Defining Developmental Regression in Rare Neurodevelopmental Disorders of Genetic Etiology: A Scoping Review

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Abstract: *Background*: Some genetic neurodevelopmental disorders (NDDs) are linked to a loss of acquired abilities. No universal term or severity measure exists for this phenomenon. This scoping review aims further to define developmental regression in NDDs of genetic etiology.

Method: We used the PRISMA checklist and searched PubMed, medRxiv, and Google Scholar for developmental regression literature. After data extraction, qualitative (e.g., assessment methods) and quantitative (e.g., mentioned NDDs) data were analyzed.

Results: A total of 59 relevant articles from 2074 unique records were identified, associating 18 NDDs of genetic etiology with developmental regression. Multiple terms (e.g., loss of skills, deterioration) and definitions were used across syndromes.

Conclusions: A uniform definition of developmental regression was formulated based on literature diversity and NDD heterogeneity. The study also offers guidance on identifying and monitoring developmental regression and its underlying causes.

Keywords: Clinical genetics, intellectual disability, developmental disability, neurodevelopmental disorders, developmental regression, scoping review.

1. INTRODUCTION

Neurodevelopmental disorders (NDDs) are conditions that typically manifest during the early developmental years. These are characterized by somatic, cognitive, neurological, and psychological abnormalities with a variety of substantial adverse effects on communication, learning, social interaction, and social participation [1]. Some NDDs are associated with the occurrence of so-called regressive symptoms, typically understood as a loss of functions that may or may not be related to the etiological condition [2-4]. Autistic regression is probably the most famous form of regression, in which there is a loss of previously acquired skills, mainly language and/or social communication skills. It occurs in =30% of young children with the heterogeneous condition of autism spectrum disorders and has a mean age of onset of 21 months [5]. However, its definition is applied in different ways, as are the methods used to investigate this phenomenon. Presently, its etiology remains unresolved [6]. The definition of autistic regression is insufficient for NDD cases in which regression occurs later or presents with a broader loss of skills [7, 8]. Other types of regression have been described with a clear somatic cause [9, 10] and are outside the scope of this review.

Presently, the total incidence in subjects with genetic origins of NDDs is unknown. For several NDDs, a (mono)genetic etiology has been demonstrated, and with advancements in genetic diagnostic approaches, NDDs of genetic origin are more frequently diagnosed [11]. Even at adult ages, and with the improvement of care in all medical areas, life expectancy has also increased for individuals with NDDs [12-14]. Therefore, more individuals with potential regressive symptomatology are expected to be detected [11, 15,

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16]. Regression is a term often used in research and clinical settings regarding individuals with NDDs (of genetic origin) that show a loss in functional capacities. It is defined as *a return to earlier, especially to infantile patterns of thought or behavior or stage of functioning* [17]. However, the use of this term and its definition are not universally applied, as many different terms are used to describe this same regression of development (e.g., decline of functioning, loss of skills, (neuro) degeneration, and deterioration). Additionally, in the NDD literature, several seemingly similar terms have fundamentally different meanings. For example, 'neurodegeneration', i.e., the *progressive loss of neural cells and tissue* [18], where the somatic aspect is the main element of the definition. Developmental regression should also be distinguished from developmental delay or a developmental plateau, where a child is not able to reach certain milestones. Moreover, there is no commonly acknowledged way of objectifying the (degree of) regression, which may cause issues with the interpretation of IQ measures and scores, as they are based on the population average. Since subjects with NDD of genetic origin may have a different pace of development, the gap between their scores and those of typical developing peers increases with biological age. For this reason, IQ scores seem to decrease in time in individuals with (genetic) NDDs. This decrease may be interpreted as developmental regression, whereas in reality may be the result of a 'growth into deficit', are relative increase of the developmental delay [19].

Objectives

The present scoping review gathers the terms and definitions used to describe episodes of developmental regression in NDDs of genetic origin.

To this end, we shall catalog (1) the NDDs that are associated with developmental regression and are of genetic origin, (2) the methods used to assess/objectify the developmental regression, and (3) the factors that play a part in the etiology of the regression itself. Ultimately, our goal is to establish a definition for the term 'Developmental regression' that focuses on the non-somatic aspects of the decline of functioning and can be utilized in the fields of genetic and neuropsychiatric research.

2. METHODS

This scoping review was carried out via the PRISMA-ScR checklist as established by Tricco *et al*. [20].

Protocol and Registration

For this review, we registered no formal a priori review protocol.

Eligibility Criteria

Articles were screened based on title and abstract and deemed eligible when written in English with a full-text version available. Since the term 'regression' was already used in post-war clinical and psychoanalytic settings, and since it can be relevant to establish a historical framework, we did not limit the number of years considered. Moreover, the most recent articles in this rapidly growing field of clinical research are also important to consider. Therefore, we included articles in pre-print in addition to those already published, provided that they have been in pre-print no longer than 2 years. At this stage, papers were excluded if the title and abstract of the paper indicated that the material was obviously irrelevant to our review (e.g. when the term 'regression' solely referred to the statistical analysis). In addition, articles solely mentioning an isolated motor regression were excluded, as isolated motor regression can very often be traced back to a clear somatic substrate.

Further exclusion criteria were formulated as follows:

- Intellectual disability/developmental delay without genetic etiology.
- Animal studies and translational research have no clinical part or a clear link to clinical practice.
- Alzheimer's disease (also in combination with Down syndrome).
- Schizophrenia, with first symptoms arising after the age of 30.
- Regression with an identifiable somatic substrate, such as metabolic disorders/storage diseases.
- Regression with a clear epileptic and/or neuronal degeneration etiology.
- Search strategy and Information sources

Concrete search strategies for Pubmed, medRxiv, and Google Scholar were drafted and refined by three members of the research team [J.K., E.W., and K.V.-K]. To identify potential relevant articles, the research

question was broken down into (a) terms referring to NDDs of genetic origin and (b) terms relating to developmental regression. To ensure we included all possible terminology, an exploratory search prior to the main search was conducted to map which terms are actually used in the literature.

This initial search was conducted in PubMed and the Google Scholar database from October 2021 to January 2022. The electronic database search was supplemented by a search of medRxiv in February 2022. The main search was executed in PubMed on June 14, 2022. A similar search was done for Google Scholar and medRxiv on October 4, 2022, but it yielded no relevant results.

Additionally, the 'cited by' section in Pubmed was manually scanned for other relevant publications not yet captured. The complete search strategies for Pubmed, medRxiv and Google Scholar can be found in Appendices 1 and 2. The final results were exported to Endnote after which duplicates were removed.

Selection of Sources of Evidence

After the comprehensive search of the literature was completed, [EvdW] and [JK] independently screened each article based on title and abstract, after which any discrepancies were discussed with [KVK]. In a similar process, [EvdW] and [JK] subsequently assessed the found literature for eligibility based on the full-text articles and again discussed discrepancies with [KVK]. A meeting with all authors was organized to discuss the selection made by [EvdW], [JK], and [KVK] and to establish a final selection of articles.

Data Items and Data Charting Process

A data charting form was composed with the input of [JK], [KVK], [JE], and [TK] to determine the relevant data to extract. It was revised during the data charting process when deemed necessary. From each of the selected sources, the following data was collected: title, author, year of publication, country of origin, aims of the study, study population/NDDs addressed and sample size, used definition of regression, suspected etiology of the regression itself, age of onset and duration of the regressive period, method of assessment, therapies used/mentioned, and efficacy of therapy. [LV] and [EvdW] manually extracted the needed data for this review from the articles that were found relevant. Another reviewer [JK] double-checked the manually extracted data.

