was worst on the Gift Delay task and best on the Pen Prohibition task (33.3% vs. 85.7%).

**Table 5.4** Descriptive statistics for play-based assessments.

| Task             | Completion <sup>a</sup> | Demonstrate Inhibitory Control <sup>b</sup> |
|------------------|-------------------------|---------------------------------------------|
| Toy Retraction   | 7/8 (87.5%)             | -                                           |
| Toy Prohibition  | 8/8 (100.0%)            | 3/8 (37.5%)                                 |
| Marshmallow Task | 6/8 (75.0%)             | 3/6 (50.0%)                                 |
| Pen Prohibition  | 7/8 (87.5%)             | 6/7 (85.7%)                                 |
| Gift Delay       | 6/8 (75.0%)             | 2/6 (33.3%)                                 |

<sup>a</sup>Task completion is shown as the number of participants who attempted the task/the total number of participants.

<sup>b</sup>The proportion of participants who demonstrated inhibitory control on each task is shown as the number of participants who passed the task according to task description/the total number of participants who attempted the task.

### 5.3.3 Aim 2: Feasibility of Micro-analytic Coding of Self-Regulation Strategies

#### 5.3.3.1 Feasibility

We applied a micro-analytic approach to code children's behaviour during the first 60 seconds of the 3-minute wait period on Gift Delay task. The modified coding scheme comprised 48 distinct codes (see **Table 5.2**). Across all 72 epochs (12 epochs per participant, 6 participants in total), only 9 codes were unused, suggesting that children displayed a wide range of behaviours that were adequately captured by the coding scheme. However, two methodological challenges were encountered when applying the coding scheme. First, in some instances it was difficult to determine the direction of speech (i.e., whether the child was talking to themselves or to someone else). Second, multiple behaviours were recorded in each 5-second epoch. To more accurately capture dynamic, moment-to-moment changes in behaviour, a more fine-grained coding approach, such as using shorter 1-second epochs, may be more informative.

#### 5.3.3.2 Observations

Visualisation of self-regulation strategies revealed variability in behaviour over the first 60 seconds of the Gift Delay task, both within and between children with rare ID-associated genetic conditions (see **Figure 5.6**). We observed some similarities between Participants C and F, who successfully withheld touching the gift during the delay period. Within a single epoch, these children engaged self-regulatory strategies across several of the code categories. These children also demonstrated behaviours within the 'Hand – Withhold' category, something that wasn't observed in children who failed the task, with the exception of Participant A.

We also found that children who failed the task typically touched the gift within the first four epochs (i.e., the first 20 seconds of the delay period). According to the coding scheme, there were several different ways a child could fail the Gift Delay task. These are visualised in **Figure 5.7**. Most children touched or moved the gift, while only one child (Participant E) opened the gift and used the bubbles. Interestingly, Participant A engaged in game-like behaviour with the researcher (AMF) during the delay period. For instance, after they pushed or threw the gift bag off the play table and it was replaced, they repeated this behaviour.

### **5.3.4 Aim 3: Wearable Devices – Feasibility, ECG Data Quality and Preliminary Analysis**

We found all children were able to tolerate the wearable device. Although many children initially displayed signs of distress during its application (e.g., crying, hand-flapping), in most cases, children recovered within a few minutes and were effectively distracted either once their t-shirt was pulled down over the device or through parental support. Some children required ongoing distraction during the play-based assessments or naturalistic recording sessions. It is also possible that the wearable device was removed by parents in some instances; however, such events were not systematically recorded. Additionally, we found one child who was unable to participate in the play-based assessments due to their severity of physical disability (see Section 5.3.1), but was able to tolerate the wearable device. Their data were excluded from the analyses below for comparability.

There was generally high continuity of ECG recordings – the average proportion of missing HR data was 2.09% ( $SD = 3.43$ , range = 0-10.75) during the play-based assessments and 9.43% ( $SD = 15.45$ , range = 0-41.47) during one hour of naturalistic recording (see **Figures 5.8 and 5.9**). Visual inspection of the HR data reveals significant variability both within and between participants across the play-based and naturalistic recording sections of the protocol.

To determine whether it would be feasible to generate an arousal composite, we examined the relationships between HR, HRV, and movement signals recorded by the wearable device. As expected, based on prior findings (Wass et al., 2015, 2016), the peak cross-correlation between HR and movement occurred around zero lag (**Figure 5.10a**), with a mean zero-lag correlation of  $r = 0.59$  (**Figure 5.10c**). This indicates a strong, synchronous positive relationship between these variables, likely reflecting the immediate influence of physical activity on HR.

In contrast, the cross-correlation between HR and HRV did not show a consistent peak at zero lag (**Figure 5.10d**). The mean zero-lag correlation was  $r = -0.20$ , with substantial variability between

participants (**Figure 5.10f**). This finding differs from previous research in typically developing infants and children that reported a negative association between HR and HRV (Goldenberg et al., 2024; S. V. Wass et al., 2015, 2016). It remains unclear whether this inconsistency represents a baseline difference between study populations or if other factors could influence HRV in children with rare-ID associated genetic conditions. As a result, it may not be practical or informative to generate an arousal composite of physiological measures to study self-regulation in this population.

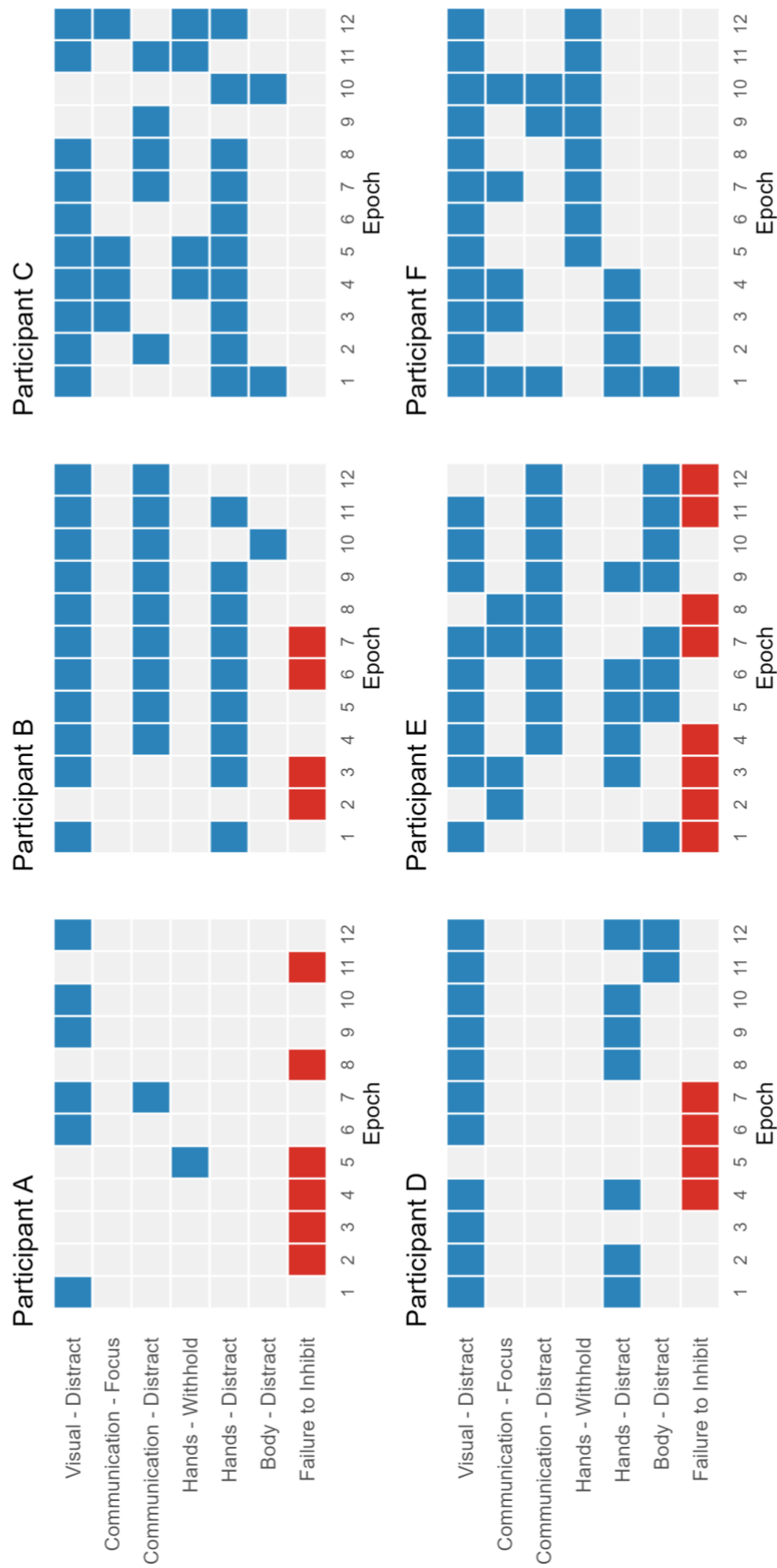


**Figure 5.6** Self-regulation strategies and inhibitory control ability during the Gift Delay task for each participant. Data are segmented into 5-second epochs, representing the first 60 seconds of the 3-minute delay period. Blue shading indicates the presence of a self-regulatory strategy, while red shading indicates the presence of behaviours reflecting failure to inhibit.

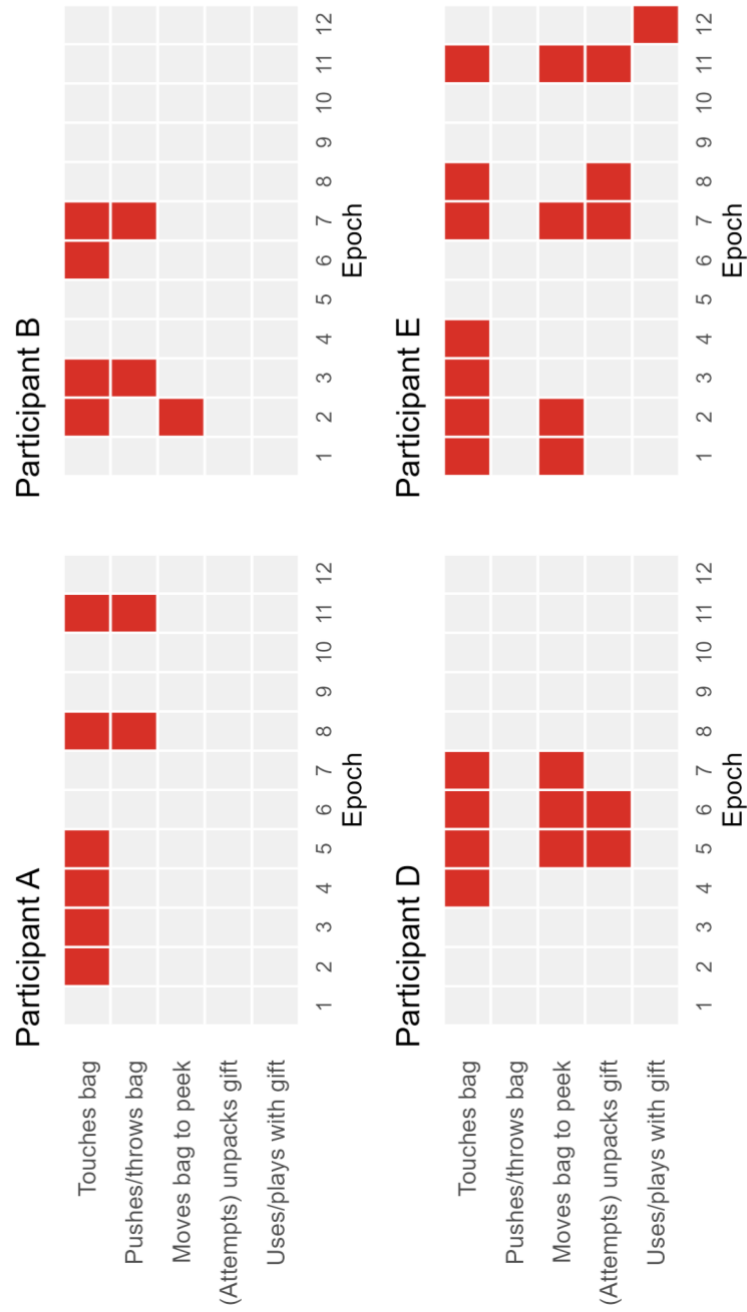


**Figure 5.7** Failure to inhibit behaviours during the Gift Delay task for each participant. Data are segmented into 5-second epochs, representing the first 60 seconds of the 3-minute delay period. Red shading indicates the presence of behaviours reflecting failure to inhibit.

