American Journal of Medical Genetics Part B: Neuropsychiatric Genetics

WILEY

RESEARCH ARTICLE OPEN ACCESS

Cognitive, Social, and Emotional-Behavioral Outcomes in Children and Adolescents With Beckwith–Wiedemann Syndrome

Niccolò Butti[1,2] | Cosimo Urgesi[3,4] | Alessandro Mussa[5] | Rosario Montirosso[1]

[1]Scientific Institute, IRCCS E. Medea, 0-3 Centre for the at-Risk Infant, Bosisio Parini, Lecco, Italy | [2]PhD Program in Neural and Cognitive Sciences, Department of Life Sciences, University of Trieste, Trieste, Italy | [3]Scientific Institute, IRCCS E. Medea, Pasian di Prato, Udine, Italy | [4]Laboratory of Cognitive Neuroscience, Department of Languages and Literatures, Communication, Education and Society, University of Udine, Udine, Italy | [5]Department of Public Health and Pediatric Sciences, School of Medicine, University of Torino, Torino, Italy

Correspondence: Niccolò Butti (niccolo.butti@lanostrafamiglia.it)

Received: 29 April 2024 | **Revised:** 6 August 2024 | **Accepted:** 23 August 2024

Funding: Associazione Italiana Sindrome di Beckwith-Wiedemann (AIBWS) partly funded a PhD scholarship (to N.B.) related to this study. This study was partly supported by grants from the Italian Ministry of Health (Ricerca Corrente 2023-2024, Scientific Institute, IRCCS E. Medea, to R.M.).

Keywords: academic skills | anxiety | autistic traits | Beckwith–Wiedemann syndrome | emotional-behavioral problems | social perception | social withdrawal

ABSTRACT

Although Beckwith–Wiedemann syndrome spectrum (BWSp) is not usually associated with intellectual disability, recent evidences calls for further investigation of cognitive development and academic skills in children with BWSp. Moreover, research has documented social difficulties and emotional-behavioral problems associated with BWSp. Nevertheless, a full characterization of socio-emotional development in BWSp is still lacking. In the current study, cognitive and socio-emotional development was assessed in 29 children with BWSp aged 5–18 years, using a test of nonverbal intelligence, a neuropsychological battery covering multiple domains, academic skills tests, and questionnaires evaluating autistic traits and emotional-behavioral problems. As expected, most participants showed adequate performance in cognitive tests. However, the findings also highlighted greater difficulties in language than visuospatial processing, strengths in social perception, as well as slowness in reading and mental calculation. The assessment of emotional-behavioral difficulties indicated a prevalent phenotype characterized by increased anxiety, low self-esteem, social withdrawal and a tendency to control externalizing reactions, but no associations with autistic traits, cognitive outcomes, and the clinical score proposed by the recent Consensus statement. Increased social perception and internalization problems likely result from coping strategies with social and care-related stress. Overall, the findings of this study inform clinical management and genetic counseling for children and adolescents with BWSp.

1 | Introduction

Beckwith–Wiedemann syndrome (BWS) is an imprinting disorder that leads to overgrowth, with an estimated prevalence of 1:10,500 newborns (Mussa et al. 2013). BWS is linked to genetic and epigenetic changes on chromosome 11p15.5, germline or somatic, respectively (Shuman, Kalish, and Weksberg 2023). Most affected individuals have an altered expression of the growth suppressor gene *CDKN1C*, mainly due to loss of methylation at the *KCNQ1OT1* differentially methylated region (DMR) (also known as IC2) in the maternal allele. Other acknowledged causes are a gain of methylation in the *H19/IGF2* DMR (also known as IC1), associated with increased expression of the growth promoter gene *IGF2* in the paternal allele,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Author(s). *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* published by Wiley Periodicals LLC.

and Uniparental Paternal Disomy of the 11p15.5 chromosomal region (UPD(11)pat). The heterogeneity in its molecular causes and the mosaic distribution result in a multifaceted spectrum of clinical manifestations (the so-called BWS spectrum, BWSp), with cardinal and suggestive features including macroglossia, abdominal wall defects, lateralized overgrowth, and a heightened risk of developing embryonal tumors in infancy. According to the scoring system proposed by a recent Consensus statement (Brioude et al. 2018), these features are summarized with a clinical score to facilitate the diagnostic process. A score of ≥2 indicates the need for genetic testing, while a score of ≥4 supports a clinical diagnosis of BWS, even in the absence of positive molecular test results. Thus, the BWSp encompasses patients with typical BWS features, regardless of whether molecular confirmation of an 11p15.5 anomaly is present, those with atypical BWS features but with epigenetic changes at the BWS locus, and individuals with isolated lateralized overgrowth likely associated with an 11p15 abnormality.

BWSp is not usually associated with intellectual disability, unless secondary to severe unrecognized hypoglycemia, prematurity, unbalanced chromosome rearrangements, and genome-wide paternal uniparental isodisomy (Brioude et al. 2018; Kalish et al. 2013; McElroy et al. 2023). However, a recent study found that developmental difficulties in language and motor skills for preschool-age children with BWS may depend on typical features of BWSp—macroglossia and lateralized overgrowth (Butti, Castagna, and Montirosso 2022). A diagnosis of chronic disease such as BWSp is considered a risk factor for educational outcomes at primary school entry (Bell et al. 2016). A survey-based study reported learning difficulties in nearly 20% of adult patients with BWS (Drust et al. 2023). Other research has suggested that epigenetic mechanisms associated with BWS may play a role in the development of learning difficulties (Choufani et al. 2021; Slavotinek, Gaunt, and Donnai 1997). These pieces of evidence call for further characterization of cognitive development and academic skills in children with BWSp.

Socio-emotional development has long been neglected in clinical practice and research on BWSp. A study conducted in 2008 documented increased emotional problems and difficulties in peer relations in children with BWS, suggesting a heightened risk of Autism Spectrum Disorder (ASD) in this population (Kent et al. 2008). Research examining specific features of BWSp, such as macroglossia, abdominal wall defects, and increased tumor risk, has also indirectly provided evidence of emotional-behavioral problems and psychosocial risk (Burnett et al. 2018; Duffy et al. 2018; Shipster, Morgan, and Dunaway 2012). More recently, difficulties in social development and an increased incidence of internalization problems have been documented in a preschool-age sample of children with BWS, even after excluding those with secondary diagnoses of neurodevelopmental disorders (Butti, Castagna, and Montirosso 2022). In the survey by Drust et al. (2023), over a third of the adult participants reported having faced psychiatric issues and negative social experiences in their lives, such as bullying, teasing, and social isolation (Drust et al. 2023). These results suggest that, similar to other pediatric chronic physical illnesses (Pinquart and Teubert 2012), social difficulties and emotional-behavioral problems may be more closely related to the experience of having BWSp rather than to genetic and epigenetic causes. Nevertheless, a full characterization of the socio-emotional development of school-age children with BWSp is still lacking.