Synthesis of Results

Quantitative analysis was performed on publication characteristics, e.g. year and place of publication. Qualitative analysis comprised descriptions or definition of regression, suspected etiology of the regression and therapies used/mentioned. Key components were processed by mapping in the online Mindmeister [21] mind map tool. Furthermore, descriptive statistics were used to summarize the main findings.

3. RESULTS

Selection of Sources of Evidence

The literature search yielded a total number of 2074 unique records. After screening based on abstracts, 10 articles were excluded as they were not available in English, and 1712 were excluded as they clearly did not fit the scope of the review (e.g., the term 'regression' solely referred to the performed statistical analyses). When assessing for eligibility, 293 articles were excluded for various reasons (i.e., full text not available (n=26), authors did not give a relation between NDD and regression (n=217), focus on dementia/late-onset schizophrenia (n=24) or somatic substrates (n=26)), leaving 59 articles. A full overview of the exact proceedings per review phase can be found in the established flowchart below (Figure **1**).

Characteristics of included articles

The year of publication ranged from 1981 to 2022, with a high representation of more recent articles (Skewness: -1.93; Mean: 2013.5). The included articles comprised 25.4% of case reports originating mainly from North America and Europe. No publications from Africa or South America were included. A more detailed overview can be found in Figure **2**— Publication characteristics.

Results of Individual Sources of Evidence

A definition of the observed developmental regression was given in 45 studies (76.3%). In 29 (49.2%) of the articles, a (possible) explanation for the observed regression– e.g., psychosocial stressors, epilepsy, infections, sleep disturbances, and psychotic symptoms – was given. In addition, the age of onset of the period of developmental regression ranged from 9 months to 32 years, and the duration of this period ranged from weeks to years. A complete overview of definitions and age of onset/duration of the regressive period mentioned in the included articles can be found in Table **1**. Explanations/hypotheses for the cause of

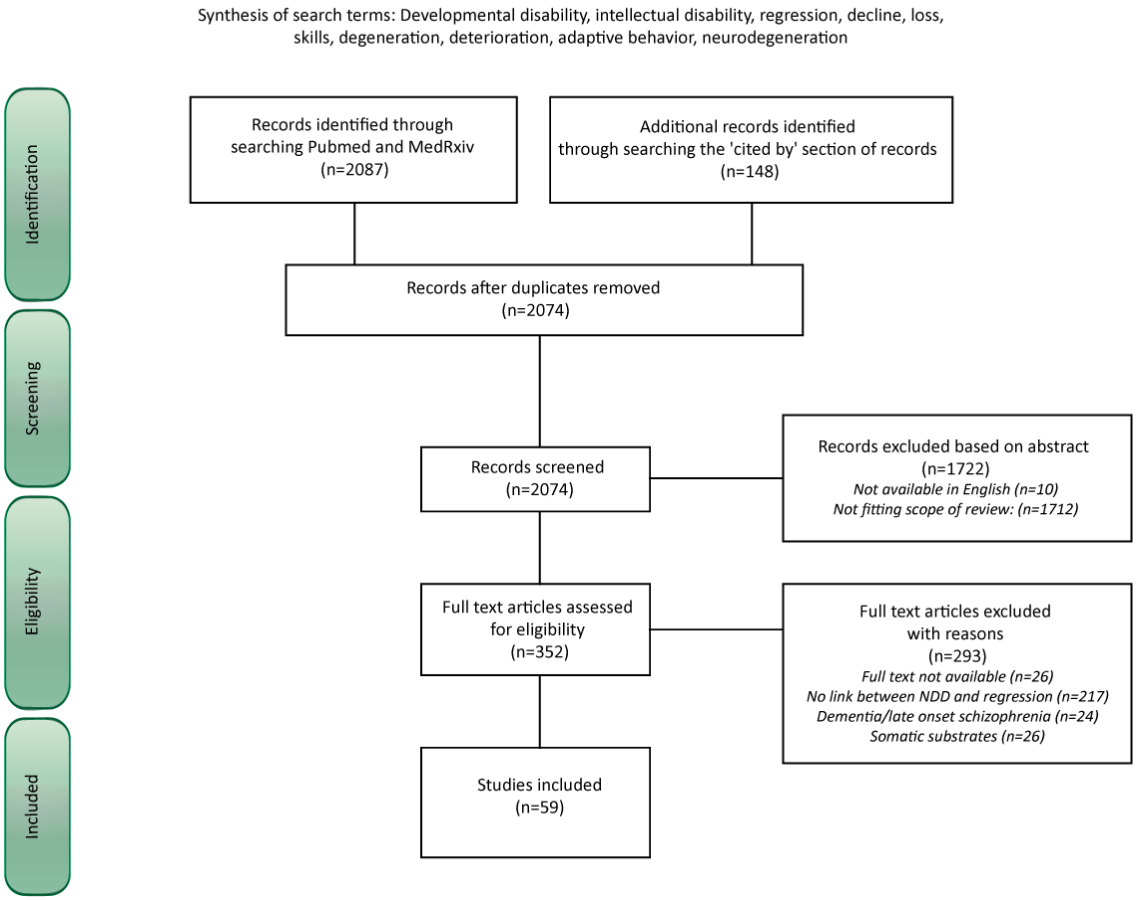

Figure 1: PRISMA Flow Diagram.

Diagram showing the number of papers identified, screened, deemed eligible, and eventually included in the scoping review.

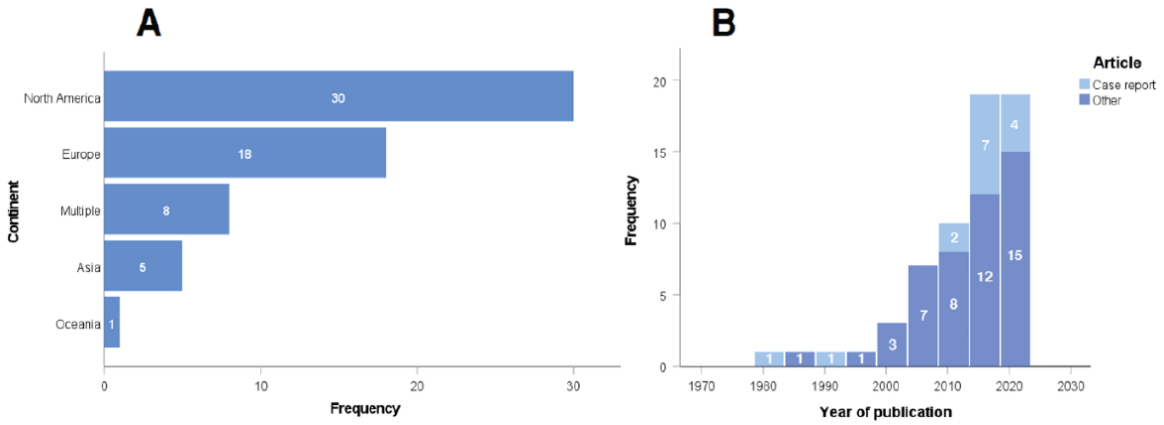

Figure 2: Publication Characteristics.

A: Bar chart displaying the continents where the included articles were published. **B**: Histogram displaying the publishing year of the included articles. Case reports (n=15, (24.2%)) are indicated in light blue. Other types of articles (e.g., systematic reviews) (N=47, (75.8%)) are indicated in dark blue.

regression that were mentioned can be found in 'Appendix 3 – Causes'.

The included articles used many different terms (e.g., loss of acquired skills, deterioration, progressive dysfunction) to describe the regression phenomenon. Figure **3** provides an overview of all these terms and their underlying word associations.

