**Clinical Research on the Lives of Individuals Diagnosed with Rare Genetic Syndromes**

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Thesis submitted in partial fulfilment of the requirements of Staffordshire University for the degree of Doctorate in Clinical Psychology

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**THESIS PORTFOLIO: CANDIDATE DECLARATION**

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| **Declaration and signature of candidate** |
| I confirm that the thesis submitted is the outcome of work that I have undertaken during my programme of study, and except where explicitly stated, it is all my own work.  I confirm that the decision to submit this thesis is my own.  I confirm that except where explicitly stated, the work has not been submitted for another academic award.  I confirm that the work has been conducted ethically and that I have maintained the anonymity of research participants at all times within the thesis.  Signed:  Date: 30.04.20 |

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| **DEDICATION** |

For my parents

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| **ACKNOWLEDGMENTS** |

Firstly, I would like to acknowledge the support of my research supervisor Dr Jane Waite. Thank you for agreeing to supervise me again and allowing me to contribute to the Bardet-Biedl syndrome project. Your guidance and feedback has been greatly appreciated.

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| **PREFACE** |

Chapters one and two are written in accordance with author guidelines for the American Journal of Medical Genetics Part A. The submission guidelines for this journal can be found in chapter one: Appendix A.

**Word Count**

Literature Review: 7261

Empirical Paper: 7999

Executive Summary: 1783

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| **THESIS ABSTRACT** |

This thesis was completed as part of the Professional Doctorate in Clinical Psychology at Staffordshire University.

Chapter one is a literature review that systematically evaluates fourteen empirical research studies that report on the behavioural, cognitive, emotional and social characteristics observed in individuals diagnosed with Rubinstein-Taybi syndrome (RTS). The results suggested that repetitive behaviour and challenging behaviour are likely to be specific features of RTS. High levels of sociability were also identified; however, the findings also reported a high prevalence of autism characteristics which seemingly contradicts the findings of heightened sociability. Similarly, several studies highlighted a heightened prevalence of anxiety, specifically obsessive compulsive disorder (OCD) in people with RTS; however, given the high levels of repetitive behaviour, it is possible that repetitive behaviours are being misattributed as OCD. These findings, along with their clinical implications, limitations and directions for future research are discussed further in chapter one.

Chapter two is an empirical study investigating the prevalence and predictors of anxiety and depression in adults diagnosed with Bardet-Biedl syndrome (BBS). This study was a cross-sectional self-report questionnaire study, where eighteen individuals with BBS took part. Correlational analyses showed that the number of physical health problems, intolerance to uncertainty, autism characteristics and executive dysfunction were positively correlated with anxiety and depression. A multiple regression analysis was conducted on the data, which revealed that the number of health problems and executive dysfunction predicted higher levels of both anxiety and depression in adults with this syndrome. Degree of visual impairment was also a predictor of depression. The results, clinical implications, limitations and future research are discussed further in chapter two.

Chapter three is an executive summary of the empirical research presented in chapter two. This has been written in an accessible format intended for dissemination to adults with BBS, their family members/carers and the general population.

**CHAPTER ONE:**

THE BEHAVIOURAL PHENOTYPE OF RUBINSTEIN-TAYBI SYNDROME: A LITERATURE REVIEW

**Abstract**

Rubinstein-Taybi syndrome (RTS) is a rare genetic syndrome associated with growth delay, phenotypic facial characteristics, microcephaly, developmental delay, broad thumbs and big toes. To date, the majority of research on RTS has focused on the physical characteristics and genetic components associated with the syndrome. However, a small number of studies have investigated the behavioural, cognitive, emotional and social characteristics of RTS (n=14), which are reviewed in this paper. The characteristics that are reported most commonly throughout the literature include repetitive behaviour, challenging behaviour, intellectual disability, mental health problems, Autism Spectrum Disorder (ASD) traits and heightened sociability. Due to several methodological limitations, which are discussed in the review, it is difficult to conduct comparisons between the studies; therefore the behavioural phenotype of RTS is yet to be established.

Keywords: Rubinstein-Taybi syndrome, behavioural phenotype, repetitive behaviour, autism, sociability, challenging behaviour, mental health

**Introduction**

RTS is a multiple congenital syndrome that was first described in 1958 by three Greek surgeons. The condition was later named after the two medical doctors (Jack Rubinstein and Hooshang Taybi) from the United States of America, who described the syndrome after they assessed two children with a number of shared clinical characteristics including specific facial features, developmental delay, delayed growth of height and weight, microcephaly, broad thumbs and big toes (Beets, Rodriguez-Fonseca, & Hennekam, 2014; Hennekam, 2006; Udwin & Dennis, 1995). Following this, another five individuals with very similar profiles were identified and the two doctors published the first research on RTS by documenting the condition in those seven individuals (Rubinstein & Taybi, 1963).

**Prevalence and Genetic Cause**

RTS is now estimated to occur in approximately one in 100,000 to 125,000 live births; however, confirmation of diagnosis can only be obtained in approximately 65-70% of cases (Hennekam, Van Den Boogaard, Sibbles, & Van Spijker, 1990). In 1992, the first genetic anomalies for RTS were discovered in chromosome 16 including breakpoints, mutations and microdeletions (Lacombe, Saura, Taine, & Battin, 1992). Following this, a gene named CREBBP was located at 16p13.3, which has now been identified to affect approximately 60-65% of individuals with RTS. A smaller number of individuals with RTS (3-8% of cases) are affected by a mutation in the gene EP300 (Roelfsema et al., 2005; Zimmermann, Acosta, Kohlhase, & Bartsch, 2007). Subsequent research literature often refers to these two sub-types of RTS as type 1 (CREBBP) and type 2 (EP300).

**Clinical Characteristics**

Over the last 50 years, a physical, cognitive and behavioural profile of RTS has been established through the work of geneticists, researchers and other health professionals. A number of distinctive physical features have been identified in individuals with RTS including a small head and short stature, a characteristic facial appearance including downwards-slanting palpebral fissures, raised nasal bridge, arched eyebrows, small upper lip, micrognathia and finally, broad thumbs and toes (Hennekam, 2006; Rubinstein & Taybi, 1963; Schorry et al., 2008; Udwin & Dennis, 1995). A range of health difficulties have also been identified in RTS including problems with the heart and renal system, gastroesophageal reflux, recurrent respiratory infections, constipation, increased risk of both benign and cancerous tumours and finally eye, dental and skeletal abnormalities (Baker, 1987; Hennekam et al., 1990; Kinirons, 1983; Rubinstein, 1990; Stevens & Bhakta, 1995; Wiley, Swayne, Rubinstein, Lanphear, & Stevens, 2003).

Cognitive characteristics in the syndrome include intellectual disability, deficits in short term memory, delayed speech and difficulties with attention (Hennekam et al., 1992; Stevens, Carey & Blackburn, 1990; Waite, Beck, Heald, Powis, & Oliver, 2016). There are also a number of behavioural characteristics exhibited by individuals with RTS including hyperactivity, impulsivity and repetitive behaviours such as repetitive speech and body stereotypy with emerging research indicating that particular repetitive behaviours appear to be more specific to RTS compared to other rare genetic conditions and ASD (Waite et al., 2015). Age-related changes have also been described in RTS, with reports that mood difficulties and temper tantrums increase with age (Hennekam et al., 1992).

**Behavioural Phenotypes**

The concept behavioural phenotype refers to an increased likelihood of individuals with a particular condition displaying a behaviour or set of behaviours compared to individuals who do not have that condition (Dykens, 1995). The term was first introduced by Nyhan (1972) through his research into the development of self-injurious behaviour in Lesch-Nyhan syndrome. Nyhan (1972) described the behaviours as an integral part of genetic conditions and emphasised the organic factors that lead to the development of these particular behaviours. Since then a more widely accepted definition of behavioural phenotypes has been described by Dykens (1995):

“…the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural or developmental sequelae relative to those without the syndrome”.

Emotional and cognitive characteristics can also be included in the definition of behavioural phenotypes despite not being directly observable, as they often have an impact on behaviours (Flint, 1996; Waite et al., 2014).

Describing the behavioural phenotype associated with a genetic syndrome improves understanding of the condition and helps clinicians to provide specific advice and support to individuals and their families (Waite et al., 2014). Furthermore, describing behavioural phenotypes informs the development of targeted interventions. This review aims to describe the behavioural phenotype of RTS by identifying literature that comments on the behavioural, cognitive and social characteristics of RTS. Mental health problems will be included in this review as they are often closely associated with cognitive and behavioural profiles. The literature will be summarised in the results section followed by an evaluation of the quality of the studies included in this review to identify gaps for future research studies.

**Method**

**Search Strategy**

A search of CINAHL, Medline, PsychINFO and Web of Science was carried out in June 2019 using the search terms: ‘Rubinstein-Taybi syndrome’, ‘Rubinstein Taybi’, ‘Rubinstein-Taybi’, ‘Broad Thumb Hallux’ and ‘16p13.3’and limited the search to only include papers that contain these keywords in the title. Truncations (\*) were used to ensure alternative word endings were included and to allow for variations in spelling. The “AND” and “OR” functions were employed to combine relevant search terms. In order to obtain studies that commented on the cognitive, behavioural and emotional phenotype of RTS, the following search terms were also employed through the use of “AND” and the advanced search function:

[behavio\* or psychiatr\* or psycholog\* or emotion or mood or "mental health" or social\* or Autism or Autistic or "Autis\* Spectrum Disorder" or ASD or Cogniti\* or "executive function" or "attention deficit hyperactivity disorder" or ADHD or intelligen\* or intellectual\* or IQ or "mental illness" or "adaptive function" or psychosocial or affect\* or hyperactiv\* or impulsiv\* or overactiv\* or "repetitive behavio\*" or aggression or aggress\* or "problem behavio\*" or "challenging behavio\*"]

***Selection of studies***

A total of 340 articles were identified. Following the removal of duplicates, 233 articles remained and these were then screened by title and abstract. Studies were excluded based on exclusion criteria (see table 1). A total of 218 studies were excluded, including studies that did not comment on the cognitive, behavioural or emotional phenotype of RTS (n=158), case studies (n=49), animal studies (n=7) and conference abstracts (n=4). The full texts of the remaining 15 studies were accessed and one further paper was excluded as it did not comment directly on the cognitive, emotional or behavioural phenotype of RTS. The remaining 14 were deemed appropriate and were included in the review (see figure 1).

*Table 1. Exclusion Criteria*

|  |
| --- |
| Exclusion Criteria |
| Case Studies, Reviews/Meta-analyses, Books, Chapters |
| Non-Human Studies |
| Behavioural, Emotional, Cognitive, Psychiatric or Social characteristics are not the main focus of the study. |
| Study of participants without RTS |
| Studies of mixed diagnoses if RTS is not commented on separately |

Results deduplicated. (*n*=233)

Results screened by title and abstract using exclusion criteria. (*n*=15)

Full texts assessed for eligibility (*n*=14)

Total full texts excluded: (*n*=1).

Full texts were not available at the time of the review (*n*=1)

**Papers included in final review (*n*=14)**

Results from combined database searches. (*n*=340)

(CINAHL, *n*=18; MEDLINE*n*=171; PsychINFO, *n*=31; Web of Science, *n*=120)

Records excluded from screening title and abstract (*n*=218):

Did not comment on behavioural phenotype (n=158)

Case Studies (n=49)

Animal Studies (n=7)

Conference Abstract (n=4)

Duplicates removed (*n*=107)

*Figure 1. PRISMA Flowchart (Moher, Liberati, Tetzlaff, & Altman, 2009)*

**Quality Review**

The literature was appraised using quality criteria adapted from a meta-analysis on the prevalence of ASD in rare genetic syndromes (Richards, Jones, Groves, Moss, & Oliver, 2015). The quality criteria adapted for this review relates to the methodological constraints of the study in relation to answering the specific question addressed in this literature review, rather than an objective measure of the overall quality of the study per se. The framework was based on four factors, thought to reflect the key threats to internal and external validity: sample identification, confirmation of RTS diagnosis, properties of measures and inclusion of comparison groups (see table 2). Each domain was scored from 0 (poor) to 3 (excellent) producing a total score for each paper which was then divided by the highest possible score (12). This therefore produced a final score ranging from 0 (lowest possible score) and 1 (highest possible score). All scores were reported to 2 decimal places (see table 3). A second researcher also completed quality ratings using the chosen appraisal framework for 21.4% of the papers. An excellent level of inter-rater reliability (91.7%) was achieved.

More formal measures of study quality were considered, such as the Downs and Black (1998) checklist and the Appraisal Tool for Cross Sectional Studies (AXIS; Downes, Bennan, Williams, & Dean, 2016); however, these scales place emphasis on less influential factors such as the inclusion of a structured abstract and the funding source of the research, rather than factors that fundamentally impact on the reliability and validity of the findings, such as the method of recruitment and the use of standardised measures.

*Table 2. Appraisal criteria adapted from Richards et al. (2015)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 0  Poor | 1  Adequate | 2  Good | 3  Excellent |
| Sample Identification | Unreported. | Single restricted/ non-random sample (e.g. specialist clinic/previous research study).  Single non-random regional-based sample (e.g. regional family support groups). | Multiple restricted/non-random samples (e.g. multi-region specialist clinics/hospitals)  National non-random samples (e.g. national family support groups)  A combination of the above. | Random population sample.  Total population sample. |
| Confirmation of RTS Diagnosis | Unreported/ unconfirmed.  Clinical diagnosis only suspected. | Clinical diagnosis by general clinician (e.g. general practitioner, paediatrician).  Diagnosis by application of broad diagnostic criteria. | Clinical diagnosis by ‘expert’ clinician (e.g. clinical psychologist). | Genetic confirmation.  Confirmation is made clinically **and** genetic testing was carried out during the study. |
| Properties of Measures | Unreported/ unspecified.  Qualified subjectively. | Non-standardised measures developed specifically for the study, with unknown reliability/validity. | Measures with unknown/poor reliability/validity.  Assessment by an ‘expert’. | Standardised measures with moderate-good validity/reliability.  Assessment by an ‘expert’, validated by a second ‘expert’. |
| Comparison Groups | Unreported.  No control group.  Does not compare to standardized scores. | Compares to standardized scores in general population.  Compares to a historical control group (e.g. control group from previous studies). | Compares to standardized scores in comparable population (e.g. intellectual disability).  Compares to a concurrent control group. | Compares to a concurrent control group that is matched by age and gender, as well as other features pertinent to the research question. |

**Results**

***Behavioural Characteristics***

Eight of the fourteen studies presented findings relating to behavioural characteristics of RTS. The characteristics reported across studies that may be aspects of the behavioural phenotype of RTS include: self-stimulatory/repetitive behaviours, aggressive behaviour and self-injurious behaviour.

*Self-stimulatory/repetitive behaviour*

Five studies commented on self-stimulatory/repetitive behaviours, all of which report heightened levels of these behaviours in individuals with RTS. Stevens et al. (1990) reported that 65% of their sample of children with RTS displayed what they describe as “unusual behaviours” which are reported as being primarily self-stimulatory in nature, including rocking, spinning and hand flapping. Repetitive speech was reported in 57% of children with RTS and 84.6% of adults with RTS; however, repetitive movements seemed to be lower in adults (38.5%) compared to children (77.4%) (Boer, Langton & Clarke, 1999). Neither study compared these findings to typically developing individuals or individuals with other rare genetic syndromes or intellectual disability of heterogeneous aetiology.

Studies that included comparison groups also reported higher levels of self-stimulatory/repetitive behaviours in RTS. When comparing children with RTS to a comparison group of typically developing children, Galéra et al. (2009) found that children with RTS scored significantly higher on the items “flaps arms/hands when excited”; “makes off/fast movements with fingers/hands” and “pleased by movements/keeps doing them” (p<.05). Other findings showed that when matched for degree of intellectual disability, children with RTS displayed significantly more self-stimulatory behaviours compared to the children without RTS (Gotts & Liemohn, 1976).

Comparisons between RTS and other syndrome groups were carried out by Waite et al. (2015) who described a profile of repetitive behaviour in RTS by comparing to Down syndrome (DS), fragile X syndrome (FXS) and ASD. Findings indicated more frequent occurrence of stereotyped behaviour and compulsive behaviour in individuals with RTS compared to individuals with DS, which did not differ from FXS or ASD. By examining the types of repetitive behaviours displayed between the syndrome groups, at fine-grained level of description, an uneven profile of repetitive behaviour was identified with the RTS group displaying more frequent hand, object and body stereotypy, hoarding and repetitive questioning compared to the DS group. However, RTS had lower levels of restricted conversation and echolalia when compared to FXS and ASD. The RTS group also showed lower levels of adherence to routine and hand stereotypy than individuals with FXS.

*Aggressive and Self-Injurious Behaviour*

Seven studies commented on challenging behaviour including aggressive behaviours and self-injurious behaviours. The prevalence of challenging behaviours varies across the studies with common behaviour problems reported to occur in 25% of individuals with RTS (Hennekam et al., 1992) and 10% of maladaptive behaviours reported to be moderate to severe (Stevens et al., 1990). Boer et al. (1999) reported high levels of ‘verbal abuse’ in both children and adults with RTS (86.2% and 84.6% respectively) with other studies reporting less prevalent aggressive behaviour in adults with RTS (10.8%) (Schorry et al., 2008). One study reported age related differences in RTS with older individuals with RTS (>13 years) displaying significantly more aggressive behaviour that younger individuals with RTS (Yagihashi et al., 2012). When compared with a comparison group matched for intellectual ability, the comparison group showed significantly lower levels of residual anger than the RTS group (Gotts & Liemohn, 1976). However, in contrast to these findings, Galéra et al. (2009) found no significant difference between the RTS children and the typically developing children for ‘temper tantrums or hot temper’.

Only three studies commented specifically on self-injurious behaviour in RTS and the prevalence estimates varied across the studies, ranging from 6.5% to 53.8% (Boer et al., 1999; Schorry et al. 2008). Boer et al. (1999) reported a lower prevalence of self-injurious behaviour in children with RTS (45.2%) compared to adults with RTS (58.3%); however Stevens, Pouncey and Knowles (2011) reported a lower prevalence of self-injurious behaviour (32%) of their sample of adults with RTS, which may be due to the use of different measures. These findings differed from Schorry et al. (2008) who reported that only 6.5% of their sample of individuals with RTS displayed self-injurious behaviours; however, the age range of the sample is unknown and the estimate of self-injurious behaviour was produced by examining developmental and school performance data. None of the studies reported the topography of self-injurious behaviour in RTS.