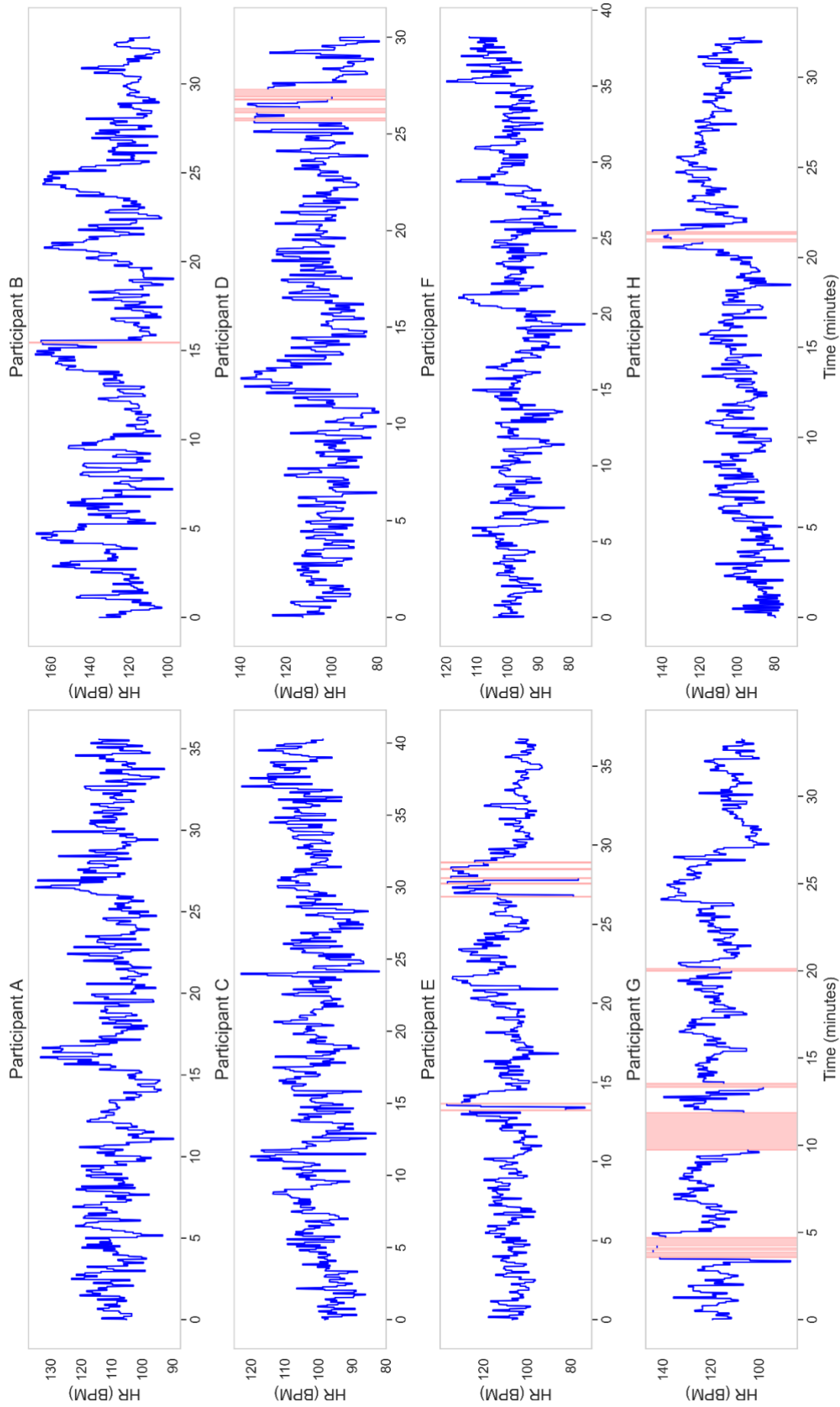


**Figure 5.8** Heart rate (HR in beats per minute, BPM) during play-based assessments for 8 participants. Shaded regions represent missing data (i.e., poor ECG data signal).

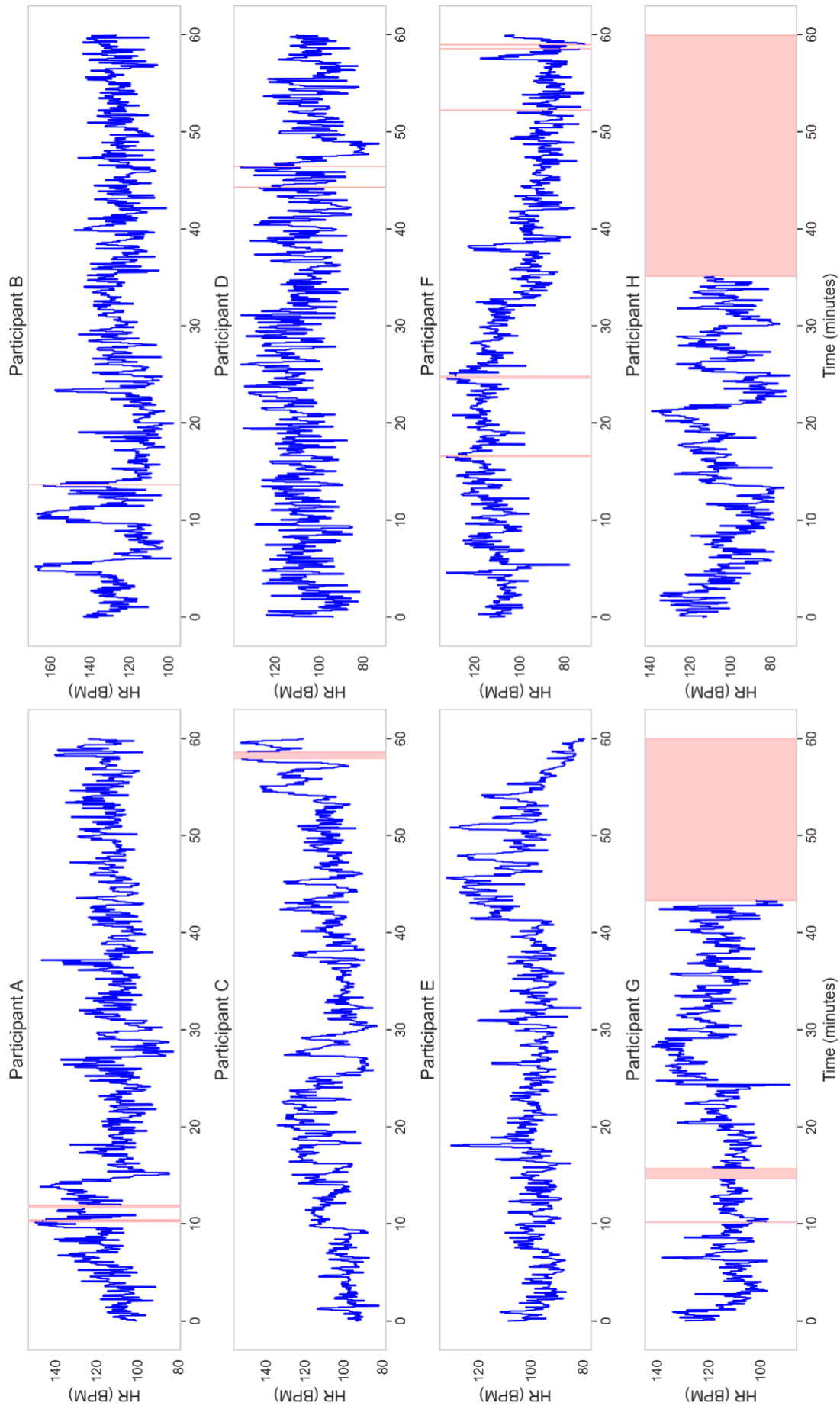


**Figure 5.9** Heart rate (HR in beats per minute, BPM) during naturalistic recording for 8 participants. Shaded regions represent missing data (i.e., poor ECG data signal).

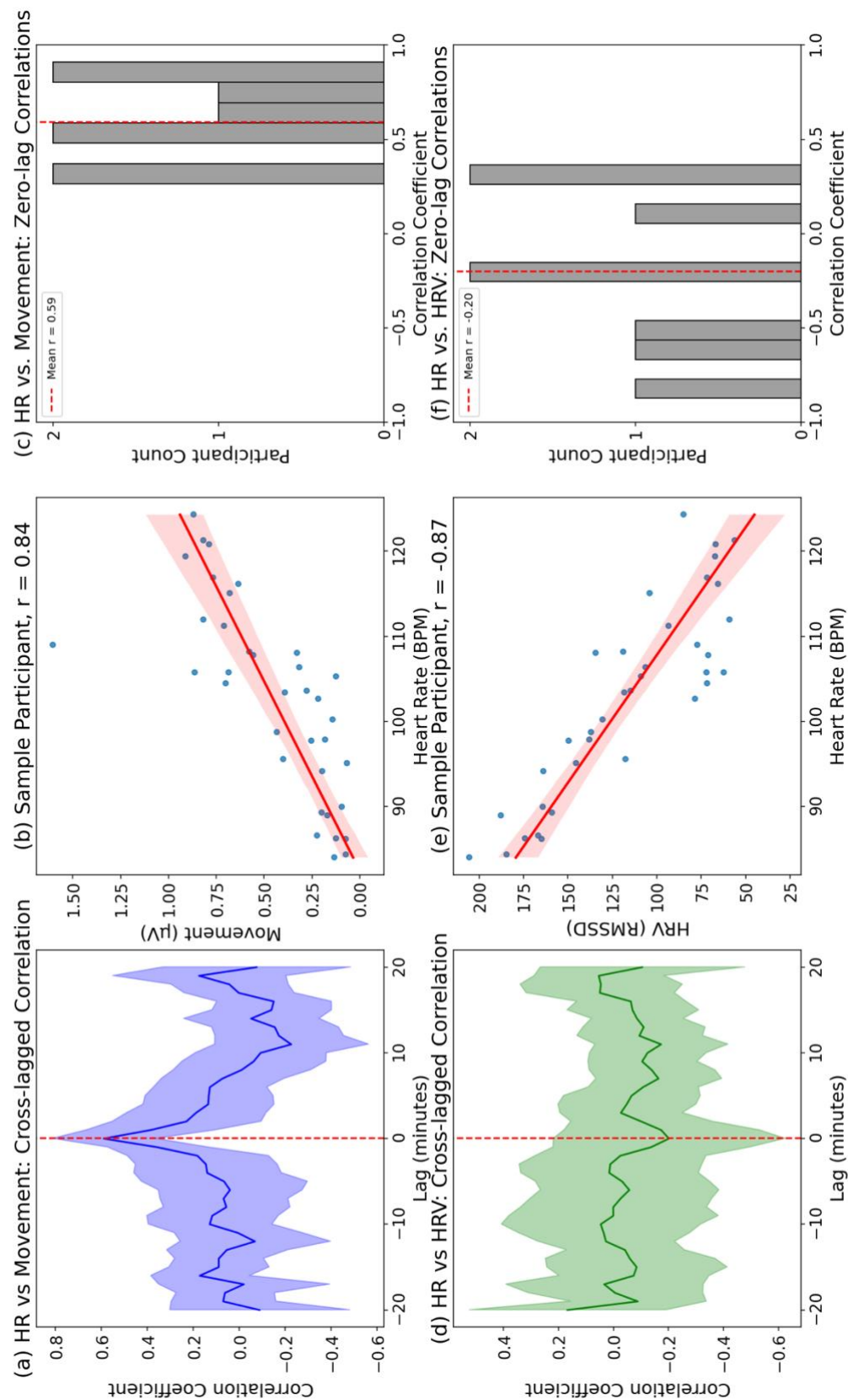


**Figure 5.10** Relationship between physiological measures. (a) Mean cross-lagged Spearman correlation between heart rate (HR) and movement (actigraphy) across participants, plotted over a  $\pm 20$ -minute lag window. Shaded areas represent the standard deviation (SD) of correlations at each lag. (b) Scatterplot illustrating the relationship between HR and movement for a single participant, with each point representing a 60-second epoch. The red line denotes the linear regression fit. (c) Histogram showing the distribution of zero-lag Spearman correlations between HR and movement across all participants. Dashed red line indicates the mean correlation coefficient. (d)-(f) Equivalent plots for HRV (in BPM) and HRV (measured via RMSSD).

## **5.4 Discussion**

This pilot study examined the feasibility of play-based assessments (predominately measures of inhibitory control) and wearable devices (physiological measures) in children with rare ID-associated genetic conditions. It also explored whether a micro-analytic coding approach can capture self-regulation strategies in this population. In this section, we discuss preliminary findings, provide recommendations, and propose alternative approaches for future studies.