The current study investigates cognitive and socio-emotional development in 29 children with BWSp aged 5–18 years. The cognitive assessment encompassed a test of nonverbal intelligence, a co-normed battery covering multiple neuropsychological domains, and academic skills tests of reading, comprehension, and mathematics. The neuropsychological testing included social perception, namely, a set of cognitive abilities that enable understanding others' emotions and mental states. This domain has long been considered a weakness in individuals with an ASD (Baribeau et al. 2015; Baron-Cohen, Leslie, and Frith 1985; Happé and Frith 2014). Two parent–report and standardized questionnaires were used to investigate the presence of autistic traits and emotional-behavioral problems. Please note that, despite evaluating social perception skills and autistic traits, a clinical assessment of ASD was outside the scope of this study.

2 | Materials and Methods

2.1 | Participants

Twenty-nine children and adolescents were recruited in collaboration with the Italian Association of Beckwith–Wiedemann Syndrome (AIBWS). Inclusion criteria were: (i) confirmed clinical and/or genetic diagnosis of BWSp (Brioude et al. 2018); (ii) age from 5 to 18 years. All children had a clinical score ≥2, with the exception of one participant whose diagnosis of BWSp was confirmed by genetic testing. This child was tested because her twin sister had BWSp (subjects #9 and #10 in Table S1). One 5-year-old child had lateralized overgrowth (clinical score = 2) and was waiting for the results of genetic testing, while two children had a clinical diagnosis with negative molecular tests (clinical score ≥4). Most of the sample presented with macroglossia. Among them, seven children underwent tongue reduction surgery, while the remaining children were routinely followed by a multidisciplinary team including a surgeon, orthodontists, and speech therapists, in accordance with the Consensus recommendations (Brioude et al. 2018). When present, neonatal hypoglycemia was transient and did not require treatment beyond the first week of life. Although preterm birth was relatively common in the sample, none of the children were born very or extremely preterm (gestational age range: 32–36 weeks). The sample included participants with comorbid diagnoses of neurodevelopmental disabilities. In detail, one child had been diagnosed with ASD, and five had a diagnosis of learning difficulties from a child psychiatry service. Among them, one was also affected by epilepsy and one had an additional diagnosis of attention deficit. These previous clinical diagnoses were collected through chart review and were not independently verified by our study. A resume of the demographic, genetic, and clinical features of the sample is reported in Table 1 (please see Table S1 for individual features).

2.2 | General Procedure

Families affiliated with AIBWS were informed of the possibility of participating in the study. All interested families were

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Demographic and clinical features of the recruited sample.

	Mean (SD)/*N* (%)
Sex (females)	18 (62%)
Age (years)	9.4 (3.5)
Genetic diagnosis	
Gain of methylation at the IC1	2 (7%)
Loss of methylation at the IC2	18 (62%)
UPD(11)pat	6 (21%)
Other/unknown	3 (10%)
Clinical features	
Macroglossia	25 (86%)
Lateralized overgrowth	18 (62%)
Macrosomia at birth	9 (31%)
Omphalocele	4 (14%)
Neonatal hypoglycemia	12 (41%)
Tumor onset	3 (10%)
Clinical score as per consensus statement (Brioude et al. 2018)	5.7 (2.5)
Preterm birth	10 (34%)
Neurodevelopmental disabilities	6 (21%)

contacted by a researcher to be further informed about aims and methods of the study and to arrange their visit to the Scientific Institute, IRCCS E. Medea, where all procedures were carried out. The cognitive assessment was usually conducted over two consecutive days, adjusting duration and number of sessions to each child's characteristics (e.g., age, behavior). At the same time, questionnaires were administered to evaluate autistic traits and emotional-behavioral problems.

Parents were asked to sign an informed consent form before starting any assessment. All procedures were in accordance with the Declaration of Helsinki and its later amendments and were approved by the Ethical Committee of the Scientific Institute, IRCCS E. Medea (Prot. 18/21 CE).

2.3 | Cognitive Assessment

2.3.1 | Intelligence Quotient (IQ)

The standard or colored Raven progressive matrices were administered according to the child's age (Raven 1982). Raven matrices are considered a time-wise, nonverbal tool for assessing IQ, providing classifications comparable to those of the gold-standard Wechsler scales (Mungkhetklang et al. 2016). On the basis of the raw score, the normative standardization manuals were used to obtain an IQ score (mean = 100, SD = 15). IQs below 1 SD (i.e., 70–84) denote borderline intellectual functioning, and IQs below 2 SD (i.e., <70) indicate intellectual disability.

2.3.2 | Neuropsychological Profile

Selected subtests of the Italian version of the NEPSY-II battery were administered (Korkman, Kirk, and Kemp 2007; Urgesi, Campanella, and Fabbro 2011). These subtests can be administered to children of different ages and provide a detailed description of specific domains and abilities (Table 2).

Raw scores were converted into scaled scores (mean = 10, SD = 3, range = 1–19) according to the Italian normative tables (Urgesi, Campanella, and Fabbro 2011). The use of scaled scores allows comparisons of performances across different subtests or domains with no need for control groups (Russell, Russell, and Hill 2005). Scaled scores >13 indicate strengths, and scaled scores <4 indicate weaknesses.

2.3.3 | Academic Skills

The Italian standardized tests MT-3 and AC-MT (Cornoldi, Pra Baldi, and Giofrè 2017; Cornoldi, Mammarella, and Caviola 2020; Cornoldi and Carretti 2016) were administered to assess reading, comprehension, and mathematics according to each participant's school grade. For reading, both speed and accuracy were considered. Mathematics tests included arithmetical facts (i.e., calculation and knowledge of basic arithmetic rules) and mental calculation. In this latter, accuracy and speed were evaluated when the participant achieved correct results on at least one-third of the items. Raw scores were used to derive a four-level classification based on the percentile distributions reported in the normative tables: Fully achieved criterion (percentile >75), sufficient performance (percentile 11–75), request for attention (percentile 6–10), request for immediate intervention (percentile ≤5). This classification is widely adopted for screening children with learning difficulties in Italy (Barbiero et al. 2019). These tests were administered to children already enrolled in primary school ($N = 21$, 14 females; mean age = 10.8, SD = 3.2), of which five had a previous diagnosis of learning difficulties (24%).

2.4 | Socio-Emotional Assessment

2.4.1 | Autistic Traits

The Italian version of the autism quotient (AQ) questionnaire was administered to assess traits associated with ASD (Auyeung et al. 2008; Baron-Cohen et al. 2006; Ruta et al. 2012). The AQ is a 50-item self- or parent-report (according to the participant's age) questionnaire that evaluates autism-like traits. Answers are provided on a Likert scale from 0 = 'Strongly agree' to 3 = 'Strongly disagree', with some items reversely scored. A total AQ score is calculated by summing all item scores. The higher the score, the more the autistic traits. A cut-off of 76 has demonstrated high sensitivity (95%) and specificity (95%) in identifying children with ASD (Auyeung et al. 2008). However, it is important to stress that the AQ was

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | Domain and selected subtests of the NEPSY-II.

