REVIEW EMOTION & DYSREGULATION

Systematic Review: Emotion Dysregulation in Syndromic Causes of Intellectual and Developmental Disabilities

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Objective: To summarize the current state of the literature regarding emotion dysregulation (ED) in syndromic intellectual disabilities (S-IDs) in 6 of the most common forms of S-IDs—Down syndrome, fragile X syndrome (FXS), tuberous sclerosis complex, Williams syndrome, Prader-Willi syndrome, and Angelman syndrome—and to determine future research directions for identification and treatment of ED.

Method: PubMed bibliographic database was searched from date of inception to May 2021. PRISMA 2020 guidelines were followed with the flowchart, table of included studies, list of excluded studies, and checklist provided. Filters applied included human research and English. Only original research articles were included in the final set, but review articles were used to identify secondary citations of primary studies. All articles were reviewed for appropriateness by 2 authors and summarized. Inclusion criteria were met by 145 articles (Down syndrome = 29, FXS = 55, tuberous sclerosis complex = 11, Williams syndrome = 18, Prader-Willi syndrome = 24, Angelman syndrome = 8).

Results: Each syndrome review was summarized separately and further subdivided into articles related to underlying neurobiology, behaviors associated with ED, assessment, and targeted intervention. FXS had the most thorough research base, followed by Down syndrome and Prader-Willi syndrome, with the other syndromes having more limited available research. Very limited research was available regarding intervention for all disorders except FXS.

Conclusion: Core underlying characteristics of S-IDs appear to place youth at higher risk for ED, but further research is needed to better assess and treat ED in S-IDs. Future studies should have a standard assessment measure of ED, such as the Emotion Dysregulation Inventory, and explore adapting established curricula for ED from the neurotypical and autism spectrum disorder fields.

Key words: Down syndrome; emotion dysregulation; fragile X syndrome; intellectual disability; Williams syndrome

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Emotion regulation (ER) is the process of modifying the intensity of and/or response to emotional experiences.[1,2] This process occurs at both conscious and unconscious levels[3] and can occur reactively, after an emotional experience, or proactively, before an emotional experience. For most individuals, an ER style emerges that is either adaptive or maladaptive. Adaptive ER begins early in development progressing through emotion identification, recognition of a regulation need, and learning and using coping strategies.[4] Adaptive ER is associated with better problem solving, ultimately leading to more positive outcomes. Psychopathology, such as depression and anxiety, and problem behaviors, such as irritability and aggression, have been associated with maladaptive ER styles, or emotion dysregulation (ED).[4] ED is a commonly identified reason for treatment, manifesting with a host of concerns such as physical/verbal aggression, self-injury, high reactivity, and suicidality.[5,6] A growing body of research suggests that ED is a transdiagnostic mechanism that plays an underlying role in a variety of disorders.[7-10] Though ED is associated with higher rates of comorbid diagnoses and maladaptive behaviors across a broad range of psychiatric diagnoses, it is not yet clear if it is present and/or impairing in developmental or syndromic diagnoses, outside of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).[11,12]

Intellectual disability (ID), marked by both cognitive and adaptive deficits, impacts between 1% and 3% of the population and is frequently caused by genetic abnormalities.[13] Across genetic or syndromic intellectual disabilities

(S-IDs), affected individuals are predisposed to experience ED owing to cognitive impairment, communication difficulties, rigid behavior and thought, poor social insight/skills, processing difficulties, impulsivity, disinhibition, and impaired problem solving. Language particularly is a critical component of learning ER, including internal self-talk and verbalization of feelings or experiences. Furthermore, the 5 categories of effective ER strategies (situation selection, situation modification, attentional deployment, cognitive change, and response modulation) described by Gross and Thompson[2] all involve complex cognitive and problem-solving skills, suggesting they may be underused in individuals with S-IDs. Co-occurring disorders across S-IDs, notably ADHD, ASD, anxiety, and depression, often have prominent ED. In addition, alterations in the neural anatomy, circuitry, and function have been implicated in diagnoses associated with ED, and these neural alterations have also been implicated in S-IDs.[14,15] For example, increased rigidity, reactivity, and emotional lability, thought to stem from neural hyperresponsiveness to environmental and sensory changes, and/or impaired inhibitory and executive control are common in S-IDS.[16] The transdiagnostic theory of ER by Nolem-Hoeksema and Watkins[17] would suggest that an S-ID is a risk factor for ED itself, which is then an underlying risk factor for psychopathology.

Through S-ID populations, researchers can begin to identify common disrupted biological pathways underlying ED. As ED is prevalent across multiple conditions, including S-IDs and other mental health conditions (eg, anxiety, ADHD, ASD), there may be multiple underlying biological pathways that ultimately converge to result in symptoms of ED. Although the preliminary work to identify the genetic etiology of ED has been established in general psychiatry,[18,19] examining ED in S-IDs could begin to delineate distinct clinical and behavioral phenotypes and their role in the development of ED in individuals with ASD and ID. This is a parallel to work as done with monogenetic disorders, ASD, and ID.[20,21] Further, by delineating different phenotypes of ED in S-IDs, future research can begin to advance improvements in clinical care and provide an opportunity for the development and assessment of novel targeted interventions for ED within S-IDs.

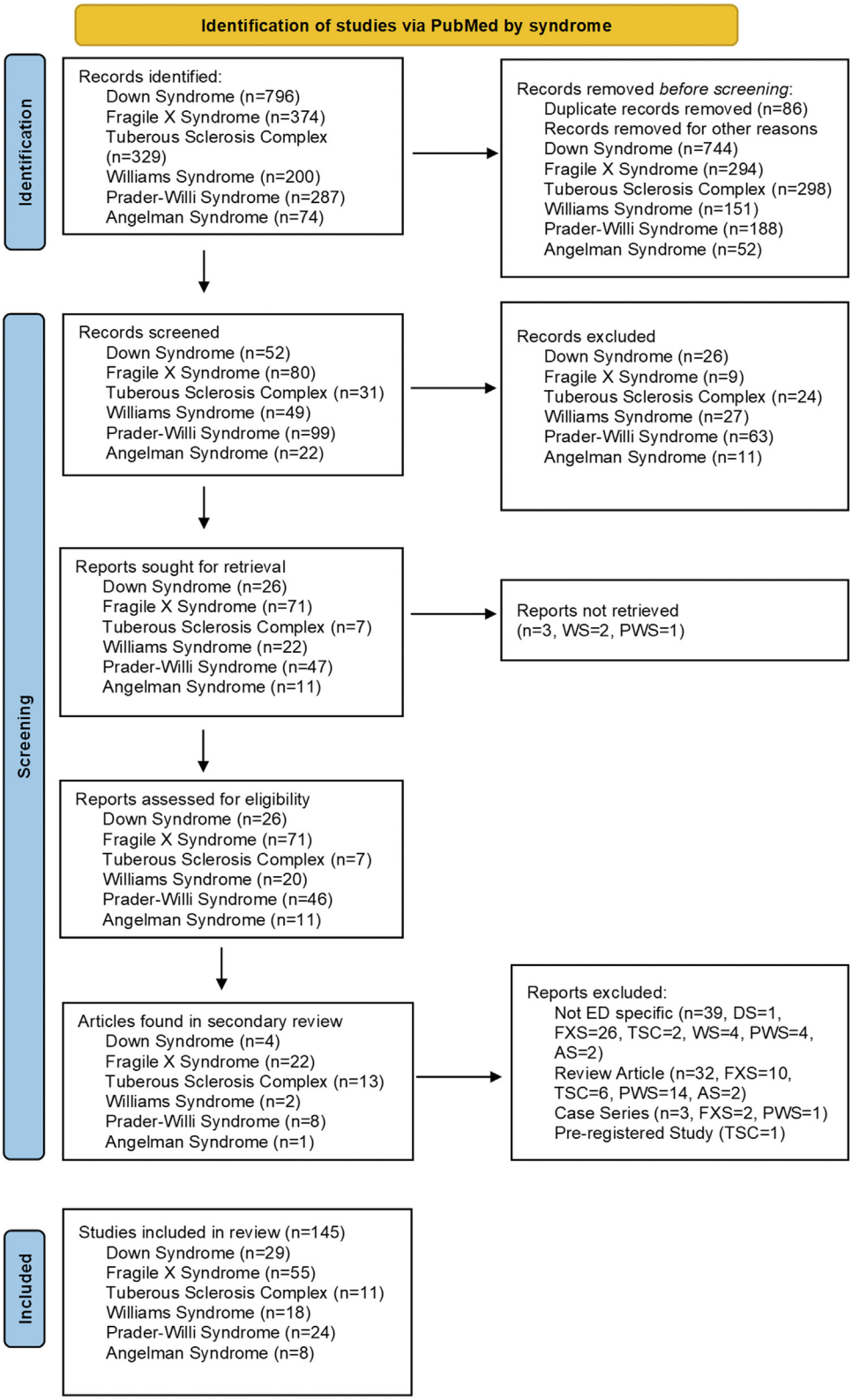
Purpose of this Review

Research in typical development and ASD has demonstrated the poor outcomes associated with ED (eg, higher rates of psychopathology, high medication rates, suicidality, and utilization of crisis services), underscoring the importance of valid assessment and effective treatment.[5,6] Examinations of similarities and differences across S-IDs in expression of ED and available treatment may offer insight regarding mechanisms of ED across diagnoses and development. To our knowledge, a review has not yet been conducted to better understand ED in S-IDs. We conducted a systematic review of 6 of the most common and behaviorally impacted forms of S-IDs (Down syndrome [DS], fragile X syndrome FXS, tuberous sclerosis complex [TSC], Williams syndrome [WS], Prader-Willi syndrome [PWS], and Angelman syndrome [AS]) to better understand the state of ED in S-IDs research.

METHOD

A systematic review of the literature was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The checklist is provided in Table S1, available online. The PubMed bibliographic database was searched from date of inception to May 2021. An initial search was conducted and discussed among the authors. The following final search strategy was used: "reactivity" or "dysregulat*" or "coping" or "autonomic arousal" or "executive function" or "emotion regulat*" or "irritability" or "emotional control" or "emotion control" or "tantrum" or "outburst" along with each syndrome name. Filters applied included human research and English. Only original research articles were included in the final set, but review articles were used to identify secondary citations of primary studies. Abstracts were retrieved from the search results, and all duplicates were removed. Inclusion criteria included participants with one of the chosen syndromes and prevalence, assessment, or intervention related to emotion dysregulation. Exclusion criteria included adults only in the study, studies assessing only emotion identification/recognition and no mention of regulation or coping, studies unavailable in English, and case studies. Reference lists of all included studies were also searched for secondary citations. Articles for each syndrome were reviewed by 2 authors (FXS: L.S., D.R.; DS: A.E., R.C.S.; WS: E.S., M.C.; TSC: E.S., M.C.; AS: K.D., M.L.; PWS: K.D., M.L.) to assess appropriateness, and the first author (R.C.S.) made final decisions on questionable inclusion across all syndromes. For the purposes of this study, articles were separated by syndrome diagnosis, then further subdivided into underlying neurobiology, syndrome-specific behaviors related to ED, assessment, and targeted interventions. Figure 1 shows the flowchart of the search strategy and article inclusion. Table 1 lists all articles included in the study, including characteristics of participants, assessment tools, and study outcomes. For studies in

FIGURE 1 Identification of Studies Flowchart



Note: AS = Angelman syndrome; DS = Down syndrome; ED = emotion dysregulation; FXS = fragile X syndrome; PWS = Prader-Willi syndrome; TSC = tuberous sclerosis complex; WS = Williams syndrome. *(From Page* et al., *2021.*[190] https://doi.org/10.1136/bmj.n71. *Published under Creative Commons license CC BY: https://creativecommons.org/.)*

TABLE 1 Overview of Studies Examining Emotion Dysregulation by Syndromic Intellectual Disability