### **5.4.1 Feasibility and Performance on Inhibitory Control Tasks**

The first aim of this study was to assess the feasibility of using play-based inhibitory control tasks in young children with rare ID-associated genetic conditions. Feasibility was highest for the prohibition tasks, with all children in the pilot study completing the Toy Prohibition task (100%). This is consistent with findings from a previous study in children with DS, which reported completion rates between 97-100% on two modified versions of this task (Walsh et al., 2025).

In addition to similar completion rates, task performance on the Toy Prohibition task was also comparable to previous studies. In this pilot, we found 37.5% of children waited the full 30 seconds on the Toy Prohibition task – similar to rates reported in children with DS (21.92-24.66%, Walsh et al., 2025) and typically developing toddlers (35.8%, Devine et al., 2019). This finding suggests that in addition to feasibility, the Toy Prohibition task is sensitive to individual differences in inhibitory control, and may be suitable for studying self-regulation in this population.

Children's performance also varied across the different inhibitory control tasks. Within the prohibition tasks, performance was greater on the Pen Prohibition task (85.7%) than the Toy Prohibition task (37.5%). The Pen Prohibition task, developed by Fiske et al. (in prep), was designed to be more ecologically valid and resemble everyday situations in which children must refrain from touching an attractive but prohibited object (e.g., a parent's hot cup of tea). Additionally, unlike the single-trial format of Toy Prohibition task, the Pen Prohibition task includes multiple opportunities for children to hear tasks instructions and demonstrate inhibitory control. While repeated trials may introduce practice effects, they also provide an opportunity to measure children's best performance. This aligns with previous findings suggesting that children with ID often perform better on executive function measures when given repeated exposure or practice (Brkić et al., 2022; Hessel et al., 2016).

In contrast, the delay of gratification tasks were less feasible (i.e., had lower completion rate) than the prohibition tasks. These tasks involve more complex instructions and longer delay periods, placing greater demands on receptive language and cognitive skills, which may be particularly challenging for

some children with rare ID-associated genetic conditions. Additional factors, such as age and fatigue, may have played a role in task completion. For example, younger children appeared more fatigued toward the end of the testing session, which may have affected their ability to complete the Gift Delay task.

Across all tasks, we noted that engagement and interest played a substantial role in task completion. We found that this varied between children and tasks, from complete disinterest to such intense excitement that it interfered with experimenter's ability to administer task instructions. For example, we were unable to complete the Marshmallow Task with one participant because they immediately ate the reward upon presentation. Conversely, another participant was uninterested in playing with any of the three balls used in the Toy Retraction task and consistently returned them to the experimenter, rendering the task impossible.

Although the tasks were administered in a familiar environment (i.e., the children's homes), it is noteworthy that the testing session itself was somewhat atypical. The novelty of the testing equipment (e.g., cameras and wearable devices) and the presence of unfamiliar researchers may have influenced children's participation. While a brief five-minute free play period was included in the protocol to build rapport, this may have been insufficient. Such contextual influences are consistent with findings from the broader literature, which show that young children's performance on delay of gratification tasks is affected by their perception of the trustworthiness of task administrators (Ma et al., 2018; Michaelson & Munakata, 2016). This suggests that greater familiarisation time may have improved completion rates in some cases.

#### **5.4.2 Micro-analytic Coding of Self-regulatory Behaviours**

A key aim of this pilot study was to explore approaches which move beyond binary pass/fail measures to better capture the dynamic nature of self-regulation. Specifically, in Aim 2 we examined whether a micro-analytic coding approach, previously used to characterise self-regulatory behaviours in typically developing toddlers (see Fiske, 2023; Mulder et al., 2019), could be applied to children with rare ID-associated genetic conditions. Our findings indicate that this method successfully captured the broad range of behaviours displayed by children during the wait period of the Gift Delay task.

Importantly, we observed differences in self-regulatory strategies that may be related to task performance. Anecdotally, children who successfully withheld from touching the gift for the full delay period were more likely to actively withhold their hands from the gift, compared to children who failed.

This pattern is consistent with Mulder et al. (2019), who found that the percentage of time typically developing toddlers withheld their hands predicted tasks success.

One potential challenge of adopting this approach relates to performance on the Gift Delay task. In this pilot study, we found that most children touched the gift and that typically this occurred within the first 20 seconds of the delay period, providing only a short time-window within which to observe self-regulation strategies and apply the micro-analytic coding scheme. In contrast, most typically developing toddlers can manage the full delay period (~70%; Mulder et al., 2019), providing more instances in which successful regulatory behaviour can be coded. As few children with rare ID-associated genetic conditions can demonstrate self-regulation on this task, it may be less suitable to apply a micro-analytic coding scheme to this task, as recorded self-regulatory behaviour would not be representative of the population. Instead, a different task may be required to examine how these children behave whilst exerting self-regulation.

#### **5.4.3 Wearable Devices**

Our study also showed that wearable devices can be used to collect ECG and actigraphy data at-home from young children with rare ID-associated genetic conditions whilst they complete experimenter-initiated tasks and every-day activities.

All of the children who participated in the play-based assessments were able to wear the device, although many experienced distress when it was applied and were distracted by the device when completing the play-based assessment battery. Resistance to wearing ECG monitors has also been observed in typically developing 4-5 year olds, leading to elevated study drop out (Goldenberg et al., 2024).

On the contrary, the one child who was unable to participate in the structured testing session due to physical disability could tolerate the device for several hours, albeit with some mild discomfort. This suggests that wearable devices may facilitate research with children who would otherwise be excluded from conventional testing. Going forward, it will be important to determine the quality of ECG data and establish whether a physiological composite is informative for this sub-population of children with rare ID-associated genetic conditions.

For children who were included in our analyses, there was minimal ECG data loss during the play-based assessments. However, data quality dropped substantially during the naturalistic recording phases. Unlike the majority of previous studies using these wearable devices in infants, the children in this

study were mobile, and electrodes may have detached due to increased movement or because children pulled them off. As researchers were not present during the naturalistic recording phases, it remains unclear whether the drop in ECG data quality was due to random technical issues (e.g., poor electrode adhesion) or to children's discomfort with wearing the device for an extended period. Therefore, wearable devices may be more suitable for data collection during structured assessments or shorter periods of naturalistic recording in children with rare ID-associated genetic conditions.

Whilst we found HR was correlated with movement, we were unable to recapitulate the cross-correlation between HR and HRV expected from studies in typically developing infants and children (Goldenberg et al., 2024; Wass et al., 2015, 2016). It is possible that alternative physiological composites are more informative for children with rare ID-associated conditions, and it may be necessary to assess this in further pilot studies.

#### **5.4.5 Future Directions**

Several broader considerations emerged from this pilot study that should inform future research using these methods in children with rare ID-associated genetic conditions.

First, task performance in this pilot study was measured using a crude, dichotomous outcome (i.e., whether or not children touched a prohibited object). While practical for examining the suitability of these tasks, such binary coding may obscure subtler differences in regulatory ability. Latency to touch is a continuous and more sensitive measure of task performance that is commonly used, and has shown promise in similar contexts. For example, a recent pilot study used latency to touch to examine the feasibility of two modified toy prohibition tasks in 2-year-old children with DS, including reliability of performance across tasks, and relationship with chronological and mental age (Walsh et al., 2025). Whether variability in performance relates to psychopathology remains to be explored.

Second, future research may consider employing embedded delay tasks in naturalistic settings, delivered by familiar individuals such as parents or caregivers. The pen prohibition task is a promising candidate, as it mirrors everyday scenarios in which parents or caregivers are engaged in an activity and children attempt to access a restricted object (Fiske, 2023). Emerging evidence suggests that prohibition tasks can be successfully administered by parents, with remote support from researchers, to individuals with ID with and without a genetic cause (Lavery et al., In Review; Shelley, 2024). This may increase ecological validity and reduce the potential influence of unfamiliar researchers on task performance.

Third, interpreting children's behaviour remains a key challenge when using inhibitory control measures. In our study, it was difficult to determine the extent to which children's behavioural responses accurately reflected their inhibitory control abilities. Researchers have traditionally confirmed children's understanding of task instructions by directly asking them (e.g., Mischel et al., 1972). However, this was not possible in the present pilot study due to variability in participant's verbal communication skills. It therefore remains unclear how to interpret certain behaviours. For example, a child who remained still with a flat affect may have demonstrated strong inhibitory control, or may have been disengaged. Conversely, a child who immediately touched the prohibited item may have misunderstood the task demands, rather than lacking inhibitory control. Some researchers have addressed this ambiguity by incorporating additional observational measures into their protocol. For example, Walsh et al. (2025) included experimenter ratings of children's engagement. Future studies might benefit from adopting similar approaches to improve the validity of interpretations based on task performance.

These interpretive challenges are not limited to binary pass/fail outcomes. Even when using more fine-grained micro-analytic coding to capture behaviours like fidgeting, self-talk and gaze aversion, the function of each behaviour might vary between children, or even within children across contexts. For example, in our pilot study, one child pushed the gift bag off the play table during the Gift Delay task. While this was interpreted as game-like behaviour by experimenters and their parent, it could also reflect an adaptive self-regulatory strategy, perhaps serving to manage temptation or redirect attention away from the reward. It would have been informative to observe what this child might have done if the bag had not been replaced: would they have stood up to look for the gift, or remained seated for the remainder of the delay period? Such observations could have offered deeper insight into the strategies used by this child.

Given the challenges of obtaining sufficient analysable data from delay tasks (see section 5.4.2) an alternative approach is to code children's behaviours in tasks which elicit emotions that require self-regulation, rather than tasks explicitly designed to assess executive processes (i.e., inhibitory control) that underlie self-regulation. Examples of such tasks include interactions with unfamiliar strangers, such as the "Clown" and "Lion" paradigm described by Morales et al. (2017) that are designed to elicit fear, and frustration-inducing tasks like the Toy Retraction task piloted here (also see Suata, 2024). In this study, we found that frustration-eliciting tasks are feasible in young children with rare ID-associated genetic conditions (7/8 participants attempted the Toy Retraction task), and therefore could be used to study self-regulatory behaviour. However, careful risk assessment should be carried out

before applying these methods in samples who may engage in BtC, as frustration and blocked goals have been identified as triggers of emotional outbursts in several rare genetic syndromes (Cressey et al., 2019; Shelley, 2024). In addition, utilising tasks which causes significant distress might not be ethical, and requires appropriate consideration.

Beyond observing how children exert self-regulation in emotion-eliciting tasks, these tasks can be used to study self-regulation as a dynamic system. Cole and colleagues argue that self-regulation is the dynamic process in which executive processes are engaged to modulate prepotent (i.e., reflexive) emotional and behavioural responses to challenging situations (Cole et al., 2004; Morales et al., 2017). In this framework, the influence of regulatory behaviours (e.g., gaze aversion, fidgeting or self-talk) on emotional responses (e.g., facial affectivity) is modelled mathematically over time. Using tasks designed to elicit anger, fear and frustration, they have shown that self-regulation emerges from the moment-to-moment coupling of executive processes and prepotent responses (Cole et al., 2017, 2020; Morales et al., 2017). These dynamics change across early childhood, whereby executive processes exert stronger regulatory effects with age (Cole et al., 2020; Morales et al., 2017). This approach might be particularly informative for examining self-regulation as a dynamic, ongoing ability in children with rare ID-associated genetic conditions in the future.

#### **5.4.6 Conclusions**

The findings of this pilot study were mixed, highlighting both the potential opportunities and challenges of using play-based assessments and wearable devices to investigate self-regulation in children with rare ID-associated genetic conditions.

First, we found prohibition tasks, but not delay of gratification tasks, were feasible in this population. Second, we demonstrated that a micro-analytic coding approach can successfully capture a broad range of self-regulatory behaviours, but this method may be best suited to study self-regulation in children who can engage meaningfully with delay of gratification tasks, limiting its wider applicability. Finally, we reported that most children tolerated the wearable devices, and that good-quality ECG and actigraphy data were collected in naturalistic settings. Nonetheless, further work is needed to determine the most appropriate contexts for deploying these devices, and to develop methods for analysing physiological data in this population. Practical challenges, such as high attrition rates, also raise concerns about the scalability and generalisability of these methods.

Overall, this pilot study underscores both the promise and practical challenges of implementing these tools in rare ID-associated genetic condition research and these findings offer important insights to guide future larger-scale studies.