Domain	Subtest	Part	Main assessed ability
Attention and executive functions	*Visual attention*		Visual and selective attention
	Inhibition	*Naming*	Verbal response control
		Inhibition	Inhibitory control of verbal response
		Switching	Flexibility in verbal response control
Language	*Comprehension of instructions*		Receptive language
	Speeded naming		Rapid semantic access and production
Memory and learning	*Memory for faces*		Encoding and immediate/delayed retrieval of facial stimuli
	Memory for designs	*Immediate*	Immediate visual–spatial memory
		Delayed	Delayed visual–spatial memory
Sensorimotor functions	*Imitating hand positions*		Imitation
	Manual motor sequences		Encoding and retrieval of rhythmic motor programs
Social Perception	*Theory of Mind*	*Verbal part*	Understanding mental functions (e.g., beliefs, motivations, etc.)
		Contextual part	Understanding the emotional states of others in relation to the social context
	Affect recognition		Facial affect recognition
Visuospatial processing	*Design copying*		Graphomotor control and visual-perceptual analysis
	Block construction		Visuospatial construction skills
	Geometric puzzles		Mental rotation

designed for research purposes. Although it provides a quantitative measure of autistic traits, the AQ is not intended for clinical diagnosis of ASD.

2.4.2 | Emotional-Behavioral Problems

According to the child's age, parents filled out the 1½-5 or 6–18 Italian versions of the Child Behavior Checklist (CBCL) (Frigerio et al. 2004, 2006), an internationally adopted, standardized questionnaire designed to assess emotional-behavioral problems (Achenbach 2011). As the two versions provide slightly different scales and most participants were administered with the CBCL 6–18, specific emotional-behavioral problems were investigated only in this subsample ($N = 24$, 15 females; mean age = 10.2, SD = 3.3). In detail, the following scales were obtained from the CBCL 6–18: Anxiety/depression, social withdrawal, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviors, and aggressive behaviors. However, both the 1½–5 and 6–18 versions also provide two aggregated scales, internalization, and externalization, which were calculated across the whole sample. These aggregated scales indicate the tendency to problematize a situation as an internal problem and focus on oneself, or to react externally (Achenbach et al. 2016). For each scale, raw scores were converted into *T*-scores (mean = 50, SD = 10) according to the normative values, with higher *T*-scores indicating greater levels of emotional-behavioral problems on that scale. Also, the CBCL provides borderline and clinical cut-off scores to detect children who exhibit persistent behavioral problems.

2.5 | Data Handling and Statistical Analysis

For the NEPSY-II, scaled scores obtained from different parts of the same subtest (i.e., inhibition, memory for designs) were averaged into a single scaled score. Similarly, a domain score was computed as the average of the scaled scores from the subtests

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 | Performance at the NEPSY-II. Scaled scores are reported as mean (SD).

Domain	Subtest	Scaled score	Participants with individual strengths (% >13)	Participants with individual weaknesses (% <4)
Attention and executive functions		9.6 (2.4)	3	3
	Visual attention	10.3 (3.6)	14	3
	Inhibition	8.8 (2.4)	0	3
Language		8.7 (2.7)	3	3
	Comprehension of instructions	9.2 (2.8)	7	3
	Speeded naming	8.1 (3.1)	3	10
Memory and learning		9.8 (2.9)	14	0
	Memory for faces	10.7 (2.7)	14	0
	Memory for designs	8.9 (4.1)	17	10
Sensorimotor functions		9.5 (2.6)	7	0
	Imitating hand positions	9.4 (2.9)	3	7
	Manual motor sequences	9.6 (3)	10	0
Social Perception		11.2 (2.7)	10	0
	Theory of Mind	11.7 (2.4)	21	0
	Affect recognition	10.8 (2.4)	10	0
Visuospatial processing		10.4 (3.2)	17	7
	Design copying	9 (3.9)	14	7
	Block construction	10.4 (3.7)	17	7
	Geometric puzzles	11.8 (3.5)	34	3

within each neuropsychological domain. Descriptive statistics and the percentage of children with IQ above or below the mean, and with strengths or weaknesses in subtests and domains of the NEPSY-II, were calculated. A hierarchical analysis approach was then used for describing the neuropsychological profile obtained at the NEPSY-II. First, an RM-ANOVA was conducted inserting the six domain scores as dependent variables. To account for potential differences related to biological sex and the presence of secondary neurodevelopmental disabilities, these variables were included as categorical factors in separate mixed-model ANOVAs with domain as a within-subject variable. Then, a series of paired-sample *t*-tests and an RM-ANOVA (for visuospatial processing) were run to compare subtests of the same domain. The percentage of participants at each of the four performance levels was calculated for academic skills.

For the socio-emotional assessment, descriptive statistics were calculated including the percentage of children exceeding the cut-off for the total AQ and the borderline and clinical thresholds for each CBCL scale. Next, the CBCL aggregated scales (i.e., internalization and externalization) were compared by means of a paired-sample Student's *t*-test. Sex and comorbidity with neurodevelopmental disabilities were inserted as categorical factors in separate mixed-model ANOVAs with internalization and externalization as within-subject variables. To further describe the behavioral profile, the CBCL 6–18 scales were inserted as within-subject variables into an RM-ANOVA.

To investigate whether internalization and externalization problems were associated with demographic and clinical features, Spearman's *r* correlations were run with age, clinical score, IQ, social perception, and total AQ.

The analyses were performed by means of Statistica 8.0 (Statsoft, Tulsa, OK), with alpha set at $p < 0.05$. Bonferroni post hoc tests were used to analyze the significant effects of the ANOVAs. For the correlation analyses, the Bonferroni correction was adopted to adjust the standard p according to the number of comparisons for each scale (corrected $p = 0.010$). Effect sizes were estimated as partial eta squared (n^2_p) for ANOVA designs, and as Cohen's d for pairwise comparisons, adopting conventional cut-offs (Lakens 2013).

3 | Results

3.1 | Cognitive Assessment

The performance on the Raven matrices indicated a group IQ aligned with the normative mean and distribution (mean = 107, SD = 16, range 75–135). Three participants (10%) presented borderline intellectual functioning; all of them had a previous diagnosis of neurodevelopmental disability (one with ASD, one with learning difficulties and epilepsy, one with learning difficulties and attention deficit). None of these children had hypoglycemia

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 | Percentage of participants for each performance level at academic skills tests.