***Cognitive Characteristics***

Four studies commented on the cognitive characteristics associated with RTS; however, there was variability in the extent of cognitive impairment reported across the studies. Levitas and Reid, (1998) reported that 33.3% of their sample had a mild intellectual impairment, 16.7% had a moderate intellectual impairment and 50% had a severe/profound intellectual impairment. However, Schorry et al. (2008) reported that 44.3% of their sample had an IQ below 50, 53.2% with an IQ between 50 and 75 and 2.5% with an IQ above 75. Another study reported a mean IQ of 35.6 (range 25-79) and a sharp decline in IQ as age increased (Hennekam et al., 1992)

Other studies that have focused on more specific cognitive impairments have reported impairments in the working memory trajectory of individuals with RTS (Waite et al., 2016). For example, Waite et al. (2016) found that there were no significant differences between the RTS group and the matched control group on the visuo-spatial working memory tasks at the youngest developmental age of measurement (3 years old); however, the typically developing group’s cross sectional trajectory has a positive slope with age, whereas this remains flat for the RTS group. This suggests a specific visuo-spatial working memory difficulty in RTS.

***Emotional and Psychiatric Characteristics***

Six studies discussed psychiatric or emotional difficulties in individuals with RTS. Levitas and Reid (1998) reported 61% of individuals with RTS were identified as having a ‘mood disorder’ and 31% were identified as having tics or OCD. Another study reported that 31% of adults with RTS had received a psychiatric diagnosis, mostly OCD, anxiety or depression (Stevens at al., 2011). Age related differences were also reported in one study, with older individuals with RTS (>13 years) displaying higher levels of anxiety, depression, nervousness and fearfulness compared to younger individuals (<13 years) with RTS (Yagihashi et al., 2012).

Studies that compared emotional and psychiatric characteristics in RTS to individuals without RTS have shown mixed results. Two studies compared anxiety in individuals with RTS and typically developing individuals, yet produced contrasting results. Crawford, Waite and Oliver (2017) reported significantly lower levels of social phobia in individuals with RTS, and significantly higher levels of panic/agoraphobia and OCD; however they noted that an OCD diagnosis in RTS should be applied extremely cautiously given that repetitive behaviour in the syndrome may be misattributed as a symptom of OCD. As well as including a typically developing comparison group, Crawford et al. (2017) also included a comparison group of typically developing individuals who had a diagnosis of anxiety. Galéra et al. (2009) found significantly lower levels of anxiety in the RTS group compared to a control group of typically developing children. It is important to note that Crawford et al., (2017) had a broader age range of participants with RTS including some adults; Galéra et al. (2009) only included children with RTS, which might explain the different findings. Another study controlled for the degree of intellectual disability and found that the comparison group of individuals with ID of heterogeneous aetiology had significantly lower levels of anxiety symptoms compared to the children with RTS (Gotts & Liemohn, 1976).

***Social Characteristics***

Eight studies reported findings related to social characteristics including difficulties with social skills and ASD. Stevens et al. (2011) reported behaviours pertaining to autism including requiring strict routines (62%), difficulty with tolerating noises and crowds (62%) difficulty with tolerating unexpected change (62%) and self-stimulatory behaviours (61%), however, the authors reported that only 19% of adults with RTS were diagnosed with autism. Another study reported that 43.75% of individuals with RTS met the cut off for ASD (Crawford et al., 2017) using the ASD screening tool Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003). Waite et al. (2015) reported that individuals with RTS on average had a moderate score on SCQ for social and communication difficulties; although, they also reported that scores on the SCQ were likely elevated due to repetitive behaviour in RTS rather than social-communication difficulties.

Heightened levels of sociability or enhanced social skills were reported in five studies. Individuals with RTS showed higher levels of social competence compared to individuals without RTS and when compared to typically developing children, social contact and interest were found to be significantly higher in the RTS group (Hennekam et al., 1992; Galéra et al., 2009). These findings are consistent across all the studies measuring social characteristics with over friendliness reported in 77.3% of children with RTS (Boer et al., 1999) and the RTS group were found to ‘accepts social contacts readily’ significantly more than the matched comparison group (Gotts & Liemohn, 1976). Cross syndrome comparisons also showed heightened levels of sociability in individuals with RTS when compared to individuals with Cornelia de Lange syndrome (CdLS), FXS and ASD (Moss et al., 2016).

An additional study aimed to further the understanding of varied profiles of sociability observed in rare genetic syndromes by identifying whether the social impairment observed in CdLS and the heightened sociability observed in RTS are subcortically or cognitively mediated through the use of a face scanning task. No significant differences were observed between the two syndromes indicating that the contrasts in sociability between the two syndromes are unlikely to be subcortically mediated (Crawford et al., 2015).

*Table 3. Summary of all studies and quality scoring.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Authors (year)** | **Study Aims** | **RTS Sample**  **N**  **(age range)** | **Comparison Group**  **N**  **(age range)** | **Measures** | **Main Findings** | **Quality Score** |
| **Boer, Langton & Clarke (1999)** | To describe the developmental and behavioural aspects of RTS. | 44  (3-51 years):  31  (children 3-16 years)  13  (adults 17-51 years) | None | The Study of Behavioural Phenotypes Postal Questionnaire (SSBP-PQ; O’Brien, 1995) | Repetitive speech: children (57%) and adults (84.6%)  Repetitive movements: children (77.4%) and a  dults (38.5%)  Self-injurious behaviour: children (45.2%) and adults (53.8%)  Verbal abuse in children (86.2%) and adults (84.6%)  “Too friendly with strangers”: children (77.3%) and adults (33.3%) | 0.42 |
| **Crawford et al (2015)** | To further the understanding of whether the documented differences in social behaviour in RTS and CdLS are subcortically or cognitively mediated. | 17  (4-37 years) | CdLS: 15  (6-33 years) | Eye-Tracking Task  Social Communication Questionnaire (SCQ; Rutter et al, 2003)  Vineland Adaptive Behaviour Scale (VABS; Sparrow, Cicchetti & Balla, 2005) | No significant differences between the RTS group and the CdLS group on the amount of time spent looking at the face stimuli.  Both groups spent more time looking at disgust faces compared to neutral faces but not a higher amount of time looking at happy faces compared to disgust faces.  Conclusion: differences in sociability between RTS and CdLS are unlikely to be subcortically mediated. | 0.75 |
| **Crawford, Waite & Oliver (2017)** | To enhance understanding of anxiety in individuals with RTS, FXS and CdLS by investigating anxiety at symptom level. | 17  (mean age: 23.55 years) | CdLs:13  FXS:19  Typically developing children: 261  Typically developing children with anxiety: 484 | VABS  SCQ  The Spence Child Anxiety Scale (Spence, 1999) | High levels of social phobia in the RTS group compared to the typically developing control group.  Lower levels of panic/agoraphobia and OCD in the RTS group compared to typically developing control group.  No differences between the RTS group and the typically developing participants with anxiety for panic/agoraphobia and OCD.  43.75% of RTS group met the cut off for ASD | 0.67 |
| **Galéra et al (2009)** | To determine whether behavioural features in children with RTS, differ from those found in children with intellectual disability of heterogeneous aetiology. | 39  (4.3-15.8 years) | Typically developing children:39  (4.4-15.5 years) | Child Behavior Checklist (CBCL; Achenbach, 1991)  Children’s Social Behavior Questionnaire (CBSQ; Lutejin et al. 1998) | Lower levels of anxiety in the RTS group compared to the control group.  Poorer attention and concentration in the RTS group than the control group.  RTS group displayed significantly more motor stereotypies including “flaps arms and hands when excited”, “makes odd or fast movements with fingers or hands” and “extremely pleased by certain movements/keeps doing them” than the control group.  Higher levels of sociability in the RTS group compared to the control group.  No differences for mood or temper disturbances between RTS group and the control group. | 0.83 |
| **Gotts & Liemohn (1976)** | To document the behavioural characteristics of children with RTS. | 3  (7-10 years) | Children with intellectual disability of heterogeneous aetiology: 15 | Leary & Coffey (1955) Behavioral Checklist | The matched control group showed significantly lower levels of the following compared to the RTS group:  Anxiety symptoms  Short attention span difficulties  Overreaction to stimulation/being highly excitable  Accepting social contact  Residual anger | 0.42 |
| **Hennekam et al (1992)** | To document the psychological examinations of individuals with RTS. | 40  (2.7-60.3 years) | None  For analysis of social competency and temperament only, compared RTS to existing data from “a group of persons with mental retardation” | Weschler’s Intelligence Scale for Children Revised (WISC-R; Weschler, 1973)  Weschler’s Preschool & Primary Scale of Intelligence (WPPSI; Weschler, 1989)  Stutsmans Intelligence Test (Cattell, 1940)  Bayley Scales of Infant and Toddler Development (Bayley, 1969)  Achenbach Behavior Checklist (Achenbach, 1979) | RTS IQ mean = 35.6; range=25-79  There is a sharp decline in IQ as age increases  RTS group displayed higher levels of social competence when compared to control group data.  Common behaviour problems occurred in over 25% of the RTS group.  41% of the RTS group were reported to have “temper tantrums.” | 0.58 |
| **Levitas & Reid (1998)** | To report the psychiatric evaluation of individuals with RTS. | 13  (24-51 years) | None | Psychiatric Assessment | IQ ranged from mild to severe.  No association between IQ and psychiatric diagnosis.  Mood disorders prevalence (61%)  Tic/OCD prevalence (31%)  Schizophrenia, Generalised Anxiety Disorder and panic were not observed | 0.42 |
| **Moss et al (2016)** | To examine the nature and developmental trajectory of sociability in AS, CdLS, DS, FXS and RTS. | 88  (4-49 years) | AS: 66  (aged 4-48 years)  CdLS: 98  (4-43 years)  FXS: 142  (9-49 years)  DS: 117  (4-62 years) | Sociability Questionnaire for People with Intellectual Disability (SQUID; Moss et al, 2016)  Wessex Scale (Kushlick, Blunden & Cox, 1973)  SCQ | Higher levels of sociability in RTS, Angelman syndrome and Down syndrome compared to CdLs, fragile X syndrome and ASD in various social contexts.  Individuals with RTS and Angelman syndrome shared a similar level of sociability except for “initiating interaction” where the Angelman syndrome group scoring significantly higher.  High levels of “extreme socialibility” in RTS group during familiar and unfamiliar social situations. | 0.67 |
| **Schorry et al (2008)** | To evaluate the genotype-phenotype correlations in individuals with RTS. | 93 | None | Developmental and school performance data were examined.  Autism features were assessed via physician interview | Self-injurious behaviour (6.5%)  Aggressive behaviour (10.8%)  IQ <50: (44.3%)  IQ 50-75: (53.2%)  IQ >75: (2.5%) | 0.42 |
| **Stevens, Carey & Blackburn (1990)** | To document the development and behaviour of individuals with RTS living in institutions. | 50  (1-26.5 years) | None | Parental Questionnaire (no further details provided)  The Inventory for Client & Agency Planning – maladaptive behaviour section only (Bruininks, Hill, Weatherman & Woodcock, 1986) | IQ mean = 51 (range= 30-79)  Short attention span: (90%)  Sensitivity to sound: (46%)  “Unusual behaviours” including self-stimulatory behaviours: (65%)  Moderate- serious maladaptive behaviours: (10%) | 0.58 |
| **Stevens, Pouncey & Knowles (2011)** | To document the medical issues, education, independence and behaviour problems in adults with RTS. | 61  (18-67 years) | None | Caregiver questionnaire (no further details provided) | Attention span: (72%)  Distractibility: (70%)  Impulsivity (56%)  Disruptive actions: (29%)  Psychiatric diagnosis: the majority of which were OCD, anxiety, or depression: (31%)  Self-injury: (32%)  Autistic type behaviours: - needing a strict routine: (62%); intolerance of noise/crowds: (62%); difficulty with change in the environment: (62%); and self-stimulation behaviours: (61%). | 0.42 |
| **Waite et al (2015)** | To compare the profile of  repetitive behaviours in RTS, ASD, DS and FXS; to explore the association between repetitive behaviour and  ASD phenomenology  across groups; to  explore associations between repetitive behaviour and  degree of disability across groups. | 87  (aged 4-59 years) | ASD: 228  (4-45 years)  Fragile X syndrome:196  (aged 6-47 years)  Down syndrome: 132  (4-62 years) | Wessex Scale  SCQ  Repetitive Behaviour Questionnaire (RBQ; Moss et al, 2009) | RTS group scored higher on stereotyped behaviour and compulsive behaviour compared to Down syndrome group.  RTS had significantly higher levels of repetitive speech than Down Syndrome.  No differences were found for restricted preferences and insistence on sameness for RTS compared to other syndromes.  RTS group showed heightened levels of stereotypy, hoarding, preference to routine, repetitive questions and phrases compared to Down syndrome group.  RTS had lower levels of restricted conversation, repetitive phrase and echolalia than ASD and fragile X syndrome, lower levels of adherence to routine and hand stereotypy than fragile X syndrome.  RTS had heightened scores on body stereotypy compared to Down syndrome. Lower levels of restricted conversation and repetitive phrases relative compared to ASD group and fragile X syndrome. | 0.75 |
| **Waite et al (2016)** | To explore the cross sectional developmental trajectories of working memory domains in RTS. | 21  (aged 6-37 years) | Typically developing children: 89  (3-7 years) | Mullen Scales of Early Learning (Mullen, 1995)  Wechsler’s Abbreviated Scale of Intelligence (WASI-II)  VABS  Verbal Animal Scan (Bull et al. 2004)  Corsi Blocks (Pickering, Gathercole & Peaker, 1998)  Scrambled Boxes (Diamond, 1990) | RTS working memory varied depending on the aspect of working memory measured.  The typically developing control group consistently outperform RTS group with higher mental age performed better than on verbal and visuo-spatial working memory.  Differences in the trajectory of working memory- RTS trajectory remains flat in contrast to a positive slope in the control group group. | 0.67 |
| **Yagihashi et al (2012)** | To compare behavioural difficulties in children and adults with RTS | 63  (1-38 years) | None | CBCL (Achenbach, 1991) | Older individuals (>13 years) with RTS scored higher on anxiety, depression, nervous highly strung or tense, attention difficulties, too fearful/anxious compared to younger group (<14 years) with RTS.  Older individuals with RTS showed significantly more aggressive behaviour than the younger individuals (p=0.036) | 0.5 |

**Discussion**

The results suggest that several behavioural, cognitive, social and psychiatric characteristics are commonly present in individuals with RTS, including repetitive behaviour, challenging behaviour, intellectual disability, ASD characteristics, heightened sociability, mood disorders and anxiety including OCD. However, these findings should be treated with caution as the lack of replication and comparison groups in many of the studies makes it difficult to ascertain whether these characteristics are more likely to occur in individuals with RTS compared to people with intellectual disability of heterogeneous aetiology. Moreover, the measures and method used to obtain the data varies between the studies making comparison of the reported characteristics more difficult. It is also important to note that the characteristics reported in the studies have been separated into categories for brevity; however, there is likely to be interaction between these characteristics.

A variety of methods were employed to measure behavioural, cognitive, social and psychiatric aspects of RTS, which may have impacted the findings that were reported. For example, prevalence estimates for repetitive movements varied between 31% and 77.4% across the studies (Boer et al., 1999; Galéra et al., 2009). The variability in estimates may partly be explained by the different measures employed to identify repetitive movements. Certain measures such as the Study of Behavioural Phenotypes Postal Questionnaire (SSBP-PQ; O’Brien, 1995), ask respondents to report the presence of repetitive movements using ‘yes/no’ responses, whereas other measures such as the Child Behavior Checklist (CBCL; Achenbach, 1991) and Repetitive Behaviour Questionnaire (RBQ; Moss, Oliver, Arron, Burbidge, & Berg, 2009) ask respondents to indicate the type of repetitive movement displayed. Moreover, the RBQ measures the frequency of repetitive behaviours allowing for a more detailed understanding of repetitive behaviour.

The large differences in the prevalence of challenging behaviour may be explained by the lack of a clear definition of challenging behaviour across the studies and the different methods used to identify such behaviours. Challenging behaviours are considered to be “behaviours of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy” (Emerson, 1995). Research studies focusing on the epidemiology of challenging behaviour identified specific behaviours that are considered to fall within the category of challenging behaviour, including aggression, self-injurious behaviour and property destruction (Borthwick-Duffy, 1994; Kiernan & Qureshi, 1993; Qureshi, 1994; Qureshi & Alborz, 1992). Hennekam et al. (1992) reported that common behaviour problems occurred in 25% of individuals with RTS; however, closer inspection of their chosen tool (Achenbach Behavior Checklist; Achenbach & Edelbrock, 1983) revealed a variety of behaviours that may not necessarily involve any aggression, self-injurious behaviour or destruction of property. Examples of these behaviours include ‘wets bed’, ‘thumb-sucking’, ‘picks nose’ and ‘temper tantrums’.

All of the studies that have reported on aggressive behaviour and self-injurious behaviour have used different methods for data collection, none of which included direct observations of challenging behaviour. Two studies did not clearly report the measures or method used to identify challenging behaviour in RTS; for example, Schorry et al. (2008) provided no clear information on how the challenging behaviour data was collected. Similarly, Stevens et al. (2011) provided no information on the method of identifying and measuring challenging behaviours other than using an informant questionnaire and subsequently, both studies received the lowest scores on the quality assessment tool (0.42). Although overall the findings point towards the presence of challenging behaviours in RTS, it is very difficult to ascertain a detailed profile of these behaviours without a clear definition of what is defined as a behaviours that challenge as well as incomplete information on the methods used to identify them.

The results also identified a high prevalence of ASD characteristics in RTS including restricted preferences, sensitivity to noise, difficulties with unexpected change and self-stimulatory behaviours (Stevens et al., 2011). These findings are not unexpected as research has shown higher rates of ASD in rare genetic conditions compared the general population (Richards et al. 2015); however, it is important to recognise that none of the studies used comprehensive observational assessments to identify ASD, such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). All of the studies used informant questionnaires to identify the presence of characteristics associated with ASD.

Some of these measures may not be validated for the identification of autism characteristics; for example, Stevens et al. (2011) used a parental questionnaire; however, they did not elaborate on whether this was a standardised questionnaire designed to assess behavioural difficulties and ASD traits in rare genetic syndromes. The article subsequently received a low score for the domain ‘properties of measures’ and the lowest total score on the quality assessment tool (0.42) (see Appendix B). On the other hand, two studies (Crawford et al., 2017; Waite et al., 2015) used the SCQ (Rutter et al., 2003), which is a well-validated tool that identifies ASD characteristics in individuals with intellectual disability. The measure has high concurrent validity with the ADOS, as the total score on the SCQ is strongly related to the total score on the ADOS (Berument, Rutter, Lord, Pickles, & Bailey, 1999; Lord, Rutter, & Le Couteur, 1994), which is a strength of the papers that chose to use this measure. Both papers received the highest possible score for the domain ‘properties of measures’ (3; excellent) and scored “good” for the overall quality of the papers (0.67 and 0.75, respectively). However, the studies using the SCQ have only reported the total cut off scores to show the level of ASD characteristics present; they have not reported ASD traits at a domain level. Repetitive behaviour, for example, is a common feature of autism spectrum phenomenology, and given that many of the studies have identified a heightened prevalence of repetitive behaviours in individuals with RTS, it is likely that many individuals with RTS meet the cut off for ASD due to the presence of repetitive behaviour alone.