## Chapter 6 | General Discussion

This thesis had two overarching aims. First, to characterise anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder compared to other rare ID-associated genetic conditions. Second, to investigate temperament-based self-regulation (e.g., effortful control) in rare ID-associated genetic conditions, given its significance as an early-emerging ability linked to anxiety in typically developing and autistic populations. Here, I provide a summary of key observations from each chapter, and reflect on the methodological and conceptual challenges of understanding mental health in rare ID-associated genetic conditions.

### 6.1 Summary of Key Observations

#### 6.1.1 Chapter 2

We did not replicate any of the group differences reported by Ng-Cordell et al. (2023) between *DDX3X*-related disorder and other rare ID-associated genetic conditions. However, we did replicate a significant association between greater autism-related traits and anxiety across these groups. Our network analysis, including data from individuals with *DDX3X*-related disorder, *CASK*-related disorder and other rare ID-associated genetic conditions, also revealed a link between greater sensory avoiding (an autism-related characteristic), anxiety and self-injury. While these findings should be interpreted with caution, given the small sample size and focus on children and adolescents, they raise important questions: How robust are comparative findings in the literature on mental health in rare ID-associated genetic conditions? And what role does autism play in shaping mental health in these conditions?

#### 6.1.2 Chapter 3

Using interview methodology grounded in a formulation framework, we identified common patterns of anxiety-related behaviours (e.g., non-verbal vocalisations, crying and BtC), triggers (e.g., new situations, sensory overload and routine changes) and parent-coping strategies (e.g., reassurance and avoidance) across children with rare ID-associated genetic conditions. The frequency of these factors suggests they should be considered in clinical settings. These findings also raise important questions about possible mechanisms involved in the emergence and maintenance of anxiety in children with rare ID-associated genetic conditions: What is the role of Intolerance of Uncertainty (IU) and Family Accommodation (FA)? Are these mechanisms particularly elevated, or vulnerable in this population? And can existing IU- or FA-based interventions be modified or repurposed for children with rare ID-associated conditions, potentially offering scalable alternatives to condition-specific interventions?

### **6.1.3 Chapter 4**

Our review of existing literature (Part A) highlighted some evidence that effortful control may be atypical in rare genetic syndromes, but findings varied based on assessment method and participant characteristics. In contrast to literature in typically developing and autistic children, few studies found a relationship between effortful control and anxiety in this population. Rather, effortful control might be linked to neurodevelopmental or externalising difficulties in rare ID-associated genetic conditions, and anxiety may be predicted by negative affect. Consistent with existing literature, in Part B we found that negative affect, but not effortful control, predicted anxiety in young children with rare ID-associated genetic conditions. This pattern appeared to be conserved across rare genetic diagnosis groups. Although this latter observation requires formal testing, these findings suggest that negative affect may be a cross-condition correlate of anxiety in rare ID-associated genetic conditions.

### **6.1.4 Chapter 5**

The results of our pilot study were mixed, and suggest that play-based assessments and wearable devices may be feasible and acceptable methods for investigating self-regulation in some, but not all, children with rare ID-associated genetic conditions. For example, we found prohibition tasks were more feasible than delay of gratification tasks, and whilst a micro-analytic coding approach captured a broad range of self-regulatory behaviours, this method might only be applicable to a subset of children who can demonstrate inhibitory control on delay tasks. In addition, most children were able to tolerate the wearable device, but further consideration of what contexts these should be used in, and how to analyse physiological data in this population is required before embarking on a larger, full-scale study utilising these sensors. Our pilot study therefore highlights the potential challenges and opportunities in analysing and interpreting the data collected via these methods.

### **6.1.5 Summary**

Overall, this thesis has furthered our understanding of anxiety, BtC and temperament-based self-regulation in children with rare ID-associated genetic conditions. Conducting the research presented in this thesis highlighted several methodological challenges and important areas for future research on mental health in this population, including the value of comparative studies, in-depth phenotyping, and the possibility of shared developmental mechanisms underpinning anxiety. Each of these areas will now be discussed in more detail.

## **6.2 The Value and Challenges of Comparative Research**

Individuals with rare ID-associated genetic conditions are at increased risk of mental health difficulties, including anxiety and BtC. However, this risk is not uniformly distributed: some genetic conditions are associated with a significantly higher risk than others. Identifying which groups are at elevated risk, and understanding the factors that contribute to this increased vulnerability, is a key goal of research in this area (Waite et al., 2014) and a central motivation for this thesis.

Behavioural phenotyping provides a framework that links genetic variation to specific behavioural traits. This research approach involves systematically characterising behavioural traits that occur more frequently in individuals with a specific rare ID-associated genetic condition compared to those without that condition (Dykens et al., 2000; Oliver et al., 2010). By directly contrasting two or more genetic diagnosis groups, researchers can in turn determine whether certain mental health difficulties (e.g., anxiety and self-injury) are elevated in a given condition, or common across multiple conditions. Comparative designs also allow researchers to identify condition-specific correlates, which may form the targets of interventions. This knowledge can support early identification of emerging mental health difficulties and inform the development of targeted, condition-specific interventions.

However, it is important to recognise that intervention research remains limited, and that the development of targeted treatments for adverse condition-specific traits is still in its early stages (Assadourian & Martinez-Agosto, 2025). As such, identification of high-risk groups and correlates of mental health problems does not yet result in tailored interventions. Nevertheless, comparative research remains crucial for highlighting similarities and differences between conditions, thereby supporting the development of a more nuanced and realistic understanding of condition-specific profiles (e.g., the range of expected strengths and difficulties). Such insights can inform clinical formulation and guide the interpretation of behavioural and mental health presentations, even in the absence of condition-specific interventions.

### **6.2.1 Methodological Challenges in Conducting and Interpreting Comparative Studies**

Despite their potential value, comparative studies face several methodological challenges. Studies often have small sample sizes and limited statistical power due to the difficulty of recruiting participants with rare genetic conditions. They also typically involve several statistical comparisons, but rarely apply corrections for multiple testing (e.g., Ng-Cordell et al., 2023; O'Brien et al., 2019; Watkins et al., 2019). This may reflect the fact that the majority of these studies are exploratory in nature and aim to characterise broad behavioural profiles. Applying strict correction procedures (e.g.,

Bonferroni) in these cases could further reduce statistical power and increase the likelihood of Type II errors (i.e., failing to detect true group differences). Nevertheless, the absence of correction increases the risk of Type I errors – that is, detecting group differences where none exist. As such, researchers have to strike a balance between sensitivity and statistical stringency, but this raises concerns about the reliability and replicability of findings.

Pooling results from multiple studies is one approach to dealing with small sample sizes. However, even when multiple studies compare the same condition, they often employ different measurement tools, control groups and inclusion criteria. For example, there has been a growing number of studies examining the behavioural phenotype of *SYNGAP1*-related ID in the past two years (Bednarczuk et al., 2024; Frazier et al., 2025; D. Wright et al., 2024, 2025). For example, Wright et al. (2024) compared children with *SYNGAP1*-related ID to typically developing controls and found significantly elevated internalising and externalising behaviours on the Child Behavior Checklist (CBCL, Achenbach & Rescorla, 2001), with even higher scores among those with co-occurring epilepsy. In contrast, Bednarczuk et al. (2024) compared children with *SYNGAP1*-related ID to children with other rare ID-associated genetic conditions that were matched on chronological age and severity of ID. They found no significant differences in emotional-behavioural problems on the Strengths and Difficulties Questionnaire (SDQ, Goodman, 2001), despite a markedly higher prevalence of epilepsy in the *SYNGAP1*-related ID group. These studies not only differ in their outcome measures and comparison groups, but also in their analytic focus: for instance, in addition to group differences, Wright et al. (2024) examined within group variation in *SYNGAP1*-related ID. This methodological variability makes it difficult to synthesise findings and draw consistent conclusions across studies.

As such, methodological rigour and replication are critical, not only to distinguish robust, condition-specific findings from spurious or sample-specific effects, but also to accurately identify groups at high risk of mental health difficulties.

These issues are exemplified in Chapter 2, which aimed to replicate previous findings in *DDX3X*-related disorder (Ng-Cordell et al., 2023). Ng-Cordell et al. (2023) found that anxiety and self-injury were elevated in this group, relative to individuals with other rare ID-associated genetic conditions, and that these difficulties were associated with distinct, condition-specific correlates (e.g., a relationship between lower adaptive ability and higher anxiety in the *DDX3X*-related disorder group). However, our findings in Chapter 2 did not support this pattern, and instead suggest that anxiety and self-injury are similar across rare ID-associated genetic conditions, and that autism-related traits may be a shared

developmental correlate of these mental health difficulties. By failing to replicate these findings in a new sample, we not only tested the robustness of group differences in anxiety and BtC, but also highlighted the risks of interpreting comparative findings based on studies that have small sample sizes, limited mental health measures and that lack statistical rigour.

### 6.2.2 Questioning the Limits of Comparative Studies

In addition to methodological concerns, the use of comparative studies raises important conceptual issues. Many such studies are motivated by the search for condition-specific traits (whether this is influenced by long-standing scientific norms such as deficit-based models, a reliance on frequentist statistics, or modern publication pressures is up for debate), and often overlook within-condition variability, and cross-condition similarity. For example, as one recent study put it: *‘There is a need to systematically compare the characteristics of SYNGAP1 with other monogenic causes of ID and [developmental delay] DD to identify features unique to the SYNGAP1 phenotype.’* (Bednarczuk et al., 2024, pg. 1). However, this kind of reasoning aligns with a more deterministic view of genetic difference, whereby specific genes are presumed to lead to discrete and distinct behavioural phenotypes.

As outlined in the Chapter 1, with the increased diagnostic yield of NGS technologies, the phenotypic spectrum of many rare ID-associated genetic conditions is expanding. For example, *CASK*-related disorder, once primarily linked to severe neuroanatomical abnormalities, is now understood to encompass a broader spectrum of neurodevelopmental presentations (Dubbs et al., 2022; Martin et al., 2024). Expanding phenotypes have also been observed in other conditions, such as *STXBP1*-associated disorder (Stamberger et al., 2022; Xian et al., 2022) and *SYT1*-associated disorder (Melland et al., 2022; Norwitz et al., 2025), highlighting increased within-condition variability. At the same time, overlapping behavioural traits across different genetic conditions are becoming more apparent. This raises questions about the long-term utility of cross-syndrome comparisons if both within-group variability and between-group similarity continue to grow.

Crucially, the presence of both within-group heterogeneity and between-group overlap also implies that genetic diagnosis alone does not fully explain variability in mental health difficulties. In support of this, Cunningham et al. (2020) found that genotype only explained 16.4% of the variance in emotional-behavioural difficulties in individuals with CNVs associated with NDDs (termed ND-CNVs). Similarly, although not focused on mental health, Ali et al. (2025) found between-group variation in autism-related characteristics in individuals with ND-CNVs was significantly smaller than the within-group variation (21.4% vs. 73.7%). These findings challenge the assumption of narrow gene-behaviour

relationships. Instead, they highlight the likely contribution of shared developmental mechanisms, such as autism-related traits and negative affect, in shaping mental health vulnerability across conditions, regardless of specific genetic diagnosis (for further discussion see Section 6.3).

### **6.2.3 The Future of Comparative Studies: To Lump or Split?**

These challenges highlight the need for reflection on how to best conduct research in this field. A central dilemma is whether to study rare ID-associated genetic conditions in isolation ('split'), or aggregate across diagnostic groups ('lump'). While this challenge is not new, it becomes increasingly relevant as more rare and ultra-rare genetic causes of ID are identified.

While a condition-specific focus may provide valuable insights into genotype-phenotype correlations, there is a risk of over-interpreting specificity. A shift towards cross-condition research on the other hand may allow researchers to identify shared mechanisms that may be translated into more broadly applicable interventions, but this broader view may also risk obscuring syndrome-specific features that could have diagnostic or prognostic utility (Waite et al., 2014).

Additionally, the decision of which conditions to study is rarely neutral. It is often shaped by factors such as funder preference, pre-existing research networks, and participant availability. These practical constraints may lead to an uneven research landscape, where a small subset of rare genetic conditions are disproportionately represented. Totsika et al. (2022) have argued that, in the context of evaluating mental health interventions, condition-specific research should not come at the cost of more widely applicable interventions. Given limited research resources and expanding diagnostic diversity, future research should openly reflect on questions of representation, equality and impact: who gets included in research and why?

#### **6.2.3.1 At What Level Should We Group?**

Even when researchers decide to 'lump', a further challenge arises: at what level should we aggregate rare genetic causes of ID? Common strategies include grouping individuals by specific clinical syndromes (e.g., Williams syndrome), the affected gene (e.g., *LIMK1*), or chromosomal region (e.g., 7q11.23). Each approach comes with trade-offs in terms of statistical power, biological relevance, and clinical utility.