	Fully Achieved	Sufficient	Request for Attention	Immediate Intervention
Word reading				
Accuracy	10%	62%	24%	4%
Speed	10%	43%	28%	19%
Reading comprehension	14%	57%	10%	19%
Mathematics				
Arithmetic facts	4%	76%	10%	10%
Mental calculation				
Accuracy	10%	76%	4%	10%
Speed	0	26%	32%	42%

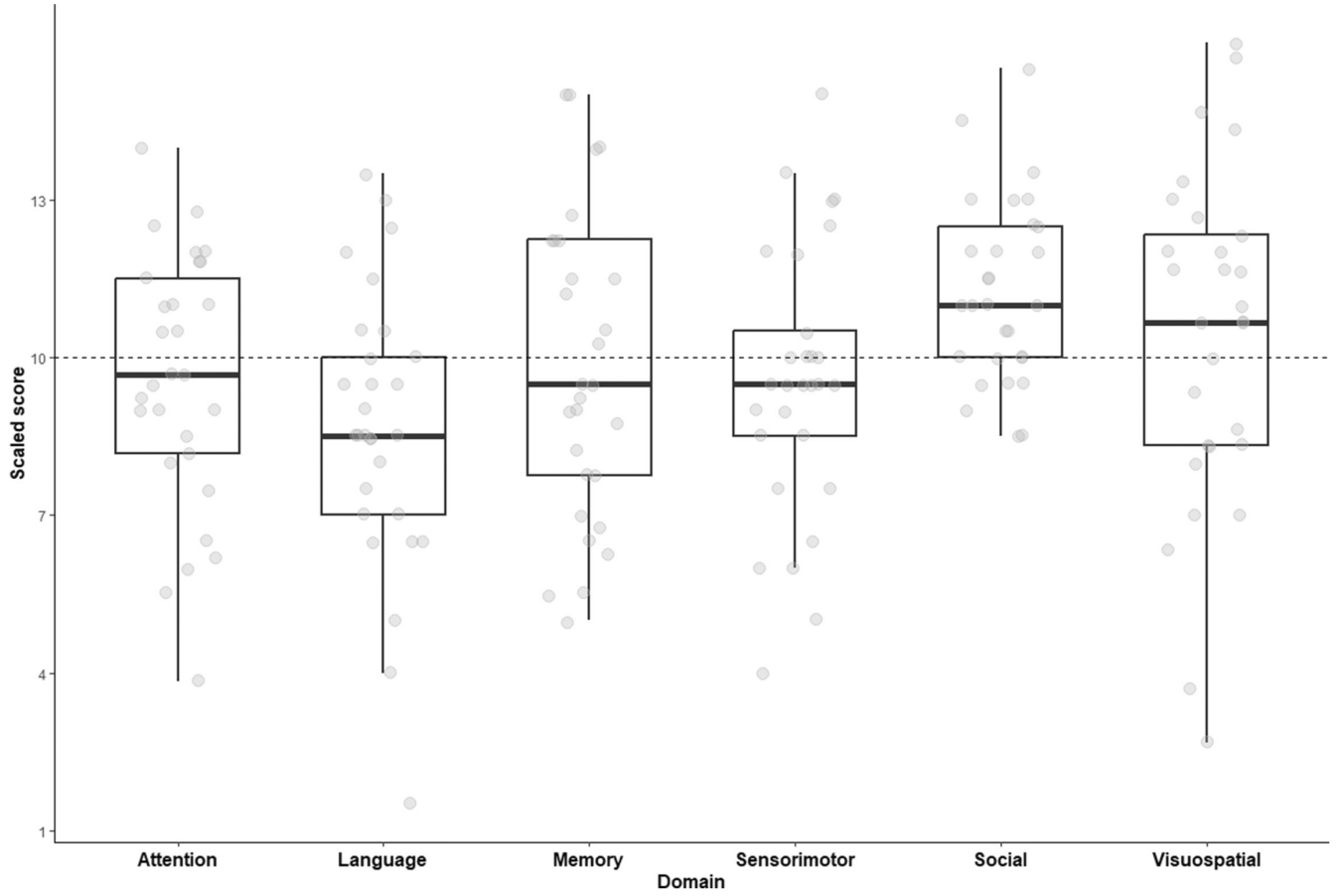

FIGURE 1 | Boxplot of the scaled scores at the NEPSY-II domains. Gray dots represent individual observations and the dotted black line represents the normative mean.

at birth, and only one was born preterm (late). Two of them presented with macroglossia, with one undergoing two surgical interventions for tongue reduction. Eighteen participants (62%) showed average intellectual functioning, and the remaining eight children (28%) had above-average IQ (please see Table S2 for individual performance of each participant).

Table 3 reports the scaled scores and the percentage of participants showing individual strengths or weaknesses in each subtest and domain of the NEPSY-II.

The comparison between neuropsychological domains highlighted significant differences ($F_{5,140} = 6.56, p < 0.001, n^2_p = 0.19$). Social perception obtained higher scores than all other domains (all $p < 0.046$), except for visuospatial processing ($p > 0.999$). The latter domain obtained higher scores than language ($p = 0.007$) (Figure 1).

Visuospatial processing showed the highest percentage of participants with strengths (17%). Across domains, the percentage of participants with individual weaknesses was very low (range 0%–7%).

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The follow-up analyses with sex and comorbidity with neurodevelopmental disabilities as categorical factors confirmed the between-domain differences (all $F > 5.56$, all $p < 0.001$). Although children with neurodevelopmental disabilities obtained lower scores than participants with no secondary diagnoses across domains ($F_{1,27} = 11.05$, $p = 0.003$, $n^2_p = 0.29$), the main effect of sex and the interactions with domain were non-significant (all $F < 2.04$, all $p > 0.076$). These results indicated that the differences between neuropsychological domains were observed regardless of sex and secondary diagnosis of neurodevelopmental disabilities.

The analysis within the attention and executive functions domain revealed a better performance in visual attention compared to inhibition ($t_{28} = 2.27$, $p = 0.031$, Cohen's $d = 0.51$). Similarly, within the language domain, comprehensions of instructions obtained higher scores than speeded naming ($t_{28} = 2.46$, $p = 0.020$, Cohen's $d = 0.39$). Also, a better performance was detected in memory for faces over memory for designs ($t_{28} = 2.55$, $p = 0.017$, Cohen's $d = 0.51$). For sensorimotor functions, similar scores were recorded in imitating hand positions and manual motor sequences ($t_{28} = 0.27$, $p = 0.786$, Cohen's $d = 0.05$). No difference emerged between social perception subtests ($t_{28} = 1.55$, $p = 0.132$, Cohen's $d = 0.40$), indicating comparable abilities to understand another's mental states and emotions from verbal, contextual and facial cues. Concerning visuospatial processing, a significant within-subject effect ($F_{2,56} = 13.49$, $p < 0.001$, $n^2_p = 0.33$) showed a better performance in geometric puzzles than all other subtests (all $p < 0.040$) and in block construction than design copying ($p = 0.033$). On an individual level, the highest percentage of participants with strengths was estimated in geometric puzzles (34%) and theory of mind (21%). The percentage of participants with individual weaknesses was ≤10% across all subtests.

The percentage of participants for each classification at the academic skills tests is reported in Table 4.

Participants with previous diagnoses of neurodevelopmental disabilities showed consistent difficulties across tests (see Supplementary table for individual performances). Beyond those with a previous diagnosis, a high percentage of children with difficulties was observed in reading speed (47%) and calculating speed (74%). In accuracy measures and the other tests, a large majority of the sample (>70%) showed sufficient-to-fully achieved abilities.