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Down syndrome					
Alsaied *et al.*, 2016[44]	1,092 DS	NR (0-18 y)	Chart review; within-group comparison	BRIEF EC	There were no differences in BRIEF EC across children with DS with (n = 26) or without (n = 78) congenital heart defects.
Bieberich and Morgan 2004[33]	15 DS 14 ASD	DS: 8 y (5-12 y) ASD: 8 y (5-12 y)	Between-group comparison	MN-PARS	DS group demonstrated stability across 2 time points on irritability. There were no group differences on negative affect (including irritability) between DS and ASD groups.
Camp *et al.*, 2016[45]	47 WS 31 DS 34 TD (MA-matched)	WS: 17.33 y (12-22 y) DS: 18 y (12-23 y) TD: 8.25 y (4-11 y)	Between-group comparison	BRIEF EC	Worse BRIEF EC scores were found in WS group compared with DS group; scores in DS group were equal to controls.
Capone *et al.*, 2016[59]	23 DS	7 y (4-12 y)	Treatment	ABC-I	Guanfacine decreased irritability by 25% on ABC-I in children with DS+ADHD.
Clark and Wilson, 2003[55]	60 DS	12 y (4-21 y)	Within-group comparison	Reiss Scales	Higher score for temper tantrums contrasted with other subscale items.
Daunhauer *et al.*, 2014[50]	25 DS 23 TD (MA-matched)	DS: 96 mo (61-133 mo) TD: 39 mo (30-46 mo)	Between-group comparison	BRIEF EC	DS and TD groups had comparable BRIEF EC symptoms.
Daunhauer *et al.*, 2017[54]	42 DS 38 TD (MA-matched)	DS: 91 mo (61-133 mo) TD: 40 mo (30-46 mo)	Between-group comparison	BRIEF EC	The correlation between BRIEF EC and planning laboratory task found in TD group was not replicated in DS group.
Didden *et al.*, 2008[152]	129 AS 90 nonspecific ID 398 DS 235 ASD	17.4 y (2-52 y)	Between-group comparison	BFRS-R	Individuals with DS and AS demonstrated more behavioral flexibility than those with nonspecific ID and those with ASD.
Dimitropoulos *et al.*, 2001[36]	56 DS 105 PWS 76 TD	DS: 3 y (2-5 y) PWS: 3 y (2-6 y) TD: 3 y (2-5 y)	Between-group comparison	Tantrum behavior survey	Age of tantrum onset in DS group was equal to PWS group, and both were greater than TD group. Latency of tantrum onset was greater in PWS group, and DS group was equal to TD group.
Dykens and Kasari, 1997[27]	43 PWS 43 DS 43 ID	11 y (4-19 y)	Between-group comparison; within-group comparison	CBCL	Children with DS demonstrated lower scores in all 3 CBCL domains (internalizing, externalizing, and total score) compared with children with PWS.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Eden *et al.*, 2014[121]	43 DS 37 TSC 61 CdLS 112 FXS 188 ASD	DS: 9.0 y TSC: 10.08 y CdLS 10.10 y FXS 10.88 y ASD 9.37 y (4-15 y)	Between-group comparison	Challenging Behaviour Questionnaire	Rates of self-injury and aggression were similar to TSC group. Rates of self- injury were lower than FXS group.
Edgin *et al.*, 2017[53]	54 DS	13 y (7-20 y)	Within-group comparison	BRIEF EC	BRIEF EC subtest had adequate retest reliability and feasibility in DS.
Esbensen *et al.*, 2019[34]	84 DS	11 y (6-18 y)	Within-group comparison	BRIEF EC	BRIEF EC subtest had adequate interrater reliability and internal consistency across parent and teacher report for DS, no differences by sex or IQ and no correlation with age.
Fidler *et al.*, 2006[39]	24 DS 33 TD (MA-matched)	~12 mo at time 1	Longitudinal	Infant Temperament Questionnaire —Revised	Infant temperament was predictive of maladaptive behavior 45 mo later, but findings were stronger in mixed group than with DS alone.
Ghezzo *et al.*, 2014[38]	67 DS	31 y (11-66 y)	Within-group comparison	VABS	There was no change in coping skills with age.
Gilmore and Cuskelly 2017[41]	25 DS	5 y (4-6 y) at time 1 13 y (11-15 y) at time 2 24 y (23-26 y) at time 3	Longitudinal	Goodman Lock Box; Self-Control Rating Scale; AIR Self-Determination Scale	Self-regulation was predictive of adult outcomes.
Hattier *et al.*, 2012[47]	27 DS 18 CP 29 TD with seizures	25 mo (17-35 mo)	Between-group comparison	Tantrum/Conduct Behavior subscale of BISCUIT	Children with seizures had more tantrums than those with CP or DS.
Jahromi *et al.*, 2008[58]	19 DS 20 ID 22 TD	DS: 96 mo (72-130 mo) ID: 110 mo (66-137 mo) TD: 44 mo (37-57 mo)	Between-group comparison	Behavioral coding of videos performing puzzle task (coping/emotion regulation strategies)	DS group demonstrated more frustration and orienting to examiner without asking for help. DS group also demonstrated limited repertoire for coping with frustration.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Joyce *et al.*, 2020[43]	80 DS	56 mo (36-71 mo)	Within-group comparison	BRIEF EC	BRIEF EC was a relative strength compared with working memory. BRIEF EC was higher among children with DS with OAHI >1.5 than OAHI <1.5.
Lee *et al.*, 2011[48]	26 DS	75 mo (48-129 mo)	Within-group comparison	BRIEF EC	BRIEF EC was within expected norms for typical development.
Loveall *et al.*, 2017[49]	112 DS	12 y (2-35 y)	Within-group comparison	BRIEF EC	BRIEF EC was within expected norms for typical development.
Määttä *et al.*, 2006[32]	129 DS	NR (0-66 y)	Chart review	Rating of behavior based on chart review	Prevalence for irritability in individuals with DS was only 9%.
Memisevic and Sinanovic 2014[52]	30 DS 30 ID known 30 ID unknown	DS: 11 y ID known: 10 y ID unknown: 11 y	Between-group comparison	BRIEF EC	BRIEF EC symptoms were worse in DS group than ID known and ID unknown groups. There were no gender differences.
Nevill and Benson 2018[40]	80 DS	32 y (16-68 y)	Within-group comparison	ABC-I	Recent negative life events and stressors predicted ABC-I. Individuals with DS had lower ABC-I scores than the normative comparison sample.
Rice *et al.*, 2015[37]	72 DS 51 PWS 63 FXS 62 WS	NR	Longitudinal	DBC	Physical aggression and temper tantrums declined with age before age 19 y for DS as well as FXS and WS groups but after 19 y for PWS group.
Schworer *et al.*, 2019[51]	42 DS 28 TD (MA-matched)	DS: 90 mo (59-118 mo) TD: 38 mo (30-49 mo)	Between-group comparison	Modified Parent-Child Challenge Task with video coding	Children with DS had worse compliant behavior than TD children but were similar for persistence, noncompliance, and disengagement.
Stores *et al.*, 1998[35]	91 DS 54 siblings 78 TD 71 ID	DS: 10 y (4-19 y) Siblings: 11 y (3-19 y) TD: 9 y (4-15 y) ID: 10 y (3-18 y)	Between-group comparison	ABC-I	Children with DS had increased ABC-I scores compared with siblings and TD children. Children with ID had more irritability than those with DS. There were no age differences for DS on irritability. Male participants were more irritable than female participants with DS.
Walz and Benson, 2002[151]	68 AS 28 PWS 91 DS	AS: 10.01 y PWS: 11.5 y DS: 10.09 y	Between-group comparison	Nisonger Child Behavior Rating Form	Children with DS had lower ratings of problem behaviors and self-injurious behaviors compared with those with AS

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
	24 ID	ID: 12.29 y (5-19 y)			and ID. Ratings of overly sensitive behavior were lower compared with PWS group. Children with DS were similarly compliant and calm compared with PWS group and more so compared with ID group.
Wilde and Oliver, 2017[46]	17 DS 13 SMS	DS: 107 mo (38-135 mo) SMS: 93 mo (36-189 mo)	Between-group comparison	BRIEF EC	Children with SMS had increased EC symptoms. EC in children with DS was within expected norms for TD children.
Fragile X syndrome					
Arron *et al.*, 2011[147]	104 AS 101 CdLS 58 CdCS 191 FXS 56 LS 189 PWS 42 SMS	16.46 y (4-52 y)	Between-group comparison	Challenging Behaviour Questionnaire	51% and 52% of individuals with FXS exhibited self-injurious behaviors and physical aggression, respectively. Physical aggression was more likely to be present in younger children with FXS. Higher impulsivity and overactivity scores also were related to rates of physical aggression.
Backes *et al.*, 2000[65]	49 FXS 16 TSC	FXS: 8.6 y (5-16 y) TSC: 9.5 y (5-17 y)	Between-group comparison	Kinder-DIPS; CBCL	The most common diagnoses in FXS group included ADHD (74%) and ODD (29%). Significant differences were found between FXS and TSC groups in proportion of ADHD diagnoses. Overall, boys with FXS exhibited more behavioral problems than TSC group. Nearly 90% of boys with FXS had elevated total problems on CBCL, with a significant difference emerging between FXS and TSC groups.
Bailey *et al.*, 2000[80]	41 males FXS (mothers)	49 mo (23-84 mo)	Descriptive longitudinal	Parent Interview; BSQ	Irritability and crankiness were among initial concerns/presenting problems; temperament style did not relate to social support, maternal age, birth order, or maternal education.
Bailey *et al.*, 2008[90]	1,491 FXS 176 Non-FXS	NR (birth to ≥30 y)	Descriptive, within-group comparison	Parent interview	Parent ratings of their child's ability to adapt to new situations correlated with the number of co-occurring conditions