There is some evidence that grouping individuals by the affected gene may not be sufficiently specific for understanding behaviour. Within-group heterogeneity is substantial (for example, see Chapter 2, Section 2.3.2.2, **Figure 2.3** and **Figure 2.4**), and variant levels differences (i.e., variant type or location)

may partially explain this variability. For example, in *DDX3X*-related disorder, missense variants have been associated with more severe adaptive function impairments than protein truncating variants (Ng-Cordell et al., 2023; Radford et al., 2023; Tang et al., 2021). In *SYNGAP1*-related disorder, recent evidence suggests that neither variant type nor domain is linked with the behavioural phenotype, but that the specific location of loss of function variants (i.e., whether they occur in exons 1-4 vs. exons 5-19) may be linked to differences in verbal communication ability (Wiltrout et al., 2024). These findings suggest that more granular genetic distinctions may explain within-group heterogeneity. However, such grouping often comes at the cost of further reducing sample sizes, and for most rare ID-associated genetic conditions, there may be an insufficient number of cases to conduct analysis at the level of variant type or exon location.

Another alternative approach is to group genetic conditions based on shared biological mechanisms. This approach is known as gene functional network (GFN) phenotyping, and assumes that genetic variants impacting similar pathways (e.g., synaptic function and transcriptional regulation) may give rise to converging phenotypes (Baker et al., 2015; Eck et al., 2024). This may offer a more scalable way to identify shared multi-level mechanisms, and ultimately interventions, than gene-by-gene approaches. However, gene functional networks are not discrete, and genes involved in chromatin regulation, for example, may indirectly affect synaptic function. Therefore, careful consideration must be given to how and why we group individuals, recognising the trade-offs between precision, power, and clinical relevance.

#### **6.2.4 Summary**

Together, these reflections highlight both the value and limitations of comparative research approaches. While such studies remain essential for determining whether mental health difficulties are elevated within a given rare ID-associated genetic condition, they are often limited by methodological challenges, and a narrow interpretive focus on condition-specificity may overlook important within-condition variability and between-condition similarities. Moreover, as the number of individual genetic diagnoses and their phenotypic diversity continues to grow, this raises important questions about which level of grouping is most appropriate, and what constitutes a relevant comparison group. An alternative approach is to examine patterns of mental health difficulties by looking across, rather than between, rare genetic groups.

In the next section, we explore how the use of deep phenotyping methods in this thesis has shed light on the presentation of anxiety-related traits in rare ID-associated genetic conditions, as well as the mechanisms that might maintain or contribute to these behaviours across diagnostic groups.

### **6.3 Insights from Deep Phenotyping**

A key aim of this thesis was to characterise anxiety in *DDX3X*-related disorder and *CASK*-related disorder through a deep phenotyping approach, particularly the use of semi-structured interviews (Chapter 3). One of the key strengths of interview methodology is its ability to elicit fine-grained, context-rich information about specific behaviours (Bull et al., 2021; Cressey et al., 2019; Royston et al., 2021; Tunnicliffe et al., 2014; Woodcock et al., 2009).

By combining this data from semi-structured interviews with broader questionnaire-based data, we were able to generate a detailed description of the range of social, emotional and behavioural presentations in children with *DDX3X*-related disorder and *CASK*-related disorder with reference to other rare ID-associated genetic conditions. This information is useful for both families and clinicians, by both validating their experiences and providing expectations about the range of challenges likely to be experienced by individuals with these conditions.

The use of deep phenotyping is particularly valuable in rare ID-associated genetic conditions, where behavioural profiles are often heterogeneous and poorly captured by standardised tools. As previously discussed (see Chapter 2, Section 2.1.3 and Chapter 3), diagnostic-based measures of anxiety may not adequately assess atypical anxiety symptoms in this population (e.g., increased non-verbal vocalisations and BtC, as well as unusual fears), and questionnaire-based measures often struggle to capture the complexity of behaviour (e.g., the context in which it emerges). In contrast, our work and others (Mingins et al., 2024; Royston et al., 2021) shows that semi-structured interviews capture nuanced aspects of anxiety-related traits and allow for the identification of meaningful profiles of behaviour, antecedents and coping strategies in rare-ID associated genetic conditions.

Importantly, the value of deep phenotyping extends beyond the description of behavioural profiles in individual conditions. In this thesis, we looked across different conditions and identified specific patterns of behaviour that may link to the emergence or maintenance of anxiety in this population. In particular, common parent-reported triggers such as new situations, sensory overload, and changes to routine suggest a role of intolerance of uncertainty (IU), while reported parent coping responses like reassurance and avoidance point to family accommodation (FA). Both IU and FA have been linked to

anxiety among typically developing and autistic populations (see Sections 3.4.2 and 3.4.4). While speculative, this raises the possibility that these may be shared mechanisms across diverse developmental populations, and could be elevated in rare ID-associated genetic conditions who are at increased risk of anxiety.

By generating hypotheses about the mechanisms that contribute to or maintain anxiety in these populations, our findings also highlight potential interventions. In our case, IU- and FA-based interventions have been shown to reduce anxiety symptoms in both typically developing and autistic populations (see Sections 3.4.2 and 3.4.4). This raises the question of whether these existing interventions could be modified or repurposed for individuals with rare ID-associated genetic conditions. The ability to repurpose existing treatments may be particularly valuable for rare ID-associated genetic conditions given the unprecedented cost of developing therapeutic interventions, whilst the effectiveness of these interventions could provide empirical support for our hypotheses about the mechanisms underpinning anxiety in rare-ID associated conditions.

An important limitation of deep phenotyping is that it is resource intensive, often requiring a substantial time commitment from both the researcher and participants. This can limit the breadth of focus (i.e., to a single difficulty), reduce scalability, and may result in smaller, less generalisable samples. Despite these constraints, we conducted semi-structured interviews with parents of 75 individuals, 39 of whom were reported to experience anxiety. This represents one of the largest samples to date applying this methodology in rare ID-associated genetic conditions.

Taken together, our work highlights the importance of deep phenotyping in the study of mental health difficulties in rare ID-associated genetic conditions by providing detailed descriptions of behaviours and the context surrounding them. Crucially, the most valuable insights did not come from contrasting anxiety profiles between genetic diagnosis groups, but from identifying shared patterns, which when interpreted in the context of broader literature generated hypothesis about factors which may underlie anxiety in these populations, as well as interventions that may address this. In the next section, we discuss how several of the findings in this thesis suggests a role of autism-related traits in anxiety in rare-ID associated genetic conditions.

#### **6.4 Shared Developmental Mechanisms – The Role of Autism-Related Traits**

Several findings in this thesis suggest that the correlates of anxiety in young children with rare ID-associated genetic conditions are not condition-specific, but rather may be shared across diverse developmental populations (for discussion of the role of negative affect, see Section 4.3.3).

In particular, we observed a link between autism-related characteristics and anxiety across several chapters. For example, in Chapter 2, we found a robust association between greater autism-related characteristics and higher anxiety in children with *DDX3X*-related disorder and other rare ID-associated genetic conditions. Our network analysis also revealed a direct link between social communication difficulties, sensory avoiding behaviours and anxiety. In Chapter 3, we found common anxiety-related behaviours and triggers mirrored patterns consistently reported in autistic individuals. Taken together, these findings lead us to speculate that autism-related traits may play a key role in shaping anxiety in children with rare ID-associated genetic conditions.

These findings align with a broader body of literature documenting the relationship between autism and anxiety in rare ID-associated genetic conditions. For example, autism and anxiety frequently co-occur in FXS (Crawford et al., 2020), and specific autism-related traits, notably repetitive speech, have been shown to predict anxiety symptoms in this rare genetic syndrome (Crawford et al., 2023). Anxiety is also highly prevalent among autistic individuals (Hollocks et al., 2023; Kent & Simonoff, 2017; van Steensel et al., 2011), and specific autism-related characteristics, such as repetitive behaviours and sensory processing differences, have been shown to predict anxiety in this population (Bird et al., 2024; Chen et al., 2024).

However, disentangling the relationship between autism and anxiety is complicated, particularly in the context of rare ID-associated genetic conditions. One major challenge is that the conceptual boundaries between autism and anxiety are often blurred. Many behaviours, including different types of restricted, repetitive behaviours and interests, are associated with both autism and anxiety (for review see Ben-Sasson & Stephenson, 2021), and may also occur as part of the broader behavioural phenotype of some rare genetic syndromes. For example, sensory processing differences are a recognised feature of autism (APA, 2013), have been linked with anxiety in the general population (Ben-Sasson et al., 2009; Engel-Yeger & Dunn, 2011), and are commonly observed in children with obsessive compulsive disorder (OCD) and other anxiety disorders (Conelea et al., 2014; A. B. Lewin et al., 2015). Moreover, sensory features have been reported as key phenotypic characteristics of several rare genetic syndromes, such as hyperacusis in WS (Silva et al., 2021) and sensory hypersensitivity in FXS (Rais et al., 2018). This symptom overlap means that autism-related characteristics, anxiety

symptoms, and other features of rare genetic syndromes may be misinterpreted or conflated with one another, or could reflect genuine comorbidity.

Another complicating factor is the reliance on questionnaire-based measures to assess both autism-related characteristics and anxiety. These tools often assume that observable behaviours directly reflect internal mental states. Behaviours such as social avoidance or repetitive actions are frequently included in measures of autism and anxiety, such that item-overlap may lead to elevated scores on both tools. However, because a single behaviour can serve multiple functions, without additional contextual information it is challenging to know which mental state they reflect. Consequently, measurement overlap may artificially inflate correlations between these two traits and obscure the true nature of the relationship between autism and anxiety (Wood & Gadow, 2010). This issue may be particularly relevant in rare ID-associated genetic condition, where individuals often have complex neurodevelopmental and mental health profiles.

To address these limitations, more nuanced multi-method assessment approaches are needed, particularly those that consider the function and context of behaviour. Observational tools such as the Anxiety Dimensional Observation Schedule (Anx-DOS, Mian et al., 2015) have been used successfully in rare genetic syndromes (e.g., Crawford et al., 2023; Edwards, 2022; Ezell et al., 2022), and may offer a more valid means of disentangling overlapping traits in these populations.

Another conceptual challenge is that autism is often presumed to contribute to anxiety, rather than the reverse. However, it is equally plausible that anxiety contributes to the expression or severity of autism-related traits. For example, children may increasingly rely on routines to manage persistent worries or fears, which in turn could exacerbate a preference for sameness, a core feature of autism (APA, 2013). Without longitudinal data, it is difficult to determine whether autism-related traits drive anxiety, whether anxiety exacerbates these traits, or whether both are influenced by a shared underlying mechanism (for example, see literature on IU in autistic populations e.g., Rodgers et al., 2023; South & Rodgers, 2017) .

However, conducting longitudinal research in rare ID-associated genetic conditions presents several challenges. First, large samples are required to examine complex interactions over time. Second, although genetic diagnoses are generally being made earlier in development (i.e., in paediatric settings), this is not the case for all rare ID-associated genetic conditions. As a result, this limits the opportunity to study early development before the emergence of traits such as anxiety or autism-

related characteristics (for discussion of why this approach is necessary in the context of rare ID-associated genetic conditions see, Farran, 2020; Farran & Scerif, 2022). Third, longitudinal studies are resource intensive and require sustained participation over time. This may be particularly difficult for families of children with rare ID-associated genetic conditions who are often managing additional medical, behavioural and caregiving needs. Consequently, participant attrition and missing data may further impact the feasibility and interpretability of such studies.

Together, these factors pose significant barriers to understanding developmental pathways to mental health difficulties in rare ID-associated genetic conditions. While these challenges are not insurmountable, they highlight the need for strategic approaches including multi-site collaborations and data-sharing consortia. The utility of these approaches has been demonstrated in the context of understanding cognitive development in rare genetic syndromes (for examples see the LonDownS Consortium, <https://www.ucl.ac.uk/london-down-syndrome-consortium/>, and the WiSDom Network, <https://blogs.ucl.ac.uk/wisdom/>), but have yet to be applied in the context of mental health difficulties.

In summary, autism-related traits appear to play a key role in shaping anxiety in rare ID-associated genetic conditions. However, overlapping behaviours, measurement limitations, and potential bidirectional influences make it challenging to disentangle these traits. Conducting longitudinal research is also practically constrained in small, complex populations. Together, this highlights the need for multi-method assessment approaches and collaborative longitudinal studies to advance our understanding of anxiety and autism in rare ID-associated genetic conditions.