According to the DSM-V (American Psychiatric Association, 2013) and the ICD-11 (World Health Organisation, 2018), autism is classified by the presence of two core features which include deficits in social interaction and communication and the presence of restrictive and repetitive patterns of behaviour. Therefore the studies that have highlighted heightened sociability in RTS, seemingly contradict the research showing a prevalence of ASD in RTS. The high levels of repetitive behaviour but seemingly preserved social functioning suggest a dissociation of behaviours across the ASD dyad of impairments in individuals with RTS. Similar results have also been identified in other rare genetic syndromes, such as FXS (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). For example, research has identified significantly less impairments across a large number of social and communicative behaviours in FXS compared to individuals with ASD, yet many individuals with FXS still meet the cut-off for ASD using the SCQ (Hall et al., 2010). More detailed descriptions of sociability in FXS have found that although individuals with the syndrome display shyness, social anxiety and gaze avoidance, emotion sensitivity and willingness to interact may also be preserved (Cornish, Turk, & Levitas, 2007; Hall, DeBernardis, & Reiss, 2006; Turk & Graham, 1997). These characteristics are very different to the original descriptions of severe social withdrawal in ASD as noted by Leo Kanner (Kanner, 1943).

Similarly the behavioural phenotype of Angelman syndrome (AS) is characterised by excessive sociability, heightened levels of laughing and smiling behaviour and an interest in seeking out interaction with adults (Horsler & Oliver, 2006). However, studies examining the prevalence of ASD in AS have identified that ASD is strongly associated with the syndrome (Bonati et al., 2007; Trillingsgaard, & Østergaard, 2004), which seems inconsistent with the social profile that is characteristic to this syndrome. Similar findings for CdLS were reported by Moss, Howlin, Magiati, & Oliver, (2012) who compared the presentation of ASD symptomatology in CdLS to individuals with ASD using the ADOS (Lord et al., 2000). The results showed that many of the individuals with CdLS met the cut off for autism based on the total ADOS score; however, domain and item specific analysis showed that individuals with CdLS displayed more eye contact and gestures but less repetitive behaviour and stereotyped speech than the ASD group. These findings, along with research reporting prolonged eye gaze and heightened social anxiety (Collis, Oliver, & Moss 2006; Goodban, 1993), suggest that the profile of social impairments in CdLS may be different to that observed in ASD. This adds to previous findings which suggest that the repetitive and stereotyped behaviour aspect of the dyad of impairments in ASD contributes less to the ASD profile in CdLS than impairments in communication and social interaction (Oliver, Berg, Moss, Arron, & Burbidge, (2011).

Delineation of the profile of ASD in these syndromes clearly shows how subtle differences in phenomenology can be obscured if associations with ASD are based solely on clinical cut off scores and this may also be the case with RTS, as all of the studies included in this review used informant questionnaires to identify autism characteristics. The results indicate that RTS shows a dissociation across the dyad of impairments adding to the literature that suggests a fractionation in the dyad of impairments, which has implications for how ASD is researched and conceptualised.

The prevalence estimates for psychiatric difficulties in RTS varies between 31%- 61%. This is higher than the general population, which is reported at 29.2% (Steel et al., 2014), suggesting that individuals with RTS are at higher risk of developing a psychiatric illness. However, it is possible that due to the challenges associated with identifying mental health difficulties in individuals with intellectual disability, such as difficulties with providing verbal accounts of symptoms and the lack of validated diagnostic tools, mental health difficulties may be under- reported in RTS (Costello & Bouras, 2006; Moss, Emerson, Bouras, & Holland, 1997). Conversely, several studies drew particular attention to the presence of anxiety disorders and specifically to a heightened prevalence of OCD; however, given that OCD is conceptualised by the presence of obsessive, intrusive thoughts and compulsions, often described as repetitive behaviours or rituals (APA, 2013; WHO, 2011), it is possible that OCD is over-reported in RTS due to the presence of repetitive/stereotyped behaviours in the syndrome. Without controlling for repetitive behaviours in the syndrome, it is difficult to conclude that there is a heightened prevalence of psychiatric difficulties in RTS.

The findings presented by Yagihashi et al. (2012) points towards age-related differences in the psychiatric profile of RTS; however, no clear trajectory of psychiatric illness was established and depression and anxiety were not reported separately. Moreover, the chosen measure (CBCL) is not validated for use with individuals over the age of 15 years, which again highlights the need for more appropriate measures to identify behavioural, cognitive and emotional characteristics in individuals with intellectual disability, particularly as a proportion of people with RTS have severe intellectual disability. There are few measures available for detecting mental health difficulties in those with severe intellectual disability (Flynn et al., 2017).

Half of the articles in this review did not include any comparison groups, therefore 7 papers received a score of 0 (poor) for this domain. In order to establish a behavioural phenotype in any syndrome, there must be substantial evidence that the behaviour or set of behaviours is significantly more common in individuals with the syndrome than those without the syndrome, whilst controlling for the degree of intellectual disability (Dykens, 1995). The inclusion of comparison groups is therefore imperative and due to the lack of comparison groups in many of the papers included in this review, we cannot conclude that all of the characteristics discussed in this review are phenotypic of RTS.

**Clinical Implications**

The findings suggest that repetitive behaviour and challenging behaviour are likely to be specific features of RTS, thus highlighting the need for appropriate support for individuals who display these behaviours. There are effective interventions available to support those experiencing behaviours that challenge (Iwata et al., 1994), therefore it is important to understand the function of the challenging behaviour, particularly as the effectiveness of an intervention is increased when the function of a behaviour is understood (Hurl, Wightman, Virues-Ortega, & Haynes, 2016). This will allow for appropriate interventions to be used to support individuals who display these behaviours, as well as those who care for them.

There is a growing body of evidence showing that challenging behaviour can be maintained via operant reinforcement (Oliver, 1995) therefore the National Institute of Clinical Excellence have emphasised the importance of assessing the function of behaviour, changing reinforcement contingencies, teaching alternative functional communication strategies and educating families about how behaviours are shaped over time (NICE, March 2018). Challenging behaviour has been found to be higher in individuals who have an increased need of assistance and those who have restricted receptive and expressive communication (Emerson & Bromley, 1995; Emerson et al., 2001), therefore managing factors that we know are associated with challenging behaviour for example through supporting the development of communication from an early age and providing increased mobility support, will help towards preventing and managing behaviours that are challenging.

There is also evidence to show that high frequency repetitive behaviour can be a predictor of both the presence and the severity of challenging behaviour in individuals with intellectual disability (Oliver et al., 2011) therefore providing carers with support for managing repetitive behaviours such as those offered to individuals with ASD may also help with the management of challenging behaviours.

**Limitations of this review**

There are some limitations to this review that need to be considered. Despite conducting a systematic search of the literature, it is possible that some publications were missed or overlooked as some articles may not have been listed in the identified databases. Furthermore, due to limiting the search to only include papers that contain the search terms in the title, it is also possible that some papers commented on the behavioural phenotype of RTS but were screened out in the initial search. Finally, due to time constraints, unpublished theses were not searched, which may have resulted in publication bias; therefore it is possible that relevant unpublished research has been missed in the process.

**Conclusion**

The current literature has made some progress in describing the behavioural phenotype of RTS. However, very few studies have been replicated, and only a handful of studies have included comparison groups, making comparisons and interpretations very difficult, therefore further research is required to understand fully understand the behavioural phenotype of RTS but specifically the intellectual ability of individuals with RTS and the presence of mental health difficulties using appropriate methodology. Further research on these areas will allow for a better understanding the behavioural phenotype of RTS and appropriate support developed to help those with the condition and their families.

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Article** | **Sample Identification** | **Confirmation of BBS Diagnosis** | **Properties of Measures** | **Comparison Group** | **Total Score** |
| Boer, Langton & Clarke (1999) | 2 | 0 | 3 | 0 | 0.42 |
| Crawford et al (2015) | 2 | 1 | 3 | 3 | 0.75 |
| Crawford, Waite & Oliver (2017) | 2 | 1 | 3 | 2 | 0.67 |
| Galéra et al (2009) | 2 | 3 | 2 | 3 | 0.83 |
| Gotts & Liemohn (1976) | 0 | 1 | 2 | 2 | 0.42 |
| Hennekam et al (1992) | 2 | 2 | 3 | 0 | 0.58 |
| Levitas & Reid (1998) | 1 | 2 | 2 | 0 | 0.42 |
| Moss et al (2016) | 2 | 1 | 3 | 2 | 0.67 |
| Schorry et al (2008) | 2 | 2 | 1 | 0 | 0.42 |
| Stevens, Carey & Blackburn (1990) | 2 | 3 | 2 | 0 | 0.58 |
| Stevens, Pouncey & Knowles (2011) | 2 | 2 | 1 | 0 | 0.42 |
| Waite et al (2015) | 2 | 1 | 3 | 3 | 0.75 |
| Waite et al (2016) | 2 | 1 | 3 | 2 | 0.67 |
| Yagihashi et al (2012) | 2 | 2 | 2 | 0 | 0.5 |

**CHAPTER TWO:**

PREDICTORS OF ANXIETY AND DEPRESSION IN ADULTS WITH BARDET-BIEDL SYNDROME

**Abstract**

Mental health difficulties are prevalent in Bardet-Biedl syndrome (BBS); however, little is known about the factors associated with mental health problems in people with this condition. Self-reported questionnaire data was obtained from 18 adults (mean age= 39 years; range= 28-62 years) with (BBS). The results showed that 27.8% of participants met the cut off for clinically significant anxiety and 22.2% met the cut off for clinically significant depression. Correlational analyses showed that number of physical health problems, autism characteristics, intolerance of uncertainty and executive dysfunction were positively correlated with anxiety and depression. Multiple regression analyses indicated that higher rates of physical health problems and executive dysfunction predicted higher anxiety and depression. Degree of visual impairment also predicted higher depression levels. This study highlights the heightened prevalence of anxiety and depression in adults with BBS and the potential risk markers for poor mental health for people with this condition.

Key words: Bardet-Biedl syndrome, anxiety, depression, autism, intolerance of uncertainty, executive functioning, vision

**Introduction**

**What is BBS?**

BBS, also known as Laurence-Moon Bardet-Biedl syndrome, is a heterogeneous genetic syndrome that affects 1 in 100,000 individuals in North America and Europe (Forsythe & Beales, 2003) and is more prevalent in communities where consanguinity appears to be more common (Farag & Teebi, 1989; Green et al., 1989). To date, 21 BBS genes (BBS1–BBS21) have been identified in which mutations account for 80% of cases (Heon et al., 2016; Khan et al., 2016). BBS is characterised by retinal dystrophy, usually resulting in a decline in vision, as well as obesity, postaxial polydactyly, renal abnormalities, male hypogonadism, female genitourinary malformations and developmental delay, usually in the mild range (Azari et al., 2006; Deveault et al., 2011; Forsythe & Beales, 2013; Green et al., 1989). A number of secondary features have also been identified including neurological problems, speech and language difficulties, facial dysmorphism, dental anomalies, behavioural difficulties and mental health problems (Beales et al., 1999).

**Mental health in BBS**

Research examining the behavioural and emotional phenotype of BBS has identified a heightened prevalence of mental health difficulties in individuals diagnosed with this syndrome. The prevalence of mental health difficulties is estimated to range between 30% and 69.23% (Ece Solmaz et al., 2015; Moore et al., 2005). Mood disorders and anxiety disorders in particular have been identified in BBS, with anxiety reported to affect between 19% and 23.08% (Baker et al., 2010; Barnett et al., 2002; Ece Solmaz et al., 2015; Moore et al., 2005), however, the prevalence estimates for depression in BBS are more varied. Beales et al. (1999) reported that 5% of their sample of individuals with BBS experienced depression, whereas other studies have reported depression and difficulties with emotion control to affect as many as 40% (Kerr et al., 2016). The variations in prevalence estimates are likely due to differences in recruitment and methodology across the studies, but despite this, the estimates suggests that mental health difficulties might be more prevalent in individuals with BBS compared to the general population.

In the general population, mental health difficulties are estimated to affect 25% of people in the UK each year (McManus, Meltzer, Brugha, Bebbington & Jenkins, 2009) and recent research has shown that generalised anxiety disorder symptoms have been identified in 5.9% of adults in the UK and “depressive episodes” have been reported to affect 3.3% of adults in the UK (Baker, 2020). Although the overall number of people with mental health problems in the UK has not changed significantly in recent years, the number of individuals experiencing suicidal thoughts and self-harm seems to be on the rise (McManus, Bebbington, Jenkins & Brugha, 2016), which highlights the need for understanding factors associated with the development of mental health issues in the general population and in those who may be at higher risk of developing mental health difficulties, which may include individuals with BBS. The factors influencing the heightened prevalence of mental health difficulties in BBS is not understood as the majority of research to date has focused solely on reporting the prevalence of mental health difficulties in the syndrome.

**Autism Phenomenology in BBS**

One possible reason for the high prevalence of mental health difficulties is that this syndrome shares cognitive profiles with other neurodevelopmental conditions, for example autism, which has also been associated with a higher prevalence of mental health difficulties. Autism Spectrum Disorder (ASD) is a neurodevelopmental condition defined by the presence of difficulties in social interaction and communication, usually accompanied by restricted or repetitive behaviours, activities, or interests (American Psychiatric Association, 2013; World Health Organisation, 2019). Similar difficulties have been reported in individuals with BBS (Brinckman et al., 2013; Kerr et al., 2016). Research has shown that as many as 79% of individuals with ASD meet criteria for a diagnosable mental health problem at least once in their lives and at least 69% of individuals with ASD are thought to have two or more mental health conditions (Balfe & Tantam, 2010; Lever & Geurts, 2016). Co-occurring mental health problems impede quality of life and are associated with greater demands for professional help, poorer prognosis and negative outcomes, which highlights the need for better understanding of mental health risk markers for individuals with ASD and those who display similar cognitive profiles (Ghaziuddin & Greden, 1998; Hedley & Young, 2006; Matson & Cervantes 2014; Wood and Gadow 2010).

Despite variation in prevalence estimates, the evidence suggests there is a heightened prevalence of autism symptomatology in individuals with BBS, specifically difficulties with interpreting language and social communication difficulties (Brinckman et al., 2013; Kerr et al., 2016). Kerr et al. (2016) reported that 26% of their sample of individuals with BBS displayed moderate difficulties of social communication and 30.5% displayed a severe impairment. Similar findings were reported by Baker et al. (2010) who reported that 40% of their sample showed difficulties with social communication. However, the prevalence of ASD characteristics may be much higher, as there is research suggesting that as many as 80% of individuals with BBS (40% mild-moderate; 40% severe) have difficulties with social skills and also mild to moderate difficulties in other areas including social awareness, social cognition, social motivation and autistic mannerisms (Brinckman et al., 2013).

Factors influencing the high prevalence of depression and anxiety in both BBS and ASD are not fully understood; however, there is an emergence of research exploring risk factors of mental health difficulties in ASD and it is possible that these mechanisms are also present in individuals with BBS. Research has suggested that intolerance of uncertainty and difficulties with emotion regulation are risk factors for the development and maintenance of mental health difficulties in individuals with ASD, as well as in the general population (Bruggink, Huisman, Vuijk, Kraaij & Garnefski, 2016; Cai, Richdale, Dissanayake & [Uljarević](https://link.springer.com/article/10.1007/s10803-017-3318-7#auth-4), 2017; Carleton, 2016; Hodgson, Freeston, Honey & Rodgers, 2017; Swain, Scarpa, White & Laugeson, 2015). Intolerance of uncertainty is described as a cognitive bias that affects how a person perceives, interprets, and responds to novel or uncertain situations on a cognitive, emotional, and behavioural level (Dugas, Schwartz, & Francis, 2004). It has been identified as a risk factor for various anxiety disorders and depression in the general population and is also associated with anxiety in children and adults with ASD (Boulter, Freeston, South, Rodgers, 2014; McEvoy &Mahoney 2012; Wigham, Rodgers, South, McConachie & Freeston, 2015). Despite the high prevalence of ASD traits reported in BBS, intolerance of uncertainty has not been considered in relation to mental health difficulties in this syndrome.

Another factor that may influence mental health problems in BBS is difficulties with executive functioning, which is known to play a role in the regulation of mood and behaviour (Koenigs & Grafman, 2009). Executive functions refer to higher-order cognitive processes such as attention control, cognitive flexibility, and social cognition. There is general agreement that the three core areas of executive functioning include: inhibition, working memory, and cognitive flexibility; and it is from these core areas that higher order executive functions such as reasoning, planning and problem solving are developed (Lehto, Juujärvi, Kooistra & Pulkkinen, 2003; [Miyake et al. 2000](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4084861/#R190)). There is evidence to show that difficulties with executive functioning are associated with poorer mental health, specifically increased anxiety and depression in the general population (Baune, Fuhr, Air, Hering, 2014; Wallace et al. 2016). The ability to effectively manage and respond to an emotional experience, has been found to be strongly supported by several core executive functions including attention control, inhibition of behaviours, decision making and other higher cognitive processes that take place in emotionally demanding situations (Tottenham, Hare & Casey, 2011; Zelazo & Cunningham, 2007). Executive functioning problems are therefore likely to impede an individual’s ability to regulate their own mood and might be associated with mental health problems in BBS. Given the reports of difficulties in executive functioning in ASD (Zimmerman, Ownsworth, O'Donovan, Roberts & Gullo, 2016), it would seem logical to consider executive functions when understanding the mental health of individuals who are diagnosed with BBS. Difficulties with executive functioning will understandably cause distress to an individual with BBS as many day-to-day tasks rely on a number of executive functions, for example being able to time manage, use public transport, manage stressful situations and organising personal belongings.

Recent research on emotion regulation has focused on the role of intolerance of uncertainty, as this has been found to mediate the relationship between emotional regulation and symptoms of depression and anxiety in individuals with ASD (Cai et al., 2017). To date, no research has been conducted to understand the factors associated with mental health difficulties in BBS; therefore we do not know whether similar mechanisms predict mental health in individuals with this syndrome. An alternative consideration is whether physical health problems and in particular visual impairment directly impact mental health difficulties in BBS.

**Visual Impairment and Health Problems**

Sight loss affects the majority of individuals with BBS and is likely to impact upon mental health, but despite this, it has rarely been considered in the research investigating the emotional experiences of individuals with BBS. Research investigating sight loss in the general population has found that the prevalence of mental health difficulties is reported to be higher in individuals with low vision than those without a visual impairment. The majority of studies examining the relationship between visual impairment and mental health difficulties have focused on rates of depression in the older adult population; however, there is evidence showing that the prevalence of mental health problems in working-age adults with vision loss may be higher (Pinquart & Pfeiffer, 2011). Symptoms of depression are reported to affect 40-45% of adults with vision loss and 20% are reported to display moderate to severe anxiety symptoms (Brennan & Cardinali, 2000). Sight loss is likely to affect an individual’s ability to read, write and socialise and requires a considerable amount of adjustment in day-to-day life and may have a negative impact on psychological wellbeing.