3.2 | Socio-Emotional Assessment

Regarding the presence of autistic traits, the group's mean AQ score was well below the cut-off (mean = 55.6, SD = 11.7). Only two participants obtained a score above this cut-off, and one of them had a previous diagnosis of ASD.

For the CBCL, the significant *t*-test ($t_{28} = 5.05$, $p < 0.001$, Cohen's $d = 1.10$) indicated greater problems for internalization (mean = 61.4, SD = 9.6) than externalization (mean = 51.2, SD = 8.9). Neither sex nor the presence of comorbid neurodevelopmental disabilities influenced this difference (all $F < 2.59$, all $p > 0.119$), which was still observed (all $F > 10.67$, all $p < 0.003$). Accordingly, 19 participants (66%) had internalization problems, while only four (14%) obtained borderline or clinical scores in externalization. Among these four children, three showed internalization problems as well. The *T*-scores obtained at the CBCL 6–18 scales are represented in Figure 2.

The RM-ANOVA indicated significant differences between scales ($F_{7,161} = 4.63$, $p < 0.001$, $\eta^2_p = 0.17$). That is, higher scores emerged in anxiety/depression and in social withdrawal than in rule-breaking and aggressive behaviors (all $p < 0.008$). Half of the sample (50%) exhibited problems in the anxiety/depression scale, with seven and five children showing scores beyond the borderline and clinical thresholds, respectively. In the social withdrawal scale, 42% of participants were above the borderline threshold. A relatively high percentage of participants showed thought problems (29%). Conversely, only one child showed problems above the clinical threshold in both rule-breaking and aggressive behaviors, and another participant reached the borderline threshold in aggressive behaviors.

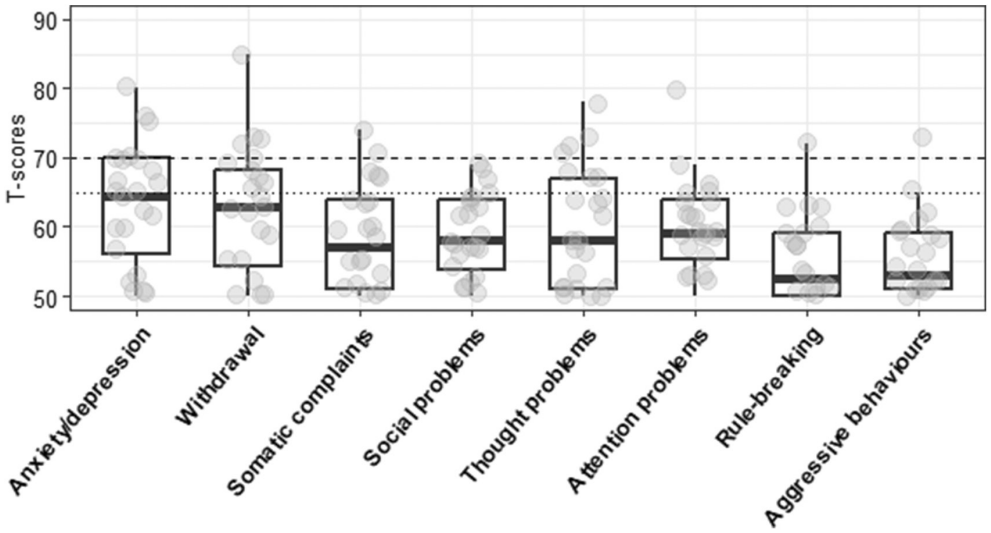

FIGURE 2 | Boxplot of *T*-scores at the CBCL 6–18. Gray circles represent individual scores, with higher scores reflecting more problematic behavior; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 5 | Correlations between behavioral problems and demographic and clinical features.

	Internalization		Externalization	
	r	*p*	*r*	*p*
Age	0.39	0.034	0.19	0.333
Clinical score	0.09	0.645	0.1	0.623
IQ	0.27	0.151	−0.18	0.359
Social perception	0.07	0.727	−0.2	0.305
Autism quotient	0.15	0.444	0.16	0.393

All correlations between either the aggregated CBCL scale and the selected variables were nonsignificant after controlling for multiple comparisons (all $p > 0.033$), with only age showing a medium but nonsignificant association with internalization problems (Table 5).

4 | Discussion

In this study, a cognitive and socio-emotional assessment was performed on 29 children and adolescents with BWSp. In terms of general intellectual functioning and specific neuropsychological abilities, few participants showed a performance lower than the age-expected mean. The three participants with borderline intellectual functioning, each with distinct BWSp clinical features, had prior diagnoses of neurodevelopmental disabilities. While confirming that BWSp is not usually associated with cognitive impairments (Mussa et al. 2016; Wang et al. 2020), the results also highlighted greater difficulties in language than visuospatial processing, strengths in social perception, and slowness in reading and mental calculation. The emotional-behavioral assessment indicated a prevalent phenotype characterized by greater internalization than externalization, with increased anxiety, low self-esteem, and social withdrawal behaviors. Overall, the findings of this study call for a wider consideration of psychological functioning, in terms of both cognitive and socio-emotional outcomes, of children and adolescents with BWSp.

As regards the cognitive outcomes in BWSp, a weakness emerged in language compared to visuospatial skills. The worst performance was recorded at the speeded naming subtest, in which rapidity in semantic access and verbal response strongly contribute to performance. Speech difficulties due to macroglossia may partially explain the weak performance in this language timed subtest as well as in reading speed at the academic skills tests (Butti, Castagna, and Montirosso 2022; Shipster, Morgan, and Dunaway 2012). Nevertheless, many participants of this study showed low performance also in calculation speed. These results point to heightened learning difficulties in BWSp, specifically when considering execution speed, even in children with no previous diagnosis of learning difficulties. However, as for other chronic illnesses, the findings of reduced speed in word reading and mental calculation should be read in the light of a complex relationship between genetic predisposition, psychosocial factors and educational outcomes (Bell et al. 2016; Pinquart and Teubert 2012). For instance, people with cleft lip/palate often experience a negative bias in the educational system due to speech difficulties and atypical facial features (Dardani et al. 2020). This may trigger a vicious circle, ultimately leading to lower educational attainments. In a recent survey-based study (Drust et al. 2023), adult people with BWS reported a lack of accommodation in the educational system for people with speech difficulties. Future research using wider samples should address the prevalence of learning difficulties in BWSp and the underlying factors that can contribute to educational attainment.

Social perception skills emerged as a relative peak at the neuropsychological profile, suggesting that children with BWSp are particularly able to understand others' emotions and mental states. It is important to stress that higher social perception skills do not imply fewer emotional-behavioral problems, as also suggested by the nonsignificant associations between social perception and both internalization and externalization scales. Rather, the findings reported here extend the results of previous studies documenting internalization problems in individuals with BWSp (Butti, Castagna, and Montirosso 2022; D'Onofrio et al. 2024; Kent et al. 2008), mainly represented by anxiety symptoms, low self-esteem feelings, and social withdrawal behaviors, like shyness and difficulty in adapting to new contexts.