## **6.5 Conclusions**

There is an ever-increasing imperative to understand mental health in rare ID-associated genetic conditions, in order to develop effective interventions and, ultimately, improve quality of life for this population. This thesis contributes to this goal by utilising multiple methods to characterise anxiety and BtC in children with *DDX3X*-related disorder and *CASK*-related disorder, as well as exploring temperament-based self-regulation as a predictor of anxiety across rare ID-associated genetic conditions.

Findings from this multi-method thesis suggest that both anxiety and BtC are prominent and highly variable across and within these conditions. Notably, results from both the comparative questionnaire-based analyses and the condition-specific presentation of interview data highlighted a predominance

of similarities rather than differences between the groups. In particular, autism-related traits emerged as a shared correlate of anxiety across conditions.

By applying a developmental framework centred on temperament-based reactivity and self-regulation, this thesis also found that negative affect was associated with anxiety – a pattern consistent with findings in typically developing and autistic children. Importantly, this relationship did not appear to be condition-specific, suggesting that the early-emerging traits contributing to anxiety in children with rare ID-associated genetic conditions may be consistent across broader developmental populations. Moreover, the use of novel analytical approaches and wearable physiological devices showed promise for studying self-regulation in this population, offering dynamic, multi-level insights that traditional methods may not capture.

Building on these findings, this thesis also highlights several key challenges and opportunities for future research. One major challenge lies in balancing condition-specificity, within-condition variability, and cross-condition similarity. While comparative studies are clinically valuable for mapping the profile of difficulties associated with specific genetic conditions – particularly when considered relative to expectations based on ID severity – this thesis suggests that understanding mental health in this population may benefit from a shift toward exploring shared behavioural phenotypes and transdiagnostic mechanisms.

Such an approach may also offer opportunities to adapt existing interventions developed in other populations. This direction holds particular promise given the increasing number of rare and ultra-rare causes of ID for which detailed genotype-phenotype mapping is not feasible. As a result, effectively addressing the complexity of mental health difficulties in rare ID-associated genetic conditions, as demonstrated in this thesis, requires the integration of multiple methodologies. This presents exciting opportunities for collaboration and large-scale research consortia.

Ultimately, this thesis contributes to our understanding of anxiety and BtC in *DDX3X*-related disorder and *CASK*-related disorder, highlights possible cross-condition mechanisms underlying anxiety in rare ID-associated genetic conditions, and evaluates possible methodological approaches for future research. It also offers conceptual insights that may guide future research, including the value of cross-condition similarity and the importance of focusing on early-emerging traits.

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# Appendices

## Appendix A: Supplementary Information for Chapter 2

### A1. Reliability and Validity of the CIASP-ID

The Clinical Anxiety Scale for People with Intellectual Disabilities (CIASP-ID, Mingins et al., 2024) is a novel measure of anxiety. It was specifically designed to assess anxiety in individuals with moderate to severe ID, including those who speak no or few words, and have a co-occurring autism diagnosis. In their paper, Mingins et al. (2024) showed that the CIASP-ID subscales demonstrated good internal consistency ( $\alpha = 0.82 - 0.92$ ) and validity, when compared to existing measures of emotional difficulties (the anxiety and depression subscales from the Anxiety, Depression and Mood Scale, ADAMS, Esbensen et al., 2003), as well as a bespoke measure of health severity. This thesis offers the opportunity to evaluate the reliability and validity of the CIASP-ID in an independent sample of children with varying severity of ID and autism characteristics (for participant characteristics see Section 2.2.1, **Table 2.1**).

To examine the internal consistency of each of the CIASP-ID subscales – anxiety, pain, low energy/withdrawal and consolability – we calculated the Cronbach's alpha. Subscale-wise missing data were handled by removing participants with incomplete responses, resulting in a minimum of 88 complete cases per subscale. Further, to examine the convergent and divergent validity of the CIASP-ID, the anxiety and low energy/withdrawal subscale scores were correlated against scores on the anxiety and social relating subscales of the DBC2 and total scores on the ASC-ASD. Due to availability of alternative measures, we were unable to examine the validity of the pain and consolability subscales within this study. Spearman's rho correlations were calculated with available pairwise data.

Internal consistency of the anxiety subscale was good ( $\alpha = 0.86$ ), and the low energy/withdrawal subscale was acceptable ( $\alpha = 0.78$ ). Cronbach's alphas for the pain and consolability subscales were poor ( $\alpha = 0.54 - 0.59$ ). We found evidence of good convergent and divergent validity for the anxiety subscale, which correlated significantly with the DBC2 anxiety subscale ( $r_s = .67, p < .001$ ) and the ASC-ASD total score ( $r = .66, p < .001$ ), but lower with the DBC2 social relating subscale ( $r_s = .34, p = .002$ ). There was also good evidence of convergent and divergent validity for the low energy/withdrawal subscale, which significantly correlated with the DBC-2 social relating subscale ( $r_s = .54, p < .001$ ), but lower with the ASC-ASD total score ( $r_s = .23, p = .03$ ). The low energy/withdrawal subscale was not significantly correlated with the DBC2 anxiety subscale ( $r_s = .18, p = .09$ ).

Taken together these findings, provide further evidence that the CIASP-ID is a reliable and valid measure, which can be used to screen anxiety in children with ID, variable verbal communication abilities and high levels of autism characteristics. However, caution should be taken when using the pain and consolability subscales.

## A2. Network analysis edge and node stability estimates

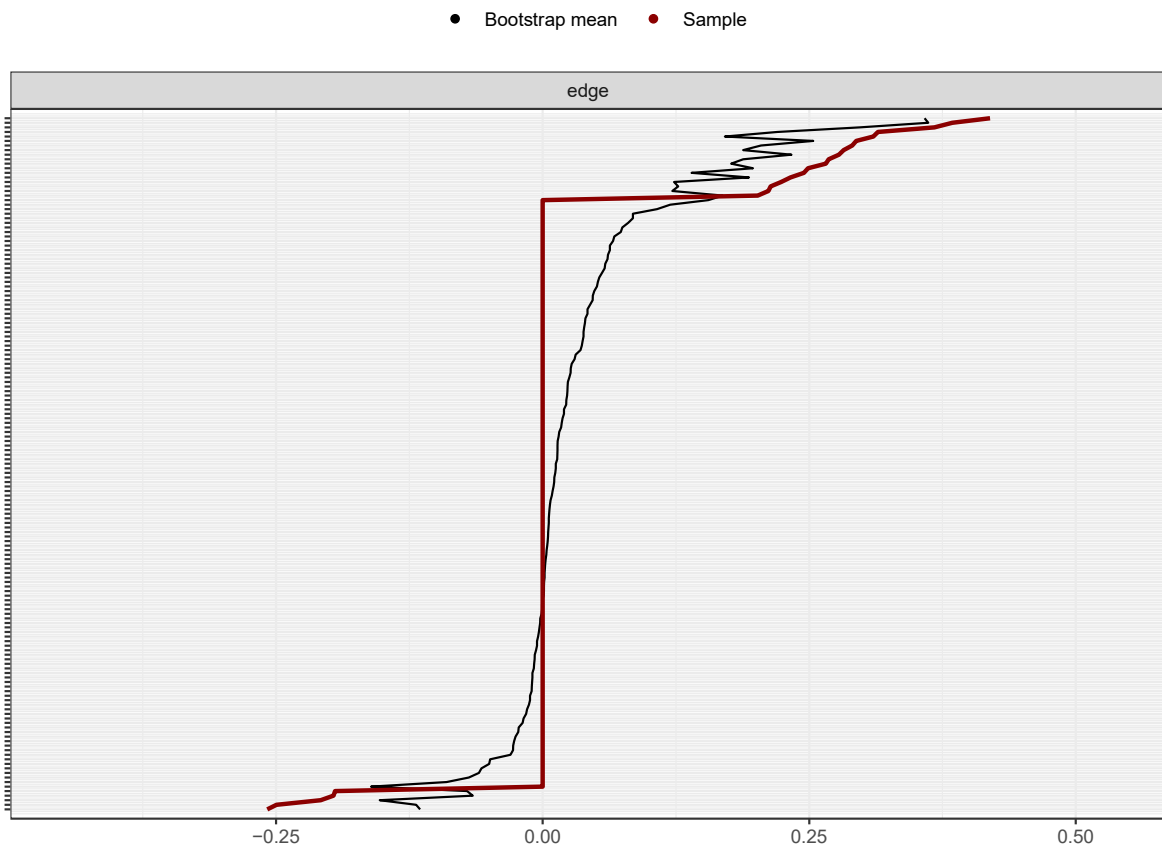


**Figure A2.1** Edge weights for all edges in the network with bootstrapped 95% confidence intervals.

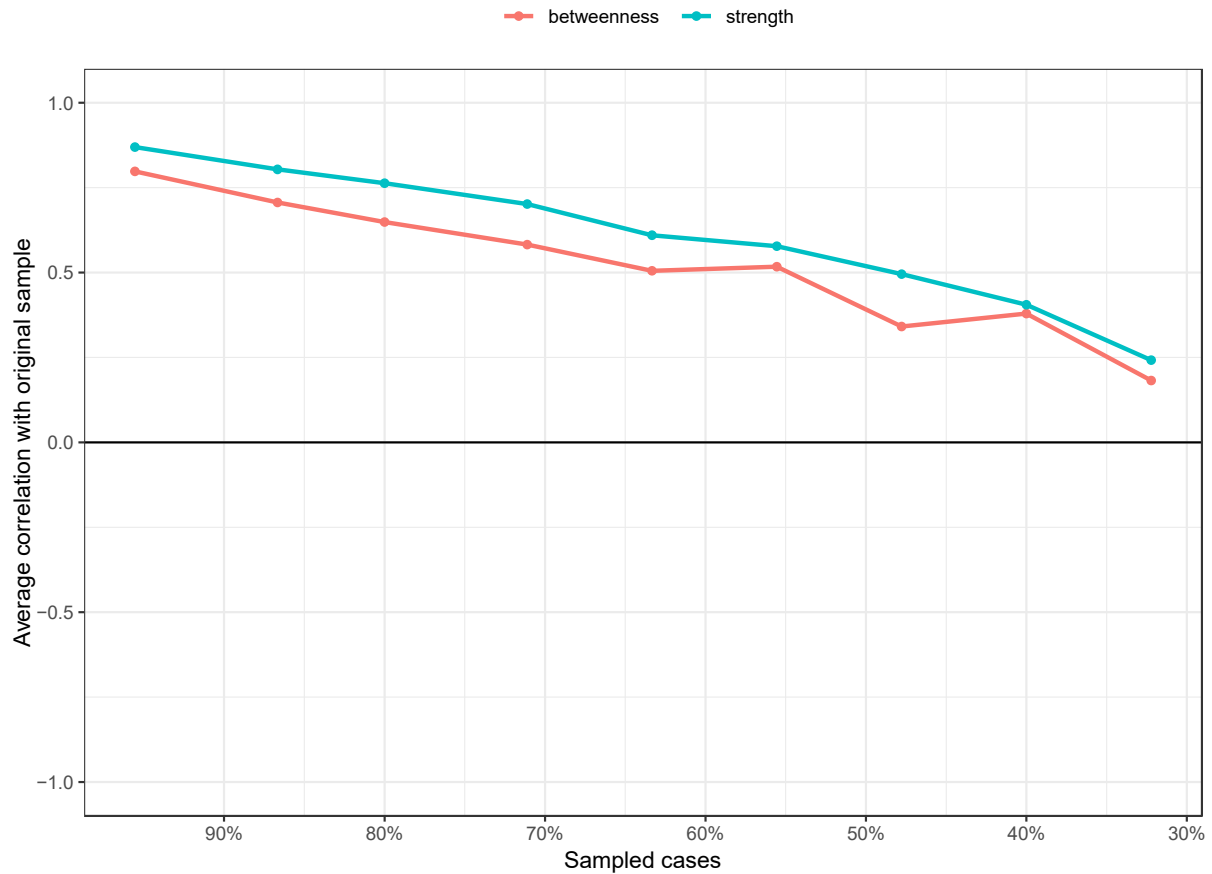


**Figure A2.2** Stability of node-level centrality estimates. Correlation-Stability Coefficients (CS-Coefficients) were calculated by correlating the original centrality estimate with centrality estimates generated by dropping subsequent proportions of participants from the original sample (Epskamp et al., 2018). The x-axis refers to the percentage of participants dropped from the sample, and the y-axis represents the CS-coefficient (i.e., the correlation with the original sample). Shaded areas represent the 95% confidence interval.