It is important to understand the impact of sight loss on individuals with BBS particularly because retinal degeneration is the most highly penetrant feature of the syndrome (Stone et al., 2017). Retinitis pigmentosa typically develops in the first 10 years of life in BBS and often by the time they reach their 20s to 30s, most individuals with BBS are considered to be legally blind (Adams, Awadein & Toma, 2007). There is evidence to show that self-reported functional vision loss in adults is significantly associated with depression rather than visual acuity itself (Zhang et al., 2013) suggesting that individuals with BBS are particularly vulnerable to developing mental health difficulties such as depression and anxiety, given that their eyesight deteriorates over time. Losing the ability to drive, see family members or play certain sports may cause an individual with BBS considerable distress. Moreover, learning to rely on other senses, family members and adaptive equipment such as a cane may have a negative psychological impact on those with this condition. The risk of mental health difficulties in those with vision loss is associated with poorer quality of life and reduced social activity, therefore understanding the profile of mental health difficulties in adults with BBS is very important (Burmedi, Becker, Heyl, Wahl & Himmelsbach, 2002).

Understanding the impact of other physical health problems on the mental health of individuals with BBS is also important given the various health issues commonly reported in BBS. The association between physical health problems and mental health problems in the general population is well documented, and although the relationship is thought to be bi-directional, there is research showing that depression increases as the number of chronic physical health issues rise (Gunn et al., 2012; Stegmann et al., 2010). Furthermore, mental health difficulties can be associated with specific genetic syndromes, as there is evidence to show that mental health problems can be associated with a number of emotional, behavioural and cognitive structures (Royston et al., 2017; Crawford et al., 2017). Research has also shown mental health difficulties are associated with intolerance of uncertainty, poor emotional regulation and sensory difficulties in neurodevelopmental disorders (e.g. autism) in individuals with rare genetic syndromes, as well as in the general population (Joyce, Honey, Leekam, Barrett & Rodgers, 2017; Dugas, Gosselin & Ladouceur, 2001). This highlights the importance of understanding the behavioural, cognitive and emotional phenotype of genetic syndromes for early intervention and improving clinical outcomes (Waite et al., 2014).

To date, studies investigating the cognitive, behavioural and emotional features of BBS have focused on describing the prevalence of specific difficulties rather than trying to characterise the factors that lead to the development of these difficulties. On the whole, studies have relied on carers or family members to report the presence of difficulties; however, given the subjectivity associated with mental health problems, it is important to obtain self-reported accounts of mental health issues; this should be seen as the gold standard of assessment where an individual is able adequately self-report. In this study, self-report data is used to investigate the associations between autism characteristics, intolerance of uncertainty, executive functioning, health problems, visual impairment and anxiety and depression. The focus was specifically on adults with BBS because of the high prevalence of mental health problems reported in this group.

The aims of the study are:

* To document the prevalence of anxiety and depression in a sample of adults with BBS.
* To assess whether autism characteristics, intolerance of uncertainty, executive functioning, visual impairment and physical health problems predict anxiety and depression in adults with BBS.

**Epistemological Position**

The researcher’s epistemological position sits between the positivist and interpretative approach. The positivist position assumes that the view that all behaviour can be observed, identified, reliably measured and empirically tested and therefore generalizable to a specified population and aims to produce objective knowledge, with the researcher as the external observer (Finlay, 2006; Willig, 2008). The interpretivist approach assumes the view that reality is subjective and therefore differs between people (Guba & Lincoln, 1994) and is constructed through the use of language (Scotland, 2012).

The methodology for this research sits more towards the positivist approach, due to the use of quantitative methodology through standardised questionnaires. This approach was intentionally adopted by the researcher to objectively document mental health difficulties in BBS; however, the reliance on self-report data reduces the likelihood of achieving absolute objective truth, as self-report methods may be influenced by the subjectivity of the participants’ experiences.

**Method**

**Ethical Approval**

Ethical approval was obtained from the NHS Research and Ethics Committee (REC): Wales REC5 (appendix A) and was subject to scientific review by Aston University (appendix B).

**Recruitment**

Participants were recruited from the BBS UK support group. This support group was set up by individuals with BBS and their family members to allow for people diagnosed with the syndrome to be able contact and meet others diagnosed with this condition. The support group is available on social media but the organisation also have an annual conference where people with the syndrome, their families and professionals who work with individuals with BBS can meet and discuss issues relevant to BBS.

The syndrome support group holds a database of people with BBS who are interested in research and have agreed to be contacted about upcoming research projects. Eighty recruitment packs, containing information about the study (appendix C) and an expression of interest form (appendix D) were posted to participants on the database. In accordance with BBS UK policy, all information was posted to potential participants regardless of vision; however, participants were given the option to receive an audio information sheet via email as many individuals with visual impairment have reading software on their computers. Participants were able to express an interest in the study by posting the expression of interest form back to the research site using a pre-paid envelope provided by the researchers. Participants were also able to express an interest in the study via telephone or email.

**Inclusion Criteria**

In order to be eligible to take part in the study, all participants had to be 18 years old at the time of expressing an interest in the study, have a formal diagnosis of BBS from a clinical geneticist, paediatrician or General Practitioner (GP) and provide informed consent regarding their participation in the study.

**Participants**

Eighteen participants with BBS completed the study (12 females; mean chronological age: 39 years; age range: 28 – 62 years). Eight participants have BBS1; three participants have BBS2; two participants have BBS10 and five participants reported the type of BBS as “unknown”. None of the participants in this study reported having a diagnosis of an intellectual/learning disability. All participants had received a diagnosis of BBS from a clinical geneticist, paediatrician or GP.

**Measures**

***The Background Questionnaire (Arron, Oliver, Moss, Berg & Burbidge, 2011; Appendix E)*** collects demographic information about the person with BBS including age, gender, educational level, living arrangement, intellectual disability, autism diagnosis and age at diagnosis of BBS.

***Beck Anxiety Inventory (BAI; Beck & Steer, 1993; Appendix F)*** is a 21-item standardised questionnaire that measures symptoms of generalised anxiety disorder using a four-point likert scale. A higher score indicates higher levels of generalised anxiety. Scores between 0 and 7 suggests minimal anxiety; 15 to 18 suggests mild anxiety; 16 to 25 suggests moderate anxiety; and scores of 26 and above suggests severe anxiety. The cut off for clinically significant anxiety is 16 (Beck & Steer, 1993). It has a one-week test-retest reliability of r= 0.75 and an internal consistency α=.92 (Beck, Epstein, Brown & Steer, 1988). Similarly, in the current study, the internal consistency was excellent (α=.92).

***Beck Depression Inventory (BDI-II; Beck, Steer & Brown, 1996; Appendix G)*** is a 21-item standardised questionnaire that measures symptoms of depression using a four-point Likert scale. A higher score indicates higher level of depression. Scores between 0 and 13 suggest minimal depression; 14 to 19 indicate mild depression; 20 to 28 are suggestive of moderate depression; and 29 or more and suggestive of severe depression (Beck, Steer & Brown, 1996). The cut off for clinically significant depression is 20 (Kendall, Hollon, Beck, Hammen, & Ingram, 1987). It has a one-week test–retest reliability of r = 0.93 and an internal consistency α=.91 (Beck, Steer & Brown, 1996). Similarly, in the current study, the internal consistency was excellent (α=.95).

***Cardiff Visual Ability Questionnaire for Children (CVAQC; Khadka, Ryan, Margrain & Woodhouse, 2010; Appendix H)*** is a 25-item standardised questionnaire that has been developed for children with visual impairment. It measures the degree of difficulty in completing tasks due to a visual impairment and has good reliability (.84). The measure has been adapted for this study so that it can be used with adult samples. The education subscale has been removed and items regarding ‘textbooks’ were adapted to ‘books’ to make the measure more age appropriate. The adapted version of the measure has 21 items. The lowest possible score on the measure is 21 and the highest possible score is 84. A higher score is indicative of greater difficulty with day-to-day tasks due to visual impairment. In the current study, the adapted version of the measure has excellent internal consistency (α=.95).

***The Autism Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, Clubley, 2001; Appendix I)*** is a 50-item standardised self-report questionnaire measuring the degree of autistic traits in adults across 5 domains relevant to autism traits (social skill, attention switching, attention to detail, communication, and imagination). Participants are asked to rate the extent to which they agree with each statement on a four point likert scale ranging from “definitely disagree” to “definitely agree”. The lowest possible score is 0 and the highest possible score is 50. A higher score indicates greater presence of autism characteristics. A score of 32 and above suggests further assessment for an autism spectrum condition (Baron-Cohen et al., 2001). The internal consistency in the current study was good (α=.85).

***The Health Questionnaire (HQ; Hall, Arron, Sloneem & Oliver, 2008; Appendix J)*** is a standardised questionnaire that measures the presence and severity of current (in the last month) and lifetime health problems in children and adults. The questionnaire consists of 15 health problems scored on a scale of 0 = “never affected” to 3 = “severely affected”. Scores are summed to obtain an overall health score. Item level reliability was .72 for lifetime problems and .76 for current problems (Hall et al., 2008). This measure has been adapted for this study to include a question about polycystic ovarian syndrome and diabetes given that these are common health conditions in people with BBS. The lowest possible score is 0 and the highest possible score is 54. In the current study, the adapted version of the measure has good internal consistency (α=.88).

***The Intolerance of Uncertainty Scale (IU; Boulter et al.***[***2014***](https://link.springer.com/article/10.1007/s10803-016-2721-9#CR5)***; Appendix K)*** is a 12-item standardised measure that reflects levels of intolerance of uncertainty. Participants are asked to rate how much they agree with 12 statements on a scale of 1 “not at all characteristic of me” to 5 “entirely characteristic of me”. The lowest possible score is 12 and the highest possible score is 60. Higher scores indicate greater levels of intolerance of uncertainty. In the current study, the scale has good internal consistency (α = 0.88).

***Behaviour Rating Inventory of Executive Functioning – Adult Version (BRIEF-A; Roth, Isquith & Gioia, 2005; Appendix L)*** is a 75 item standardised measure that is used in clinical practice to assess executive functioning across nine subscales (see Table 1 for a description of the subscales). Participants are asked to rate the frequency of each statement on a three-point likert-scale ranging from “never” to “often”. The items in each subscale are summed to create a total score for each domain. A Behaviour Regulation Index (BRI) score is created through totalling the score from four subscales and this reflects an individual’s general ability to regulate or control their emotional and behavioural responses. A Metacognition Index (MI) score is created though totalling the score from five subscales, which reflects an individual’s ability to get started on an activity, to hold information in working memory, to plan, organise and solve problems; and to maintain organisation. A Global Executive Composite (GEC) score is created from summing the BRI and MI; this is an overall score of executive functioning. The internal consistency in the current study was excellent (α=.95).

*Table 1. Descriptions of the BRIEF-A Subcales*

|  |  |  |
| --- | --- | --- |
| BRIEF-A Subscales | Description |  |
| Inhibit | This domain assesses inhibitory control and impulsivity, which can be described as the ability to resist impulses and to stop one’s own behaviour at the appropriate time. | **Behavioural Regulation index (BRI)**  BRI captures the ability to maintain appropriate regulatory control of one’s own behaviour and emotional responses. |
| Shift | This domain assesses the ability to move with ease from one situation, activity, or aspect of a problem to another, as required. This includes the ability to (a) make transitions; (b) tolerate change; (c) problem-solve flexibly; (d) switch or alternate attention; and (e) change focus from one topic to another. |
| Emotional Control | This domain assesses an individual’s ability to modulate or control his or her emotional responses. |
| Self-Monitor | This domain assesses aspects of social or interpersonal awareness. It captures the degree to which an individual perceives him/herself as aware of the effect that their behaviour has on others. |
| Initiate | This domain assesses an individual’s ability to begin a task or activity and to independently generate ideas, responses, or problem-solving strategies. | **Metacognition Index (MI)**  MI reflects the individual’s ability to initiate activity and generate problem-solving ideas, to sustain working memory, to plan and organize problem-solving approaches, to monitor success and failure in problem solving, and to organize one’s materials and environment. |
| Working Memory | This domain assesses the capacity to hold information in mind for the purpose of completing a task, encoding information, or generating goals, plans, and sequential steps to achieving goals. |
| Plan/Organise | This domain measures an individual’s ability to manage current and future-oriented task demands. The Plan component captures the ability to anticipate future events, to set goals, and to develop appropriate sequential steps ahead of time in order to carry out a task or activity. The Organize component refers to the ability to bring order to information and to appreciate main ideas or key concepts when learning or communicating information. |
| Task Monitor | This domain reflects the ability to keep track of one’s problem-solving success or failure, and to identify and correct mistakes during behaviours. |
| Organisation of Materials | This domain measures orderliness of work, living, and storage spaces (e.g., desks, rooms). |

**Procedure**

Consent to participate in the study was obtained over the telephone, due to visual impairment. Telephone calls were recorded to ensure there was a record of obtained consent. The researcher explained the aims of the research, the involvement of participants, the potential risks and benefits associated with the research, the right to withdraw and who to contact to ask further questions. Following this, the participants were able to ask any further questions and then the researcher checked whether they were still interested in taking part in the study. In order to assess their understanding and capacity to consent, participants were asked to explain what the research asks them to do, the purpose of the study and whether there are any risks associated with taking part in the study (Appendix M).

Once capacity had been determined to the satisfaction of the researcher they went through the consent form and asked the participant to respond either “yes” or “no” to each item. If the participant provided consent to all the relevant items, it was agreed that they were able and willing to participate. The participants were able to fill in the questionnaires either manually and return them via post, electronically (using electronic aids to complete the questionnaires), or over the telephone with a researcher, at a mutually convenient time. Data were collected between October 2019 and March 2020.

**Data Analysis**

The data were entered into SPSS Version 26 and each entry was checked a second time in case any errors occurred during the initial data entry. Total scores were created for all measures. For the BRIEF-A, domain scores, BRI, MI and GEC raw scores were created. These were then converted into T-Scores to allow executive functioning to be interpreted. T-scores between 60 and 65 were considered as mildly elevated and t-scores above 65 were considered as clinically elevated (Roth et al. 2005).

Multiple regression analyses were used to identify whether the predictor variables: degree of visual impairment, level of autism traits, executive functioning, intolerance of uncertainty and number of total health problems; predicted the two criterion variables: anxiety and depression in individuals diagnosed with BBS.

Data checks were carried out to ensure that they did not violate assumptions for regression including normality of residuals, independence and homoscedasticity through inspection of P-P plots and scatterplots (Appendix N). The P-P plots indicated some deviation of residuals for both anxiety and depression; however, tests of normality showed the residuals had not significantly departed from normality. Multicollinearity was checked by examining correlation coefficients and variance inflation factor (VIF) values, which identified acceptable levels of correlation between predictors.

**Results**

**Descriptive Statistics**

The results for the all variables are displayed in Table 2. They show that five participants (27.8%) met the cut off for clinically significant anxiety. In total, one participant met the cut off for mild anxiety, two participants met the cut off for moderate anxiety and three participants met the cut off for severe anxiety. Four participants (22.2%) met the cut off for clinically significant depression. Two participants met the cut off for mild depression, one met the cut off for moderate depression and three met the cut-off for severe depression. Two participants met the cut-off for further assessment of autism characteristics and four participants had clinically elevated scores on the BRIEF.

*Table 2. Descriptive statistics for all variables*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | BAI | BDI | CVAQ | HQ | AQ | IU | BRIEF |
| Mean | 10.1  (10.4) | 12.3  (13.9) | 61.9 (9.2) | 10.4 (7.7) | 20.5 (8.2) | 25.4 (9.1) | 111.6 (21.8) |
| Range (min-max) | 0-32 | 0-45 | 33-79 | 0-28 | 7-39 | 13-40 | 70-142 |
| Number of participants above clinical cut-off | 5  (27.8%) | 4  (22.2%) |  |  | 2  (11.1%) |  | 4  (22%) |
| Severity of mental health difficulties:  Mild  Moderate  Severe | 1 (5.6%)  2 (11.1%)  3 (16.7%) | 2 (11.1%)  1 (5.6%)  3 (16.7%) |  |  |  |  |  |

BAI~ Beck’s Anxiety Inventory

BDI~ Beck’s Depression Inventory

CVAQ~ Cardiff Visual Ability Questionnaire

HQ~ Health Questionnaire

AQ~ Autism Quotient

IU~ Intolerance of Uncertainty

BRIEF~ Behaviour Rating Inventory of Executive Functioning

**Correlations**

Correlation analyses were employed to examine the relationship between all of the variables (see Table 3). Spearman’s Rank correlation coefficient was deemed appropriate due to the small n. The results showed a moderate positive correlation between number of health problems and anxiety (rs=.676, *p<0.01*) and depression (rs=.534, *p<.05*). Degree of autistic characteristics was also moderately positively correlated with anxiety (rs=.510, *p<.05*) and depression (rs=.497, *p<.05*). Level of intolerance of uncertainty was moderately positively correlated with anxiety (rs=.620, *p<.01*) and depression (rs=.549, *p<.05*). The level of executive dysfunction was moderately positively correlated with anxiety (rs= .673, *p<.01*) and depression (rs=.575, *p<.05*). The number of health problems was moderately positively correlated with level of intolerance of uncertainty (rs= .591, *p<.01*), whereas the degree of autism characteristics was strongly positively correlated with level of executive dysfunction (rs= .794, *p<.01*).

*Table 3. Spearman’s correlation for all variables*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | BAI | BDI | CVAQ | HQ | AQ | IU | BRIEF |
| BAI | 1 | .746\*\* | .099 | .676\*\* | .510\* | .620\*\* | .673\*\* |
| BDI |  | 1 | .274 | .534\* | .497\* | .549\* | .575\* |
| CVAQ |  |  | 1 | .362 | -.221 | .031 | -.334 |
| HQ |  |  |  | 1 | .212 | .591\*\* | .333 |
| AQ |  |  |  |  | 1 | .136 | .794\*\* |
| IU |  |  |  |  |  | 1 | .395 |
| BRIEF |  |  |  |  |  |  | 1 |

All significances are two-tailed

\*\**p<.01*

\**p<.05*

**Regression Analyses**

Multiple regression analyses using the stepwise method were carried out separately for the two criterion variables: anxiety and depression and five predictor variables: health problems, autism characteristics, intolerance of uncertainty, visual impairment and executive dysfunction (see Tables 4 and 5). As this is the first study investigating predictors of anxiety and depression in individuals with BBS, the stepwise method was used to identify a useful subset of predictors. The anxiety model was significant (F(2,15)= 8.975, *p=.003*), explaining 54.5% (R2) of variance and 48.4% when adjusted. Two variables significantly predicted anxiety in adults with BBS: number of health problems (β=.483, *p=.017*) and level of executive dysfunction (β=.45, p=.025). The depression model was significant (F(3,14)= 12.172, *p<.001*) explaining 72.3% (R2) of the variance and 66.3% when adjusted. Two variables significantly predicted depression: level of executive dysfunction (β= .681, *p=.001*) and degree of visual impairment (β=.492, *p.017*). Number of health issues also predicted depression; however, this result was not significant (β.266, *p=.149*).