As for other chronic illnesses (Pinquart and Shen 2011; van de Pavert et al. 2017), there are various potential pathways through which children with BWSp may develop internalization problems. The frequent hospital admissions, medical tests, and visits, as well as surgical interventions, are stressors for the patients and their families (D'Onofrio et al. 2024; Wolock et al. 2020). The tumor risk implies a relevant emotional burden for children with BWS and their families (Duffy et al. 2018; Kalish and Deardorff 2016). The macroglossia influences physical appearance as well as feeding, speech, and drooling functions (Shipster, Morgan, and Dunaway 2012). Hemihyperplasia may affect gross motor skills and participation in recreational and sports activities (Butti, Castagna, and Montirosso 2022). Thus, all these issues may lead these children to feel "different", namely, to perceive themselves as diverse from others, and prompt a constellation of internalization problems.

Adult people with BWS have related this sense of "feeling different" to their own perception of themselves in relation to others and to negative social reactions towards their physical features (Drust et al. 2023). In individuals with chronic illness, the perception or anticipation of social stigma related to their physical appearance and symptoms can become internalized, potentially impacting their self-esteem (O'Donnell and Habenicht 2022; Waugh, Byrne, and Nicholas 2014). The perception of 'being different' can also lead to increased shyness and social withdrawal (Rubin, Coplan, and Bowker 2009). In this light, heightened social perception in BWSp may be the result of coping strategies with social stress (Compas et al. 2012). Enhanced social perception may enable children with BWSp to anticipate others' social and emotional reactions, helping them avoid negative interactions. Similarly, controlling external reactions through less aggressive and rule-breaking behaviors may be functional for these children and their families to cope with social expectations and to facilitate continued access to medical care (Meijer

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

et al. 2000; Pinquart and Teubert 2012). However, these coping strategies may lead to increased internalization and to phobias or obsessive-like thoughts, as suggested by the relatively high incidence of thought problems in our cohort.

A previous study by Kent et al. (2008) reported a high prevalence of emotional-behavioral problems in a sample of 87 children with BWS. Among them, six children with low prosocial scores had been diagnosed with ASD. Based on these findings, they suggested that the diagnosis of ASD would not arise merely as a consequence of being "different". Instead, altered expression of imprinted genes might increase susceptibility to developmental disorders, resulting in the observed behavioral phenotype. In our study, however, only two participants showed above-threshold autistic traits and one of them had an existing diagnosis of ASD from a child psychiatry service. Although the AQ questionnaire is not a diagnostic tool (Auyeung et al. 2008), these findings, along with the observed strengths in social perception skills, suggest that autism-like behaviors were relatively infrequent in our sample. Importantly, the nonsignificant correlation with the total AQ indicated that internalization problems may be present in children with BWSp regardless of their level of autistic traits. Also, internalization did not correlate with Raven-derived IQ or the clinical score, which served as a proxy for the individual clinical burden. At the individual level, emotional-behavioral problems were observed in children with various genetic diagnoses and clinical features (see Tables S1 and S2). Overall, our results suggest that the observed social-behavioral phenotype may stem from coping strategies developed to face care-related emotional burdens, a disturbed self-perception, and the internalization of perceived social stigma. However, we cannot exclude potential (epi)genotype–phenotype associations for both cognitive and emotional-behavioral outcomes. This hypothesis should be explored in larger samples, taking into account factors such as mosaicism and the presence of multilocus imprinting disturbances in patients with IC2 loss of methylation (Brioude et al. 2018).

Limitations should be acknowledged in interpreting the findings of this study. The relatively small sample size and the wide age range ask for caution in generalizing the results. Given the wide age range within our sample, various factors could have potentially influenced cognitive and emotional-behavioral outcomes, including participation in previous rehabilitative or psychological interventions. Selection bias cannot be ruled out, as parents of children with more cognitive difficulties and emotional-behavioral problems might have been more inclined to participate in the study. Nonetheless, the results presented here align with findings from previous studies involving different age groups and nationalities (Butti, Castagna, and Montirosso 2022; D'Onofrio et al. 2024; Drust et al. 2023; Kent et al. 2008). The study adopted a cross-sectional design; longitudinal data would be useful to define the developmental trajectories of cognitive and emotional-behavioral outcomes in individuals with BWSp. A longitudinal design could also provide insights into protective factors that promote social adjustment. Lastly, the adoption of a research tool like the AQ prevented us from drawing firm conclusions on the prevalence of ASD in our sample. It is recommended that future research employs also other tools, such as the Social Responsiveness Scale, for better profiling autism-like behaviors in BWSp.

Limitations notwithstanding, these findings can drive communications and modalities of clinical management as well as genetic counseling for children and adolescents with BWSp. While BWSp is not associated with intellectual disability, this study provides the first evidence of reduced speed in reading tasks and mental calculation. Screening academic skills in school-age children with BWSp could be beneficial for early intervention, helping to implement compensatory strategies and mitigate potential prejudices or negative biases against children with otherwise appropriate skills. This study extends previous research by highlighting that BWSp is frequently associated with emotional-behavioral problems such as anxiety symptoms, depressive feelings, and social withdrawal. Administering parent-report questionnaires at various ages could help screen for emotional and behavioral problems, enabling the identification of cases that might benefit from psychological support, without increasing the overall burden of care.

Author Contributions

Niccolò Butti, Cosimo Urgesi, and Rosario Montirosso conceived the study design. Material preparation, data collection, and analysis were performed by Niccolò Butti. Niccolò Butti wrote the first draft, and all authors commented on previous versions of the manuscript. All authors critically read, improved, and approved the final manuscript.

Acknowledgments

The authors are grateful to AIBWS—Italian Association for Beckwith–Wiedemann syndrome, and particularly to Monica Bertoletti for her precious support and collaboration. The authors would also like to thank all children and families who took part in the study. Open access funding provided by BIBLIOSAN.

Ethics Statement

All procedures were in accordance with the Declaration of Helsinki and its later amendments and were approved by the Ethical Committee of the Scientific Institute, IRCCS E. Medea (Prot. 18/21 CE).

Consent

Parents were asked to sign an informed consent form before starting any assessment.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data related to this study are publicly available at this link: https://zenodo.org/records/11000908.

References

Achenbach, T. M. 2011. "Child Behavior Checklist." In *Encyclopedia of Clinical Neuropsychology*, 546–552. New York: Springer. https://doi.org/10.1007/978-0-387-79948-3_1529.

Achenbach, T. M., M. Y. Ivanova, L. A. Rescorla, L. V. Turner, and R. R. Althoff. 2016. "Internalizing/Externalizing Problems: Review and Recommendations for Clinical and Research Applications." *Journal of the American Academy of Child & Adolescent Psychiatry* 55, no. 8: 647–656. https://doi.org/10.1016/J.JAAC.2016.05.012.