Within the included articles, a total number of 18 different NDDs of genetic etiology were linked to developmental regression. Rett syndrome (n=19),

Table 1: Regression Definitions and Timing. Definitions and Age of Onset/ Duration of the Regressive Period are Mentioned in the included Articles. Keywords are in Bold

Article	NDD(s)/Study population	Definition of regression	Onset/duration of regression	Design	Study sample
Einspieler *et al.* [48]	Rett syndrome	A return to a previous, less advanced state, condition or behaviour. Implies that a function can only be lost if it was acquired before.	Duration: A period of several months or even years. Onset: Onset of regression at the age of 12 to 19 months […], lasting from 6 to 19 months.	Retrospective	Review
Eriksson *et al.* [49]		Loss of more than five spoken words used communicatively in children more than 15 months of age. In children younger than 15 months, regression was determined when there was a clear indication of loss of social interest and contact.	Onset:The onset of regression is often reported to be between the ages of 15 and 24 months.	Prospective	Clinical based
Garber *et al.* [26]			Onset; The children appear to develop normally until 6 to 18 months, then appear to arrest in development or regress in previously acquired skills.	Prospective	Clinical based
Glaze *et al.* [50]		Loss of social, cognitive, and language skills during the first 2-4 years of life.	Onset: The onset of regression is between 1 and 3 years.	Prospective	Clinical-based/animal study
Kim *et al.* [30]		Progressive regression in cognition, language, and purposeful hand skills.	-	Retrospective	Clinical based
Larsson *et al.* [51]		Stagnation of development, loss of ability, and then a more stationary lifelong situation.	-	Retrospective	Parent survey based
LeBlanc *et al.* [31]		Regression, losing expressive language and purposeful hand use and developing gait abnormalities and hand stereotypies over the course of weeks, months, or years.	Duration: […] girls with RTT undergo regression, […] over the course of weeks, months, or years.	Prospective	Clinical based
Lee *et al.* [32]		Regression in the current sample comprised a loss of previously acquired hand and speech skills, in addition to the development of hand stereotypies, social withdrawal, and inconsolable crying.	Onset: The median age at onset of regression was 18 months (range 9–34).	Retrospective	Parent survey based
Marschik *et al.* [33]		Progressive deterioration leads to dramatic loss of ability in adaptive functioning, functional hand use, mobility, language, and communicative functions.	-	Retrospective	Clinical/parent survey based
Marschik *et al.* [34]		The regression was associated with the deterioration of speech/language and communicative abilities, withdrawal from social life, and the loss of purposeful hand use.	Onset: Around the girl's second birthday.	Prospective	Clinical/parent survey based

Neul *et al.* [35]		Psychomotorregression with loss of volitional hand use and spoken language, the development of repetitive hand stereotypies, and gait impairment.	Onset/duration: A period of active regression […] typically occurs at 1 to 4 years old, although in some cases the regression may occur earlier or later.	Retrospective	Review
Nomura *et al.* [29]		Regression period: speech delay, losing purposeful hand use, pathognomonic hand stereotypies.	Onset/duration:Stage II is from 1 to 3 or 4 years and comprises a period of regression.	Retrospective	Clinical based
Peters *et al.* [52]		A partial or complete loss of skills related to language, socialization, self-help skills, and/or motor skills.	Onset: The loss of skills occurs at an early age (usually between 15 and 30 months).	Retrospective	Parent survey based
Peters *et al.* [53]		-	Average age of loss (mean, SD). Language regression: 39.12 months; 13.58 months. Range of ages (months): 24-60. Average age of loss (mean, SD). Regression in other skills: 54.57 months; 20.82 months. Range of ages (months): 30-84.	Retrospective	Clinical/parent survey based
Pohodich *et al.* [36]		Developmental regression is marked by a loss of acquired language abilities, a slowing of both head and brain growth, impaired motor skills, and loss of purposeful hand movements.	Onset: After the first 6-18 months of life. Duration: Progresses over the next few years	Retrospective	Review, epigenetic/neuronal based
Reichow *et al.* [28]		Regression in skills and abilities, including motor movements, communication, and purposeful hand movements.	-	Retrospective	Systematic review, literature/clinical-based
Sheikh *et al.* [27]		Childhood onset cognitive decline. Cognitive decline is a component of the SCZ phenotype, which starts at or soon before the onset of positive symptoms, and continues for months to years after the onset.	Duration: Continues for months to years after the onset	Retrospective	Clinical/family survey based
Sigafoos *et al.* [54]		Developmental regression refers, in part, to situations in which previously acquired skills and abilities are lost or diminish significantly in terms of their fluency and precision.	Onset: occurring between 2 and 8 years of age.	Retrospective	Systematic review, literature/clinical-based
Castillo *et al.* [55]	Down syndrome	Phenomenon characterized by deterioration of a previously acquired skill. This loss of ability can be in the areas of language, communication, or social skills.	Onset: The mean age at language loss in children with autism with Down syndrome was 61.8 months (SD = 22.9). The mean age at other skill loss was 46.2 months (SD = 19.1). Another child was reported to lose articulation and grammar skills for a prolonged period at age 13 years. Duration: at least 3 months	Retrospective	Clinical based
Fox *et al.* [56]		-	Onset:Between the ages of 24 and26 (case study)	Retrospective	Clinical based

Jacobs *et al.* [57]		A rapid and unexplained deterioration in cognitive, adaptive, and behavioral functioning. Their decline typically involves intellectual deterioration, a loss of skills of daily living, and prominent behavioral changes.	Onset:He began to show deterioration in function at 17.5 years of age. Ages 10–30 years and usually post-pubertal at the time of onset.	Retrospective	Clinical based
Lukowski *et al.* [58]		Cognitive decline over time: general intelligence/IQ, language development, recall memory, and executive functioning.	-	Retrospective	Literature based
Lyons *et al.* [22]		A slow but gradual loss of ability in previously acquired skills, speech, and spontaneous movement.	-	Retrospective	Clinical based
Rosso *et al.* [25]		Down Syndrome Disintegrative Disorder (DSDD) is a regression of previously attained skills, notably in the domains of language, communication, and social skills. No formal criteria exist within the diagnosis of DSDD to define either regression or autistic-like behavioral regression.	Duration: The acute regression appears to last for ∼6monthsand is followed by a chronic phase in which previous skills may not be completely recovered	Retrospective	Review, clinical-based
Stein *et al.* [59]		Cognitive and developmentalregression including loss of language, social, and toileting skills.	-	Retrospective	Clinical based
Walpert *et al.* [60]		Significant impacts on the person's cognitive and language functioning, their ability to perform daily tasks, a considerable loss of previously acquired daily skills, mild to severe alterations in personality and behavior, and the onset of social withdrawal.	Onset:The mean age of onset was 20.97 years.	Retrospective	Systematic review, literature-based
Worley *et al.* [23]		Loss of previously acquired language and socio-communicative skills.	Onset: The mean age at which symptoms developed was 11.4 years	Retrospective	Clinical/parent interview based
Fisch *et al.* [61]	Fragile X syndrome	Decreased cognitive ability (IQ scores) and decreased adaptive behavior levels (DQ scores).	-	Prospective	Clinical based
Fisch *et al.* [62]		Negative correlations between chronological age and adaptive behavior composite scores or age-equivalent scores of adaptive behavior leveled off as chronological age increased + IQ and DQ scoresdecline as young fra(X) males age.	-	Prospective	Clinical based
Hahn *et al.* [63]		A decline of the raw scores of adaptive behavior means that these children, according to parent reports, had regressed, losing some of these important skills.	Onset:positive trajectories until the age of 10 in males with FXS and then decline or stabilization after age 10. A subgroup of 30 participants […] showed declines in adaptive behavior raw scores starting around age 7.	Prospective	Parent interview based
Kosinovsky *et al.* [64]		The loss of milestones in the development of speech, non-verbal communication, social skills, and play.	Onset: The average age at the time of regression was 20.4 months (range 12–36, STD 5.58)	Retrospective	Clinical based