*Table 4. Multiple regression analysis of anxiety, health problems and executive dysfunction*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | B | SE B | β | Sig. | 95% CI | |
|  |  |  |  |  | **Lower** | **Upper** |
| Constant | -22.645 | 9.787 |  | .035 | -43.506 | -1.784 |
| HQ | .456 | .170 | .483 | .017 | .094 | .818 |
| BRIEF\_GEC | .467 | .187 | .450 | .025 | .069 | .864 |

*Table 5. Multiple regression analysis of depression, health problems, executive dysfunction and degree of visual impairment*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | B | SE B | β | Sig. | 95% CI | |
|  |  |  |  |  | **Lower** | **Upper** |
| Constant | -74.660 | 19.232 |  | .002 | -115.907 | -33.412 |
| HQ | .335 | .219 | .266 | .149 | -.135 | .806 |
| BRIEF\_GEC | .944 | .238 | .681 | .001 | .433 | 1.455 |
| CVAQ | .499 | .184 | .492 | .017 | .104 | .894 |

**Post-Hoc Analyses: Executive Functioning**

As executive dysfunction significantly predicted anxiety and depression in the initial multiple regression analyses, post-hoc analyses were conducted to allow for a closer inspection of the relationship between the executive functioning subscales and anxiety and depression, in order to understand the profile of executive dysfunction in individuals with BBS and to understand which areas of executive functioning were predicting anxiety and depression.

Table 6 shows the descriptive statistics for all BRIEF subscales. Four participants (22%) met the clinical cut-off for executive dysfunction (GEC). The results show that four participants (22%) met the clinical cut off for the domain BRI and one participant met the clinical cut off for MI.

*Table 6. Descriptive statistics for the BRIEF domains (T-scores).*

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Inhibit | Shift | Emotional Control | Self-Monitor | Initiate | Working Memory | Plan/ Organise | Task Monitor | Organisation Materials | BRI | MI | GEC |
| Mean | 48 | 56 | 57 | 49 | 53 | 52 | 52 | 53 | 49 | 54 | 53 | 53 |
| Range (min-max) | 36-60 | 39-77 | 38-80 | 37-67 | 37-73 | 39-83 | 38-70 | 36-72 | 36-75 | 35-67 | 36-67 | 34-67 |
| Std. Deviation | 9.4 | 11.0 | 11.9 | 10.0 | 12.8 | 11.8 | 9.0 | 9.6 | 12.5 | 10.1 | 9.9 | 10.0 |
| Number mildly elevated | 3 (17%) | 7 (39%) | 3  (17%) | 2  (11%) | 0  (0%) | 0  (0%) | 4  (22%) | 0  (0%) | 1  (6%) | 1  (6%) | 5  (28%) | 0  (0%) |
| Number above clinical cut off (%) | 0  (0%) | 2 (11%) | 4  (22%) | 1  (6%) | 6  (33%) | 4  (22%) | 1  (6%) | 2  (11%) | 3  (17%) | 4 (22%) | 1  (6%) | 4  (22%) |

Multiple regression analyses were carried for the two criterion variables: anxiety and depression using the executive functioning (BRIEF) subscales as predictor variables (see Tables 7 and 8). The anxiety model was significant (F(2, 15)= 11.976, *p=.001*), explaining 61.5% (R2) of the variance and 56.4% when adjusted. Two executive functioning (BRIEF) subscales significantly predicted anxiety in adults with BBS: “Task Monitor” (β= .994, *p<.001*) and “Organisation Materials” (β=-.535, *p=.019*). The depression model was significant (F(1, 16)= 18.427, *p=.001*), explaining 53.9% (R2) of the variance and 51% when adjusted. One executive (BRIEF) subscale variable predicted depression in adults with BBS: “Emotional Control” (β= .734, *p=.001*).

*Table 7. Multiple regression analyses of anxiety and the BRIEF subscales “Task Monitor” and “Organisation Materials”*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | B | SE B | β | Sig. | 95% CI | |
|  |  |  |  |  | **Lower** | **Upper** |
| Constant | -25.133 | 9.463 |  | .018 | -45.302 | -4.964 |
| Task Monitor | 1.074 | .220 | .994 | .000 | .604 | 1.544 |
| Organisation Materials | -.446 | .170 | -.535 | .019 | -.809 | -.084 |

*Table 8. Multiple regression analyses of depression and the BRIEF subscales “Emotional Control”*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | B | SE B | β | Sig. | 95% CI | |
|  |  |  |  |  | **Lower** | **Upper** |
| Constant | -36.815 | 11.574 |  | .006 | -61.350 | -12.279 |
| Emotional Control | .859 | .198 | .734 | .001 | .438 | 1.279 |

**Discussion**

This study aimed to examine potential predictors of depression and anxiety in 18 adults with BBS using self-report data, due to the heightened prevalence of anxiety and depression reported in the existing BBS literature (Barnett et al., 2002; Ece Solmaz et al., 2015; Kerr et al., 2016; Moore et al., 2005). The analyses focused on the degree of visual impairment, health problems, intolerance of uncertainty, executive dysfunction and autism characteristics, as these factors are known to be associated with anxiety and depression in the general population and in other genetic and metabolic syndromes (Bruining et al., 2014; Dugas et al., 2001; Joyce et al., 2017; Oliver et al., 2011).

The results show that five (27.8%) participants met the cut off for clinically significant anxiety, which is in line with existing BBS literature that has reported a prevalence of anxiety in 19% to 23.08% of individuals with BBS (Baker et al., 2010; Barnett et al., 2002; Ece Solmaz et al., 2015; Moore et al., 2005). Four (22.2%) participants met the cut off for clinically significant depression, which is in line with the estimates reported by Ece Solmaz et al. (2015) who found that 23.08% of their sample met the cut off for depression; however, this finding is considerably higher than the prevalence estimates reported by Beales et al., (1999) who found that only 5% of their BBS met the cut off for depression. The variation in estimates between the current study and Beales et al. (1999) is most likely due to varying methodology. The prevalence estimate for depression in the present study was obtained using a self-report standardised questionnaire, whereas the estimate provided by Beales and colleagues was obtained using a non-standardised parent-report questionnaire. However, it is also important to acknowledge that the sample size in the current study is small; therefore it is not possible to conclude with certainty that the prevalence estimates for anxiety and depression are representative of the BBS adult population.

Furthermore, the estimates for anxiety and depression reported in the current study are higher than those observed in the general population, where recent reports show that 5.9% and 3.3% of adults in the UK reported experiencing generalised anxiety symptoms and “depressive episodes”, respectively (Baker, 2020). The results suggest that adults with BBS may be at higher risk of anxiety and depression, which also adds to the existing literature showing higher rates of mental health problems are characteristic of some genetic syndromes (Dekker, Koot, der Ende, & Verhulst, 2002; Dykens, Hodapp & Finucane, 2000).

All predictor variables were positively correlated with both depression and anxiety; however, visual impairment did not significantly correlate with either anxiety or depression, which is contrary to previous research highlighting association between self-reported functional vision loss and mental health difficulties (Pinquart & Pfeiffer, 2011). However, the multiple regression analyses revealed that the degree of visual impairment was a significant predictor of depression, therefore indicating that degree of visual impairment might be enhancing the predictive ability of the other predictor variables.

Physical health problems in adults with BBS predicted anxiety and depression, which highlights the importance of understanding the psychological impact of physical health problems on adults with BBS. Understandably, the burden of physical symptoms and the functional difficulties caused by physical health problems are likely to provoke or worsen episodes of anxiety and depression (Katon, 2003); however, there may be other factors that mediate the relationship between physical health and mental health. Research has shown that anxiety and depression are associated with poor adherence to self-care activities including maintaining an appropriate diet, exercising, medication routines and increased physical health difficulties in individuals with chronic health problems such as those identified in BBS, and it is often these factors that contribute to increased symptom burden (Lin et al., 2004). For example, research shows that physical activity is negatively associated with anxiety disorders and depression ([De Mello et al., 2013](https://www.sciencedirect.com/science/article/pii/S0277953617306639" \l "bib11); [Hegberg & Tone, 2015](https://www.sciencedirect.com/science/article/pii/S0277953617306639#bib23)). Due to the various physical health problems identified in BBS, including low vision, people with BBS may find it difficult to participate in physical activity and this might maintain low mood and anxiety.

The results also showed that the degree of executive dysfunction predicted anxiety and depression, which is in line with the general population (Koenigs & Grafman, 2009). The BRIEF subscale regression analyses showed that emotion control significantly predicted depression in adults with BBS, and this has also been found to predict depression in the general population (Gross & Jazaieri, 2014). Keeping track of one’s problem-solving successes or failures and identifying and correcting mistakes (Task Monitor) and difficulties with organising work and living spaces (Organisation Materials) were found to predict anxiety levels in BBS. Understandably, difficulties in these areas of functioning may contribute to heightened anxiety; however, it is possible that visual impairment is impacting the relationship between executive functioning and anxiety. Low vision is likely to impact on the ability to maintain orderliness in work and living spaces and the ability to keep track of one’s own problem solving successes and failures and to correct mistakes usually requires an individual to identify one’s mistakes, which is much more difficult with little or no vision. Many participants anecdotally reported to the researcher that day-to-day tasks that use executive functions (such as finding things and being organised) are often difficult due to having a visual impairment rather than a deficit in that area of cognitive functioning. For example items on the BRIEF-A such as “I lose things” and “I make mistakes” are likely to be difficult for an individual with low vision; therefore high scores on these items may not indicate difficulties in certain areas of executive functioning and instead may be picking up on difficulties associated with having a visual impairment. This may be a confounding factor; therefore we must interpret these findings with caution.

Two (11.1%) participants met the cut off for ASD characteristics, which is much lower than prevalence estimates in the existing BBS literature, which reports ASD characteristics to be as high as 80% (Brinckman et al., 2013). One possible explanation for the differences in prevalence estimates may be due to visual impairment. Research has shown that ASD prevalence is as high as 50% in congenitally blind children (Jure, Pogonza & Rapin, 2016) compared with 1.0%–1.5% in the general population (Hobson & Bishop, 2003). Despite much of the research attributing the high prevalence of ASD traits in individuals with congenital blindness to neurological difficulties alone; recent research has found an independent relationship between congenital blindness and ASD (Begeer et al., 2014; Cass, Sonksen, & McConachie, 1994). Difficulties with facial expression, body language, and verbal and non-verbal social communication are all core features of ASD; however, these features are also affected by visual impairment (Mosca, Kritzinger & van der Linde, 2015). This highlights the considerable impact of congenital blindness on the development of the ASD phenotype and suggests that estimates of ASD in BBS are likely to be elevated due to the social communication difficulties that are also observed in individuals with congenital blindness.

The lack of appropriate ASD screening and assessment methods for individuals with visual impairment poses an additional barrier to understanding the ASD profile in BBS. The existing BBS research used informant questionnaire data to identify ASD characteristics in BBS; however, the majority of ASD screening questionnaires are designed for sighted individuals. The present study used the AQ; however, this measure also relies on participants being able to see. Items such as “I find it easy to work out what someone is thinking and feeling just by looking at their face” and “I don’t usually notice small changes in a situation or a person’s appearance” are likely to prompt responses based on the ability to see or not see, rather than difficulties in areas of functioning that are commonly observed in ASD; therefore we must remain cautious when interpreting the results.

**Clinical Implications**

The findings suggest that early intervention for mental health difficulties is important for adults with BBS who are experiencing anxiety and depression as it can often have a negative impact on emotional wellbeing and quality of life and can also have a negative impact on health, social functioning and work (Mendlowicz & Stein, 2000; Wells et al., 1989).

Individuals with more significant health problems regularly attend the BBS clinics therefore introducing mental health screening procedures or an assessment pathway for adults who regularly attend the BBS clinical would be beneficial. This would allow for timely support to be offered to those who may be struggling with their mental health.

**Directions for Future Research**

This is the first study examining predictors of mental health problems in this syndrome; further research is required on the factors associated with anxiety and depression in adults with BBS. Further research looking specifically into the relationship between health, anxiety and intolerance of uncertainty in BBS would help to develop our understanding of the profile of anxiety in individuals with BBS and longitudinal analyses would allow for the direction of the relationship between physical and mental health to be established and a better understanding of the factors that mediate the relationship between physical and mental health problems in BBS, allowing for appropriate support and intervention to be offered.

Longitudinal research on the development of social communication difficulties in children with BBS using comprehensive multidisciplinary assessments would provide a robust and more detailed understanding of the development of the autism phenotype in individuals with BBS as vision begins to decline. At present, the existing ASD assessment methods for children are not suitable for those with visual impairment. The Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) is recommended by the National Institute for Clinical Excellence (NICE; December 2017) for identifying Autism in those aged under 19; however, it requires individuals to be able to see resources as part of the assessment process. In recent years, there has been some focus on developing an autism observation tool for children with visual impairment such as the Visual Impairment and Social Communication Schedule (VISS; Absoud, Parr, Salt & Dale, 2011) which has been developed to identify autism characteristics in children without the use of visual tools or items to aid the assessment process. While the preliminary results look promising, the VISS requires further testing as an alternative for the ADOS in individuals with visual impairment.

Similarly there is a need for appropriate executive functioning measures to be developed for individuals with visual impairment due to traditional screening measures relying on informants having the ability to see.

**Strengths and Limitations**

This study is the first to explore the predictors and potential risk markers of mental health difficulties in BBS and will pave the way for future research using more in-depth methodology; however, there are several limitations that should be taken into consideration. As mentioned previously, assessment of cognitive, behavioural and emotional characteristics of BBS was based on questionnaire data rather than clinical diagnosis. Although this methodology provides us with an indication of whether individuals with BBS are experiencing clinically relevant difficulties through the use of continuous scores, it is not robust and does not include the same level of detail as a formal clinical diagnostic assessment.

A larger sample size would have been preferable for a regression analysis to ensure a greater level of statistical power. According to Austin and Steyerberg ([2015](https://link.springer.com/article/10.1007/s10803-019-04317-1#ref-CR2)), two participants per variable can be adequate to estimate regression coefficients; however, it is important not to over-generalise these findings given the sample size. Due to the exploratory nature of the study, the chosen p-value increases the likelihood of a type 1 error; the results should be interpreted having considered this. It is also important to recognise that small sample sizes are common in rare genetic syndrome research, and the sample size in this study is comparable to other studies exploring mental health difficulties in rare genetic syndromes (Barnett et al., 2002; Crawford et al., 2017; Ece Solmaz et al., 2015).

This study used cross-sectional methodology; however, longitudinal research is required to identify the associations between predictors and mental health difficulties over time. Although the prevalence of mental health difficulties in individuals with intellectual disability is estimated to be four times higher than the general population (Matson & Shoemaker, 2011), this study did not consider the influence of the level of intellectual ability on mental health difficulties in individuals with BBS. The study focused on understanding self-reported difficulties, therefore recruiting individuals who have the capacity to participate resulted in none of the participants having an intellectual disability diagnosis. The results are therefore not generalisable to individuals with BBS who also have an intellectual disability.

Finally, a study of this kind is prone to substantial sample bias as it is not possible to ascertain the proportion of individuals with BBS who chose not to take participate, the reasons behind this and how their data might have influenced the findings (Keiding & Louis, 2016).

**Summary and Conclusion**

To the author’s knowledge, this is the first study to examine the factors associated with anxiety and depression in adults with BBS. Number of physical health problems and executive dysfunction were found to significantly predict mental health in the syndrome; however, the findings should be interpreted with caution due to the small number of participants. The study has also highlighted the need for the development of assessment measures for individuals with visual impairment in order to continue the research into the risk markers of mental health problems in individuals with BBS. This will allow for further research into mental health and for targeted interventions to be developed to improve psychological wellbeing for those with the syndrome.

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 Gwasanaeth Moeseg Ymchwil

Research Ethics Service

Wales Research and Ethics Committee 5

Bangor

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22 February 2019

Dr Jane Waite

Lecturer of Psychology

Aston University

School of Life and Health Sciences

Aston Triangle

Birmingham

B4 7ET

Dear Dr Waite

# Study title: Mental health and personal characteristics in Bardet-Biedl syndrome and syndromes associated with sight loss

**REC reference: 19/WA/0055 Protocol number: 271-2018-JW IRAS project ID: 242829**

The Research Ethics Committee reviewed the above application at the meeting held on 21 February 2019. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net) outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

# Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

# Mental Capacity Act 2005

I confirm that the Committee has approved this research project for the purposes of the Mental Capacity Act 2005. The Committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

# Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The Committee made the following recommendations:

The Participant Information sheet could be laid-out in a larger more legible font and study start dates might need to be updated.

These are merely **recommendations,** not a condition of the ethical opinion, and the REC does not require perusal of the amended documentation.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*

*Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at* [*www.hra.nhs.uk*](http://www.hra.nhs.uk/) *or at* [*http://www.rdforum.nhs.uk.*](http://www.rdforum.nhs.uk/)

*Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of management permissions from host organisations.*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact [hra.studyregistration@nhs.net.](mailto:hra.studyregistration@nhs.net) The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

# It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

**Ethical review of research sites**

*NHS Sites*

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

# Extract of the meeting minutes

The Chairman welcomed the applicant and introduced the Committee members. The following issues were discussed:

Social or scientific value; scientific design and conduct of the study

The Committee discussed whether the design and methodology makes use of accepted scientific principles and methods to produce reliable and valid data.

It was noted that the primary outcome and primary outcome analysis are not very well defined, some of the outcome measures do not seem to have a matching research question/ rationale and the comparator groups are not described.

Dr Waite clarified that in stage 1 the study will be looking at clinical presentation whilst stage 2 will focus more on mental health issues. The aim is to establish the prevalence of a range of cognitive, behavioural and mood characteristics in a group of individuals with BBS and then to investigate whether these are different between syndrome groups.

A lot of the measures are interlinked and a range of measures are required to identify each trait. The second study will look at the link between mental health and anxiety, and the clinical profile of the group studied in stage 1 - and how they link to intolerance of uncertainty.