## Appendix B: Supplementary Information for Chapter 3

### B1. Anxiety Profiles

|                                             | 1                                                                                                                                   | 2                                                  | 3                                                                           | 4                                                                                                           |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Triggers                                    | Routine changes,<br>New situations,<br>Worry about future<br>events, Sensory<br>overload, SP:<br>(Babies/small<br>children)         | Routine changes                                    | Seperation/being<br>alone, Routine<br>changes, Worry<br>about future events | Social/performance<br>situations, Everyday<br>events, New<br>situations, Sensory<br>overload, SP:<br>(Dogs) |
| Physiological<br>reactions<br>(involuntary) | Trembling/shaking                                                                                                                   | Trembling/shaking                                  |                                                                             | Nausea, Headaches                                                                                           |
| Voluntary body<br>movements/actions         | Aggression, Crying,<br>Property destruction,<br>Muscle tension,<br>Jerky movements                                                  | Self-Injury,<br>Aggression, Muscle<br>tension      | Self-Injury,<br>Pacing/restlessness                                         | Crying, Maintaining<br>distance, Decreased<br>activity/movement                                             |
| Voluntary facial<br>expressions             | Tense face                                                                                                                          | Tense face,<br>Grimacing                           | Tense face                                                                  | Looks sad/worried                                                                                           |
| Communication<br>changes                    | Decreased<br>vocalising, Talks to<br>self, Repetitive<br>speech,<br>Stops initiating<br>conversations,<br>Repetitive<br>questioning |                                                    | Talks to others,<br>Repetitive speech,<br>Mumbling                          | Decreased<br>vocalising, Talks to<br>others, Repetitive<br>speech, Stops<br>initiating<br>conversation      |
| Parental coping<br>strategies               | Preparation,<br>Reassurance,<br>Physical contact,<br>Avoidance                                                                      | Preparation,<br>Physical contact,<br>Communication | Distraction,<br>Reassurance                                                 | Avoidance,<br>Distraction,<br>Removal of<br>stimulus/situation,<br>Communication                            |
| Duration<br>(minutes)                       | 5>                                                                                                                                  | Few                                                | 20-all day                                                                  | Up to a day                                                                                                 |
| Anxiety<br>severity                         | Moderate                                                                                                                            | Moderate                                           | Mild                                                                        | Moderate                                                                                                    |

|                                             | 5                                                                   | 6                                                                                             | 7                                                                                                        | 8                                                |
|---------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Triggers                                    | Routine changes,<br>New situations,<br>Worry about future<br>events | New situations,<br>Sensory Overload                                                           | Social/ performance<br>situations,<br>Seperation/being<br>alone, Routine<br>changes, Sensory<br>overload | Lack of sleep,<br>Aversive settings              |
| Physiological<br>reactions<br>(involuntary) |                                                                     | Trembling/shaking                                                                             |                                                                                                          |                                                  |
| Voluntary body<br>movements/actions         |                                                                     | Crying, Maintaining<br>distance, Self-<br>soothing, Clinging to<br>parent/carer, Bury<br>head | Pacing/restlessness,<br>Muscle tension                                                                   | Crying, Defiance,<br>Muscle tension              |
| Voluntary facial<br>expressions             | Looks worried/sad                                                   | Looks worried                                                                                 |                                                                                                          | Tense face,<br>Grimacing, Frowning               |
| Communication<br>changes                    | Talks to others                                                     | Repetitive speech                                                                             | Dereased vocalising,<br>Increased vocalising,<br>Repetitive shouting                                     | Mumbling,<br>Whining/complaining<br>sounds       |
| Parental coping<br>strategies               | Calming presense,<br>Distraction                                    | Avoidance,<br>Distraction, Physical<br>contact,<br>Reassurance                                | Avoidance, Removal<br>of stimulus/from<br>situation, Distraction,<br>Physical contact                    | Physical contact,<br>Distraction,<br>Reassurance |
| Duration<br>(minutes)                       | Extended periods                                                    | Situational                                                                                   | 10-15                                                                                                    | 20                                               |
| Anxiety<br>severity                         | Moderate                                                            | Mild                                                                                          | Moderate                                                                                                 | Moderate                                         |

|                                       | 9                                                                                 | 10                                          | 11                                                                                       | 12                                           |
|---------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------|
| Triggers                              | Social/performance situations, Routine changes, New situations, Aversive settings | Seperation/being alone                      | Seperation/being alone, Routine changes, New situations, Lack of sleep, Sensory overload | Sensory overload                             |
| Physiological reactions (involuntary) |                                                                                   |                                             | Palpitations                                                                             |                                              |
| Voluntary body movements/actions      | Aggression, Crying, Maintaining distance                                          | Self-Injury, Crying                         | Maintaining distance, Pacing/restlessness, Muscle tension, Removing clothing, Bruxism    | Aggression, Crying, Clinging to parent/carer |
| Voluntary facial expressions          |                                                                                   |                                             |                                                                                          |                                              |
| Communication changes                 | Increased vocalising                                                              | Talks to others, Whining/complaining sounds | Talks to others, Repetitive speech, Reports feeling anxious                              | Increased vocalising                         |
| Parental coping strategies            | Distraction, Child's pace                                                         | Distraction, Physical contact               | Reassurance, Distraction, Removal of stimulus/from situation, Avoidance, Communcation    | Distraction                                  |
| Duration (minutes)                    | 30                                                                                | 10-15                                       | Situational                                                                              | Situational                                  |
| Anxiety severity                      | Mild                                                                              | Moderate                                    | Mild                                                                                     | Severe                                       |

|                                       | 13                                                          | 14                                                                                           | 15                                                                 | 16                                                 |
|---------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------|
| Triggers                              | Social/ performance situations,<br>New situations           | Aversive settings, SP: (High objects/ceilings),<br>SP: (Hospital linked to tests being done) | Seperation/being alone, Aversive settings                          | Sensory overload                                   |
| Physiological reactions (involuntary) |                                                             |                                                                                              |                                                                    | Bulging vein                                       |
| Voluntary body movements/actions      | Self-Injury                                                 | Self-Injury, Aggression, Muscle tension                                                      | Crying, Repetitive behaviours, Pacing/restlessness, Muscle tension | Self-Injury, Crying, Walking with curled toes      |
| Voluntary facial expressions          |                                                             | Tense face                                                                                   | Tense face, Looks worried                                          | Tense face                                         |
| Communication changes                 | Talks to others, Repetitive speech, Reports feeling anxious | Increased vocalising                                                                         | Repetitive speech                                                  | Talks to others, Repetitive speech, Talking faster |
| Parental coping strategies            | Reassurance, Communication, Physical contact                | Removal of stimulus/ from situaiton, Physical contact, Distraction                           | Distraction, Reassurance, Removal of stimulus/from situation       | Physical contact, Communication, Distraction       |
| Duration (minutes)                    | Few                                                         | Situational                                                                                  | Situational                                                        | Situational                                        |
| Anxiety severity                      | Mild                                                        | Moderate                                                                                     | Mild                                                               | Mild                                               |

|                                             | 17                                                                | 18                                                                        | 19                                                                                    | 20                                                                                                                                    |
|---------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Triggers                                    | New situations,<br>Sensory overload                               | Sensory overload                                                          | New situations                                                                        | Separation/being<br>alone, Every day<br>events, New<br>situations, Sensory<br>overload, SP:<br>parent/carer using<br>specific objects |
| Physiological<br>reactions<br>(involuntary) |                                                                   |                                                                           |                                                                                       | Blushing,<br>Trembling/shaking,<br>Difficulty breathing,<br>Jumpy/on edge                                                             |
| Voluntary body<br>movements/actions         | Crying, Maintaining<br>distance, Defiance,<br>Muscle tension      | Self-soothing, Arches<br>back                                             | Maintaining distance,<br>Defiance, Muscle<br>tension, Clinging to<br>parent/caregiver | Aggression,<br>Maintaining distance,<br>Clinging to<br>parent/carer                                                                   |
| Voluntary facial<br>expressions             | Crying, Not looking<br>like they would be like<br>to be somewhere | Whining face                                                              | Looks worried                                                                         | Looks sad                                                                                                                             |
| Communication<br>changes                    | Decreased vocalising                                              | Talks to others,<br>Repetitive speech,<br>Whining/complaining<br>sounds   | Increased vocalising,<br>Reports feeling<br>anxious,<br>Tone change                   | Increased vocalising                                                                                                                  |
| Parental coping<br>strategies               | Preparation,<br>Physical contact                                  | Distraction,<br>Communication,<br>Breathing/<br>mindfulness<br>techniques | Preparation,<br>Communication,<br>Reassurance                                         | Avoidance, Removal<br>of stimulus/from<br>situation, Physical<br>contact, Distraction                                                 |
| Duration<br>(minutes)                       | Situational                                                       | Situational                                                               | Situational                                                                           | Situational                                                                                                                           |
| Anxiety<br>severity                         | Mild                                                              | Mild                                                                      | Mild                                                                                  | Severe                                                                                                                                |

|                                       | 21                                                                           | 22                               | 23                                                 | 24                                                                                                  |
|---------------------------------------|------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Triggers                              | Seperation/being alone                                                       | New situations, Sensory overload | Routine changes, New situations, Aversive settings | N/A                                                                                                 |
| Physiological reactions (involuntary) | Difficulty breathing                                                         |                                  | Palpitations                                       | Palpitations                                                                                        |
| Voluntary body movements/actions      | Self-Injury, Crying, Property destruction                                    | Crying, Muscle tension           | Self-Injury, Crying                                | Crying, Defiance, Pacing/ restlessness, Withdrawn                                                   |
| Voluntary facial expressions          |                                                                              | Tense face                       |                                                    | Looks sad                                                                                           |
| Communication changes                 | Increased vocalising                                                         | Decreased vocalising             | Increased vocalising                               | Decreased vocalising, Talks to others, Stops initiating conversation, Constant bids for reassurance |
| Parental coping strategies            | Avoidance, Removal of stimulus/from situation, Physical contact, Reassurance | Distraction, Physical contact    | Distraction, Avoidance                             | Distraction, Communication, Time and space                                                          |
| Duration (minutes)                    | 15-20                                                                        | 5-10                             | Situational                                        | N/A                                                                                                 |
| Anxiety severity                      | Moderate                                                                     | Moderate                         | Moderate                                           | Moderate                                                                                            |

|                                             | 25                                                                      | 26                                                                                                                  | 27                                                                                   | 28                                                                                      |
|---------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Triggers                                    | SP: loft hatch                                                          | Routine changes,<br>New situations                                                                                  | Routine changes,<br>New situations                                                   | Seperation/being<br>alone, Routine<br>changes, New<br>situations, Sensory<br>overload   |
| Physiological<br>reactions<br>(involuntary) | Difficulty breathing                                                    |                                                                                                                     | Palpitations                                                                         | Palpitations, Difficulty<br>breathing, Sweating,<br>Dilated pupils                      |
| Voluntary body<br>movements/actions         | Decreased<br>activity/movement,<br>Muscle tension,<br>Hands behind head | Aggression, Crying,<br>Defiance, Property<br>destruction, Muscle<br>tension, Applying<br>deep pressure,<br>Freezing | Maintaining distance,<br>Defiance, Decreased<br>activity/movement,<br>Muscle tension | Crying, Muscle<br>tension                                                               |
| Voluntary facial<br>expressions             |                                                                         | Looks angry                                                                                                         | Tense face,<br>Frowning                                                              | Looks scared                                                                            |
| Communication<br>changes                    |                                                                         | Increased vocalising                                                                                                | Repetitive speech,<br>Tone change, Says<br>"no"                                      | Increased vocalising,<br>Talks to others,<br>Unhappy sounds                             |
| Parental coping<br>strategies               | Calming presence,<br>Physical contact,<br>Distraction,<br>Avoidance     | Distraction,<br>Preparation,<br>Physical contact                                                                    | Child's pace,<br>Distraction                                                         | Distraction,<br>Reassurance,<br>Physical contact,<br>Removal from<br>stimulus/situation |
| Duration<br>(minutes)                       | <1                                                                      | 15                                                                                                                  | Up to 45                                                                             | 5-20                                                                                    |
| Anxiety<br>severity                         | Mild                                                                    | Moderate                                                                                                            | Mild                                                                                 | Severe                                                                                  |