Maltman *et al.* [65]		One behavioral phenotype that may evidence change over time among PM carriers is verbal disinhibition.	-	Prospective	Clinical based
Warren *et al.* [66]		declines in adaptive behavior// lose adaptive behavior skills.	Onset: 56% of children showed declines in adaptive behavior at or before the age of 10	Prospective	Clinical based
Biswas *et al.* [67]	22q11.2 deletion syndrome	Depending on the study discussed: decline in VIQ, PIQ and FIQ // detoriationin global functioning.	Onset:Some children assessed at 7.5 and 9.5 years showing actual deterioration	Retrospective	Review
Davies *et al.* [68]		A decline represents a negative deviation from the expected decline in this population (defining VIQ decline as a binary variable operationalized as any negative change in z scores exceeding 1 s.d. difference).	-	Retrospective	Clinical based
Engebretsen *et al.* [69]		Severe fall in global functioning.	Onset: At age 19 (case report)	Prospective	Clinical based
Evers *et al.* [70]		Intellectual/cognitive decline (premorbid IQ >70).	-	Retrospective	Clinical based
Kohlenberg *et al.* [2]	Phelan-McDermid syndrome (PMS)	A prolonged loss of previously acquired skills that either (a) began when the individual was psychiatrically well or (b) began during a psychiatric episode, with loss of skills persisting for at least 6 months beyond the resolution of the psychiatric episode.	Onset: Onset of psychiatric symptoms occurred at a mean age of 15.4 years (range = 7 to 32). Duration: Loss of skills persisting for at least 6 months beyond the resolution of the psychiatric episode.	Retrospective	Caregiver survey based
Kolevzon *et al.* [7]		Typically, loss of skills is thought ofas a prolonged loss of skills previously acquired and the term is consistently used in conjunction with a clear history of specific skills lost for a prolonged period. The amount of time defined as “prolonged” can vary, but typically a minimum of 3 months is required.	Onset:Clinical presentations […] occurring at a mean age of 20 years. Duration: The episodes lasted for periods of weeks. […] most of the available reports do not clarify whether symptoms persisted beyond the acute psychiatric episodes.	Retrospective	Systematic review, literature-based
Philippe *et al.* [71]		Progressive loss or marked impairment of spoken language, loss of play, loss of social skills, and loss of bowel and bladder control.	Onset:Between 5 and 6 years of age.	Retrospective	Clinical based
Serret *et al.* [72]		Progressive loss of skills (verbal, motor, and autonomy) associated with catatonia features, behavioral disorders, and sleep disturbances are suggestive of "catatonia-like deterioration".	Onset:From age 13 to 15	Retrospective	Clinical based
Paganoni *et al.* [73]	SEMA3E-related syndrome	Worsening of his social, adaptive, and personal autonomy skills, cognitive regression according to scores on intelligence scales, ID, and tics.	-	Retrospective	Clinical based

Srivastava *et al.* [74]	Cornelia de Lange syndrome	This age-related “decline," starting in adolescence may reflect (1) a plateauing of skill acquisition in adolescence, creating a relative deficit in adaptive functioning relative to neurotypical controls; (2) a true regression in acquired skills; (3) the emergence offactors precipitating maladaptive behaviors such as GI reflux; (4) syndrome-specific accelerated aging affecting multiple organ systems associated with cognitive and behavioral decline; or (5) a combination of these factors.	Onset:starting in adolescence	Retrospective	Clinical/interview-based
Vermeulen *et al.* [38]	Kleefstra syndrome	Lost skills.	Onset: 18 years (case report); around 20 years (case report) Duration: 6 months (Case report); years (case report)	Prospective	Clinical based
Kernohan *et al.* [75]	PAK1-related syndrome	Behavioral problems include difficulties with transitioning and subsequently losing most of her expressive language.	Onset: age of 3	Retrospective	Clinical based
Verhoeven *et al.* [76]	HNMT-related syndrome	developmental regression: global deterioration with loss of previously acquired capacities.	Onset:global regression occurred around the age of 4 years,	Retrospective	Clinical based
Weerts *et al.* [77]	SETD1B-related syndrome	Regression of previously acquired skills.	-	Retrospective	Clinical based
Srivastava *et al.* [78]	IQSEC2-related syndrome, KCNB1-related syndrome	Regression in language and hand use.	-	Retrospective	Clinical based

Figure 3: Word Association Web

Overview of terminology used in included articles. The search terms included in the search strategy are underlined in red.Made with the online MindMeister mind map tool [21].

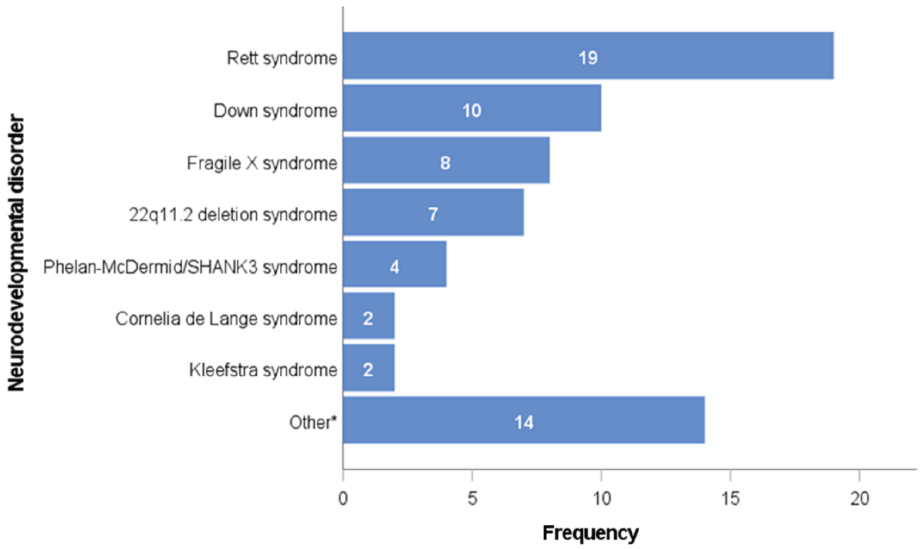

Figure 4: Study Population.

A bar chart displaying the different NDDs of genetic etiology was found. 'Other*' consists of 15q11.2 BP1-BP2 Burnside-Butler deletion syndrome, 17p13.3 duplication syndrome, 2q23 microdeletion syndrome, HNMT homozygous variant, IQSEC2, KNCB1/DEE-26, MBD5, MECP2 duplication syndrome, Mohr-Tranebjaerg syndrome/DDON, PAK1 Variant, SEMA3E syndrome, and SETD1B-related syndrome.