The comparator groups have not been firmly defined yet as they need to be matched to the characteristics of the BBS group as per the outcomes of stage 1. They would be recruited from a syndrome group with a comparable level of sight loss and mild cognitive impairment. If the results of stage 1 demonstrate a more sever cognitive impairment then the comparison group might need to be adjusted so that it is truly matched to the BBS grp.

The Committee concluded that the conduct of the study is appropriately described in the protocol, the study design robust and the proposed analysis adequate to answer the research question.

*Relevance of the research to the impairing condition*

The Committee agreed the research is connected with an impairing condition affecting persons lacking capacity or with the treatment of the condition.

*Justification for including adults lacking capacity to meet the research objectives*

The Committee agreed the research could not be carried out as effectively if it was confined to participants able to give consent.

Informed Consent process and the adequacy and completeness of participant information The Committee discussed the provision of information to research participants about the purpose of the research, and whether it includes all procedures as described in the protocol.

The Committee noted that written informed consent is taken as part of a process - with participants having adequate time to consider the information, and opportunity to ask questions. There is no inducement or coercion.

The Committee requested a clarification in relation to the requirement for parents to make a determination of the child’s capacity and competency to understand the study information.

Dr Waite clarified that this requirement relates to the consent process for stage 1, where parents are asked to make a determination on whether their child can understand the study information and meaningfully assent to taking part. However, for participants over 16 years old, the team will discuss the study over the telephone and assess capacity. If it is determined that the young person lacks capacity a consultee will be appointed.

*Information for consultees*

The Committee reviewed the information to be provided to consultees about the proposed research and their role and responsibilities as a consultee.

The Committee was satisfied that the information was adequate to enable consultees to give informed advice about the participation of persons lacking capacity.

The Committee thanked Dr Waite for her availability to speak to this submission and gave her an opportunity to ask questions.

The applicant did not raise any issues.

The Committee considered the researcher’s responses.

# Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

No ethical issues were raised in relation to the following:

* Recruitment arrangements and access to health information; fair participant selection

*Arrangements for appointing consultees*

The Committee considered the arrangements set out in the application for appointing consultees under Section 32 of the Mental Capacity Act to advise on whether participants lacking capacity should take part and on what their wishes and feelings would be likely to be if they had capacity.

After discussion the Committee agreed that reasonable arrangements were in place for identifying personal consultees and for nominated consultees independent of the project where no person can be identified to act as a personal consultee.

* Favourable risk benefit ratio; anticipated benefit/risks for research participants

*Balance between benefit and risk, burden and intrusion*

The Committee noted that while the research would not benefit participants lacking capacity it is intended to provide knowledge of the causes or the treatment or care of the impairing condition.

After discussion, the Committee agreed that the risk to participants is likely to be negligible and the research will not significantly interfere with their freedom of action or privacy or be unduly invasive or restrictive.

* Care and protection of research participants; respect for participants’ welfare and dignity; data protection and confidentiality

*Additional safeguards*

The Committee was satisfied that reasonable arrangements would be in place to comply with the additional safeguards set out in Section 33 of the Mental Capacity Act.

* Suitability of the applicant and supporting staff
* Independent review
* Suitability of supporting information
* Other study procedures
* Other general comments missing information/ typographical errors/ application errors
* Suitability of the study summary

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

# Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

No declarations of interest have been made in relation to this application

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

# After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed

guidance on reporting requirements for studies with a favourable opinion, including:

* Notifying substantial amendments
* Adding new sites and investigators
* Notification of serious breaches of the protocol
* Progress and safety reports
* Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

# User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-> assurance/

# HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee’s best wishes for the success of this project.

Yours Sincerely,

# Dr Philip Wayman White, MBChB, FRSM

# General Practitioner

**Chair Wales REC 5**

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# 19th March 2019

# Dr Jane Waite

**School of Life and Health Sciences**

Dear Jane,

|  |  |
| --- | --- |
| **Study title:** | Mental health and personal characteristics in Bardet-Biedl syndrome and syndromes associated with sight loss |
| **IRAS project ID:** | 242829 |
| **Protocol number:** | 271-2018-JW |
| **REC reference:** | 19/WA/0055 |
| **AURIO reference:** | 271-2018-JW |
| **Research Sites:** | Generic approval to approach syndrome support groups for participation. Site specific approvals to be added when management approval confirmed. |
|  | Professional networks |

I am writing to confirm permission for your project to proceed on behalf of the Sponsor, Aston University.

This approval is subject to the project being undertaken in accordance with:

* The REC Approval Letter dated 22nd February 2019 and documents listed therein
* Delegation of Duties and Authorised Persons Logs (Appendix 1)
* Aston University Quality Management System requirements as outlined in the site file standard operating procedures and if applicable the Aston University Quality Manual: Acquisition, Storage, Use and Disposal of Human Tissue.
* The [UK Policy Framework for Health and Social Care Research](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/)

Continued Sponsorship is subject to the following, post approval:

Reporting

* Submission of Annual Reports to the NHS Ethics Committee that gave a favorable opinion to the study and a copy of the report being sent to [AURIOgovernance@aston.ac.uk](mailto:ahricgovernance@aston.ac.uk).

Protocol amendments

Any protocol amendments being submitted for approval according to SOP AURIO107 before they are implemented.

Changes to study personnel

Updated Delegation of Duties Logs and Authorized Persons Logs being submitted to [research\_governance@aston.ac.uk](mailto:research_governance@aston.ac.uk) with associated supporting documents for approval prior to personnel changes being made.

Adverse Event Reporting

Any Adverse Events being reported according to SOP AURIO104

Study Closure

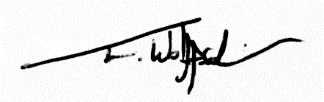
At the end of data collection (and if applicable data cleansing) an end of study report being is submitted to the REC and [research\_governance@aston.ac.uk](mailto:research_governance@aston.ac.uk) . Note: data analysis can continue after submission of this report.

Archiving

Archiving of the study in according to SOP AURIO106.

# Failure to comply with the terms of this approval will result in withdrawal of approval and indemnity for the project.

May I take this opportunity to wish you well with your study. Yours sincerely,



Professor James Wolffsohn

Associate Pro-Vice Chancellor, Research Integrity

**Mental health and personal characteristics in Bardet-Biedl syndrome** **and syndromes associated with sight loss**

**Participant Information Sheet**

**Questionnaire Study (Stage 1): Adult with BBS**

**Invitation**We would like to invite you to take part in a research study.

**If you have questions or would like a verbal explanation of this study, contact Jane Waite (Lead Researcher) on 0121 204 4307 or** [**j.waite@aston.ac.uk**](mailto:j.waite@aston.ac.uk) **or Joanne Tarver on 0121 204 4386 or j.tarver@aston.ac.uk. Accessible and full-length versions of this information sheet are available in an audio format at the following web address: [insert link].**

**If you are a parent/carer of an individual with Bardet-Biedl syndrome who is unable to understand this information sheet and decide whether they would like to take part, you can still take part as their parent/carer. Information sheets for those acting as a personal or nominated consultee are available at [insert link] or from Jane Waite (Lead Researcher) on 0121 204 4307 or j.waite@aston.ac.uk.**

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

**What is the purpose of the study?**

We are inviting individuals with Bardet-Biedl syndrome (BBS) and parents of individuals with BBS to take part in a questionnaire study about behaviour, emotion and cognition. We hope that the study will help health care professionals working with individuals with BBS to understand the factors that influence the well-being and outcomes of individuals with this condition.

The aim is to examine which person characteristics are common in children and adults with BBS and learn how these characteristics impact well-being.

The study is part of a longitudinal follow-up study that is taking place over 6 years. This will allow us to look at characteristics and changes in behaviour over time. If you decide to take part in this stage of the research, we will ask you if you also want to be involved in the other later aspects of this research project.

**Why have I been invited?**

You are being invited to take part in this study because records held by [name of support group] indicate that you are an adult with BBS and that you are happy to be contacted for research purposes. We will ask you to complete some questionnaires over the phone and nominate a person that knows you well to complete some questionnaires.

**What will happen to me if I take part?**

If you want to take part in the questionnaire study, you will need to provide your consent. Please complete the expression of interest form enclosed and a member of the research team will phone you. Alternatively, you can contact Dr Jane Waite on 0121 204 4307 or j.waite@aston.ac.uk or Dr Joanne Tarver on 0121 204 4386 or [j.tarver@aston.ac.uk](mailto:j.tarver@aston.ac.uk). We will ask you to provide consent over the phone and we will need to record the phone call. Once you have provided consent, we will send you some questionnaires in the post. The questionnaires will need to be given to your parent/carer to be completed. Once completed, the questionnaires should be returned back to the research team in the prepaid envelope. We will also arrange a time for you to answer some questions on the phone, if you are happy to. As part of the questionnaire, we will also ask your parent/carer to answer some additional questions over the phone about your ability.

The consent forms and questionnaires can be completed at a location and time convenient to you and your parent/carer.

Dr Jane Waite (study lead) is part of the team at the NHS BBS multi-disciplinary clinics. In the future, as part of the broader project, we may wish to gather some additional health related information about you (e.g. results from vision, hormone and genetic tests) from the records held at these clinics. This information may help us understand the results of the current questionnaire study. You will be asked to indicate whether you consent to us contacting you in the future to discuss how to arrange this. This is optional.

If you answer some questions on the phone this will take approximately 30 minutes. Taking part in the paper questionnaire study will take your parent/carer no longer than 45 minutes. Your parent/carer does not have to complete the questionnaire in one go. If your parent/carer decide to speak to a researcher on the phone this takes 20-25 minutes.

For the current questionnaire study, we are collecting data from participants from November 2018 until November 2019. After that we will spend some time understanding the data and writing reports. This means that the study will be finished in September 2020. This study is part of a broader study of behaviour, emotion and cognition in people with BBS that is ongoing until 2024. You will be given the option for us to retain your details if you would like to be invited to take part in other aspects of the study.

**Do I have to take part?  
  
No.** It is up to you to decide whether or not you wish to take part. If you do decide to participate, you will be asked to complete a consent form on the phone with the research team. We will record the phone call. You would still be free to withdraw from the study at any time without giving a reason.

**Will my taking part in this study be kept confidential?  
Yes.** A code will be attached to all the data you provide to maintain confidentiality. Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits or collect data by phone. Analysis of your data will be undertaken using coded data. The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the research Aston University may need to access your data to check that the data has been recorded accurately. If this is required your personal data will be treated as confidential by the individuals accessing your data.

**Will my GP be informed of my involvement in the study?**

With your consent your GP will be notified of your participation in the study. A copy of the feedback report will be shared with you GP at the end of this study. If we become aware that you may be experiencing an undiagnosed health difficulty, Dr Jane Waite will write to your GP to pass on this information.

It can also be useful for some doctors involved in your usual care to see the results of some of the questionnaires and assessments we do as part of this study. We will ask you whether it is ok to notify them of your participation and share the data we collect from you with other professionals or clinicians who usually work with you. This is optional.

**What happens if something is discovered during the study which requires further clinical investigation?**

The investigations undertaken during this study are not intended to be diagnostic but occasionally we discover something unusual that we feel should be investigated. We call these incidental findings.

Should this occur we will write to your GP who will be able to arrange further investigations for you.

**What happens if I tell you something that concerns you about my health or welfare or that of the person I care for?**

In the unlikely event of this happening, we will discuss with you how this should be addressed. If necessary, to protect you and the person you care for, we will report your concern to the appropriate person or bodies.

If you request advice this will be passed on to Dr Jane Waite who is a Clinical Psychologist, who will provide information about accessing local support.

**What are the possible benefits of taking part?**

You will receive two copies of an individualised feedback report summarising the results of the study. You can share one of the feedback reports with your parent/carer if you wish. This study will help us to find out more about the lives and needs of people with BBS and other groups who experience sight loss.

**What are the possible risks and burdens of taking part?**

We will be asking you and your parent/carer to think about times when you may feel distressed. This can sometimes be upsetting. Your decision to participate in this study will not impact your right to access services.

**What will happen to the results of the study?**

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential. Research findings may also be published in newsletters of support groups and educational institutions. Data will also be included in student dissertations.A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

**Expenses and payments**

There will be no payments made to participants for taking part in this study. Participants will not incur any expenses as a result of taking part in this study.

**Who is funding the research?**The study is being funded by the Baily Thomas Charitable Fund.

**Who is organising this study and acting as data controller for the study?**Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

**Who has reviewed the study?**This study was given a favorable ethical opinion by the Wales Research and Ethics Committee.

**What if I have a concern about my participation in the study?**If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet. If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Director of Governance, Mr. John Walter, j.g.walter@aston.ac.uk or telephone 0121 204 4869.

**Research Team**

This research is being conducted by:

Jane Waite (Lead Researcher)

Telephone: 0121 204 4307. Email: [j.waite@aston.ac.uk](mailto:j.waite@aston.ac.uk)

Joanne Tarver (Research Associate)

Telephone: 0121 204 4386. Email: [j.tarver@aston.ac.uk](mailto:j.tarver@aston.ac.uk)

**Thank you for taking time to read this information sheet. If you have any questions regarding the study please don’t hesitate to ask one of the research team.**

**Person characteristics and well-being in Bardet-Biedl Syndrome**

**EXPRESSION OF INTEREST FORM**

The research team are hoping to recruit parents, carers and individuals with Bardet-Biedl Syndrome (BBS) to take part in our questionnaire study about behaviour, emotion and cognition. We hope that the study will help health care professionals working with individuals with BBS to understand the factors that influence the well-being and outcomes of individuals with this condition.

If you would like to take part in this questionnaire study, or learn more about it, you can do so in the following ways.

1. Telephoning Dr Jane Waite (0121 204 4307) or emailing (j.waite@aston.ac.uk) to register your interest and receive paper copies of the questionnaires. You can also give consent over the phone
2. Complete the form below and a member of the research team will call you to provide more information about the research

*Completing this form does not commit you to taking part. You will have a chance to make your decision about getting involved once you have read the information sheets.*

Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Email address:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Telephone number:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Most convenient time to contact you:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Thank you very much for your interest**

**Background Information**

**Consenting adults**

**Please tick or write your response to these questions concerning background details:**

**Please answer the following about you:**

1. **Today’s date:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. **Gender:** Male Female
3. **Date of Birth**: \_\_\_/\_\_\_/\_\_\_\_ **Age:\_\_\_\_\_\_\_\_\_\_\_\_\_\_**
4. **Are you able to walk unaided?**

Yes/No (delete as appropriate)

1. **Have you been diagnosed with a syndrome?** Yes/No (delete as appropriate)

*If yes, please indicate which syndrome and answer questions 7 to 9. If no, please move on to question 10*

|  |  |  |  |
| --- | --- | --- | --- |
| BBS 1 |  | BBS 9 |  |
| BBS 2 |  | BBS 10 |  |
| BBS 3 |  | BBS 11 |  |
| BBS 4 |  | BBS 12 |  |
| BBS 5 |  | BBS 13 |  |
| BBS 6 |  | BBS 14 |  |
| BBS 7 |  | BBS 15 |  |
| BBS 8 |  | BBS gene unknown |  |
|  |  | Autism |  |
|  |  | Insert syndrome name |  |

1. **What is the genetic mechanism causing the syndrome?**

Uni-parental disomy Sequence repetition

Deletion Translocation

Unknown Other \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **When were you diagnosed?** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. **Who diagnosed you?**

Paediatrician Clinical Geneticist

GP Other \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **Have you had any medical/health difficulties in the last six months? If yes, please give details:**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

*We need to contact your GP to notify them of your participation (see consent form and information sheet for more information). Please complete the relevant details below:*

1. **Name of your GP\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**GP Address\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**GP Telephone number\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

*It can also be useful for some doctors involved in your usual care to see the results of some of the questionnaires and assessments we do as part of this study (see consent form and information sheet for more information). If you are happy for us to share your research data and notify your usual care team of your participation, please complete the information below:*

1. **Name of Clinician\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Clinic name and address \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Telephone number\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**NHS Trust\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**13. Please tick the highest level of your educational qualifications.**

No formal educational qualifications.......................................................................................... 🞏

Fewer than 5 GCSE’s or O Level’s (grades A-C), NVQ 1, or BTEC First Diploma……. …. 🞏

5 or more GCSE’s or O Level’s (grades A-C), NVQ 2, or equivalent…………………..…….. 🞏

3 or more ‘A’ Levels, NVQ 3, BTEC National, or equivalent.................................................. 🞏

Polytechnic/University degree, NVQ 4, or equivalent................................................................. 🞏

Masters/Doctoral degree, NVQ 5, or equivalent…………........................................................ 🞏

**14. In total how many people currently live in your home?** \_\_\_\_\_\_\_\_\_ Adults \_\_\_\_\_\_\_ Children

**15. Which of these best describes your current living situation?**

Married, and living with spouse..................................................................... 🞏

Living with partner....................................................................................... 🞏

Living alone with assistance from support worker................................................. 🞏

Living alone with no assistance from support worker ................................................ 🞏

Divorced/Separated/Widowed/Single and NOT living with a partner............... 🞏

Living with Parent/Family Member/Friend.......................................................... 🞏

Living in Residential/Care settings............................................................................ 🞏

**Beck Anxiety Inventory**

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today by circling the number in the corresponding space in the column next to each symptom.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Not at all | Mildly but it didn’t bother me much | Moderately it wasn’t pleasant at times | Severely- it bothered me a lot |
| 1. Numbness or tingling | 0 | 1 | 2 | 3 |
| 1. Feeling hot | 0 | 1 | 2 | 3 |
| 1. Wobbliness in legs | 0 | 1 | 2 | 3 |
| 1. Unable to relax | 0 | 1 | 2 | 3 |
| 1. Fear of worst happening | 0 | 1 | 2 | 3 |
| 1. Dizzy or lightheaded | 0 | 1 | 2 | 3 |
| 1. Heart pounding/racing | 0 | 1 | 2 | 3 |
| 1. Unsteady | 0 | 1 | 2 | 3 |
| 1. Terrified or afraid | 0 | 1 | 2 | 3 |
| 1. Nervous | 0 | 1 | 2 | 3 |
| 1. Feeling of choking | 0 | 1 | 2 | 3 |
| 1. Hands trembling | 0 | 1 | 2 | 3 |
| 1. Shaky/unsteady | 0 | 1 | 2 | 3 |
| 1. Fear of losing control | 0 | 1 | 2 | 3 |
| 1. Difficulty in breathing | 0 | 1 | 2 | 3 |
| 1. Fear of dying | 0 | 1 | 2 | 3 |
| 1. Scared | 0 | 1 | 2 | 3 |
| 1. Indigestion | 0 | 1 | 2 | 3 |
| 1. Faint/lightheaded | 0 | 1 | 2 | 3 |
| 1. Face flushed | 0 | 1 | 2 | 3 |
| 1. Hot/cold sweats | 0 | 1 | 2 | 3 |

**Beck Depression Inventory II**

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including item 16 (changes in sleeping pattern) or item 18 (changes in appetite).