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					across full mutation and premutation male and female participants. 38% of male and 43% of female participants with the full mutation exhibited aggression in contrast to 19% of males and 4% of females with premutation. 41% of males and 10% of females with the full mutation exhibited self-injurious behaviors in contrast to 8% of males and 3% of females with the premutation. Aggression and self-injury were higher in both males and females with the premutation compared with non-FXS controls.
Bailey *et al.*, 2008[78]	108 FXS	6 y (1-15 y)	Within-group comparison	CBCL	Behavior problems were significantly correlated with maternal stress, depressive symptoms, and anxiety. They were moderately correlated with anger and quality of life.
Bailey *et al.*, 2012[94]	1,363 FXS	Males: 15.5 y Females: 16.3 y (0-≥30 y)	Descriptive	Parent survey	Treatment for anger or aggression was reported for 24% of male and 7% of female participants and was significantly associated with age for males and autism ratings in both males and females. Medication use to treat anger or aggression in males increased significantly between birth and age 15 y and then remained stable into adulthood. Families with income >$50,000 were less likely to use medication to treat their son's anger or aggression problems.
Baker *et al.*, 2020[91]	62 FXS	NR (3-32 y)	Within-group comparison	ABC-FXS	Mosaic FXS resulted in lower ABC-FXS Irritability and Total scores. No difference on ABC-FXS was found between incomplete or complete silencing of *FMR1* in FXS. Elevated *FMR1* was associated with more severe irritability and ABC-FXS Total scores in the incomplete silencing FXS group.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Baumgardner *et al.*, 1995[92]	31 FXS 30 ID	FXS: 8.7 y ID: 9.3 y	Between-group comparison	ABC; teacher and parent	Compared with ID controls, children with FXS exhibited more ABC Hyperactivity but similar Irritability scores based on both parent and teacher ratings. Parent-rated Irritability scores were associated with lower IQ in ID control group, but teacher-rated Irritability scores were associated with higher IQ in FXS group. No differences were found between children with mosaic FXS and nonmosaic FXS, but findings were limited by small sample sizes.
Berry-Kravis *et al.*, 2008[186]	15 FXS	11 y (6-30 y)	Treatment	ABC; VABS	Significant improvement in ABC Total score was seen between pre- and post-treatment with lithium. Trending improvements were noted on ABC-I subscale. No significant difference was observed on VABS coping subscale.
Berry-Kravis *et al.*, 2016[105]	175 FXS adults 139 FXS adolescents	24.2-26.9 (18-45 y) 14.4-14.6 (12-17 y)	Treatment	ABC-I	There were no treatment effects on ABC total score or Irritability score, with the placebo group having more improvement than treatment groups.
Berry-Kravis *et al.*, 2012[187]	63 FXS	NR (6-39 y)	Treatment	ABC-I; VAS	No treatment effects were found on ABC-I subscale in intent-to-treat groups. STX209 was associated with improvement on VAS problem behavior ratings.
Dominick *et al.*, 2018[102]	21 FXS	14 y (3-31 y)	Treatment	CGI-I with focus on irritability	Improvement with use of risperidone was regarded as minimal with average CGI-I scores of 3.27, and only 30% of the sample were identified as treatment responders. Treatment response was higher in individuals younger than age 12 y.
Eckert *et al.*, 2019[73]	415 FXS	NR (1-57 y)	Descriptive; within-group comparison	ABC-FXS Irritability	Individuals with FXS and IAAS receiving drug treatment had significantly higher mean scores on the ABC-FXS Irritability subscale.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Eden *et al.*, 2014[121]	43 DS 37 TSC 61 CdLS 112 FXS 188 ASD	DS: 9.0 y TSC: 10.08 y CdLS 10.10 y FXS 10.88 y ASD 9.37 y (4-15 y)	Between-group comparison	Challenging Behaviour Questionnaire	Children with FXS had higher risk of self-injury than those with TSC and those with DS.
Einfeld *et al.*, 1994[67]	48 FXS 454 ID	FXS: 13.4 y ID: 11.7 y	Between-group comparison	DBC	31.2% of individuals with FXS met clinical cutoff for behavioral and emotional disturbance compared with 40.7% in ID controls.
Einfeld *et al.*, 1999[85]	61 FXS 569 ID	FXS: 15 y ID: 11 y	Longitudinal	DBC	No significant changes occurred in overall behavioral and emotional disturbance across 7 y in FXS group. A significant decline in the disruptive subscale was found. FXS group had significantly less overall behavioral and emotional disturbance in relation to ID controls and this remained across time.
Erickson *et al.*, 2009[104]	6 FXS + ASD	18.3 y (13-22 y)	Treatment	ABC	No statistically significant changes were observed from pre- to post-treatment using memantine on any of the ABC subscales.
Erickson *et al.*, 2010[100]	8 FXS	NR (6-35 y)	Treatment	ABC-I	All subjects demonstrated more than 25% improvement on ABC-I subscale.
Erickson *et al.*, 2011[101]	12 FXS	14.3 y (6-25 y)	Treatment	ABC-I; CGI-I with a focus on irritability	Parent-rated ABC-I subscale scores declined 72% from baseline to post-treatment using aripiprazole. 10 of 12 participants were rated as "much improved" or "very much improved" on CGI-I in regard to irritability, aggression, self-injury, and tantrums.
Ethridge *et al.*, 2019[62]	38 FXS 40 TDC	FXS: 25.5 y (10-53 y) TDC: 27.7 y (12-57 y)	Between-group comparison	ABC-I	Increased parent-rated ABC-I subscale scores were related to increased single-trial high-frequency gamma power during a passive auditory EEG task in FXS group.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Freund *et al.*, 1993[68]	17 FXS 17 TD	FXS: 12.8 y (4-27 y) TDC: 11.5 y (7-27 y)	Between-group comparison	DICA-P; Revised Behavior Problem Checklist	Almost half of females with FXS met criteria for a past and/or current mood disorder. Both parent and teacher reports on Revised Problem Behavior Checklist differentiated females with FXS and TD females on the Anxiety/Withdrawal scale. On average, females with FXS were rated 2 SD above mean on Anxiety-Withdrawal scale. No difference between females with FXS and TD females was found on other subscales.
Frolli *et al.*, 2015[86]	36 FXS	10.25 y at time 1 (9-11 y)	Descriptive; longitudinal	SDQ	Males with FXS exhibited significant improvement in hyperactivity/lack of attention across time, whereas emotional symptoms, behavioral problems, problems with peers, and prosocial behavior remained stable.
Hatton *et al.*, 2002[84]	59 FXS	86.6 mo (48-152 mo)	Descriptive; within-group comparison	CBCL; BSQ	In males with FXS, scores on CBCL (summary and subscale) were stable across time. Within the sample, 44% were rated in the clinical range for total behavior problems, 17% for internalizing problems, and 19% for externalizing problems. Delinquent and aggressive syndrome scales were within the average range. Total problem behavior was significantly related to autistic behavior, adaptability, medication status, and maternal education. Internalizing behaviors were predicted by adaptability and medication status, whereas externalizing behaviors were predicted by only adaptability.
Hauser *et al.*, 2014[99]	18 FXS	15.68 y (11-20 y)	Longitudinal	PBS; CBCL	Maternal mental health did not predict change in challenging behavior in subjects with FXS. Increased challenging behavior in subjects with FXS at time 1 predicted improvements in maternal depression and increased feelings of maternal closeness.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Hessl *et al.*, 2006[95]	90 FXS 90 unaffected siblings	FXS: 10.89 y Unaffected siblings: 11.13 y (6-17 y)	Between-group comparison	ABC; CBCL	Cortisol reactivity to a social challenge was not related to ABC or CBCL scores for FXS and unaffected sibling groups.
Hessl *et al.*, 2008[188]	50 FXS	15.6 y (8-24 y)	Within-group comparison	BPI	The most common aggressive behaviors included hitting (49%) and kicking others (30%). Aggression toward others was observed in 75% of sample during the 2-mo period. Regarding frequency of aggression, one-third demonstrated daily aggression; one-third, weekly; and one-third, monthly. Aggressive behavior in individuals with FXS appeared to be dependent on genotype differences in the serotonin transporter polymorphism (5-HTTLPR), with those homozygous for the L genotype having significantly higher levels of aggressive behavior.
Heussler *et al.*, 2019[107]	20 FXS	10.40 y (6-17 y)	Treatment	ABC-FXS; VAS	Statistically and clinically significant reductions in all ABC-FXS subscales, including Irritability. Significant improvement on VAS hyperactivity/impulsivity and tantrum/mood lability subscales.
Hustyi *et al.*, 2014[87]	124 FXS	11 y (2-26 y)	Longitudinal	ABC	At age 10, ABC-I and Hyperactivity/Noncompliance subscale scores were significantly higher in males compared with females with FXS. ABC-I declined at a similar rate over time for both males and females. In contrast, ABC Hyperactivity/Noncompliance scores declined at a greater rate over time for males than females. Higher developmental level predicted lower Irritability subscales in both males and females and lower Hyperactivity in only

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					male individuals. In both males and females with FXS, developmental age and medication status did not impact the trajectory of problem behavior. In female participants only, greater FMRP expression as associated with a faster decline in Hyperactive behavior.
Kau *et al.*, 2004[182]	41 FXS 14 FXS+ASD 11 DLD 7 DLD+ASD	FXS: 56.4 mo FXS+ASD: 60.1 mo DLD: 102.4 mo DLD+ASD: 59.q mo	Within-group comparison	CBCL; ABC-I	CBCL Total scores, driven by higher Internalizing Problems, were higher in FXS+ASD group. No differences across FXS+ASD, FXS, and DLD+ASD groups were found for externalizing behaviors. On ABC-I, no statistically significant group differences were found.
Kaufmann *et al.*, 2004[189]	56 FXS	57.1 mo (13.9 mo)	Descriptive	CBCL; ABC-I	No significance differences were found on the ABC-I and CBCL (Internalizing and Externalizing problems) between FXS+ASD, FXS+PDD, and FXS groups.
Leigh et al., 2013[108]	55 FXS	9.2 y (3-16 y)	Treatment	ABC; ABC-FXS; VAS	Average VAS scores improved on minocycline compared with placebo, but this difference did not reach significance. Specifically, significantly greater improvement in anxiety and mood-related behaviors was reported on minocycline. Greater improvement also was found for the "other" category on the VAS, which included self-calming/self-soothing, noncompliance/defiance, and self-injury. No significant treatment effects were found using the ABC or ABC-FXS.
Ligsay *et al.*, 2017[106]	59 FXS	Placebo-treatment: 11.3 y Treatment-placebo: 10.6 y (6-17 y)	Treatment	PARS-R; VAS; ADAMS; ABC; ABC-FXS; SNAP-IV	PARS-R total score did not statistically differ between ganaxolone and placebo. For the ADAMS, the depressed mood was higher at the end of ganaxolone treatment compared with placebo. No other measures (eg, ABC, ABC-FXS, VAS, or SNAP-IV) showed statistically

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					significant difference between ganaxolone treatment and placebo periods.
McCarthy *et al.*, 2006[98]	40 FXS	10.4 y (4-17 y)	Descriptive; within-group comparison	BASC	More children with FXS were rated as at risk based on mother and father reports of internalizing behaviors, externalizing behaviors, and the behavioral index compared with clinically significant on the BASC. Fathers, but not mothers, had greater psychological stress with more severe problem behaviors in their children.
Muller *et al.*, 2019[81]	53 FXS	9.5 y (8-10 y)	Descriptive	Parent interview	89% of mothers indicated defiance was most prevalent followed by 77% indicating tantrums, 57% indicating verbal aggression, and 55% indicating physical aggression.
Ouyang *et al.*, 2014[77]	189 FXS 185 ASD 177 ID 178 ASD + ID	NR (5-17 y)	Between-group comparison	ABC-I; additional laboratory-generated survey questions	Nearly half of caregivers reported behavior problems in children with FXS, and 67.2% of children with FXS were reportedly diagnosed with anxiety. Higher levels on ABC-I in FXS group were related to reduced work hours for caregivers with children ages between 5 and 11 y. In children with FXS between ages 12 and 17 y, a co-occurring diagnosis (anxiety, depression) was associated with perceived financial burden.
Paribello *et al.*, 2010[109]	19 FXS	18 y (13-32 y)	Treatment	ABC-I; VAS	Statistically significant changes were observed on ABC-I and VAS from baseline to post-treatment using minocycline. No significant differences were found on the outcome measures between high- and low-dose groups, raising the possibility of a placebo effect.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Prinzie *et al.*, 2002[171]	39 PWS 48 VCFS 32 FXS 28 WS 240 TD	PWS: 10 y (3-20 y) VCFS: 8.3 y (3-14 y) FXS: 10.5 y (3-18 y) WS: 9.4 y (2-19 y) TD: 8.4 y (3-14 y)	Between-group comparison	CCQ	Children with FXS exhibited lower Emotional Stability and higher Irritability scores compared with TD group, but scores similar to PWS, WS, and VCFS groups. Age was not significantly correlated with Emotional Stability in FXS group. A decline in Irritability across age in FXS group was not found.
Rice *et al.*, 2015[37]	72 DS 51 PWS 63 FXS 62 WS	NR	Longitudinal	DBC	Physical aggression and temper tantrums both declined with age in FXS group.
Roberts *et al.*, 2009[97]	93 mothers with *FMR1* premutation	NR	Within-group comparison	CBCL	Increased child problem behaviors were positively associated with a diagnosis of anxiety disorder in mothers with *FMR1* premutation.
Roberts *et al.*, 2013[96]	23 FXS 27 TD	FXS: 4.91 y TD: 4.62 y (1-10.5 y)	Within-group comparison	Change in heart rate (IBI); behavioral reactivity	No significant group differences were found in behavioral reactivity, latency to react, or latency to recover. Physiological variables were not correlated with behavioral variables.
Robinson *et al.*, 2018[93]	97 FXS 32 TD	FXS: 3.82 y TD: 2.58 y (1-9 y)	Longitudinal	TBAQ-R; CBQ	Boys with FXS showed lower levels of effortful control with little change over time and the gap between TD and FXS groups increasing across time. Greater ASD symptoms were associated with lower effortful control but did not affect rate of growth.
Sansone *et al.*, 2012[69]	630 FXS 601 ID	11 y	Descriptive; within-group comparison	ABC-I; ABC-FXS	No significant differences were found between FXS and ID groups on the ABC-I except in boys between ages 12 and 13 y.
Shanahan *et al.*, 2008[76]	25 FXS 64 TD	FXS: 34.76 mo TD: 36.25 mo (30-40 mo)	Between-group comparison	CBQ	Boys with FXS had significantly lower scores on the CBQ Anger/Frustration scale. MA and ASD symptoms were not correlated with the CBQ Anger/Frustration scale in the FXS group.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Simko *et al.*, 1989[79]	20 FXS	NR (1-7 y)	Descriptive	Parent interview	60% of children with FXS were reported to be difficult to discipline, 55% exhibited temper tantrums, 40% exhibited self-injurious behavior, and 15% were reported to fight with others.
Smith *et al.*, 2012[74]	30 FXS+ASD 106 FXS 135 ASD	FXS+ASD: 18.47 y FXS: 21.62 y ASD: 31.37 y	Between-group comparison	SIB-R Behavior Problems subscale; CBCL Externalizing Behaviors subscale	All 3 groups exceeded the clinical cutoff score for the SIB-R with the FXS+ASD group exhibiting significantly more behavior problems. FXS+ASD also had significantly higher rates of aggressive behavior. Younger age and ID were significantly associated with more behavior problems.
Smith *et al.*, 2016[88]	147 FXS	20.6 y (12-48 y)	Longitudinal	SIB-R Behavior Problems subscale; CBCL Externalizing Behaviors subscale	Severity in problem behavior decreased across time. Females with FXS had lower levels of problem behavior. Greater number of medications was associated with more problem behavior. Higher levels of criticism in the home were associated with more severe behavior problems. Increases in warmth were associated with less severe behavior problems. Higher levels of maternal depressive symptoms and criticism were associated with greater externalizing problems.
Sullivan *et al.*, 2007[83]	43 FXS	10 y (6-14 y)	Descriptive	CBCL; CSI-PC	Avoidance behaviors, confrontational and nonconfrontational, but not behavioral dysregulation, predicted anxiety problems in children with FXS as rated by teachers and parents.
Thurman *et al.*, 2014[75]	41 FXS 41 Non-S-ID ASD	FXS: 7.2 y Non-S-ID ASD: 7.5 y (4-10 y)	Between-group comparison	ADAMS	Males with FXS exhibited higher mean ratings on the ADAMS General Anxiety subscale and trended higher on the Manic/Hyperactive subscale compared with the CA-matched nonsyndromic ASD group. Males with FXS exhibited higher Manic/Hyperactive and General