|                                             | 29                                                                                        | 30                                                                                                           | 31                                                  | 32                                                                                                                                                                |
|---------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Triggers                                    | Everyday events,<br>Routine changes,<br>Worry about future<br>events, Sensory<br>overload | Seperation/being<br>alone,<br>New situations,<br>Dark/loud settings                                          | N/A                                                 | Everyday events,<br>New situations,<br>Worry about future,<br>SP: (Umbrellas),<br>SP: (Airplanes/<br>helicopters)                                                 |
| Physiological<br>reactions<br>(involuntary) | Blushing, Nausea                                                                          | Difficulty breathing                                                                                         |                                                     | Palpitations,<br>Bedwetting                                                                                                                                       |
| Voluntary body<br>movements/actions         | Aggression,<br>Maintaining distance,<br>Muscle tension                                    | Self-Injury,<br>Aggression towards<br>others, Crying,<br>Property distruction,<br>Muscle tension,<br>Bruxism | Self-soothing                                       | Repetitive<br>behaviours,<br>Maintaining<br>distance,<br>Defiance,<br>Pacing/restlessness,<br>Clinging to<br>parent/carer,<br>Uncoordinated<br>movement, Freezing |
| Voluntary facial<br>expressions             | Tense face, Wide<br>eyes                                                                  |                                                                                                              |                                                     | Looking through<br>others                                                                                                                                         |
| Communication<br>changes                    | Decreased<br>vocalising, Increased<br>vocalising,<br>Repetitive speech                    | Increased vocalising                                                                                         | Reassurance<br>seeking                              | Decreased<br>vocalising, Talks to<br>others, Repetitive<br>speech, Tone<br>change                                                                                 |
| Parental coping<br>strategies               | Reassurance,<br>Physical contact,<br>Removal of<br>stimulus/from<br>situation             | Distraction, Physical<br>contact, Time and<br>space                                                          | Reassurance,<br>Communcication,<br>Physical contact | Avoidance, No/late<br>disclosure of<br>upcoming event,<br>Physical contact,<br>Reassurance                                                                        |
| Duration<br>(minutes)                       | 10-15                                                                                     | 30                                                                                                           | N/A                                                 | Varies                                                                                                                                                            |
| Anxiety<br>severity                         | Moderate                                                                                  | Severe                                                                                                       | N/A                                                 | Severe                                                                                                                                                            |

|                                             | 33                                                                 | 34                                                                                                                         | 35                                                      | 36                                                                                                              |
|---------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Triggers                                    | New situations,<br>Aversive settings                               | Seperation/being<br>alone, Routine<br>changes, New<br>situations, SP:<br>(Airport security)                                | Everyday events,<br>New situations,<br>Sensory overload | Routine changes                                                                                                 |
| Physiological<br>reactions<br>(involuntary) | Blushing                                                           | Palpitations,<br>Sweating                                                                                                  | Trembling/shaking                                       | Blushing                                                                                                        |
| Voluntary body<br>movements/actions         | Self-Injury,<br>Aggression, Crying,<br>Clinging to<br>parent/carer | Self-Injury, Crying,<br>Repetitive<br>behaviours,<br>Decreased activity/<br>movement, Self-<br>soothing, Muscle<br>tension | Crying, Muscle<br>tension, Bruxism                      | Self-Injury, Crying,<br>Muscle tension                                                                          |
| Voluntary facial<br>expressions             |                                                                    | Frowning, Looks<br>worried                                                                                                 |                                                         | Tense face                                                                                                      |
| Communication<br>changes                    | Tense face,<br>Frowning                                            | Repetitive speech,<br>Repetitive<br>questionning                                                                           | Decreased<br>vocalising                                 | Increased vocalising,<br>Tone change,<br>Shorter with words,<br>Unreasonable when<br>talking to<br>parent/carer |
| Parental coping<br>strategies               | Preperation,<br>Reassurance,<br>Physical contact                   | Distraction, Physical<br>contact,<br>Reassurance, Child's<br>pace                                                          | Reassurance,<br>Child's pace                            | Time and space,<br>Breathing/<br>Mindfulness<br>techniques                                                      |
| Duration<br>(minutes)                       | 3                                                                  | 5-10                                                                                                                       | 5-10<br>to a few hours                                  | Dependent on<br>who is intervening                                                                              |
| Anxiety<br>severity                         | Severe                                                             | Moderate                                                                                                                   | Severe                                                  | Mild                                                                                                            |

|                                             | 37                                                                                                       | 38                                                                                                             | 39                                                                                                        |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Triggers                                    | Sensory overload,<br>Aversive settings                                                                   | Social/performance<br>situations, Everyday<br>events, Routine<br>changes, New<br>situations, Lack of<br>sleep  | Social/performance<br>situations, Welfare of<br>significant others,<br>Lack of sleep,<br>Sensory overload |
| Physiological<br>reactions<br>(involuntary) |                                                                                                          | Blushing,<br>Trembling/shaking,<br>Skin blotching                                                              |                                                                                                           |
| Voluntary body<br>movements/actions         | Aggression,<br>Maintaining distance,<br>Shaking head,<br>Cracking knuckles,<br>Fidgeting with<br>fingers | Self-Injury,<br>Pacing/restlessness,<br>Increased<br>activity/movement                                         | Impulsive<br>behaviours                                                                                   |
| Voluntary facial<br>expressions             | Twitching nose,<br>Sniffing, Tightly<br>shutting eyes                                                    | Looks<br>worried/scared                                                                                        | Smiles more                                                                                               |
| Communication<br>changes                    | Talking less,<br>Increased vocalising,<br>Throat noises                                                  | Mumbling, Attempts<br>to communicate<br>problem, Bids for<br>parent/carer's<br>attention                       | Increased vocalising,<br>Tone change,<br>Inappropriate<br>laughter                                        |
| Parental coping<br>strategies               | Communication,<br>Distraction                                                                            | Keep routine,<br>Reassurance,<br>Communication,<br>Physical contact,<br>Removal of stimulus/<br>from situation | Removal of<br>stimulus/from<br>situation, Distraction,<br>Positive<br>reinforcement                       |
| Duration<br>(minutes)                       | 15-30                                                                                                    | Situational                                                                                                    | N/A                                                                                                       |
| Anxiety<br>severity                         | Moderate                                                                                                 | Severe                                                                                                         | Severe                                                                                                    |

## B2. Categorising and cleaning coded items

**Table B2.** Process of categorising and cleaning codes.

| Interview Question                                                                             | Description of Changes                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Code Categorisation</i>                                                                     |                                                                                                                                                                                                                                                                                                                             |
| Section B – Question 6<br>Section C – Question 3                                               | Age was categorised using 1-year age bands. If multiple ages, or an age range was reported, we categorised age based on the youngest reported age (i.e., 5-6 would be categorised as 5).                                                                                                                                    |
| Section B – Question 19<br>Section C – Question 15                                             | Participants were coded as having either a first degree, other, or no relative(s) with a history of anxiety.                                                                                                                                                                                                                |
| <i>Code Cleaning</i>                                                                           |                                                                                                                                                                                                                                                                                                                             |
| Section A – Question 1, Prompt 1                                                               | Blank coding schemes were updated to reflect the subsequent interview section completed by parents/carers (i.e., if section B was completed, this would be recorded as bursts, aka. anxiety triggered by a specific stimulus).                                                                                              |
| Section B – Question 1, Prompt 2                                                               | If multiple responses were noted on the coding scheme (e.g., at least once a week, and at least once a month), a conservative estimate was taken. Additionally, the code 'Never' was updated to 'Never/less than once a month' to reflect events which were reported by parents/carers as having occurred only a few times. |
| Section B – Question 5; Question 16, Prompt 2<br>Section C – Question 7; Question 13, Prompt 2 | If multiple responses were noted on the coding scheme (e.g., mild and moderate), a conservative estimate was taken.                                                                                                                                                                                                         |
| Section B – Question 18<br>Section C – Question 14                                             | If a range of values were noted, then the higher score, reflecting more control, was taken.                                                                                                                                                                                                                                 |
| Section B – Question 7, Prompt 1<br>Section C – Question 4, Prompt 1                           | Responses were updated if they were illogical (i.e., if NA was marked, but a specific event or comment had also been noted).                                                                                                                                                                                                |
| Section B – Question 10<br>Section C – Question 5                                              | Responses were updated if written comments were reflected in the specific codes pre-determined by (Royston et al., 2021) (e.g., hyperventilation, updated to be coded as difficulty breathing).                                                                                                                             |

### B3. Interview item level agreement for coded items

**Table B3.1** Presenting Issue

| Item                           | % Agreement |
|--------------------------------|-------------|
| Anxiety                        | 100.00      |
| Anxiety Type                   | 100.00      |
| <b>Behaviours</b>              | -           |
| <i>Communication Changes</i>   | -           |
| Decreased vocalising           | 96.97       |
| Increased vocalising/shouting  | 84.85       |
| Talks to self                  | 100.00      |
| Talks to others                | 75.76       |
| Repetitive speech              | 93.94       |
| Reports feeling anxious        | 96.97       |
| Tone change                    | 93.94       |
| Stops initiating conversation  | 96.97       |
| Mumbling                       | 93.94       |
| Other <sup>a</sup>             | 75.76       |
| <i>Facial expressions</i>      | -           |
| Tense face/furrowed brow       | 93.94       |
| Grimacing                      | 100.00      |
| Frowning                       | 100.00      |
| Other <sup>a</sup>             | 100.00      |
| <i>Movements/actions</i>       | -           |
| Self-injury                    | 84.85       |
| Aggression                     | 90.91       |
| Crying                         | 93.94       |
| Repetitive behaviours          | 96.97       |
| Maintaining distance           | 96.97       |
| Defiance                       | 90.91       |
| Decreased activity/movement    | 87.88       |
| Pacing/restlessness            | 93.94       |
| Self-soothing behaviour        | 78.79       |
| Property destruction           | 96.97       |
| Muscle tension                 | 84.85       |
| Other <sup>a</sup>             | 72.73       |
| <i>Physiological Reactions</i> | -           |
| Blushing                       | 96.97       |
| Trembling/shaking              | 93.94       |
| Dizzy/unsteady                 | 100.00      |
| Palpitations                   | 96.97       |
| Difficulty breathing           | 96.97       |
| Chills/hot flushes             | 100.00      |
| Sweating                       | 100.00      |
| Nausea                         | 100.00      |
| Chest pain                     | 100.00      |
| Numbness/tingling              | 100.00      |
| Appetite change                | 100.00      |
| Increased urination            | 100.00      |
| Jumpy/on edge                  | 96.97       |

|                    |       |
|--------------------|-------|
| Other <sup>a</sup> | 93.94 |
| Frequency          | 93.75 |
| Severity           | 93.94 |
| Impact on CYP      | 96.97 |
| Impact on Family   | 93.94 |

<sup>a</sup>Presence of comment.

**Table B3.2** Predisposing Factors

| Item                | % Agreement |
|---------------------|-------------|
| Depression/low mood | 100.00      |
| Family History      | 96.97       |

**Table B3.3** Precipitating Factors

| Item                                    | % Agreement |
|-----------------------------------------|-------------|
| Age of Onset                            | 100.00      |
| <b>Events</b>                           | -           |
| Family relationship difficulty          | 96.97       |
| Chronic ill-health                      | 100.00      |
| School/work routine difficulty          | 100.00      |
| School/work difficulty + transitions    | 93.94       |
| Friendship difficulty/social isolation  | 96.97       |
| Lack of care/inappropriate parenting    | 100.00      |
| Poverty/inadequate living conditions    | 100.00      |
| Parent marital difficulties             | 100.00      |
| Death of a pet                          | 100.00      |
| Death of a relative/friend/known person | 100.00      |
| Other chronic adversity                 | 100.00      |
| Predominantly good experience           | 100.00      |
| NA                                      | 72.73       |
| <b>Antecedents/triggers</b>             | -           |
| Social/performance situations           | 90.91       |
| Welfare of significant others           | 96.97       |
| Separation/being alone                  | 87.88       |
| Every day events                        | 84.85       |
| Routine changes                         | 81.82       |
| New situations                          | 93.94       |
| Anticipatory worry about future events  | 96.97       |
| Health worries                          | 100.00      |
| Lack of sleep                           | 96.97       |
| Sensory overload                        | 87.88       |
| Aversive settings                       | 96.97       |
| Illness                                 | 100.00      |
| Specific phobias                        | 87.88       |

**Table B3.4** Coping Strategies

| Item                  | % Agreement |
|-----------------------|-------------|
| Perception of Control | 84.85       |

**Table B3.5** Other information

| Item                           | % Agreement |
|--------------------------------|-------------|
| <b>Intervention</b>            | -           |
| Medication                     | 96.97       |
| Behavioural                    | 100.00      |
| Onset – Gradual/Sudden         | 90.91       |
| Time of day                    | 81.82       |
| Behaviours occur in a sequence | 96.97       |
| Behaviours occur in a pattern  | 96.97       |
| Impact Change Over Time        | 96.97       |