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Auyeung, B., S. Baron-Cohen, S. Wheelwright, and C. Allison. 2008. "The Autism Spectrum Quotient: Children's Version (AQ-Child)." *Journal of Autism and Developmental Disorders* 38, no. 7: 1230–1240. https://doi.org/10.1007/S10803-007-0504-Z/TABLES/4.

Barbiero, C., M. Montico, I. Lonciari, et al. 2019. "The Lost Children: The Underdiagnosis of Dyslexia in Italy. A Cross-Sectional National Study." *PLOS One* 14, no. 1: e0210448. https://doi.org/10.1371/JOURNAL.PONE.0210448.

Baribeau, D. A., K. A. R. Doyle-Thomas, A. Dupuis, et al. 2015. "Examining and Comparing Social Perception Abilities Across Childhood-Onset Neurodevelopmental Disorders." *Journal of the American Academy of Child & Adolescent Psychiatry* 54, no. 6: 479–486. e1. https://doi.org/10.1016/J.JAAC.2015.03.016.

Baron-Cohen, S., R. A. Hoekstra, R. Knickmeyer, and S. Wheelwright. 2006. "The Autism-Spectrum Quotient (AQ)—Adolescent Version." *Journal of Autism and Developmental Disorders* 36, no. 3: 343–350. https://doi.org/10.1007/S10803-006-0073-6/TABLES/4.

Baron-Cohen, S., A. M. Leslie, and U. Frith. 1985. "Does the Autistic Child Have a "Theory of Mind"?" *Cognition* 21, no. 1: 37–46. https://doi.org/10.1016/0010-0277(85)90022-8.

Bell, M. F., D. M. Bayliss, R. Glauert, A. Harrison, and J. L. Ohan. 2016. "Chronic Illness and Developmental Vulnerability at School Entry." *Pediatrics* 137, no. 5: 20152475. https://doi.org/10.1542/peds.2015-2475.

Brioude, F., J. M. Kalish, A. Mussa, et al. 2018. "Expert Consensus Document: Clinical and Molecular Diagnosis, Screening and Management of Beckwith–Wiedemann Syndrome: An International Consensus Statement." *Nature Reviews Endocrinology* 14, no. 4: 229–249. https://doi.org/10.1038/nrendo.2017.166.

Burnett, A. C., J. K. Gunn, E. A. Hutchinson, et al. 2018. "Cognition and Behaviour in Children With Congenital Abdominal Wall Defects." *Early Human Development* 116: 47–52. https://doi.org/10.1016/j.earlhumdev.2017.11.002.

Butti, N., A. Castagna, and R. Montirosso. 2022. "Psychosocial Difficulties in Preschool-Age Children With Beckwith–Wiedemann Syndrome: An Exploratory Study." *Children* 9, no. 4: 1–10. https://doi.org/10.3390/children9040551.

Choufani, S., J. M. Ko, R. Weksberg, Y. Lou, C. Shuman, and L. Fishman. 2021. "Paternal Uniparental Disomy of the Entire Chromosome 20 in a Child With Beckwith–Wiedemann Syndrome." *Genes* 12, no. 2: 172. https://doi.org/10.3390/GENES12020172.

Compas, B. E., S. S. Jaser, M. J. Dunn, and E. M. Rodriguez. 2012. "Coping With Chronic Illness in Childhood and Adolescence." *Annual Review of Clinical Psychology* 8, no. 1: 455–480. https://doi.org/10.1146/annurev-clinpsy-032511-143108.

Cornoldi, C., and B. Carretti. 2016. *Prove MT-3-Clinica per la scuola primaria e secondaria di I grado*. Firenze, Italy: Giunti Edu.

Cornoldi, C., I. C. Mammarella, and S. Caviola. 2020. *Act-MT-3*. Trento, Italy: Centro Studi Erickson.

Cornoldi, C., A. Pra Baldi, and D. Giofrè. 2017. *Prove MT Avanzate-3-clinica per il biennio della scuola secondaria di II grado*. Firenze, Italy: Giunti Edu.

Dardani, C., L. J. Howe, N. Mukhopadhyay, et al. 2020. "Cleft Lip/Palate and Educational Attainment: Cause, Consequence or Correlation? A Mendelian Randomization Study." *International Journal of Epidemiology* 49, no. 4: 1282–1293. https://doi.org/10.1093/IJE/DYAA047.

D'Onofrio, G., A. Mastromatteo, A. Di Francesco, et al. 2024. "Depression and Anxiety in Pediatric Patients With Beckwith–Wiedemann Syndrome: A Pilot Study." *Children* 11, no. 3: 342. https://doi.org/10.3390/children11030342.

Drust, W. A., A. Mussa, A. Gazzin, et al. 2023. "Adult Experiences in Beckwith–Wiedemann Syndrome." *American Journal of Medical Genetics, Part C: Seminars in Medical Genetics* 193, no. 2: 116–127. https://doi.org/10.1002/ajmg.c.32046.

Duffy, K. A., K. L. Grand, K. Zelley, and J. M. Kalish. 2018. "Tumor Screening in Beckwith–Wiedemann Syndrome: Parental Perspectives." *Journal of Genetic Counseling* 27, no. 4: 844–853. https://doi.org/10.1007/S10897-017-0182-8/TABLES/5.

Frigerio, A., C. Cattaneo, M. G. Cataldo, A. Schiatti, M. Molteni, and M. Battaglia. 2004. "Behavioral and Emotional Problems Among Italian Children and Adolescents Aged 4 to 18 Years as Reported by Parents and Teachers." *European Journal of Psychological Assessment* 20: 124–133. https://doi.org/10.1027/1015-5759.20.2.124.

Frigerio, A., P. Cozzi, V. Pastore, M. Molteni, R. Borgatti, and R. Montirosso. 2006. "La valutazione dei problemi emotivo comportamentali in un campione italiano di bambini in eta prescolare attraverso la Child Behavior Checklist e il Caregiver Teacher Report Form." *Infanzia e Adolescenza* 5, no. 1: 24–37. https://www.amazon.com.br/Infanzia-adolescenza-Anna-Freud/dp/8833923215.

Happé, F., and U. Frith. 2014. "Annual Research Review: Towards a Developmental Neuroscience of Atypical Social Cognition." *Journal of Child Psychology and Psychiatry and Allied Disciplines* 55, no. 6: 553–577. Blackwell Publishing Ltd. https://doi.org/10.1111/jcpp.12162.

Kalish, J. M., L. K. Conlin, T. R. Bhatti, et al. 2013. "Clinical Features of Three Girls With Mosaic Genome-Wide Paternal Uniparental Isodisomy." *American Journal of Medical Genetics Part A* 161, no. 8: 1929–1939. https://doi.org/10.1002/AJMG.A.36045.

Kalish, J. M., and M. A. Deardorff. 2016. "Tumor Screening in Beckwith–Wiedemann syndrome—To screen or Not to Screen?" *American Journal of Medical Genetics Part A* 170, no. 9: 2261–2264. https://doi.org/10.1002/AJMG.A.37881.