|  |  |  |  |
| --- | --- | --- | --- |
|  | 1. **Sadness** |  | **6. Punishment Feelings** |
| 0 | I do not feel sad. | 0 | I don’t feel I am being punished. |
| 1 | I feel sad much of the time. | 1 | I feel I may be punished. |
| 2 | I am sad all the time. | 2 | I expect to be punished. |
| 3 | I am so sad or unhappy that I can’t stand it. | 3 | I feel like I am being punished. |
|  |  |  |  |
|  | 1. **Pessimism** |  | **7. Self-dislike** |
| 0 | I am not discouraged about my future. | 0 | I feel the same about myself as ever. |
| 1 | I feel more discouraged about my future than I used to be. | 1 | I have lost confidence in myself. |
| 2 | I do not expect things to work out for me. | 2 | I am disappointed in myself. |
| 3 | I feel my future is hopeless and will only get worse. | 3 | I dislike myself. |
|  |  |  |  |
|  | 1. **Past failure** |  | **8. Self-Criticalness** |
| 0 | I do not feel like a failure. | 0 | I don’t criticize or blame myself more than usual. |
| 1 | I have failed more than I should have. | 1 | I am more critical of myself than I used to be. |
| 2 | As I look back, I see a lot of failures. | 2 | I criticize myself for all of my faults. |
| 3 | I feel I am a total failure as a person. | 3 | I blame myself for everything bad that happens. |
|  |  |  |  |
|  | 1. **Loss of pleasure** |  | **9. Suicidal Thoughts or Wishes** |
| 0 | I get as much pleasure as I ever did from the things I enjoy. | 0 | I don’t have any thoughts of killing myself. |
| 1 | I don’t enjoy things as much as I used to. | 1 | I have thoughts of killing myself, but I would not carry them out. |
| 2 | I get very little pleasure from the things I used to enjoy. | 2 | I would like to kill myself. |
| 3 | I can’t get any pleasure from the things I used to enjoy. | 3 | I would kill myself if I had the chance. |
|  |  |  |  |
|  | 1. **Guilty Feelings** |  | **10. Crying** |
| 0 | I don’t feel particularly guilty. | 0 | I don’t cry anymore than I used to. |
| 1 | I feel guilty over many things I have done or should have done. | 1 | I cry more than I used to. |
| 2 | I feel quite guilty most of the time. | 2 | I cry over every little thing. |
| 3 | I feel guilty all of the time. | 3 | I feel like crying but I can’t. |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
|  | **11. Agitation** |  | **17. Irritability** |
| 0 | I am no more restless or wound up than usual. | 0 | I am no more irritable than usual. |
| 1 | I feel more restless or wound up than usual. | 1 | I am more irritable than usual. |
| 2 | I am so restless or agitated that it’s hard to stay still. | 2 | I am much more irritable than usual. |
| 3 | I am so restless or agitated that I have to keep moving or doing something. | 3 | I am irritable all the time. |
|  |  |  |  |
|  | 1. **Loss of interest** |  | **18. Changes in Appetite** |
| 0 | I have not lost interest in other people or activities. | 0 | I have not experienced any change in my appetite |
| 1 | I am less interested in other people or things than before. | 1a  1b | My appetite is somewhat less than usual.  My appetite is somewhat greater than usual. |
| 2 | I have lost most of my interest in other people or things. | 2a  2b | My appetite is much less than before.  My appetite is much greater than usual. |
| 3 | It’s hard to get interested in anything. | 3a  3b | I have no appetite at all.  I crave food all the time. |
|  |  |  |  |
|  | **13. Indecisiveness** |  | **19. Concentration Difficulty** |
| 0 | I make decisions about as well as ever. | 0 | I can concentrate as well as ever. |
| 1 | I find it more difficult to make decisions than usual. | 1 | I can’t concentrate as well as usual. |
| 2 | I have much greater difficulty in making decisions than I used to. | 2 | It’s hard to keep my mind on anything for very long. |
| 3 | I have trouble making any decisions. | 3 | I find I can’t concentrate on anything |
|  |  |  |  |
|  | **14. Worthlessness** |  | **20. Tiredness or Fatigue** |
| 0 | I do not feel I am worthless. | 0 | I am no more tired or fatigued than usual. |
| 1 | I don’t consider myself as worthwhile and useful as I used to. | 1 | I get more tired or fatigued to do a lot of the things I used to do. |
| 2 | I feel more worthless compared to other people. | 2 | I am too tired or fatigued to do a lot of the things I used to do. |
| 3 | I feel utterly worthless. | 3 | I am too tired or fatigued to do most of the things I used to do. |
|  |  |  |  |
|  | **15. Loss of energy** |  | **21. Loss of interest in sex** |
| 0 | I have as much energy as ever. | 0 | I have not noticed any recent change in my interest in sex. |
| 1 | I have less energy than I used to have. | 1 | I have not noticed any recent change in my interest in sex. |
| 2 | I don’t have enough energy to do very much. | 2 | I am much less interested in sex now. |
| 3 | I don’t have enough energy to do anything. | 3 | I have lost interest in sex completely. |
|  |  |  |  |
|  | **16. Changes in sleeping pattern** |  |  |
| 0 | I have not experienced any change in my sleeping pattern. |  |  |
| 1a  1b | I sleep somewhat more than usual.  I sleep somewhat less than usual. |  |  |
| 2a  2b | I sleep a lot more than usual  I sleep a lot less than usual |  |  |
| 3a  3b | I sleep most of the day.  I wake up 1/2 hours early and can’t get back to sleep |  |  |

**Cardiff Visual Ability Questionnaire**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Because of your eye sight and with your glasses or low vision aids if you use them, how difﬁcult do you ﬁnd:** | **Very Easy** | **Easy** | **Difficult** | **Very Difficult** |
| 1. Reading books and documents (e.g. bank statements) |  |  |  |  |
| 1. Reading the smallest print in books or on documents |  |  |  |  |
| 1. Drawing, colouring or painting |  |  |  |  |
| 1. Reading text messages on your mobile phone |  |  |  |  |
| 1. Reading restaurant menus |  |  |  |  |
| 1. Reading information on a board from a distance |  |  |  |  |
| 1. Watching television |  |  |  |  |
| 1. Watching a film at the cinema |  |  |  |  |
| 1. Going out alone in daylight |  |  |  |  |
| 1. Walking in a crowded place |  |  |  |  |
| 1. Using public transport (bus/train) |  |  |  |  |
| 1. Reading a bus/train timetable on a screen at a station |  |  |  |  |
| 1. Chatting with your friends |  |  |  |  |
| 1. Recognising faces or identifying your friends at arms-length |  |  |  |  |
| 1. Seeing your friend at a social event |  |  |  |  |
| 1. Playing video games, e.g., a PlayStation |  |  |  |  |
| 1. Using a computer or IPad? |  |  |  |  |
| 1. Using an iPod/MP3/MP4 to listen to music |  |  |  |  |
| 1. Swimming |  |  |  |  |
| 1. Exercising |  |  |  |  |
| 1. Playing or doing sports |  |  |  |  |

The Adult Autism Spectrum Quotient (AQ)

Ages 16+

**How to fill out the questionnaire**

*Below are a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer.*

**DO NOT MISS ANY STATEMENT OUT.**

*Examples*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| E1. I am willing to take risks. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| E2. I like playing board games. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| E3. I find learning to play musical instruments easy. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| E4. I am fascinated by other cultures. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 1. | I prefer to do things with others rather than on my own. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 2. | I prefer to do things the same way over and over again. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 3. | If I try to imagine something, I find it very easy to create a picture in my mind. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 4. | I frequently get so strongly absorbed in one thing that I lose sight of other things. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 5. | I often notice small sounds when others do not. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 6. | I usually notice car number plates or similar strings of information. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 7. | Other people frequently tell me that what I’ve said is impolite, even though I think it is polite. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 8. | When I’m reading a story, I can easily imagine what the characters might look like. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 9. | I am fascinated by dates. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 10. | In a social group, I can easily keep track of several different people’s conversations. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 11. | I find social situations easy. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 12. | I tend to notice details that others do not. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 13. | I would rather go to a library than a party. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 14. | I find making up stories easy. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 15. | I find myself drawn more strongly to people than to things. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 16. | I tend to have very strong interests which I get upset about if I can’t pursue. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 17. | I enjoy social chit-chat. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 18. | When I talk, it isn’t always easy for others to get a word in edgeways. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 19. | I am fascinated by numbers. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 20. | When I’m reading a story, I find it difficult to work out the characters’ intentions. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 21. | I don’t particularly enjoy reading fiction. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 22. | I find it hard to make new friends. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 23. | I notice patterns in things all the time. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 24. | I would rather go to the theatre than a museum. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 25. | It does not upset me if my daily routine is disturbed. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 26. | I frequently find that I don’t know how to keep a conversation going. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 27. | I find it easy to “read between the lines” when someone is talking to me. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 28. | I usually concentrate more on the whole picture, rather than the small details. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 29. | I am not very good at remembering phone numbers. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 30. | I don’t usually notice small changes in a situation, or a person’s appearance. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 31. | I know how to tell if someone listening to me is getting bored. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 32. | I find it easy to do more than one thing at once. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 33. | When I talk on the phone, I’m not sure when it’s my turn to speak. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 34. | I enjoy doing things spontaneously. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 35. | I am often the last to understand the point of a joke. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 36. | I find it easy to work out what someone is thinking or feeling just by looking at their face. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 37. | If there is an interruption, I can switch back to what I was doing very quickly. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 38. | I am good at social chit-chat. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 39. | People often tell me that I keep going on and on about the same thing. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 40. | When I was young, I used to enjoy playing games involving pretending with other children. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 41. | I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.). | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 42. | I find it difficult to imagine what it would be like to be someone else. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 43. | I like to plan any activities I participate in carefully. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 44. | I enjoy social occasions. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 45. | I find it difficult to work out people’s intentions. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 46. | New situations make me anxious. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 47. | I enjoy meeting new people. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 48. | I am a good diplomat. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 49. | I am not very good at remembering people’s date of birth. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |
| 50. | I find it very easy to play games with children that involve pretending. | definitely  agree | slightly  agree | slightly  disagree | definitely  disagree |

**Health Questionnaire**

**PART A**

**Instructions:**

* Have these problems **EVER** affected your child or person you care for?
* Please rate as **0** – if the problem has never affected the person you care for, **1** – if it has been a mild problem, **2** - if the problem has been moderately serious, or **3** – if the problem has been severe.
* If the person you care for has had these problems please state whether any treatment has been implemented by circling **yes** or **no**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Never** | **Mild** | **Moderate** | **Severe** |
| **1a.** Eye Problems (e.g. glaucoma / blocked tear duct/s)....................................................... | **0** | **1** | **2** | **3** |
| **1b.** Corrective surgery / medication / treatment: **yes / no** |  |  |  |  |
| **2a.** Ear Problems (e.g. infections, glue ear) ......................................................................... | **0** | **1** | **2** | **3** |
| **2b.** Corrective surgery / medication / treatment (e.g. grommets): **yes / no** |  |  |  |  |
| **3a.** Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed  eruption of teeth).................................................................................................. | **0** | **1** | **2** | **3** |
| **3b**.Dental surgery / treatment (e.g. teeth removal): **yes / no** |  |  |  |  |
| **4a.** Cleft Palate................................................................................................. | **0** | **1** | **2** | **3** |
| **4b.** Repaired: **yes / no** |  |  |  |  |
| **5a.** Gastrointestinal Difficulties (e.g. reflux / stomach problems)........................................ | **0** | **1** | **2** | **3** |
| **5b.** Corrective surgery / medication / treatment (e.g. nissen fundoplication): **yes / no** |  |  |  |  |
| **6a.** Bowel Problems (e.g. obstruction).................................................................................. | **0** | **1** | **2** | **3** |
| **6b.** Corrective surgery / treatment: **yes / no** |  |  |  |  |
| 7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or  murmur)........................................................................................................................... | **0** | **1** | **2** | **3** |
| **7b.** Corrective surgery / medication / treatment: **yes / no** |  |  |  |  |
| **8a.** Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended  testes) ………………………………………………………………………………….. | **0** | **1** | **2** | **3** |
| **8b.** Corrective surgery / treatment: **yes / no** |  |  |  |  |
| **9a.** Hernia (e.g. inguinal or hiatal)........................................................................................ | **0** | **1** | **2** | **3** |
| **9b.** Repair / treatment: **yes / no** |  |  |  |  |
| **10.** Limb Abnormalities (e.g. malformed arm)..................................................................... | **0** | **1** | **2** | **3** |
| **11a.** Epilepsy / Seizures / Neurological Referrals................................................................ | **0** | **1** | **2** | **3** |
| **11b.** Medication: **yes / no** |  |  |  |  |
| **12a.** Lung or Respiratory Problems (asthma/bronchitis)...................................................... | **0** | **1** | **2** | **3** |
| **12b.** Corrective surgery / medication / treatment: **yes / no** |  |  |  |  |
| **13a.** Liver or Kidney Problems............................................................................................. | **0** | **1** | **2** | **3** |
| **13b.** Corrective surgery / medication / treatment: **yes / no** |  |  |  |  |
| **14a.** Diabetes………………………………............................................................ | **0** | **1** | **2** | **3** |
| **14b.** Corrective surgery / medication / treatment: **yes / no** | **0** | **1** | **2** | **3** |
| **15a.** Thyroid Function Problems…………………………………………………………...  **15b.** Corrective surgery / medication / treatment: **yes / no** | **0** | **1** | **2** | **3** |
| **16a.** Polycystic Ovary Syndrome………….……………………………………………….  **16b.** Corrective surgery / medication / treatment: **yes / no** | **0** | **1** | **2** | **3** |
| **17a.** Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)………………........................ | **0** | **1** | **2** | **3** |
| **17b.** Medication / treatment: **yes / no** |  |  |  |  |
| **18a.** Other (please specify problem, severity from 0-3)....................................................... | **0** | **1** | **2** | **3** |
| **18b.** Corrective surgery / medication / treatment: **yes / no** |  |  |  |  |

**PART B**

**Instructions:**

* Have these medical problems affected the person you care for in thepast**MONTH**
* Please rate as **0** – if your child has not been affected by this problem in the past month, **1** - if they have been mildly affected, **2** – if the problem has moderately affected your child and **3** - if your child has been severely affected by the problem.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | No | Mild | Moderate | Severe |
| 19. Eye Problems (e.g. glaucoma / blocked tear duct/s)...................................................... | 0 | 1 | 2 | 3 |
| 20. Ear Problems (e.g. infections, glue ear)......................................................................... | 0 | 1 | 2 | 3 |
| 21. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth)...................................................................................................................................... | 0 | 1 | 2 | 3 |
| 22. Cleft Palate.................................................................................................................. | 0 | 1 | 2 | 3 |
| 23. Gastrointestinal Difficulties (e.g. reflux / stomach problems)........................................ | 0 | 1 | 2 | 3 |
| 24. Bowel Problems (e.g. obstruction).................................................................................. | 0 | 1 | 2 | 3 |
| 25. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or  murmur)………………………………………………………………………………... | 0 | 1 | 2 | 3 |
| 26. Problems with Genitalia (e.g. prostate / testicular problems i.e. undescended testes).... | 0 | 1 | 2 | 3 |
| 27. Hernia (e.g. inguinal or hiatal)........................................................................................ | 0 | 1 | 2 | 3 |
| 28. Limb Abnormalities (e.g. malformed arm).................................................................... | 0 | 1 | 2 | 3 |
| 29. Epilepsy / Seizures / Neurological Referrals.................................................................. | 0 | 1 | 2 | 3 |
| 30. Lung or Respiratory Problems (asthma / bronchitis)...................................................... | 0 | 1 | 2 | 3 |
| 31. Liver or Kidney Problems............................................................................................... | 0 | 1 | 2 | 3 |
| 32.Diabetes......................................................................................................... | 0 | 1 | 2 | 3 |
| 33. Thyroid Function Problems.................................................................................. | 0 | 1 | 2 | 3 |
| 34. Polycystic Ovary Syndrome………................................................................................ | 0 | 1 | 2 | 3 |
| 35. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin).................................................. | 0 | 1 | 2 | 3 |
| 36. Other (please specify problem and severity from 0-3) ……………………………….. | 0 | 1 | 2 | 3 |

###### Intolerance of Uncertainty Scale - Short Form

###### (Carleton, Norton, & Asmundson, 2007)

###### Please circle the number that best corresponds to how much you agree with each

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Not at all characteristic of me | A little characteristic of me | Somewhat characteristic of me | Very characteristic of me | Entirely characteristic of me |
| 1. Unforeseen events upset me greatly. | 1 | 2 | 3 | 4 | 5 |
| 2. It frustrates me not having all the information I need. | 1 | 2 | 3 | 4 | 5 |
| 3. Uncertainty keeps me from living a full life. | 1 | 2 | 3 | 4 | 5 |
| 4. One should always look ahead so as to avoid surprises. | 1 | 2 | 3 | 4 | 5 |
| 5. A small unforeseen event can spoil everything, even with the best of planning. | 1 | 2 | 3 | 4 | 5 |
| 6. When it’s time to act, uncertainty paralyses me. | 1 | 2 | 3 | 4 | 5 |
| 7. When I am uncertain I can’t function very well. | 1 | 2 | 3 | 4 | 5 |
| 8. I always want to know what the future has in store for me. | 1 | 2 | 3 | 4 | 5 |
| 9. I can’t stand being taken by surprise. | 1 | 2 | 3 | 4 | 5 |
| 10. The smallest doubt can stop me from acting. | 1 | 2 | 3 | 4 | 5 |
| 11. I should be able to organize everything in advance. | 1 | 2 | 3 | 4 | 5 |
| 12. I must get away from all uncertain situations. | 1 | 2 | 3 | 4 | 5 |

**Behaviour Rating Inventory Of Executive Function- Adult Version**

Self-Report Form

Instructions

On the following pages is a list of statements. We would like to know if you have had any problems with these behaviours over the past month. Please answer all the items the best you can. Please DO NOT SKIP ANY ITEMS. Indicate your response by selecting:

**N** if the behaviour is **N**ever a problem

**S** if the behaviour is **S**ometimes a problem

**O** if the behaviour is **O**ften a problem

For example, if you never have trouble making decisions, you would select N for this item:

|  |  |  |  |
| --- | --- | --- | --- |
|  | N | S | O |
| I have trouble making decisions | X |  |  |

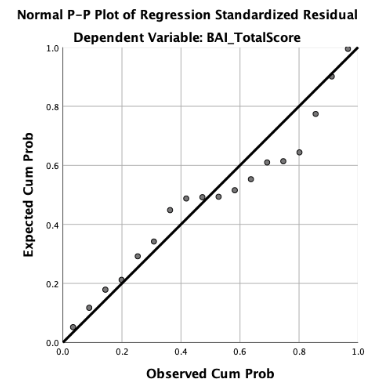
During the past month, how often has each if the following behaviours been a *problem*?