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					Anxiety subscales scores compared with nonsyndromic males matched on CA, nonverbal IQ, and autism severity.
van Lieshout *et al.*, 1998[71]	32 FXS 39 PWS 28 WS 460 TD	FXS: NR (3-18 y) PWS: NR (3-20 y) WS: NR (2-19 y) TD: NR (3-16 y)	Between-group comparison	Family Context and Parents Behaviour Questionnaire; CCQ	All 3 groups had lower emotional stability compared with controls, but were similar to each other. Irritability in FXS group was higher compared with TD group but lower compared with WS and PWS groups. Across groups, increasing age was associated with less emotional stability and less irritability. Emotional stability and irritability were found to be related to parent anger, but not family stress or marital conflict.
Von Gontard *et al.*, 2002[72]	49 FXS 46 SMA 32 TDC	FXS: 8.6 y (5-16 y) SMA: 12.7 y (6-18 y) TDC: 11.2 y (6-17 y)	Between-group comparison	CBCL; Kinder-DIPS	On CBCL, 89.9% of boys with FXS had a Total Problems score in the borderline or clinical range with two-thirds reaching clinically relevant scores in both internalizing and externalizing behaviors. Total Problem scores in FXS group did not differ based on age, but were significantly higher than in SMA and TD groups. On the Kinder-DIPS, the 2 most common diagnoses for boys with FXS were ADHD in 73.5% and ODD in 28.6%. In FXS group, increased parental stress and reduced coping abilities were associated with more severe externalizing behaviors.
Wheeler *et al.*, 2007[70]	24 FXS	45.3 mo (18-72 mo)	Descriptive	CBCL	On average, CBCL Total Problems and Internalizing Behaviors scores were reported in the borderline range. CBCL scores did not relate to autism symptoms, Mullen Early Learning Scales scores, gender, or age. However, child problem behaviors were a significant predicator of maternal stress.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Wheeler *et al.*, 2014[89]	350 FXS	Males: 19.7 y (5-66 y) Females: 17.1 y (6-44 y)	Within-group comparison	ABC-I; ADAMS	In males, age was negatively correlated with ABC-I. Further, ABC-I was moderately correlated with anxiety and ADHD symptoms across males and females. Higher ABC-I scores in males were associated with greater caregiving hours, number of specialist visits in the past year, higher rates of medication use, greater risk of causing injuries of caregivers, and perceived financial burden.
Wheeler *et al.*, 2016[82]	774 FXS	Males: 19.8 y Females: 16.33 y (3-67 y)	Within-group comparison	Behavior survey completed by caregivers	90% of individuals with FXS were reported to engage in at least 1 aggressive act in the past year (92% male; 83% female). 38% of males and 18% of females were found to engage in severe aggressive behavior. Temper tantrums, defiance, and arguing were the most common across both genders. Young children and adolescents were more frequently reported to engage in aggressive acts. Frequency of the most problematic behaviors remained greater than 50% throughout adulthood.
Woodcock *et al.*, 2009[168]	33 FXS 26 PWS	FXS: 14.0 y (9-19 y) PWS: 14.1 y (6-19 y)	Between-group comparison	Semistructured interview with coding for: changes in routines/plans, temper outbursts, and repetitive questioning	24% of children with FXS showed anger, nearly 40% showed temper outburst, and 75% exhibited repetitive questioning. 79% of children with FXS showed negative emotional behavior following changes in their routine. Anger and temper outbursts were higher in PWS group than FXS group, but anxiety following changes was more common in FXS group than PWS group. When anxious, repetitive speech and repetitive self-injurious behavior was shown in 55% of FXS. Anxiety in social/high stimulatory situations was nearly 40% in children

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					with FXS. Overall, temper outbursts did not follow same course or include the same behaviors in children with FXS.
Tuberous sclerosis complex					
Backes *et al.*, 2000[65]	49 FXS 16 TSC	FXS: 8.6 y (5-16 y) TSC: 9.5 y (5-17 y)	Between-group comparison	Kinder-DIPS; CBCL	In the TSC group, 75% had a diagnosable mental health disorder; most common were ADHD (44%), ODD (25%), and SAD (19%).
Cervi *et al.*, 2020[117]	42 TSC 42 NF1	FXS: 11.36 y NF1 11.33 y (4-20 y)	Between-group comparison	TAND	Anxiety, temper tantrums, rigidity, and hyperactivity were not associated with seizure severity and were increased in the TSC group. Depressed mood was also increased but was associated with seizure severity. 50% of individuals with TSC had ADHD, 16.6% had an anxiety or mood disorder, 54.8% had temper tantrums, 45% had anxiety, and 40.5% had aggressive outbursts.
de Vries *et al.*, 2007[120]	265 TSC	NR (0-18 y)	Within-group comparison	Postal survey	Problems in children with TSC with anxiety and depression were independent of ID.
Eden *et al.*, 2014[121]	43 DS 37 TSC 61 CdLS 112 FXS 188 ASD	DS: 9.0 y TSC: 10.08 y CdLS 10.10 y FXS 10.88 y ASD 9.37 y (4-15 y)	Between-group comparison	Challenging Behaviour Questionnaire	In the TSC group, 27% were reported to have self-injurious behaviors, and 50% were reported to have aggression, but there were no differences from the other syndromes.
Kopp *et al.*, 2008[122]	99 TSC	TSC 7.7 y	Chart review	BASC	40% of individuals with TSC were rated in the clinically significant range on BASC for the Behavior Problems Index. Behavioral problems were associated with parental stress, seizures, and IQ.
Krueger *et al.*, 2017[127]	47 TSC	12.68 y (6-21 y)	Treatment	BRIEF; BASC	No differences were found between placebo and treatment groups on the BRIEF or BASC.
Leclezio *et al.*, 2015[124]	20 TSC	14.25 y (3-42 y)	Within-group comparison	TAND Checklist; BRIEF; SDQ	Measures had high face, content, and external validity and acceptable internal consistency for measuring behaviors related to ED. 90% of participants had at

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					least 1 identified behavioral difficulty as measured by the TAND Checklist.
Leclezio *et al.*, 2018[125]	56 TSC	NR (4-42 y)	Factor analysis	TAND Checklist	6 clusters (mood/anxiety, behavioral dysregulation, hyperactive/impulsive, scholastic, ASD-like, and neuropsychological) were produced, 3 of which are related to ED: mood/anxiety, behavioral dysregulation, hyperactive/impulsive.
Peron *et al.*, 2018[126]	65 TSC1 125 TSC2 22 NMI	27.2 y (0-80 y)	Within-group comparison	TAND Checklist	No difference was found in rates of the TAND Checklist between TSC1, TSC2, and NMI.
Smalley *et al.*, 1994[119]	17 TSC 16 non-TSC related kindred	NR	Between-group comparison	SADS; K-SADS	Higher rates of mood and anxiety disorders were found in individuals with TSC compared with related kindred without TSC.
van Andel *et al.*, 2020[128]	13 TSC	12.9 y (8-21 y)	Treatment	ABC-I	ABC-I scores improved in 11/13 participants during an open-label trial.
Williams syndrome					
Braga *et al.*, 2018[134]	8 WS	60 mo (48-72 mo)	Descriptive	CBCL	Children with WS demonstrated the greatest rates of impairment in anxiety/depression subscales and overall elevations in internalizing, externalizing, and total scores on the CBCL.
Camp *et al.*, 2016[45]	47 WS 31 DS 34 TD (MA-matched)	WS: 17.33 y (12-22 y) DS: 18 y (12-23 y) TD: 8.25 y (4-11 y)	Between-group comparisons	BRIEF EC	Worse EC scores were found in WS group than DS and TD groups.
Greer *et al.*, 1997[137]	15 WS	9.5 y (4-18 y)	Descriptive	CBCL	Children with WS were rated as having significant levels of attention problems on the CBCL. No significant difficulties were found in internalizing or externalizing behaviors.
Järvinen *et al.*, 2015[131]	12 WS 17 ASD 20 TD	WS: 11.4 y (9-13 y) ASD: 10.6 y (7-13 y) TD: 10.7 y (7-13 y)	Between-group comparison	Electrodermal activation, electrocardiogram	Compared with TD controls, children with WS showed an increase in arousal when viewing happy faces and a decrease in arousal for fearful faces. In contrast to TD controls, children with WS did not show increased autonomic arousal to auditory

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					stimuli or a significant difference between visual compared with auditory stimuli.
Järvinen *et al.*, 2015[132]	24 WS 17 TD	WS: 10.65 y (15-56 y) TD: 27.18 y (19-43 y)	Between-group comparison	Electrodermal activation; electrocardiogram	Compared with TD controls, children with WS and ASD showed increased autonomic arousal to emotional vocalizations. Children with WS demonstrated increased arousal to emotional music, in contrast to a decrease in arousal in children with ASD and TD.
John and Mervis, 2010[139]	78 WS	6.53 y (4-10 y)	Within-group comparison	Conners' Parent Rating Scale —Revised	Children with WS were rated as having higher levels of sensory problems. Those with higher levels of sensory problems had higher levels of oppositional behavior, anxiety, social problems, restlessness-impulsivity, and inattention.
Klein-Tasman and Lee, 2017[136]	35 WS	4.47 y (2-6 y)	Within-group comparison	CBCL	Compared with females with WS, males had more parent-reported affective problems on the CBCL. No gender differences were observed on the CBCL teacher ratings. Teachers reported higher overall ratings on anxious/depressed, attention, aggressive behavior, externalizing, and total problems subscales than parents.
Leyfer *et al.*, 2012[140]	192 WS	7.28 y (5-10 y)	Within-group comparison; factor analysis	ADIS; Children's Behavior Questionnaire	Children with WS who had a fearful temperament were more likely to receive anxiety diagnoses. The most common anxiety disorder diagnosis in WS was specific phobia.
Martens *et al.*, 2013[141]	512 WS	17.2 (0-61 y)	Descriptive; within-group comparison	Caregiver survey	27% of respondents were prescribed ADHD medications. The majority of respondents reported the medications were helpful. Irritability was the primary reported side effect.
Neo and Tonnsen, 2019[150]	30 AS	AS: 30.5 mo (22-41 mo)	Between-group comparison	CBCL	Children with WS and AS displayed greater total problems on the CBCL than