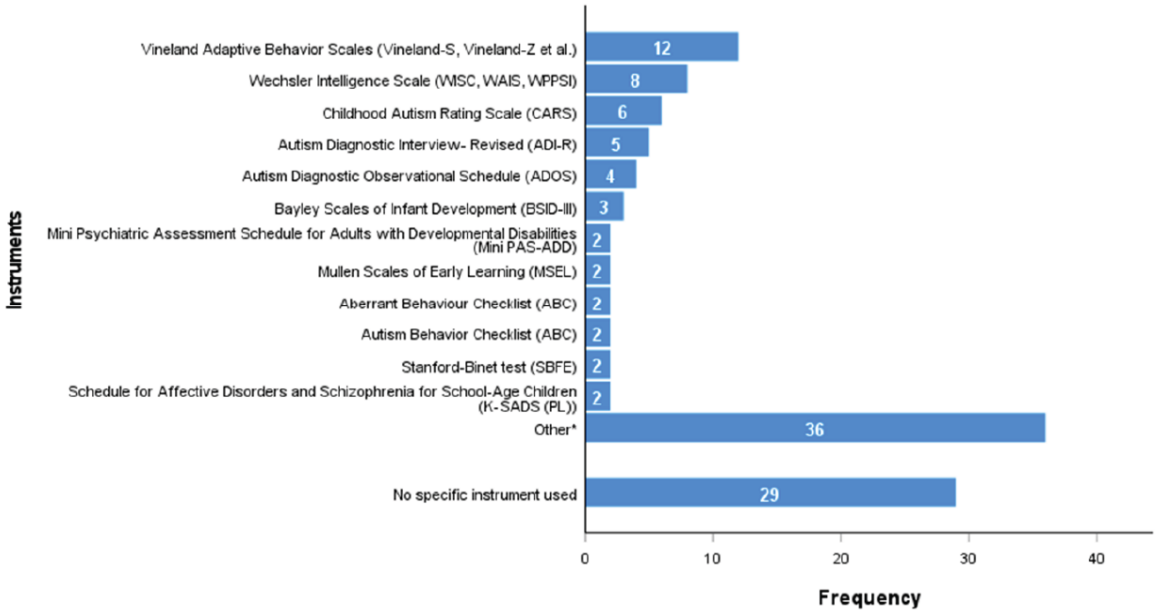

Figure 5: Instruments.

Bar chart displaying the specific instruments being used in the included studies. 'Other*' consists of: Adaptive Behavior Assessment System – II (ABAS-II), Brief Psychiatric Rating Scale (BPRS), Broad Autism Phenotype Questionnaire (BAPQ), Challenging Behavior Questionnaire (CBQ), Child Behavior Checklist (CBCL), Child Health Questionnaire (CHQ), Clinical Severity Score (CSS), Comprehensive Assessment of At-Risk Mental States (CAARMS), Continuous Performance Test (CPT), Diagnostic inventory for children and adolescents (DICA), Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV), Dutch scale for emotional development in people with intellectual disability (ESSEON-R), Dutch scale for social life skills (SRZ), Neuropsychological Assessment of Executive Functions battery for Children (ENFEN), Hayling Sentence Completion Task (HSCT), Inventory of Potential Communicative Acts (IPCA), Learning Accomplishment Profile for Infants (LAPI), MacArthur-Bates Communicative Development Inventories (ACDI), Mini-Mental State Examination (MMSE), Motor Behavioral assessment scale (MBA), Positive and Negative Syndrome Scale (PANSS), Premorbid Adjustment Scale (PAS), Psycho-Educative Profile (PEP-R), Repetitive Behavior Questionnaire (RBQ), Rett Syndrome Behaviour Questionnaire (RSBQ), Rett Syndrome Severity Scale (RSSS), Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Screen for Social Interaction (SSI), Short Sensory Profile (SSP-NL), Test of Memory and Learning (Tomal-2), the Sensorimotor Communication Profile, Uzgiris-Hunt (U-H) Scales, and one nameless self-made questionnaire.

Down syndrome (n=10), Fragile X syndrome (n=8), 22q11.2 deletion syndrome (n=7), Phelan-McDermid/SHANK3 syndrome (n=4), Cornelia de Lange syndrome (n=2), and Kleefstra syndrome (n=2) were mentioned in more than one article (Figure **4**).

In 32 (54.2%) articles, a total of 46 different instruments (including adaptive behavior scales, intelligence scales, and instruments focusing on autism spectrum traits) were mentioned. Twenty-seven (45.8%) articles did not specify an instrument (Figure **5**).

Fourteen (23.7%) articles mention therapies for regressive symptoms, ranging from treating the underlying (somatic) illness to solely treating symptoms with psychopharmaceutic agents. Efficacy of therapy was mentioned in 10 (16.9%) of the articles. A summary of the therapies mentioned and their efficacy can be found in Appendix 4—therapies.

DISCUSSION

Summary of Terms and Definitions

A large amount of literature is available concerning developmental regressive aspects in NDDs spanning several distinctive etiologies. Many articles from our initial search mentioned the loss of functioning without further specification and, therefore, were excluded from further analyses. From our systematic search, we identified 18 distinct NDDs of genetic etiology associated with developmental regression.

Several (psycho)biological factors/mechanisms are mentioned as possible explanations for the onset of regressive symptoms in the identified NDDs (see Table **1**). While some of these processes seem to be shared and common luxating factors – e.g., psychosocial stressors, epilepsy, infections, sleep disturbances, and psychotic symptoms– others seem to be syndrome-specific. For example, auto-immune thyroiditis in Down syndrome [22-24]. In addition, the age of onset of the developmental regression differs between syndromes. Developmental regression is mentioned in several developmental stages, ranging from toddler/preschool age in Rett syndrome, puberty in Kleefstra syndrome and Phelan McDermid syndrome, and adulthood in Down syndrome [2, 25, 26].

Multiple articles mention the duration of the period of developmental regression, ranging from weeks to several years. Three articles were found that mentioneda minimum duration of regressive symptoms as part of their definition used. The primary subject was either Rett syndrome or Phelan-McDermid, and the durations were a “minimum of 3 months”, “at least 6 months”, and “months to years” [2, 7, 27].

When considering the various luxating factors, the wide range of age of onset, and the minimum duration of developmental regression, we have formulated the following overarching term and definition: **“*Developmental regression*:** an absolute[1] decline of functioning in at least one of the adaptive behavior domains of practical, conceptual or social-emotional skillsin the individual, which left untreated would last at least several months.”

[1]This decline is an absolute decline within the individual, and does not refer to a decline relative to peers.

The term 'developmental regression' was chosen to distinguish it from (1) functional declines directly related to somatic substrates, (2) growth into deficit, (3) the neurodegenerative process due to dementia, and (4) the natural cognitive decline of the elderly.

The array of definitions used in the included studies all mention a certain loss of previously attained skills in one of the domains – i.e., social, communication, and practical – of adaptive behavior. In some cases, specific additions are being made to the definition of regression. In RTT, often hand stereotypies/loss of hand skills are specifically mentioned [28-36]. As some of these aspects seem syndrome-specific, we decided against including these in our definition of the trans-diagnostic regression phenomenon.

Assessment Methods

There is a large variability in the assessment methods of patients experiencing developmental regression, as we found that forty-eight different instruments were implemented across the sixty-two included articles. In the majority, it was unclear if the specific instrument had been used to objectify the (degree of) developmental regression or merely to assess the status of the patient in general. Uniformity in the application of assessment tools would bring clarity to this subject in many situations. In addition, especially when using the normative scores of certain instruments for the follow-up of patients, it is occasionally unclear if developmental regression meant that the patient lost previously acquired skills or if there was a stagnation/plateauing of development instead. It is

important to make this distinction. In the latter case, the gap in functioning is more prominent compared to age-equivalent peers when a child gets older. To avoid mistaking this 'growth into deficit' phenomenon with an actual regression in development, it is advised to only use the raw/absolute scores of the instruments [19, 37]. Taking this into account, it is not advisable to implement any of the Wechsler intelligence scales if only the IQ test scores are used to objectify the (degree of) developmental regression, as they are, by definition, based on a population of peers. Ultimately, we advise using one of the available adaptive behavior scales (e.g., the Vineland Adaptive Behavior Scales, Adaptive Behavior Assessment System) to establish and monitor developmental regression. As they are comprehensive (i.e., looking into most/all domains of development), compatible for longitudinal use and follow-up, generate absolute scores, and are already used extensively in both research and clinical settings internationally.