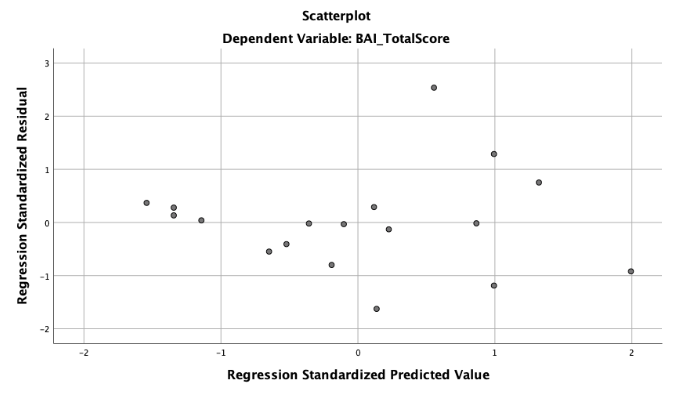
|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| 1. I have angry outbursts | N | S | O |
| 1. I make careless errors when completing tasks | N | S | O |
| 1. I am disorganised | N | S | O |
| 1. I have trouble concentrating on tasks (such as chores, reading, or work) | N | S | O |
| 1. I tap my fingers or bounce my legs | N | S | O |
| 1. I need to be reminded to begin a task even when I am willing | N | S | O |
| 1. I have a messy closet | N | S | O |
| 1. I have trouble changing from one activity or task to another | N | S | O |
| 1. I get overwhelmed by large tasks | N | S | O |
| 1. I forget my name | N | S | O |
| 1. I have trouble with jobs or tasks that have more than one step | N | S | O |
| 1. I overreact emotionally | N | S | O |
| 1. I don’t notice when I cause others to feel bad or get mad until it is too late | N | S | O |
| 1. I have trouble getting ready for the day | N | S | O |
| 1. I have trouble prioritising activities | N | S | O |
| 1. I have trouble sitting still | N | S | O |
| 1. I forget what I am doing in the middle of things | N | S | O |
| 1. I don’t check my work for mistakes | N | S | O |
| 1. I have emotional outbursts for little reason | N | S | O |
| 1. I lie around the house a lot | N | S | O |
| 1. I start tasks (such as cooking, projects) without the right materials | N | S | O |
| 1. I have trouble accepting different ways to solve problems with work, friends or tasks | N | S | O |
| 1. I talk at the wrong time | N | S | O |
| 1. I misjudge how difficult or easy tasks will be | N | S | O |
| 1. I have problems getting started on my own | N | S | O |
| 1. I have trouble staying on the same topic when talking | N | S | O |
| 1. I get tired | N | S | O |
| 1. I react more emotionally to situations than my friends | N | S | O |
| 1. I have problems waiting my turn | N | S | O |
| 1. People say that I am disorganised | N | S | O |
| 1. I lose things (such as keys, money, wallet, homework, etc.) | N | S | O |
| 1. I have trouble thinking of a different way to solve a problem when stuck | N | S | O |
| 1. I overreact to small problems | N | S | O |
| 1. I don’t plan ahead for future activities | N | S | O |
| 1. I have a short attention span | N | S | O |
| 1. I make inappropriate sexual comments | N | S | O |
| 1. When people seem upset with me, I don’t understand why | N | S | O |
| 1. I have trouble counting to three | N | S | O |
| 1. I have unrealistic goals | N | S | O |
| 1. I leave the bathroom a mess | N | S | O |
| 1. I make careless mistakes | N | S | O |
| 1. I get emotionally upset easily | N | S | O |
| 1. I make decisions that get me into trouble (legally, financially, socially) | N | S | O |
| 1. I am bothered by having to deal with changes | N | S | O |
| 1. I have difficulty getting excited about things | N | S | O |
| 1. I forget instructions easily | N | S | O |
| 1. I have good ideas but cannot get them on paper | N | S | O |
| 1. I make mistakes | N | S | O |
| 1. I have trouble getting started on tasks | N | S | O |
| 1. I say things without thinking | N | S | O |
| 1. My anger is intense but ends quickly | N | S | O |
| 1. I have trouble finishing tasks (such as chores, work) | N | S | O |
| 1. I start things at the last minute (such as assignments, chores, tasks) | N | S | O |
| 1. I have difficulty finishing a task on my own | N | S | O |
| 1. People say that I am easily distracted | N | S | O |
| 1. I have trouble remembering things, even for a few minutes (such as directions, phone numbers) | N | S | O |
| 1. People say that I am too emotional | N | S | O |
| 1. I rush through things | N | S | O |
| 1. I get annoyed | N | S | O |
| 1. I leave my room or home a mess | N | S | O |
| 1. I get disturbed by unexpected changes in my daily routine | N | S | O |
| 1. I have trouble coming up with ideas for what to do with my free time | N | S | O |
| 1. I don’t plan ahead for tasks | N | S | O |
| 1. People say that I don’t think before acting | N | S | O |
| 1. I have trouble finding things in my room, closet, or desk | N | S | O |
| 1. I have problems organising activities | N | S | O |
| 1. After having a problem, I don’t get over it easily | N | S | O |
| 1. I have trouble doing more than one thing at a time | N | S | O |
| 1. My mood changes frequently | N | S | O |
| 1. I don’t think about consequences before doing something | N | S | O |
| 1. I have trouble organising work | N | S | O |
| 1. I get upset quickly or easily over little things | N | S | O |
| 1. I am impulsive | N | S | O |
| 1. I don’t pick up after myself | N | S | O |
| 1. I have problems completing my work | N | S | O |

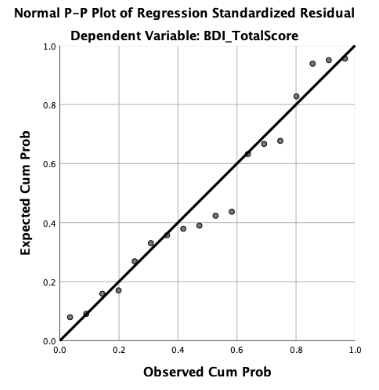
**Standard Operating Procedure (SOP)**

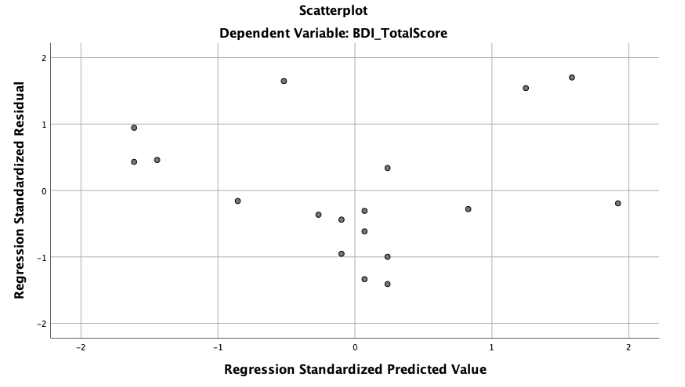
**Taking telephone consent**

1. Phone call to be taken by project lead
2. Introduce self to potential participant; enquire whether they have read information about the project
3. Briefly explain research processes to participant
   1. Aims of research
   2. What is involved for them (questionnaire completion or assessment day)
   3. What is involved for their parent/carer
   4. What are the risks
   5. What are the benefits
   6. Who to contact if questions/complaints
4. Ask participant whether they have any questions
5. Ask whether they would like to take part
6. Assess participant understanding/capacity
   1. Can they tell you what is involved in the research for them
   2. Can they tell you the purpose of the research
   3. Do they understand risks?
7. If yes and adult is deemed to have capacity, advise participant that the rest of the phone call will need to be recorded whilst you go through the consent form with them
8. Begin recording of telephone consent
9. Go through each consent item and ask participant to say yes or no
10. At the end of phone call end recording
11. If consented to all compulsory items, move recording from device onto study hard drive and label with unique ID number
12. Delete from recording device
13. Store hard drive in locked cabinet
14. If participant does not consent to compulsory consent items, explain unable to take part and reasons. End phone call and permanently delete any recording of the telephone conversation



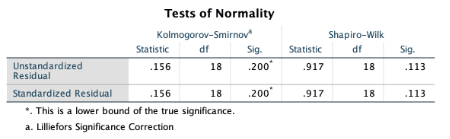




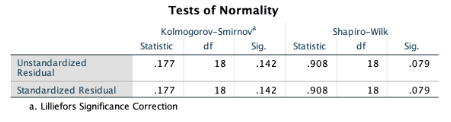


**Normality Tests of Residuals**

(Anxiety)



(Depression)

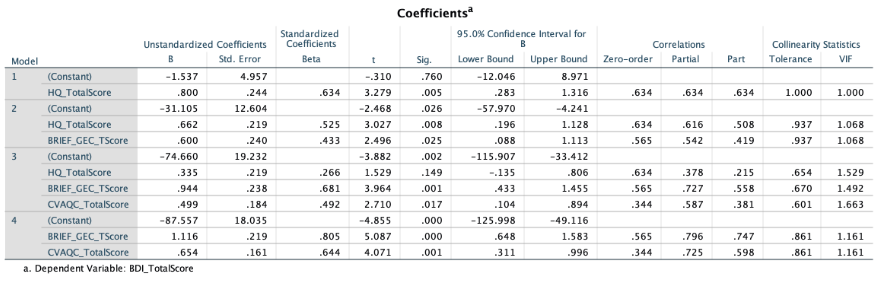


**Collinearity Statistics**

**(**Anxiety)

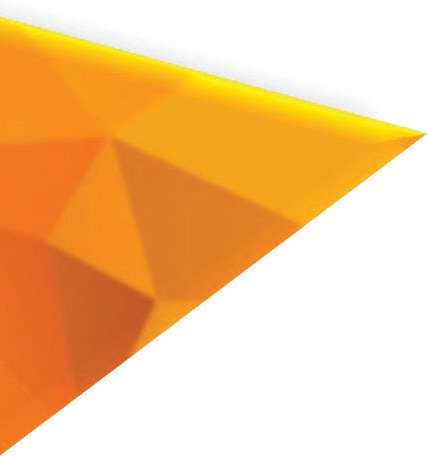


(Depression)



**CHAPTER THREE:**

**MENTAL HEALTH DIFFICULTIES IN ADULTS WITH BARDET-BIEDL SYNDROME: AN EXECUTIVE SUMMARY**



MENTAL HEALTH DIFFICULTIES IN ADULTS WITH BARDET-BIEDL SYNDROME (BBS)

**This report is a summary of a research project on anxiety and depression in adults with BBS. This summary has been written for individuals with BBS; however, it may also be of interest to family members, carers and professionals who work with adults diagnosed with this condition.**

**It has been developed collaboratively with a service user who has low vision to ensure accessibility for individuals with visual impairment and their family members and carers. The service user provided verbal feedback on one draft of this summary. Based upon feedback received, a large font size has been used throughout this report.**

**This report is not intended for publication in a scientific journal; however, it has been submitted to Staffordshire University as part of a doctoral thesis (an academic assignment) and will therefore be published on the university website for members of the public to access.**

|  |  |
| --- | --- |
| TERMINOLOGY | |
| Prevalence | Refers to how common something is. |
| Participant | Someone who consents to participate in research. |
| Autism | A developmental disability that affects how a person communicates with and relates to other people. |
| Intolerance of Uncertainty | The tendency to dislike or react negatively to new or uncertain situations. |
| Executive Functioning | **A set of** mental processes that enable us to plan, focus attention, remember instructions, behave appropriately and multi-task successfully. |
| Ethics | **Code of conduct or rules that govern an individual or group.** |
| Ethical Committee | **A group of professionals who judge whether a research study upholds ethical standards.** |

OVERVIEW

* This report summarises a research study that aimed to understand mental health difficulties in adults diagnosed with BBS.
* In 2017, researchers from the West Midlands conducted a brief survey at the BBS UK support conference with individuals with the syndrome and their parents/carers to find out where they think research should be prioritised.
* Over half of parents/carers reported that mental health difficulties should be a focus, specifically depression, anxiety and emotional outbursts. Depression and anxiety were also core themes reported by people with BBS.
* A research study focusing on factors that predict anxiety and depression in adults with the syndrome was conducted and this report provides a summary of the project.

BACKGROUND

BARDET-BIEDL SYNDROME (BBS)

* BBS is a rare genetic condition that affects approximately 1 in 100,000 people1.
* People with BBS usually have a number of health problems including sight problems, kidney problems, obesity, extra digits on the hand or feet and for some people, a learning disability2.
* There are additional difficulties that some people with BBS experience, which include speech and language difficulties, facial abnormalities, dental problems, behavioural difficulties and mental health problems3.

MENTAL HEALTH IN BBS

* Some research has shown that people with BBS have higher rates of mental health difficulties compared to the general population4,5.
* Anxiety and depression are the most commonly reported mental health difficulties in people with this syndrome6.
* We are unsure exactly why people with BBS experience anxiety and depression because most studies to date have only reported the prevalence of mental health problems in BBS.
* The majority of these studies have also relied on family members and carers accounts of mental health difficulties in this syndrome. They have not directly asked people with BBS about their experiences of mental health difficulties.

MENTAL HEALTH RISK MARKERS

* There may be a number of reasons why people with BBS experience anxiety and depression; one reason may be that people with health problems are at a higher risk of experiencing mental health problems7.
* The majority of adults with BBS have a visual impairment and research has shown that high rates of anxiety and depression in people with visual impairment8.
* A high prevalence of autism characteristics have also been reported in people with BBS10 and research suggests that mental health difficulties are more common in people diagnosed with autism9.
* Difficulties with executive functioning and intolerance of uncertainty have been associated with mental health problems in people with autism and also the general population11,12,13, but we do not know whether these factors are also associated with mental health difficulties in people with BBS.

AIMS:

* To report the prevalence of anxiety and depression in adults with BBS.
* To assess whether health problems, autism characteristics, intolerance of uncertainty, executive dysfunction (difficulties with planning things, memory, multi-tasking and managing emotions) and visual impairment predict anxiety and depression in adults with BBS.

METHOD

ETHICAL APPROVAL

* The study was given ethical approval by the Wales Research and Ethics Committee 5 and was subject to review by Aston University.

RECRUITMENT

* The study was advertised through the BBS UK support group.
* Letters containing information about the study were posted to adults with BBS.
* Those who were interested in taking part were able to express an interest in the study by posting back a form or they could contact the researchers by telephone or email.

PARTICIPANTS

* 18 adults with BBS took part in the study.
* 12 of the participants were female and 6 were male.
* The age of participants ranged from 28 years to 62 years.

PROCEDURE

* People who were interested in taking part in the study had a telephone call with a researcher to find out more about the study and they also had the opportunity to ask questions.
* The researchers checked that each participant understood what the study was about and what they were required to do.
* Participants who were willing and able to take part were asked to complete a series of questionnaires about anxiety, depression, health problems, visual impairment, autism characteristics, intolerance of uncertainty and executive functioning.
* Participants were able to complete these forms at home and post them back to the researchers. They were also given the option to complete the questionnaires electronically on a computer or over the telephone with a researcher.
* Participants were free to withdraw from the study at any time, without providing a reason.

QUESTIONNAIRES

* Beck Anxiety Inventory14
* Beck Depression Inventory15
* Cardiff Visual Ability Questionnaire16
* Health Questionnaire17
* Autism Quotient18
* Intolerance of Uncertainty Scale19
* Behaviour Rating Inventory of Executive Functioning – Adult Version20

**RESULTS**

STUDY RESULTS

* One participant (5.6%) showed mild anxiety symptoms. Two participants (11.1%) showed moderate anxiety symptoms and three participants (16.7%) showed severe anxiety symptoms.
* Two participants (11.1%) showed mild depression symptoms. One participant (5.6%) had moderate depression symptoms and three participants (16.7%) showed severe depression symptoms.
* Two participants (11.1%) displayed clinically significant autism characteristics.
* Four participants (22%) displayed clinically significant executive functioning difficulties.
* Having more health problems and difficulties with executive functioning were found to predict higher anxiety levels in adults with BBS.

***Figure 1: Diagram summarising the factors predicting anxiety***

Number of health problems

Executive Dysfunction

Anxiety Levels

* Similarly, having more health problems and difficulties with executive functioning were also found to predict higher depression levels in adults with BBS, however having a more severe visual impairment also prediction higher depression levels.

***Figure 1: Diagram summarising the factors predicting depression***

Number of health problems

Executive Dysfunction

Visual Impairment

Depression Levels

* We conducted some further analyses to understand which areas of executive functioning were impacting on anxiety and depression levels. These additional analyses showed that difficulties with problem solving and correcting mistakes, and also difficulties with keeping home and work spaces tidy and organised were found to predict higher levels of anxiety. Difficulties with managing one’s own emotions (e.g. remaining calm during an argument) were found to predict higher levels of depression.

DISCUSSION OF FINDINGS

CLINICAL IMPLICATIONS

* The results suggest that the rates of anxiety and depression in people BBS are higher when compared to the national data on anxiety and depression in the general population.
* The findings highlight the importance of understanding the impact physical health problems have on adults with BBS. BBS clinics across the UK will be able to consider the mental health of people with BBS so that they can offer or signpost people to services that can offer support.
* The findings also highlight the need for further research on anxiety and depression and in particular, how difficulties with executive functioning may impact on the development of mental health difficulties in people with this syndrome. This will further our understanding of mental health in BBS and allow for support to be offered to people with BBS.

DISSEMINATION OF FINDINGS

* All participants will be sent a summary of the research findings via post. There will also be an option to receive them electronically or via audio recording.
* The research report will be submitted for publication in an academic journal.

STUDY LIMITATIONS

* This is the first study investigating factors that predict anxiety and depression in adults with BBS; therefore we must be careful when understanding the results of this study and making decisions based on the findings. This is because further research is necessary to fully understand anxiety and depression in this syndrome.
* The number of people who took part in this study was small. Having more participants in the study would help to make the findings more accurate so that they are relevant to more people with BBS.
* The data was collected at one time point in a participant’s life; therefore there was no previous data to compare this to. This means that we are yet to understand the development of anxiety and depression in people with BBS.
* Some of the questionnaires used in this study were not designed for people with low vision. Some participants informed the researcher that certain questions were difficult to answer because the questionnaires were designed for sighted individuals. This may have made answering certain questions difficult and some participants may have answered the questions based on their ability or inability to see, rather than in response to the actual question.

CONCLUSION

* This was the first study to investigate factors that predict anxiety and depression in people with BBS.
* This study was also the first study to directly ask people with BBS about their mental health experiences.
* The findings have highlighted the impact health problems, difficulties with executive functioning and visual impairment have on anxiety and depression.
* Further research is required to understand the development of mental health in people with BBS. This will then allow for targeted interventions to be developed to support people those who are experiencing mental health difficulties.

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