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
	22 PWS 34 WS 43 LRC	PWS: 28.2 mo (24-34 mo) WS: 31.0 mo (24-42 mo) LRC: 28.7 mo (22-39 mo)			those with LRC and PWS. Inconsistencies were found in comparison to previous studies in older participants, suggesting that challenging behavior development may be nonlinear.
Ng-Cordell *et al.*, 2018[138]	26 WS	19.12 y (4-34 y) at time 1 22.86 y (8-37 y) at time 2	Longitudinal	BRIEF; Spence Children's Anxiety Scale—Parent	In a follow-up study on anxiety diagnoses, more than 70% of the follow-up sample scored above clinical cutoffs for anxiety. No clear association with age and anxiety was observed. Shifting in EF was associated with anxiety.
Pitts *et al.*, 2016[133]	194 WS	10.72 y (6-17 y)	Within-group comparison	ADIS-P; BRIEF	Gender was not related to receiving a specific phobia diagnosis. Age, intellectual ability, and behavior regulation were significantly associated with specific phobia diagnoses, with behavioral regulation problems having the strongest relationship to specific phobia diagnoses.
Prinzie *et al.*, 2002[171]	39 PWS 48 VCFS 32 FXS 28 WS 240 TD	PWS: 10 y (3-20 y) VCFS: 8.3 y (3-14 y) FXS: 10.5 y (3-18 y) WS: 9.4 y (2-19 y) TD 8.4 y (3-14 y)	Between-group comparison	CCQ	Youth with WS had less irritability and more emotional stability than the VCFS group.
Riby *et al.*, 2012[130]	13 WS 12 ASD 25 TD	WS: 23.83 y (10-37 y) ASD: 14 y (12-17 y) TD matched with ASD: 14.08 y TD matched with WS: 23.92 y	Between-group comparison	Skin conductance	When viewing affective faces either live or via video, individuals with WS had lower skin conductance than the TD group, indicating possible hypoarousal in WS.
Rice *et al.*, 2015[37]	72 DS 51 PWS 63 FXS 62 WS	NR	Longitudinal	DBC	Physical aggression and temper tantrums declined with age before 19 y for WS.
van Lieshout *et al.*, 1998[71]	32 FXS 39 PWS 28 WS	FXS: NR (3-18 y) PWS: NR (3-20 y) WS: NR (2-19 y)	Between-group comparison	Family Context and Parents Behaviour	All 3 groups were similar on emotional stability with less stability than the control group. The WS group exhibited

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
	460 TD	TD: NR (3-16 y)		Questionnaire; CCQ	lower irritability scores compared with FXS group. With increasing age across all groups, individuals with WS were found to be less emotionally stable and less irritable.
Woodruff-Borden *et al.*, 2010[135]	45 WS	6.67 y (4-13 y)	Longitudinal	ADIS-P; BRIEF	Approximately 60% of children with WS presented with a diagnosis of anxiety initially, with 82.2% meeting criteria for anxiety over time. Anxiety disorder diagnoses were persistent over time. These diagnoses were not related to age. Children with anxiety diagnoses had higher levels behavioral regulation problems.
Angelman syndrome					
Arron *et al.*, 2011[147]	104 AS 101 CdLS 58 CdCS 191 FXS 56 LS 189 PWS 42 SMS	16.46 y (4-52 y)	Between-group comparison	Challenging Behaviour Questionnaire	73% of children with AS demonstrated physical aggression, which was significantly increased compared with children with other genetic syndromes.
Didden *et al.*, 2008[152]	129 AS 90 nonspecific ID 398 DS 235 ASD	17.4 y (2-52 y)	Between-group comparison	BFRS-R	Individuals with AS demonstrated more behavioral flexibility than those with non-specific ID and those with ASD.
Neo and Tonnsen, 2019[150]	30 AS 22 PWS 34 WS 43 LRC	AS: 30.5 mo (22-41 mo) PWS: 28.2 mo (24-34 mo) WS: 31.0 mo (24-42 mo) LRC: 28.7 mo (22-39 mo)	Between-group comparison	CBCL	Children with WS and AS displayed greater total problems on the CBCL than those with LRC and PWS. Inconsistencies were found in comparison to previous studies in older participants, suggesting challenging behavior development may be nonlinear.
Sadhwani *et al.*, 2019[155]	301 AS	6 y (1-40 y) at baseline 8.7 y (1-40 y) at final visit	Longitudinal	ABC	Individuals with AS with *UBE3A* mutations demonstrate greater ABC-I scores than children with deletions or UPD/ImpD genotype. Higher cognitive functioning was related to increased irritability.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
					Irritability increased with age across all genotypes. Irritability adversely affected family quality of life and family stress.
Summers *et al.*, 1995[148]	11 AS	4.4 y	Descriptive	CBCL	Children with AS demonstrated aggressive behavior including temper tantrums, property destruction, and self-injury.
Summers and Feldman, 1999[153]	27 AS 23 Community ID 24 Clinic ID	AS: 9.08 y (2-25 y) Community ID: 9 y (4-25 y) Clinic ID: 9.17 y (3-24 y)	Between-group comparison	ABC	Children with AS had significantly lower scores on ABC-I compared with both CA-matched control groups with ID.
Walz and Benson, 2002[151]	68 AS 28 PWS 91 DS 24 ID	AS: 10.01 y PWS: 11.5 y DS: 10.09 y ID: 12.29 y (5-19 y)	Between-group comparison	Nisonger Child Behavior Rating Form	Children with AS scored significantly higher on self-injurious, attentional, and hyperactivity items compared with children with DS and PWS. They did not demonstrate the high levels of anxious or sensitive behavior associated with PWS.
Walz, 2007[149]	339 AS	10.98 y (3-22 y)	Within-group comparison	GARS	62% of children with AS in this sample showed behaviors of laughing, giggling, or crying inappropriately.
Prader Willi syndrome					
Arron *et al.*, 2011[147]	104 AS 101 CdLS 58 CdCS 191 FXS 56 LS 189 PWS 42 SMS	16.46 y (4-52 y)	Between-group comparison	Challenging Behaviour Questionnaire	51.6% of children with PWS demonstrated self-injury, which was associated with increased repetitive behaviors, impulsivity, and overactivity. Self-injurious behaviors seen in children with PWS include scratching or rubbing the skin.
Bull *et al.*, 2015[165]	16 PWS	25 y (9-47 y)	Within-group comparison	Behavioral observation	In a series of play-based challenges where a routine was established and then disrupted, increased outbursts were observed in the disruption condition with corresponding increase in emotional arousal (heart rate). In addition, results indicated that increased duration of a routine may be associated with increased outbursts when a disruption occurred.

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TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Consoli *et al.*, 2019[178]	62 PWS	23.84 y (12-43 y)	Treatment	ABC, Self-Injurious Behavior Scale	No significant differences were found in the treatment group on ABC-I or in skin picking on the Self-Injurious Behavior Scale.
Curfs *et al.*, 1995[157]	28 PWS 28 TD	11.92 y (6-18 y)	Between-group comparison	CCQ	Children with PWS had higher scores on Irritability and Immaturity on the CCQ compared with TD children. Girls with PWS scored lower on emotional stability and openness than TD girls, but no such differences were found for boys.
Dimitropoulos *et al.*, 2001[36]	56 DS 105 PWS 76 TD	DS: 3 y (2-5 y) PWS: 3 y (2-6 y) TD: 3 y (2-5 y)	Between-group comparison	Tantrum behavior survey	Significantly more compulsive behaviors were endorsed by children with PWS than both DS and TD groups. Age of tantrum onset was earlier in the DS and TD groups compared with children with PWS. Onset of tantrum behavior in children with PWS was correlated with the onset of appetite increase.
Dykens *et al.*, 2011[166]	92 PWS	21.97 y (4-50 y)	Descriptive, within-group comparison	CBCL	Polymorphisms in tryptophan hydroxylase 2 gene (*TPH2*) impact internalizing symptoms.
Dykens *et al.*, 1992[173]	21 PWS	25.8 y (13-46 y)	Descriptive, within-group comparison	CBCL	Externalizing behaviors as measured by the CBCL were significantly greater in adolescents with PWS compared with other age groups.
Dykens and Kasari, 1997[27]	43 PWS 43 DS 43 ID	11 y (4-19 y)	Between-group comparison; within-group comparison	CBCL	Children with PWS showed significantly greater scores in all 3 CBCL domains (internalizing, externalizing, and total score) compared with children with DS or ID.
Dykens and Roof, 2008[163]	88 PWS	22 y (5-51 y)	Between-group comparison	CBCL	There were no significant group differences on the CBCL and Y-BOCS across the 3 genetic subtypes, suggesting that there may not be substantial behavioral differences across the PWS paternal deletion subtypes.
Einfeld *et al.*, 2014[180]	30 PWS	17.8 y (12-29 y)	Treatment	DBC	A significant increase in temper outbursts was observed during the oxytocin treatment phase.

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TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Hiraiwa *et al.*, 2007[172]	165 PWS 42 ID adults	PWS: NR (2-31 y) ID adults: 23.6 y (18-31 y)	Descriptive	Caregiver questionnaire focusing on behavioral problems and psychiatric symptoms	More prominent behavioral problems as well as psychiatric symptoms increased with age in individuals with PWS. Adults with PWS had significantly higher rates of behavior problems and psychiatric symptoms than adults in the control ID group.
Holland *et al.*, 2003[170]	91 PWS 42 LD	PWS: 20.8 y LD: 20.2 y	Between-group comparison	Behavior diagnostic checklist, DBC (children only), ABC (adults only)	Individuals with PWS demonstrated significantly more problem behavior including temper tantrums, violence, mood fluctuations, and obsessional traits; however, there were no significant differences between children with PWS and LD individuals on any profiles of the DBC.
Kuppens *et al.*, 2016[169]	25 PWS	9.3 y (6-14 y)	Treatment	Oxytocin Study Questionnaire	There was significant reduction in anger, sadness, conflicts, and food-related behaviors in the younger age group (6-11 y) between treatment and placebo groups. No effects of oxytocin were found in the treatment group vs the control group for the broader age range.
Miller *et al.*, 2017[181]	24 PWS	8.2 y (5-11 y)	Treatment	ABC	There were no significant differences on ABC or CGI between oxytocin and placebo at day 6.
Neo and Tonnsen, 2019[150]	30 AS 22 PWS 34 WS 43 LRC	AS: 30.5 mo (22-41 mo) PWS: 28.2 mo (24-34 mo) WS: 31.0 mo (24-42 mo) LRC: 28.7 mo (22-39 mo)	Between-group comparison	CBCL	Children with PWS generally displayed similar levels of challenging behavior to children with LRC and less than those with AS and WS. Inconsistencies were found in comparison to previous studies in older participants, suggesting that challenging behavior development may be nonlinear.
Prinzie *et al.*, 2002[171]	39 PWS 48 VCFS 32 FXS 28 WS 240 TD	PWS: 10 y (3-20 y) VCFS: 8.3 y (3-14 y) FXS: 10.5 y (3-18 y) WS: 9.4 y (2-19 y) TD 8.4 y (3-14 y)	Between-group comparison	CCQ	Emotional stability as measured by the CCQ was negatively correlated with age in the PWS group.
Rice *et al.*, 2015[37]	72 DS 51 PWS 63 FXS 62 WS	NR	Longitudinal	DBC	Physical aggression and tantrums did not decline until after age 19 y

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Rice *et al.*, 2018[162]	101 PWS	16.14 y (1-64 y)	Descriptive; within-group comparison	Caregiver outburst survey	Caregivers of children younger than age 12 reported that onset of outbursts most often occurred before age 7 (89%) with most outbursts (49%) occurring between ages 4 and 6. Outburst onset was reported as occurring before hyperphagia in 68% of individuals with PWS. Outburst frequency in PWS decreases with age, while outburst duration increases in adolescents and intensity of outbursts remains stable. No differences were observed between males and females. The most common triggers involved removal of a preferred item (both food and nonfood), requests to complete a nonpreferred activity, and changes in expectations or routines.
Singh *et al.*, 2017[174]	3 PWS	17.3 y (16-19 y)	Treatment	Behavior observation	In 3 adolescents with PWS, a mindfulness intervention (Meditation on the Soles of the Feet) decreased verbal and physical aggression.
Tunnicliffe *et al.*, 2014[167]	14 PWS	NR (9-47 y)	Descriptive	Semistructured caregiver interview	The most common antecedent of tantrums/outbursts were changes in routines or to expectations. Denial/restriction of food was also a common trigger. Precursors to tantrums/outbursts included repetitive speech, increased irritability, and change in affect. There were also reported changes in emotional arousal and frequent self-injury or aggression.
van Lieshout *et al.*, 1998[71]	32 FXS 39 PWS 28 WS 460 TD	FXS: NR (3-18 y) PWS: NR (3-20 y) WS: NR (2-19 y) TD: NR (3-16 y)	Between-group comparison	Family Context and Parents Behaviour Questionnaire; CCQ	Children with PWS scored significantly higher on the irritability subscale of the Children's Personality Profile than the control and other syndromic groups. All syndromic groups had less emotional stability than the control group.