In times of somatic stress and/or psychological stress (e.g., a transition to the next stage of development or life (going to school, puberty, etc.)), it is important to monitor the patient for signs of developmental regression [2, 38]. Corollary, when there is evidence of a developmental regression, it is important to establish whether there is an underlying somatic or psychiatric illness that requires treatment [39, 40].

Characteristics of Developmental Regression and Tailored Treatments

We assume that different biological mechanisms are involved in developmental regression, as there are differences in luxating factors and age of onset. A broad differential diagnosis exists regarding the progressive decline of functioning in children [41]. To identify an underlying cause and to determine a subsequent treatment, characteristics of the developmental regression should be taken into account. Typically, developmental regression of primary metabolic originmay present at younger ages, often concurring with a progressive deterioration of physical functioning [9]. Developmental regression as a result of infections may occur at every age. However, individuals with a weakened or immature immune system are especially vulnerable (e.g., patients with a syndrome-specific immune deficiency, the elderly, and young children). At the same time, degenerative somatic mechanisms (such as the accumulation of beta-amyloid plaques in Alzheimer's disease) are generally present at older ages [42]. Developmental disorders like autism spectrum disorder often present at (pre)school ages, but severe mental illness with an episodic course tends to present from puberty and young adulthood. In addition, it is important to rule out any underlying epilepsy/epileptic encephalopathy, other developmental disorders, and severe mental illnesses (such as psychotic- and depressive disorders), as they can also result in developmental regression [43-45]. Besides treating any underlying condition, there is no standardized way of treating developmental regression in patients with an NDD of genetic etiology. Broadly, therapy should primarily focus on halting neurodevelopmental regression while considering the individual's needs and capacities.

Limitations

Writing a scoping review to get a clear view of what terms are used on a certain subject can be at risk of ascertainment bias. As many different terms are used interchangeably within the NDD literature that describe the seemingly same phenomenon (e.g., decline/fall of functioning, cognitive decline, (progressive) regression, deterioration), one may only find the terms that one is looking for. This not only compromises the understanding of developmental regression but also hampers searching and combining relevant literature. To get a broad perspective on terms and definitions used in literature, an initial exploratory research round was organized, after which any additional terms found were recorded and used in the secondary round of the literature search. Still, after our search was concluded, a few other articles came to light that could have been included if they had been found initially [46, 47]. These were not included in our scoping review, most probably due to the fact that we focused mainly on the cognitive aspect of the decline by terms such as cognitive decline, loss of cognitive faculties, and academic performance, without including other aspects of development. Not finding these articles underlines the importance of using uniform terminology. We understand that including these articles would not have substantially changed the conclusions or the formed definition of developmental regression in this scoping review. We addressed developmental regression inneurodevelopmental disorders of genetic etiology, while – for this being a scoping review – we did not specifically go into detail regarding underlying somatic processes contributing to the developmental regression. Any NDDs associated with neurodegeneration or of which the developmental

regression was directly proven to be related to a somatic substrate (e.g., Anti-NMDA receptor encephalitis, Mucopolysaccharidos is Type II) were excluded. However, the included literature on NDDs of genetic etiology and regression may also involve underlying somatic substrates, which may not have yet been uncovered.

Future research should focus on broadening perspectives on which other NDDs of genetic etiology are associated with developmental regression, as more knowledge in this area should speed up the process of recognizing and diagnosing developmental regression. Based on this, it is important to investigate what fundamental somatic or psychological substrates underlie these regressive states to arrive at possible prevention- and therapeutic strategies. Future studies may also bring more detailed knowledge on the differences and similarities between NDDs of genetic etiology that are associated with developmental regression.

CONCLUSIONS

To our knowledge, this is the first scoping review aiming to define the regressive phenomenon in NDDs of genetic etiology. Although the definition of developmental regression was established based on the aforementioned NDDs, it was formulated with the intention of creating uniformity and clarity in broader fields of NDD research and patient care. Therefore, it is possible – and even recommended – to apply this terminology to other NDDs and similar research fields.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Radboud University Medical Center (protocol code NL65650.091.18, date of approval: March 8 2019).

Consent to Participate is not applicable.

APPROVAL FOR PUBLICATION

All authors approve the publication of this manuscript.

AVAILABILITY OF DATA AND MATERIALS

After publication of the article, the study data will be available from the authors upon request.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

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VI APPENDICES

Appendix 1: Search Strategy Pubmed

Appendix 1: Search strategy PubMed. Displays all the terms that were used to search the PubMed database

Search strategy	Initial search query	Total results
#1	((disability, intellectual[MeSH Terms] OR developmental disabilities[MeSH Terms])) AND (regression psychology[MeSH Terms]) Filter: Full Text	52
#2	(loss of skills[Title/Abstract]) AND (definition[Title/Abstract])Filter: Full Text	4
Search strategy	Search query (14-06-22)	Total results
#1	("Developmental Disabilities"[Mesh]) OR "Intellectual Disability"[Mesh]	120.737
#2	(decline) AND (functi*) Filter: full text	95.705
#3	#1 AND #2	389
#4	(regressi*) AND (functi*) Filter: full text	143.601
#5	#1 AND #4	732

#6	(loss) AND (skills) Filter: fill text	7059
#7	#1 AND #6	256
#8	(Deterioration) AND ((skills) OR (functi*)) Filter: full text	43.546
#9	#8 AND #1	256
#10	(Degeneration) AND ((skills) OR (functi*)) Filter: full text	45.053
#11	#10 AND #1	236
#12	(decline) AND (adaptive behavior) Filter: full text	2402
#13	#12 AND #1	77
Search strategy	Search query (01-11-22)	
#14	(neurodegen*) AND (regressi*) Filter: full text	4220
#15	#14 AND #1	64
#16	("Intellectual Disability/genetics"[MeSH] AND ((behavi*) AND (regressi*)) AND#1) NOT motor[tw]	71

APPENDIX 2: SEARCH STRATEGY MEDRXHIV AND GOOGLE SCHOLAR

Appendix 2: Search strategy medRxhiv and Google Scholar. Displays all the terms that were used to search the med Rxhiv and Google Scholar databases on October 4, 2022

	Hits	
Initial search query	**medRxiv**	**Google Scholar (all-in title)**
for abstract or title "regression neurodevelopmental disorders" (match all words)	11	N/A
Allintitle: "neurodevelopmental disorder" AND regression OR psychosis -schizophrenia	N/A	9
Search query 4 October 2022		
Developmental Disability Regression	7	3
Developmental Disability skill loss	0	0
Developmental Disability skill decline	0	0
Developmental Disability skill deterioration	0	0
Developmental Disability skill degeneration	0	0
Developmental Disability function loss	8	2
Developmental Disability function decline	0	0
Developmental Disability function deterioration	0	0
Developmental Disability function degeneration	0	0
Developmental Disability adaptive behavior loss	0	0
Developmental Disability adaptive behavior decline	0	0
Developmental Disability adaptive behavior deterioration	0	0
Developmental Disability adaptive behavior degeneration	0	0
Intellectual Disability Regression	9	11
Intellectual Disability skill loss	0	0
Intellectual Disability skill decline	0	0
Intellectual Disability skill deterioration	0	0
Intellectual Disability skill degeneration	0	0
Intellectual Disability function loss	9	0
Intellectual Disability function decline	0	0
Intellectual Disability function deterioration	0	0