Kent, L., S. Bowdin, G. A. Kirby, W. N. Cooper, and E. R. Maher. 2008. "Beckwith Weidemann Syndrome: A Behavioral Phenotype–Genotype Study." *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 147B, no. 7: 1295–1297. https://doi.org/10.1002/ajmg.b.30729.

Korkman, M., U. Kirk, and S. Kemp. 2007. *NEPSY—Second Edition (NEPSY-II)*. San Antonio, TX: Harcourt Assessment.

Lakens, D. 2013. "Calculating and Reporting Effect Sizes to Facilitate Cumulative Science: A Practical Primer for t-Tests and ANOVAs." *Frontiers in Psychology* 4: 1–12. https://doi.org/10.3389/fpsyg.2013.00863.

McElroy, T. D., K. A. Duffy, E. R. Hathaway, M. E. Byrne, and J. M. Kalish. 2023. "Investigation of a Pervasive Immune, Cardiac, and Behavioral Phenotype in Beckwith–Wiedemann Syndrome: A Case Report." *American Journal of Medical Genetics Part A* 191, no. 4: 1107–1110. https://doi.org/10.1002/AJMG.A.63114.

Meijer, S. A., G. Sinnema, J. O. Bijstra, G. J. Mellenbergh, and W. H. G. Wolters. 2000. "Social Functioning in Children With a Chronic Illness." *Journal of Child Psychology and Psychiatry* 41, no. 3: 309–317. https://doi.org/10.1111/1469-7610.00615.

Mungkhetklang, C., S. G. Crewther, E. L. Bavin, N. Goharpey, and C. Parsons. 2016. "Comparison of Measures of Ability in Adolescents With Intellectual Disability." *Frontiers in Psychology* 7: 1–11. https://doi.org/10.3389/fpsyg.2016.00683.

Mussa, A., S. Di Candia, S. Russo, et al. 2016. "Recommendations of the Scientific Committee of the Italian Beckwith–Wiedemann Syndrome Association on the Diagnosis, Management and Follow-Up of the Syndrome." *European Journal of Medical Genetics* 59, no. 1: 52–64. https://doi.org/10.1016/j.ejmg.2015.11.008.

Mussa, A., S. Russo, A. De Crescenzo, et al. 2013. "Prevalence of Beckwith–Wiedemann Syndrome in North West of Italy." *American Journal of Medical Genetics. Part A* 161A, no. 10: 2481–2486. https://doi.org/10.1002/AJMG.A.36080.

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

O'Donnell, A. T., and A. E. Habenicht. 2022. "Stigma is Associated With Illness Self-Concept in Individuals With Concealable Chronic Illnesses." *British Journal of Health Psychology* 27, no. 1: 136–158. https://doi.org/10.1111/BJHP.12534.

Pinquart, M., and Y. Shen. 2011. "Behavior Problems in Children and Adolescents With Chronic Physical Illness: A Meta-Analysis." *Journal of Pediatric Psychology* 36, no. 9: 1003–1016. https://doi.org/10.1093/jpepsy/jsr042.

Pinquart, M., and D. Teubert. 2012. "Academic, Physical, and Social Functioning of Children and Adolescents With Chronic Physical Illness: A Meta-Analysis." *Journal of Pediatric Psychology* 37, no. 4: 376–389. https://doi.org/10.1093/jpepsy/jsr106.

Raven, J. C. 1982. "Revised Manual for Raven's Progressive Matrices and Vocabulary Scale." In *Revised Manual for Raven's Progressive Matrices and Vocabulary Scale*. Windsor, UK: NFER Nelson.

Rubin, K. H., R. J. Coplan, and J. C. Bowker. 2009. "Social Withdrawal in Childhood." In *Annual Review of Psychology* 60, no. 1: 141–171. Annual Reviews. https://doi.org/10.1146/annurev.psych.60.110707.163642.

Russell, E. W., S. L. K. Russell, and B. D. Hill. 2005. "The Fundamental Psychometric Status of Neuropsychological Batteries." *Archives of Clinical Neuropsychology* 20, no. 6: 785–794. https://doi.org/10.1016/J.ACN.2005.05.001.

Ruta, L., D. Mazzone, L. Mazzone, S. Wheelwright, and S. Baron-Cohen. 2012. "The Autism-Spectrum Quotient—Italian Version: A Cross-Cultural Confirmation of the Broader Autism Phenotype." *Journal of Autism and Developmental Disorders* 42, no. 4: 625–633. https://doi.org/10.1007/s10803-011-1290-1.

Shipster, C., A. Morgan, and D. Dunaway. 2012. "Psychosocial, Feeding, and Drooling Outcomes in Children With Beckwith Wiedemann Syndrome Following Tongue Reduction Surgery." *Cleft Palate-Craniofacial Journal* 49, no. 4: 25–34. https://doi.org/10.1597/10-232.

Shuman, C., J. M. Kalish, and R. Weksberg. 2023. "Beckwith–Wiedemann Syndrome." In *GeneReviews® [Internet]*, edited by M. P. Adam, J. Feldman, G. M. Mirzaa et al. Seattle (WA): University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/sites/books/NBK1394/.

Slavotinek, A., L. Gaunt, and D. Donnai. 1997. "Paternally Inherited Duplications of 11p15.5 and Beckwith–Wiedemann Syndrome." *Journal of Medical Genetics* 34, no. 10: 819–826. https://doi.org/10.1136/JMG.34.10.819.

Urgesi, C., F. Campanella, and F. Fabbro. 2011. *NEPSY-II, Contributo Alla Taratura Italiana*. 2nd ed. Firenze, Italy: Giunti OS.

van de Pavert, I., M. Sunderland, M. Luijten, T. Slade, and M. Teesson. 2017. "The General Relationship Between Internalizing Psychopathology and Chronic Physical Health Conditions: A Population-Based Study." *Social Psychiatry and Psychiatric Epidemiology* 52, no. 10: 1257–1265. https://doi.org/10.1007/S00127-017-1422-9/METRICS.

Wang, K. H., J. Kupa, K. A. Duffy, and J. M. Kalish. 2020. "Diagnosis and Management of Beckwith–Wiedemann Syndrome." *Frontiers in Pediatrics* 7: 562. https://doi.org/10.3389/FPED.2019.00562/BIBTEX.

Waugh, O. C., D. G. Byrne, and M. K. Nicholas. 2014. "Internalized Stigma in People Living With Chronic Pain." *Journal of Pain* 15, no. 5: 550.e1–550.e10. https://doi.org/10.1016/J.JPAIN.2014.02.001.

Wolock, E. R., A. H. Queen, G. M. Rodríguez, and J. R. Weisz. 2020. "Chronic Illness and Internalizing Symptomatology in a Transdiagnostic Clinical Sample of Youth." *Journal of Pediatric Psychology* 45, no. 6: 633–642. https://doi.org/10.1093/JPEPSY/JSAA028.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

RIGHTSLINK

1552485x, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajmg.b.33006 by Alessandro Mussa - University Degli Studi Di , Wiley Online Library on [21/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License