(*continued*)

TABLE 1 Continued

Study	Sample size	Mean age (range)	Design elements	Dependent variables	Findings
Walley and Donaldson, 2005[164]	8 PWS 15 ID	PWS: 23.5 y (16-49 y) ID: 24.5 y (18-49 y)	Between-group comparison	Series of EF tasks; ABC	Individuals with PWS had significantly higher total ABC scores than ID controls, though there were no identified EF deficits noted in the series of EF tests; suggesting that EF deficits likely do not underly behavioral problems in PWS.
Walz and Benson, 2002[151]	68 AS 28 PWS 91 DS 24 ID	AS: 10.01 y PWS: 11.5 y DS: 10.09 y ID: 12.29 y (5-19 y)	Between-group comparison	Nisonger Child Behavior Rating Form	Children with PWS had rates of externalizing, obsessive-compulsive, anxious, and overly sensitive behaviors that were significantly higher than in those with DS and AS. Their total problem score was also higher than those DS. Children with PWS had better compliant and calm behaviors compared with the ID group, but similar to DS group.
Woodcock *et el.*, 2009[168]	33 FXS 26 PWS	FXS: 14.0 y (9-19 y) PWS: 14.1 y (6-19 y)	Between-group comparison	Semistructured interview with coding for: changes in routines/plans, temper outbursts, and repetitive questioning	Anger and temper outbursts were higher in the PWS group than the FXS group. Anxiety following changes was more common in the FXS group than the PWS group.

***Note**: ABC = Aberrant Behavior Checklist; ABC-FXS = ABC for fragile X syndrome; ABC-I = ABC–Irritability Subscale; ADAMS = Anxiety, Depression, and Mood Scale; ADHD = attention-deficit/hyperactivity disorder; ADIS = Anxiety Disorders Interview Schedule for DSM-IV; ADIS-P = ADIS–Parent version; ASD = autism spectrum disorder; AS = Angelman syndrome; BASC = Behavior Assessment System for Children; BFRS-R = Behavior Flexibility Rating Scale–Revised; BISCUIT = Baby and Infant Screen for Children with aUtIsm Traits; BPI = Behavior Problems Inventory; BRIEF = Behavior Rating Inventory of Executive Function; BSQ = Behavioral Style Questionnaire; CA = chronological age; CBCL = Child Behavior Checklist; CBQ = Children's Behavior Questionnaire; CCQ = California Q-Set; CdCS = cri du chat syndrome; CdLS = Cornelia de Lange syndrome; CGI = Clinical Global Impression; CGI-I = CGI–Improvement; CP = cerebral palsy; CSI-PC = Childhood Symptom Inventories–Parent Checklist; DBC = Developmental Behavior Checklist; DICA-P = Diagnostic Interview with Children and Adolescents–Parent version; DLD = developmental language delay; EC = emotional control; EEG = electroencephalogram; EF = executive functioning; FXS = fragile X syndrome; GARS = Gilliam Autism Rating Scale; IAAS = irritability, aggression, agitation, and self-injury; IBI = interbeat interval; ID = intellectual disability; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; LD = learning disability; LRC = low-risk control; LS = Lowe syndrome; MA = mental age; MN-PARS = Minnesota Preschool Affect Rating Scale; NF1 = neurofibromatosis type 1; NMI = no mutation identified; Non-S-ID = nonsyndromic intellectual disability; NR = not reported; OAHI = obstructive apnea/hypopnea index; ODD = oppositional defiant disorder; PARS-R = Pediatric Anxiety Rating Scale–Revised; PBS = Problem Behavior Scale; PDD = pervasive developmental disorder; PWS = Prader-Willi syndrome; SAD = separation anxiety disorder; SADS = Schedule for Affective Disorders and Schizophrenia; SDQ = Strengths and Differences Questionnaire; SIB-R = Scales of Independent Behavior–Revised; SMA = spinal muscular atrophy; SMS = Smith-Magenis syndrome; SNAP-IV = Swanson, Nolan and Pelham Questionnaire–fourth edition; TAND = TSC-Associated Neuropsychiatric Disorders; TBAQ-R = Toddler Behavior Assessment Questionnaire–Revised; TD = typically developing; TSC = tuberous sclerosis complex; VABS = Vineland Adaptive Behavior Scales; VAS = visual analog scale; VCFS = velocardiofacial syndrome; WBS = Williams-Beuren syndrome; WS = Williams syndrome; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.*

which multiple disorders were compared, we included the study in each respective S-ID section of Table 1, but included only the most relevant findings in each section. A list of articles excluded after review is provided in Supplement 1, available online. Inclusion criteria were met by 145 articles (DS = 29, FXS = 55, TSC = 11, WS = 18, PWS = 24, AS = 8).

RESULTS

Down Syndrome

DS is the most prevalent genetic cause of ID; it is most frequently associated with trisomy of chromosome 21 and affects 1 in 691 live births.[22] DS is characterized by challenges in cognitive, language, and motor skills across the life span.[23,24] Individuals with DS are at higher risk of a variety of medical conditions, including congenital heart defects, obstructive sleep apnea (OSA), and dementia.

Neurobiology Related to ED. Individuals with DS demonstrate a pattern of neuroanatomic differences that could contribute to ED. For example, abnormal connections within and to the prefrontal cortex of individuals with DS likely contribute to difficulties with executive functioning, including inhibitory and emotional control, impacting behavioral compliance and self-regulation, which are commonly associated with ED.[25] Abnormalities in the cerebellum and hippocampus and disrupted synaptic function contribute to deficits in motor coordination, learning, and memory for individuals with DS. The predisposition to these challenges also may contribute to experiencing sources of frustration and subsequent display of ED.[26-31]

Behaviors Related to ED. The reported range of behavioral concerns in DS is 18% to 43%.[32] Irritability and emotional control are noted to be stable among school-age children,[33-35] and latency to tantrums is consistent with typically developing (TD) peers.[36] Temper tantrums are reported to decline with age before 19 years of age.[37] Coping skills are reported to be stable across childhood to adulthood.[38] Boys are reported to demonstrate greater symptoms of irritability than girls with DS,[35] yet no sex difference is found for ratings of emotional control on the Behavior Ratings Inventory of Executive Function (BRIEF).[34]

Longitudinal studies identify risk factors for and consequences of ED in individuals with DS. Infant temperament is predictive of subsequent maladaptive behaviors, although the finding is stronger in a mixed DS and TD group than within DS alone.[39] Recent stressors are predictive of subsequent irritability among adolescents and adults with DS,[40] and a 20-year longitudinal study demonstrated that better childhood self-regulation was predictive of increased self-determination in young adulthood.[41] A preponderance of the literature on ED in DS relates to the onset of dementia, as individuals with DS are at increased risk for dementia, but that was beyond the scope of this review focused on youth.[42]

Within-group comparisons have documented greater challenges with emotional control among children with DS with comorbid OSA than children without OSA.[43] In contrast, no differences have been documented in emotional control among children with DS with and without congenital heart defects.[44] Between-group comparisons of emotional control demonstrate fewer concerns present in DS than WS[45] or Smith-Magenis syndrome[46] and fewer tantrums in children with DS compared with children with seizures.[47] Interestingly, parent-rated emotional control in children with DS is within the normative range when scored based on both chronological age and mental age.[48-50] Video-coded behaviors also have demonstrated similar rates of noncompliance and disengagement as mental age-matched peers.[51] Yet, at least one study has reported higher concerns for emotional control on the BRIEF among children with DS compared with children with nonsyndromic ID.[52]

Assessment of ED. The predominance of research on ED in DS has focused on reporting prevalence of difficulties with emotional control or irritability using parent-report measures. The BRIEF (preschool, school-age, and adult versions) has been used most extensively, with adequate psychometric properties for use in DS,[34,53] but limited convergent validity with laboratory-based assessments in this population.[54] Greater rates of tantrums in DS have been found relative to other symptoms on the parent-report Reiss scales.[55] On the Aberrant Behavior Checklist–Irritability Subscale (ABC-I), children with DS have shown worse symptoms than TD siblings but better symptoms than children with ID.[35] New parent-report measures are being developed to capture stress management, self-regulation, and inhibition in adults with DS.[56,57] Observational studies, which may capture different features of ED compared with parent-report measures, demonstrate that children with DS show a limited repertoire of skills for coping with frustration and demonstrate greater frustration without seeking support or help.[58]

Targeted Interventions. Clinic reports of treatment of children with DS and comorbid ADHD with guanfacine note a reduction in irritability score on the ABC-I by 25%.[59]

Fragile X Syndrome

FXS is the leading inherited cause of ID and occurs secondary to an unstable trinucleotide (CGG) repeat expansion of the 5′ untranslated region of the fragile X mental retardation 1 gene (*FMR1*). This leads to hypermethylation and inactivation of the gene leading to loss of the fragile X protein, which is critical for neural development. The degree of fragile X protein loss is believed to determine the severity of the FXS phenotype. Overall, FXS is characterized by mild to severe ID along with anxiety, social and communication deficits, gaze aversion, inattention, impulsivity, aggression, and hyperactivity.[60,61]

Neurobiology of ED. Loss of fragile X protein leads to multiple changes in the brain on macroscopic, microscopic, and molecular levels, including dendritic abnormalities, changes in synaptic plasticity, and overall excitatory/inhibitory imbalance. Human brain studies in FXS have documented neural structure and function changes involving neural systems thought to influence ED, including sensory processing,[62] social and emotion identification and processing,[63] and executive function.[64] Very few studies have examined a direct link between neural changes and ED. However, recently Ethridge *et al.*[62] found that increased parent-rated irritability was associated with increased high-frequency single-trial power during a passive auditory task in adolescents and adults with FXS, suggesting that neural hyperexcitability in FXS may be a risk factor for ED.