Intellectual Disability function degeneration	0	0
Intellectual Disability adaptive behavior loss	0	0
Intellectual Disability adaptive behavior decline	0	0
Intellectual Disability adaptive behavior deterioration	0	0
Intellectual Disability adaptive behavior degeneration	0	0
Neurodevelopmental disorder Regression	12	3
Neurodevelopmental disorder skill loss	0	0
Neurodevelopmental disorder skill decline	0	0
Neurodevelopmental disorder skill deterioration	0	0
Neurodevelopmental disorder skill degeneration	0	0
Neurodevelopmental disorder function loss	10	0
Neurodevelopmental disorder function decline	0	0
Neurodevelopmental disorder function deterioration	0	0
Neurodevelopmental disorder function degeneration	0	0
Neurodevelopmental disorder adaptive behavior loss	0	0
Neurodevelopmental disorder adaptive behavior decline	0	0
Neurodevelopmental disorder adaptive behavior deterioration	0	0
Neurodevelopmental disorder adaptive behavior degeneration	0	0

APPENDIX 3: CAUSES

Appendix 3: Causes: Explanation/hypothesis for cause of regression mentioned in the included articles. Keywords are in bold

Article	NDD(s)/Study population	Explanation/hypothesis for the cause of regression?
Glaze *et al.* [50]	Rett syndrome	Abnormalities in synapse maintenance and modulation may contribute to regression in RTT and autism. [..] A similar mechanism involving MeCP2 regulation and expression may contribute to regression.
LeBlanc *et al.* [31]		The regression is accompanied by the onset of epilepsy and intellectual disabilities, reflecting excitatory-inhibitory imbalance within specific brain microcircuits.
Lee *et al.* [32]		The specific genetic mutation variant is the cause of variability between the age of onset, severity, and signs.
Nomura *et al.* [29]		The precise pathomechanism of the regression is not known.
Peters *et al.* [53]		Developmental regression is likely to coincide with the onset of epilepsy in MDS, and both are increasingly likely as participants age.
Pohodich *et al.* [36]		The developmental regression observed in patients with Rett syndrome arises from altered neuronal function and is not the result of neurodegeneration.
Sigafoos *et al.* [54]		The cause or causes of developmental regression in individuals with developmental disabilities often remain elusive, but with CDD/ASD, LKS, and RTT, it most likely has a genetic/neurological basis. However, a range of other factors, such as illness, head injury, stressful events (e.g., death in the family), or even major changes to one's daily routine, have been implicated as possible triggers for developmental regression. Environmental factors, such as early deprivation, institutionalization, and poor quality intervention/education, might also lead to developmental regression.
Castillo *et al.* [55]	Down syndrome	This delayed onset of regression may partially be explained by the overall developmental delay inherent with a diagnosis of Down syndrome.[…] The underlying developmental trajectory of the brain is also important in determining the onset of the regressive episode.
Fox *et al.* [56]		Medical examinations revealed no physical basis for the weight loss or general regressive trend.
Lyons *et al.* [22]		Differential diagnoses for young people with DS exhibiting developmental regression include systemic illness (e.g., autoimmune thyroiditis, sleep apnoea, pain), depression, psychosis, seizures, autism spectrum disorder (ASD), or other rare neuro-metabolic disorders.

Rosso *et al.* [25]		1. Immune dysregulation: The demographic profile of DSDD includes a postpubertal onset and an elevated female/male patient ratio of 2:1 in the 2 largest studies to date. This finding has raised the suspicion that inflammation may play a role in the etiology of DSDD because this demographic is mirrored in other inflammatory disorders such as multiple sclerosis and autoimmune encephalitis. // 2. Psychological stress: In their studies, Stein et al. and Mircher et al. postulated that such behavioral changes may be a way for persons with DS to express distress in the context of their developmental delays.
Stein *et al.* [59]		[...] decreases in motivation and performance were noted with a reaction to stress and multiple environmental changes as a potential causative factor. Psychiatry consultation supported this finding in that psychosocial stress temporally correlated with the patient's regression in skills.
Walpert *et al.* [60]		IRDS may be best considered as a condition triggered by stress and occurring in people with DS who have some additional genetic or acquired vulnerability (low resilience). Alternatively, IRDS is due to the occurrence of an acquired condition that results in a direct and initially adaptive response in the brain to the insult and subsequently in a temporary and adverse effect on brain function. For example, an acquired insult may lead to the development of an inflammatory response in the brain, resulting in an encephalopathy that subsequently completely or partially resolves. Triggers: Transitions, Life events, stressors.
Worley *et al.* [23]		Down syndrome disintegrative disorder was associated with thyroid autoimmunity. The prevalence of thyroperoxidase seropositivity was significantly greater in cases than in controls from our Down Syndrome Bio-Bank. A possible differential diagnosis: Alzheimer's, depression, new-onset catatonia.
Fisch *et al.* [61]	Fragile X syndrome	Defect in central nervous system development.
Fisch *et al.* [62]		Developmental deficiency in the central nervous system.
Maltman *et al.* [65]		We observed that a subset of this group, those with higher CGGs (>100 repeats) and older age (>58), exhibited declines in verbal inhibition within a threeyear period.
Warren *et al.* [66]		The underlying reasons for declines in adaptive behavior in children with FXS, as reported in several other studies, have been a mystery beyond having some relationship to autism symptoms and cognition. However, our findings suggest that parenting may play an important role in this developmental process.
Biswas *et al.* [67]	22q11.2 deletion syndrome	Neuroanatomical differences // disturbed neurotransmitter function // cognitive difficulties.
Davies *et al.* [68]		We observed a novel and significant association between VIQ decline and PS_SZ, but not PS_IQ, suggesting that common risk variants for schizophrenia contribute to cognitive decline, whereas common variants associated with cognitive ability might not. [...] Schizophrenia polygenic score was also significantly associated with cognitive (verbal IQ) decline and nominally associated with sub-threshold psychosis.
Yuen *et al.* [79]		[..] One potential predictor of psychotic illness in children with 22q11.2DS may be a decline in social and/or academic functioning between childhood and early adolescence, regardless of functioning at baseline.
Kohlenberg *et al.* [2]	Phelan-McDermid syndrome (PMS)	Several triggers were often reported as temporal antecedents to the onset of psychiatric changes. Biological: infections and changes in hormonal status // Environmental factors: stressful life events.
Kolevzon *et al.* [7]		Neuropsychiatric disorders such as bipolar disorder, catatonia, and psychosis may emerge with a loss of skills but most of the available reports do not clarify whether symptoms persisted beyond the acute psychiatric episodes.
Philippe *et al.* [71]		Our case report confirms that regression may be part of the clinical phenotype and is perhaps a hallmark symptom of SHANK3 haploinsufficiency, particularly in cases with a partial deletion or a single mutation.
Serret *et al.* [72]		Described in ASD patients after a stressful event.
Paganoni *et al.* [73]	SEMA3E-related syndrome	Given the conserved expression pattern of SEMA3E and PLXND1 in mouse and human embryonic brains and our in vitro and ex vivo experiments confirming a loss-of-function effect of the human mutation, it is plausible to hypothesize that the clinical neurological features of our patient might be due at least in part, to a defective SEMA3E signaling during embryonic brain development.
Vermeulen *et al.* [38]	Kleefstra syndrome	Severe sleep disturbances, during or post-puberty, may precede severe psychiatric disturbances and loss of functioning. //Adolescence is a critical period in the development of major psychiatric diseases.
Kernohan *et al.* [75]	PAK1-related syndrome	There were no triggering events associated with the onset of regression.
Srivastava *et al.* [78]	IQSEC2-related syndrome, KCNB1-related syndrome	Neurological impairment.

APPENDIX 4: THERAPIES

Appendix 4: Therapies: Table with therapies mentioned/efficacy of therapy. Key components are highlighted in bold

Article	NDD(s)/Study population	Therapies used/mentioned	Efficacy of therapy
Fox *et al.* [56]	Down Syndrome	Treatment program // Occupational therapy: to provide attention only contingent upon K. demonstrating appropriate behavior.	Treatment program: In addition to weight gain and increased eating rate, a number of other improvements were observed. Pants wetting decreased to once a week and then stopped entirely. Her expressive speech increased and expanded to all situations. Spontaneous bursts of laughter and generally increased activity levels were also noted. // Occupational therapy: K. responded quickly to this new contingency, and her behavior continued to show improvement, but only within the therapy sessions where the contingency was in effect.
Worley *et al.* [23]		No medication or combination of medications was consistently effective, but risperidone, fluoxetine, sertraline, trazodone, donepezil, and rivastigmine each helped at least 1 patient.	
Stein *et al.* [59]		Multimodal approach: anti-depressant medication, continuous positive airway pressure (CPAP) for OSA, increased psychosocial support, school initiatedchange in classroom placement.	Steadily improvement and returned to baseline function.
Rosso *et al.* [25]		1. Antipsychotics (e.g., risperidone) // 2. SSRIs (e.g., fluoxetine and sertraline) // 3. Anticholinergic drugs (eg donepezil and rivastigmine) // 4. Benzodiazepines (eg lorazepam) // 5. ECT // 6. Immunotherapeutic regimes (intravenous and/or oral steroids, mycophenolate mofetil, intravenous immunoglobulins, and rituximab)	Ad 1. 70% of patients experienced at least some improvement in motor symptoms, sleep disturbance, and catatonia // Ad 2. Seemed to improve mood symptoms, motor symptoms, and sleep disturbance // Ad 3. Case study of a 14-year-old boy who was treated with donepezil, which led to a complete psychosocial recovery; however, the efficacy of cholinergic medications for cognitive impairment in individuals with DS is debatable // Ad 4. 91% of patients with DSDD and catatonia demonstrated at least a partial response // Ad 5. Effective therapy for DSDD with catatonia, however, more risk of complications // Ad 6. Therapy should be chosen based on presumed etiology and clinical improvement.
Walpert *et al.* [60]		1. Anti-depressants (including clomipramine, bupropion, trazodone, fluvoxamine, desipramine, amitriptyline, nortriptyline, and citalopram) were the most commonly administered drug type. 2. Anti-anxiety drugs (mexazolam, bromazepam, benzodiazepines, lorazepam). 3. Clomipramine. 4. ECT and immunotherapy. 5. Anti-psychotic medications (clozapine, levomepromazine, haloperidol, olanzapine, aripiprazole, ziprasidone and thiothixene).	Ad 1.The effects of which were almost equal between a positive, negative and no response. Ad 2. Similar numbers of positive and negative respondents were seen.Ad 3. Positive response in all people with DS it was given to. Ad 4. Mostly positive outcomes, with all patients exhibiting a positive response, although in each treatment the numbers were small (10 and 5 cases, respectively) Ad 5. More positive responders than negative or no response.
Kohlenberg *et al.* [2]	Phelan-McDermid syndrome (PMS)	Benzodiazepines were used either regularly or on an as-needed basis in 16 of 38 cases (42%). Alpha agonists, beta-blockers, antihistamines, and trazodone were prescribed for sleep or aggression. Selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants, buspirone, lithium, cannabinoid oil, or n-acetylcysteine.	-
Philippe *et al.* [71]		Risperidone 1mg/day, later cyamemazine 10mg/day, both discontinued // Omeprazole after diagnosis of GER	Risperidone and cyamemazine showed no effect // After the introduction of omeprazole, the induced vomiting,

			merycism, and pica improved. However, the agitation was still very great, and the regression in language and autonomy were persistent // The agitation, eating disorders, and sleep problems were stabilized with the continuation of a treatment associated with risperidone (2mg), cyamemazine (25mg), carbamazepine (200mg), and omeprazole (10mg). However, her imitation and shared attention skills remained very limited.
Serret *et al.* [72]		1. Different pharmacological treatments (antipsychotics, benzodiazepines, mood stabilizer drugs, anti-depressants, and methylphenidate) // 2. Lithium therapy.	Ad 1. Failed to improve clinical symptoms and lead to multiple adverse events // Ad 2. Reversed clinical regression, stabilized behavioral symptoms, and allowed patients to recover their pre-catatonia level of functioning without significant side effects.
Kim *et al.* [30]	Rett syndrome	Valproate (10/14, 71.4%) and lamotrigine (6/14, 42.8%) were most frequently used in our patients. Carbamazepine, commonly used in Rett syndrome in other studies, was not used for this population. Oxcarbazepine and topiramate were each used in three patients. Two patients were placed on a ketogenic diet after unsuccessful multiple AED treatments, and one of them became seizure-free.	-
Lee *et al.* [32]		Strategies involving less physical contact, such as playing a DVD or music.	Effective in calming the distressed child.
Garber *et al.* [26]		Physical therapy, occupational therapy, speech-language therapy, music therapy.	Music therapy seemed to be the area in which K performed optimally. She would vocalize for the cessation of music, probably a conditioned response to years of language therapy. According to her music therapist and by observation, K increased her visual attention and acted in causal ways on musical instruments (e.g., shook bell, hit drum). //Finally, it is noted that despite the amount and variety of treatment K received for years, she did not show significant improvements.
Neul *et al.* [35]		Currently, treatment for RTT is based entirely on treating symptoms, such as treating epilepsy with anti-seizure drugs or treating constipation with laxatives. The discovery of reversibility in the mouse model of RTT has developed a strong impetus to explore treatment options directed to modify or even reverse the disease. One major focus of disease-modifying treatments is based on genetic experiments demonstrating that increasing levels of brain-derived neurotrophic factor (BDNF) improves symptoms and longevity in mice. This led to successful treatment of Rett mice with drugs that increase BDNF levels or activate a BDNF receptor.	
Engebretsen *et al.* [69]	22q11.2 Deletion Syndrome	Metyrosine, milieu therapy.	PANNS scores improved on 3 sub-scales. […] It was evident that metyrosine reduced mood cycling, psychotic symptoms, and aggressive outbursts, thus making the patient accessible to psychosocial interventions, mostly milieu therapy.
Farrell *et al.* [80]	15q11.2 BP1-BP2 Burnside-Butler deletion syndrome	Prior to age 18, she had been treated with haloperidol, fluphenazine, thioridazine, thiothixene, trifluoperazine, chlorpromazine, mesoridazine, and loxapine. // Adult: clozapine, 3 other atypicalantipsychotics, multiple typical antipsychotics, lithium, 4 anticonvulsants, 5 anti-depressants, and multiple anxiolytics // trial of a stimulant // Oral contraceptive // Behavioural interventions // Magnesium supplements	Clozapinehad little to no clinical benefit. // Trial of a stimulant: led to improved attention. // Oral contraceptive reduced irritability and anxiety.

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