Behaviors Related to ED. Across studies, children and adolescents with FXS demonstrate elevated behavioral problems associated with ED compared with TD cohorts.[65-76] Rates of behavior problems compared with other S-IDs have been variable, with several studies finding more behavioral problems in FXS compared with other S-IDs (eg, TSC[65]), nonsyndromic ID,[69,77] and ASD.[77] Yet, other studies reported that severity of problem behavior was similar to or even reduced compared with other S-IDs (eg, PWS).[71]

The types of behaviors associated with ED across development are similar to behaviors seen in TD toddlers; for example, young children with FXS exhibit irritability, temper tantrums, crankiness, and difficult temperament,[78-80] whereas adolescents and young adults exhibit defiance, tantrums, verbal aggression, and physical aggression.[79,81,82] Noncompliance, self-injurious behaviors, and interpersonal conflict are observed across the life span for individuals with FXS.[79,82,83] Longitudinal studies suggest potential improvement in behaviors over time with relatively stable severity through toddlerhood and childhood,[84-86] followed by reduction in behavioral problems into adolescence and adulthood.[37,87] Mixed findings have emerged as to whether reductions in ED in adolescence and adulthood look similar when comparing FXS and other S-IDs.[37] Studies examining sex differences have found that male participants with FXS have similar[82,87,88] or higher prevalence[87,89,90] ED-associated behaviors relative to female participants with FXS. In addition, male participants with mosaicism demonstrate lower irritability on the ABC for FXS (ABC-FXS), described below, compared with male participants with full mutations.[91]

Studies have shown a relationship between higher ABC-I scores and lower developmental age in toddlers with FXS,[87] but higher IQ in school-age male participants.[92] More severe ED also is associated with more autistic symptoms, less adaptability, and increased likelihood of taking medication.[74,75,84,93,94] Yet, cortisol reactivity and heart rate variability were not associated with ED.[95,96] ED-associated behavior problems have been significantly related to maternal psychopathology and both maternal[70,72,78,88,97] and paternal stress.[72,98] However, a smaller number of studies indicated ED was not related to family[71] or maternal stress.[98] Behavior problems are related to parental anger, reduced coping abilities and quality of life, perceived financial burden, and reduced work hours.[71,72,77,78,94,99]

Assessment of ED. Across studies reviewed, 31 different parent-report or parent interview measures, 2 teacher-report measures, and 1 clinician-rated measure were used. Only 1 parent-report measure, the ABC, has been modified and validated for use specifically within FXS using a 6- instead of 5-factor structure.[69] Irritability, as measured by the ABC (either the ABC-Community [ABC-C] or ABC-FXS), is the most common ED measure used in pharmacologic treatment trials of FXS, followed by Clinical Global Impression Scale–Improvement (CGI-I). One study[96] obtained data from individuals with FXS via observation of behavioral reactivity and heart rate monitor.

The dependent measures of ED are numerous and highly variable. Although certain subscales provide a more direct measure of ED, we found that most studies had

indirect measures of ED. Thus, it is harder to draw firm conclusions regarding whether the presence of problem behaviors stems from inherent difficulties in ED or whether they arise from other associated features of FXS, such as executive dysfunction or social anxiety.

Targeted Interventions/Psychopharmacology. There are no behavioral therapy trials examining ED-associated outcomes in FXS. Pharmacological studies of use and effectiveness of atypical antipsychotics (eg, aripiprazole[100,101]and risperidone[102]) in the treatment of irritability have pointed to a potential superiority of aripiprazole.[73] The only prospective trial of antipsychotic use in FXS examined aripiprazole in 12 participants with the ABC-I and CGI-I as outcome measures, with significant clinical improvements in irritability on both measures.[101]

Early FXS-targeted clinical trials frequently used the ABC-C irritability or total score as a primary or secondary outcome measure. This was likely influenced by drug development in ASD, but led to mixed results, likely owing to variability in irritability in FXS.[103] No clinical trials targeting the excitatory/inhibitory imbalance via alterations in glutamate/γ-aminobutyric acid (GABA) have demonstrated improvements in ED-associated behaviors as measured by the ABC-C and/or ABC-FXS,[104-106] with some potential for worsening irritability with *N*-methyl-D-aspartate (NMDA) receptor antagonism.[104] Studies exploring other treatment targets have had some mixed results, likely influenced by open-label design.[107-109]

Tuberous Sclerosis

Tuberous sclerosis, also known as TSC, is a genetic condition caused by mutations in either *TSC1* or *TSC2* genes. These mutations lead to reductions in the components of the TSC1-TSC2 protein complex, leading to hyperactivation of the mammalian target of rapamycin (mTOR) pathway.[110] This can lead to development of tubers in the brain, heart, skin, kidneys, and lungs. TSC is rare, occurring in 6.8 to 12.4 cases per 100,000 people.[111] Cognitive abilities in TSC show a bimodal distribution, with more than half of individuals with TSC meeting criteria for ID and others having average to above-average IQs.[112]

Neurobiology. Individuals with TSC have several potential underlying mechanisms for impairments in ED,[113,114] including structural and functional changes in connectivity potentially impacting top-down control of behaviors, along with gross structural changes as the result of tubers, with location of tubers likely playing a significant role.[110,115] Finally, seizures are common in TSC, affecting 72% to 85% of individuals.[116] While most behavior problems present in the disorder do not differ based on seizure status, mood disorders may be more common in individuals with TSC without seizures.[117] Given that seizure presence and age of seizure onset are associated with intellectual impairment, behavioral manifestations of ED would be expected to vary in individuals with TSC with and without seizures.[118]

Behaviors and Assessment. Comparatively fewer studies have examined ED in TSC. *DSM* diagnoses associated with ED may have increased prevalence in TSC, with about 50% of individuals meeting criteria for ADHD[65,117,119] and higher rates of anxiety and depressed mood, independent of intellectual ability or mutation locus.[120] Problem behaviors associated with ED are frequently reported by parents. For example, a survey of 265 parents of children and adolescents with TSC showed aggressive outbursts in 58% of children, temper tantrums in 57%, and self-injury in 41%. Children with TSC also show high rates of behavior problems on normed assessments, including the Challenging Behavior Questionnaire[121] and the Behavior Assessment System for Children,[122] although these may not vary significantly from other individuals with ID. Finally, the TSC-associated neuropsychiatric disorders (TAND) checklist has been created based on common behavioral and psychiatric symptoms in TSC.[123-125] The TAND checklist has been used to document high rates of problem behaviors in TSC[117] as well as mental health concerns.[126]

Targeted Interventions. There have been no studies of behavioral interventions targeting ED in TSC. Pharmacologically, seizures and tuber growth, rather than behavior problems and mental health, are the primary foci of intervention.[110] As such, mTOR inhibitors have shown promise in reducing seizures and arresting tuber growth, but have not shown effects on behavioral outcomes.[127] However, one open-label study using bumetanide showed improvements on the ABC-I in 11 of 13 participants with TSC.[128]

Williams Syndrome

WS is a rare neurodevelopmental disorder caused by a microdeletion of genes in the q11.23 region of chromosome 7. Most cases of WS (up to 95%) involve the loss of *GTF2I* and *GTF2IRD1* genes.[129] WS is characterized by unique craniofacial features (eg, elfin-like features) and cardiovascular abnormalities. Cognitively and behaviorally,

individuals with WS typically have mild to moderate ID, heightened expressive language, and hypersociability.

Neurobiology. The amygdala has been consistently implicated in neuroimaging studies of WS; however, few studies have examined amygdala activation in relation to ED-specific measures or functions in WS and instead have focused on emotion identification. Most research examining neurobiological underpinnings of ED in WS has specifically focused on autonomic arousal using physiological measures such as skin conductance, and findings have been mixed and context-specific. Relative to age-matched controls, individuals with WS show baseline hypoarousal when viewing emotional faces,[130] yet specifically demonstrate hyperarousal when viewing happy stimuli and decreased arousal when viewing fearful stimuli and similar levels of arousal when viewing faces and listening to voices.[131,132] Interestingly, compared with controls and children with ASD, children with WS often identified neutral faces as fearful; however, autonomic arousal was not significantly different from ASD or controls.[133]

Behavior. Individuals with WS demonstrate both hypersociability and higher rates of anxiety,[134] including specific phobias.[133,135] Studies across early development using the Child Behavior Checklist (CBCL) show parental concern for internalizing problems such as anxiety as well as more common ED-associated behaviors such as tantrums and aggression.[134,136] Parents of children with WS from the ages of 4 to 18 continue to report significant levels of attention problems on the CBCL overall, although mean levels of internalizing and externalizing symptoms were within normal range.[137] In addition, physical aggression and temper tantrums decline with age before 19 years of age for WS.[37] One study reported higher rates of irritability in individuals with WS compared with FXS,[71] and another study found more difficulties in emotional control in individuals with WS than in individuals with DS.[45]

An examination of the development of anxiety in children and adults with WS found that more than 70% of a cross-sectional sample was above the cutoff for anxiety disorders,[128] although the relation between age and anxiety in WS is unclear.[135,138] Children with WS with poor sensory integration have been found to have more difficulty with emotional control, emotional reactions, and problem behaviors.[139] Behavior regulation difficulties also served as the strongest predictor of a specific phobia diagnosis, whereas difficulties in shifting was the stronger predictor of an anxiety disorder diagnosis in WS.[133,135] This indicates potentially distinct behavioral phenotypes of WS, with one group experiencing more overall dysregulation.

Assessment. Behavioral assessments of ED in WS include the CBCL, Behavior Problems Inventory (BPI), and Children's Behavior Questionnaire (CBQ). The CBQ, a measure of childhood temperament, has been validated in children with WS.[140] In this factor structure, children with a diagnosed anxiety disorder demonstrated a different factor structure than children with WS without an anxiety diagnosis. Anxiety disorders in WS are commonly assessed via the Anxiety Disorders Interview Schedule. Autonomic arousal has been evaluated in relation to ED using heart rate variability, electrodermal activation, and skin conductance.

Targeted Intervention. No studies were found regarding intervention targeting ED in WS. However, parents of children with WS who are taking medication for co-occurring ADHD reported similar side effects as reported in children with ADHD but without WS, with the most common side effect being irritability.[141]

Angelman Syndrome

AS is caused by lack of expression of the maternal copy of the ubiquitin protein ligase E3A gene (*UBE3A*) in the brain.[142] AS is characterized by ID, severe speech impairment, epilepsy, motor dysfunction, and behavioral features including hyperactivity, a happy disposition, uncontrolled laughter, mouthing objects, and fascination with water.[143] AS is rare, occurring in 1:15,000 individuals, though this is likely an underestimation.[144]

Neurobiology. Voxel-based morphometry has demonstrated decreased gray matter volumes in the bilateral striatum, amygdala, hippocampus, and insular and orbitofrontal cortices, which may underlie ED in AS.[145]

Behavior and Assessment. Very few studies have directly examined ED in AS. Problem behavior in AS includes self-injury, physical aggression, hyperactivity, and inappropriate laughter.[146-149] Children with AS demonstrate increased rates of physical aggression,[147] hyperactivity, and total problem behavior compared with children with other S-IDs,[150] particularly hyperactivity and inattention.[151] However, children with AS have increased behavioral flexibility[152] and lower irritability compared with children with other S-IDs and idiopathic ID.[153] There is some evidence

that clinical features of AS are affected by type of mutations affecting the *UBE3A* gene. For example, individuals with *UBE3A* deletions have more significant developmental delay than individuals without this deletion,[154] while children with *UBE3A* mutations show greater irritability than children with deletions or UPD/impD genotypes.[155] Assessments that have parental reports of ED in AS include the CBCL, ABC, Developmental Behavior Checklist (DBC), and Behavior Flexibility Rating Scale–Revised (BFRS-R).

Targeted Intervention. There have been no studies regarding interventions specifically targeting ED in AS.

Prader Willi Syndrome

PWS is caused by lack of expression of genes on the paternally inherited 15q11-q13 region. PWS is characterized by hypotonia and failure to thrive in infancy followed by early childhood hyperphagia, developmental delay, and problem behaviors including temper outbursts or tantrums, repetitive behaviors, and skin picking[156,157]; problem behaviors increase with age.[158] PWS has an estimated prevalence of 1:22,000.[158]

Neurobiology. Hypothalamic dysfunction is thought to underlie the hyperphagia, temperature instability, endocrine abnormalities, and hypersomnia that are commonly seen in PWS.[159] There is evidence for altered GABAergic transmission underlying problem behaviors in PWS. Decreased GABA levels in the anterior cingulate cortex as measured by magnetic resonance spectroscopy were associated with increased scores on the DBC and parent-reported temper outbursts, skin picking, and depression.[160]

Behavior. Approximately 20% of children with PWS are diagnosed with a disruptive behavior disorder.[161] Problem behavior in PWS includes temper outbursts, rigidity, irritability, and extreme hyperphagia. Children with PWS show increased tantrum behavior and outbursts owing to behavioral rigidity, difficulties with changes in routine, and difficulties with cognitive tasks,[162-165] but not related to executive functioning.[164] There is ongoing debate regarding the longitudinal relationship of changes in appetite and onset of tantrum and ED behavior in PWS.[36,162,163,166,167] In comparison to other S-IDs (DS, WS, FXS) and nonsyndromic ID, children and adolescents with PWS have shown relatively higher rates of anger and tantrums than individuals with FXS[168]; more irritability than individuals with WS; and more persistent ED profile with irritability, physical aggression, and tantrums persisting through childhood and adolescence at a higher rate[27,37,71,169-172]; yet rates of externalizing behaviors are higher in adolescence than other age periods.[173]

Assessment. Assessments commonly used in PWS include the CBCL, DBC, ABC, and personality assessments such as the California Q-Set (CCQ).

Targeted Interventions. While few studies have directly assessed the effect of interventions designed to target ED in PWS, only one small study demonstrated improvement in verbal and physical aggression in 3 adolescents with PWS with a mindfulness-based intervention.[174] There also is evidence that treatment of the metabolic and endocrine dysfunction can improve cognitive and adaptive outcomes,[175,176] but it may not significantly affect problem behaviors such as tantrums.[177,178] Oxytocin also has been studied in individuals with PWS with mixed efficacy for improvement of social and disruptive behaviors.[179-181]

Comparison Across Diagnostic Groups

To further delineate the role of ED across syndromic diagnoses, studies that included comparative analyses between S-IDs subsequently were examined to identify patterns. Indeed, several clear patterns emerged, particularly for studies that included idiopathic ASD and/or ID control groups. Across studies, youth with idiopathic ASD had higher rates of ED difficulties in comparison to diagnoses in a range of syndromic causes of ID without co-occurring ASD.[33,121,152] In one of the most thorough differential analyses, Eden *et al.*[121] examined rates of self-injury and aggression across syndromes. Compared with other syndromic groups (eg, DS, TSC), individuals with FXS and idiopathic ASD showed significantly more self-injury, and autistic individuals demonstrated significantly more aggression.

Several studies also allowed comparisons of ED in an FXS-only group and in FXS+ASD or FXS+ID group. Importantly, ASD and ID both appear to be key factors related to ED in youth with FXS. At least one study showed that youth with FXS and co-occurring ID and ASD had the highest rates of irritability and aggression compared with participants without these additional diagnoses.[74] This pattern was not observed in other studies, however, which found similar rates of irritability between an FXS-alone group and FXS+ID+ASD group, but higher rates of internalizing difficulties in the FXS-alone group.[182] Furthermore, individuals with FXS and idiopathic ID have shown similar rates of irritability except during the

preadolescent age range, when children with FXS had higher rates.[65] Additionally, parents rated higher irritability in youth with FXS and lower IQ, whereas teachers rated higher irritability in youth with FXS and higher IQ.[92] Taken together, autistic features, IQ, and even age may be unique risk factors for ED in FXS.

A pattern of higher rates of irritability in idiopathic ID compared with S-IDs was consistently found across studies.[35,67,85,153] When studies compared different ID severity groups across both known etiology of ID (including DS) and unknown etiology/idiopathic ID, participants with moderate ID were more likely to have impairment in emotional control than those with mild ID.[52] Although this was the only study that examined different levels of ID, it is an important clue into the possible stepwise impact of the severity of ID on ED, highlighting the importance of including individuals with ID in interventions for ED, as this population seems to be a particularly vulnerable group that is uniquely impacted by ED.

A differential analysis across a range of disorders including DS, AS, PWS, and idiopathic ID demonstrated differentiation among the groups across 3 prosocial behaviors (follows rules, accepts redirection, helps others) and 6 problematic behaviors (high energy level, steals, puts items in mouth, talks too much, overly excited, and frequent mood changes).[151] Specifically, more difficulties with argumentativeness were demonstrated in participants with DS; difficulties with overactivity and attention were demonstrated in AS; heightened emotional sensitivity, crying and tantrums, argumentativeness, and mood lability were demonstrated in PWS; and more difficulties with attention and overactivity, mood lability, and irritability were demonstrated in idiopathic ID.

Of note, the literature examining PWS and comparison groups is quite comprehensive, including a broader range of comparison groups than other literature of disorders. Studies have consistently found that PWS groups demonstrate higher levels of emotionality, tearfulness, tantrums, sensitivity, and outbursts compared with FXS, WS, TD, ID, and ID+overweight groups.[71,157,168,170,172] Additionally, compared with other groups, PWS and idiopathic ID groups experience more significant mood changes, and ID groups demonstrate greater irritability. Only one study found participants with PWS to have fewer total ED problems than participants with WS and AS.[150] Additionally, a clear developmental pattern was found across disorders with a decrease in irritability occurring during late adolescence.[35] Yet in PWS, decline in irritability occurred at later ages than in other disorders.[37] The consistency in results across studies points to the possibility of a unique underlying biological process occurring in PWS that is not likely explained by ID alone.

While individuals with PWS present with higher rates of ED, individuals with DS appear to present with lower rates of ED compared with other groups. Studies of DS that compared ID, mental age matched, and TD groups, the DS group had similar rates of irritability and ED-related behaviors to other groups.[35,47,51] In many instances, participants with DS actually had lower rates of ED than ASD or ID groups[27,28] and in one instance had emotional control in a similar range as their TD peers.[54] In fact, DS appears to be associated with increased affective stability compared with ASD.[33] This suggests that ID alone, which is present in all youth with DS, is likely not driving ED symptoms and that perhaps there is a protective factor associated with the underlying biology of DS that leads to lower rates of ED compared with disorders such as PWS or FXS.

Distinct underlying risk factors driving ED emerge when examining specific disorders. For example, triggers for ED among specific disorders include associations for TSC with experiencing pain,[121] FXS with uncertainty,[168] DS with demands,[51] and PWS with restriction of food.[36] These disorder-specific associations may hold insight to neural pathways related to ED and specific stimuli. Together, comparison across disorders raises an important question regarding interventions for ED in S-IDs. Specifically, should interventions be tailored to each disorder, or would a modular approach with core ER intervention components and additional modules tailored specifically to ID be used for all youth with ID and ED to address ED-related difficulties unique to each disorder? Although very little research was available about coping styles or treatment, one study found that even when youth with ID or DS used coping strategies, there was not a decrease in negative affect, while TD youth did experience a decrease with coping skill use. This suggests that the youth with ID or DS were either not effectively using coping strategies or the available coping strategies were not effective for them. It is possible that coping strategies need to be tailored more directly to common triggers for each disorder to be more effective.

DISCUSSION

We conducted a systematic review of ED in 6 S-IDs including DS, FXS, TSC, WS, AS, and PWS. The state of research in this area varied across the disorders with some, such as FXS, being more extensive, and others, such as TSC and AS, being very limited. Even in the S-IDs with more available research, there was a lack of a standard definition of ED-associated behaviors and lack of gold standard ED-

specific outcome measures. Moreover, across S-IDs, behavioral and pharmacological treatment for ED is extremely limited.

We found a wide range of ED prevalence across disorders, with FXS and PWS possibly demonstrating the highest rates of irritability and behavior difficulties. However, it is possible that subgroups within disorders are more likely to experience ED, such as youth with dual diagnoses of ASD in FXS, ADHD in DS and TSC, anxiety in FXS, TSC, and WS, depression in TSC, and specific phobias in WS. As suggested in ED research of other diagnoses, it is possible that ED is a transdiagnostic characteristic of psychopathology that underlies a range of dual diagnoses. Additionally, co-occurring health conditions seen in S-IDs may be related to ED (eg, OSA in DS, seizures in TSC). Initial evidence suggests that autistic features and severity of ID may have a dose-dependent contribution to ED in S-IDs, though future research is needed to clarify.

We focused on youth in this review, but ED may play a role throughout adulthood for disorders that demonstrate co-occurring conditions, such as early dementia in DS and fragile X–associated tremor/ataxia syndrome in FXS. Regarding change in ED over time, FXS and DS provide us with the most information about the impact of ED throughout the life span through longitudinal studies. Still the results were varied, and more information is needed about the stability of symptoms and their impact into adulthood.

While studies show underlying neurobiological features of S-IDs that may be related to ED, very few studies examined possible causal pathophysiological mechanisms relating neurobiology to ED. There was a wide range of symptom manifestation of ED across disorders with some diagnoses demonstrating higher rates of behavioral concerns and others demonstrating higher rates of reported mood or anxiety symptoms. Given findings that suggest ED and related symptoms are especially common and severe in PWS, but less common and severe in DS, this suggests disorder-specific pathophysiological mechanisms may increase or decrease risk of ED. Further evidence of this notion comes from findings linking specific symptoms to ED in distinct disorders (ie, pain in TSC, anxiety in FXS). Although disentangling different pathophysiological mechanisms is beyond the scope of the current review, it remains an important area of future examination.

The broad range of symptom presentation across disorders also may be impacted by the variety of measures being used to assess ED, including the ABC-I, BRIEF Emotional Control, CBCL, Challenging Behavior Questionnaire, Behavior Assessment System for Children, and TAND. At the same time, many of these measures assess ED-related symptoms, such as irritability or anxiety, but do not directly assess ED. We demonstrate a need for a measure that can capture ED in a wide range of functioning levels and diagnoses. In the ASD field, the Emotion Dysregulation Inventory (EDI)[183] has been used widely in the ASD community, inpatient settings, and the general population. Future research of ED in S-IDs should explore the utility of the EDI across syndromes. A standard measure across disorders will help establish a common language and understanding of ED. Additionally, in both DS and FXS, behavioral observation studies identified challenges that were not captured on parent-report measures. This suggests that reliance on parent-report measures alone may not be adequate to identify and quantify ED in S-IDs. This may be a unique challenge to this population, as severe cognitive and language impairments may impact a parent's ability to identify the source of behaviors commonly associated with ED.

In the area of treatment, there are few targeted behavioral interventions for ED, with the exception of one study in PWS demonstrating improvement in problem behaviors via mindfulness therapy. Although behavioral ED intervention for S-IDS is an emerging area of research, targeted interventions in other psychiatric disorders and ASD without ID have demonstrated overwhelmingly positive results.[8,184] Moreover, given the breadth and depth of research in the general psychiatric population and early research on the utility of addressing ED in ASD, a cohesive intervention is needed that draws on research from both fields. Yet, many available interventions for youth with ED are not adapted for youth with ID or communication impairments. Early research in idiopathic ID has demonstrated that core elements of ED treatment, such as relaxation strategies and simplified cognitive-behavioral therapy skills, can be helpful, yet rigorous research has not yet been conducted.[185] As can be seen in the current review, there is a clear need for interventions that address ED in a developmentally appropriate way for a wide range of S-IDs.

In contrast, there have been relatively more studies of pharmacological trials across disorders that focused on irritability or other related disorders, though the majority of these trials have been completed in FXS. Pharmacological trials have shown some potential benefit, especially in the area of irritability. Yet, this is still a critical area of need with rigorous research designs with appropriate power and sample sizes, something that can be difficult to achieve in rare conditions. In addition, assessment of ED as a secondary outcome in intervention trials may demonstrate broader impacts of treatment, as seen in DS review studies. This may be true in other disorders.

Regarding limitations, this review took a very broad approach by examining 6 different S-IDs to obtain an overview of the state of ED research, but this may have impacted the ability to thoroughly evaluate each disorder,

particularly FXS, for which more research is available. We also limited our search to youth and did not include related research in adults with S-IDs. Finally, we searched only in PubMed vs including other databases, and this may have impacted the number of articles returned, led to exclusion of some types of articles such as dissertations, or led to a publication bias. We chose PubMed given that most research in S-IDs is medical in nature and it was the database likely to return the most results; however, a broader review may be needed in the future.

In conclusion, ED is present across many S-IDs, but a common definition and assessment tool is needed to better understand its prevalence and impact. Few interventions are available outside medication trials for related symptoms and only one psychological intervention in PWS. This represents an important area of needed research focused on both identification and treatment for ED in S-IDs.

This article is a part of a special review series devoted to child and adolescent emotion dysregulation as part of the presidential initiative of AACAP President Gabrielle A. Carlson, MD (2020-2022). Articles were selected to cover a range of topics in the area, including reviews of genetics, neuroimaging, pharmacological and nonpharmacological treatment, screening tools, and prevention, among others. The series was edited by Guest Editor Daniel P. Dickstein, MD, Associate Editor Robert R. Althoff, MD, PhD, and Editor-in-Chief Douglas K. Novins, MD.

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