Deconstructing Dravet syndrome neurocognitive development : a scoping review

Framing Dravet syndrome neurocognitive development: a scoping review

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Abstract

Dravet syndrome is a rare severe epilepsy syndrome associated with slowing of psychomotor development and behavioral disorders from the second year onwards in an apparently normal child.

Among cognitive impairments, visuo-spatial, sensorimotor integration and expressive language deficits, are consistently described. Although many authors independently suggested hypotheses to frame Dravet cognitive atypical development (dorsal stream vulnerability impairment, cerebellar-like pattern, sensorimotor integration deficit) a unified theoretical framework is still lacking.

We performed a scoping review of literature to map the state of the art on Dravet syndrome cognitive and behavioral developmental profile and summarize evidence on the main suggested theoretical frameworks.

An online databases search was carried out on PubMed, Scopus, PsycInfo and MEDLINE to identify papers focusing on cognitive deficits and/or behavioral abnormalities in Dravet syndrome published between 1978 and 15th March 2020. The Preferred-Reporting-Items-for-Systematic-Reviews-and-Meta-Analyses extension for scoping review (PRISMA-ScR) guidelines were followed. Twenty-one papers were selected and charted by three independent reviewers based on predefined data extraction and eligibility forms.

Eighteen studies assessed global intelligence quotients reporting variable degree of cognitive impairment. Eleven of these, analyzed single subitems contribution to global cognitive scores, revealing consistent higher impairment in performance scales compared to verbal ones. Studies assessing specific cognitive functions showed deterioration of early visual processing, fine and gross motor abilities, visuomotor and auditory-motor integration, spatial processing, visuo-attentive abilities, executive functions, and expressive language.

Behavioral abnormalities, assessed in 14 studies, underline a prevalence of autistic-like traits, attention and hyperactivity disorders, slightly improving with age.

The cognitive profile in DS, as well as some of the behavioral and motor abnormalities, may be enclosed within a unified theoretical framework of the three main hypotheses proposed in literature: a pervasive sensorimotor integration deficit, encompassing an occipito-parieto-frontal circuit (dorsal stream) dysfunction and a cerebellar coexistent deficit.

Keywords

Dravet syndrome; cognitive development; sensorimotor integration; dorsal stream; cerebellar impairment

Key Points

- DS is a complex developmental encephalopathy characterized among the other symptoms by cognitive stagnation and behavioral disorders
- A comprehensive theoretical framework helping understanding DS cognitive/behavioral picture to guide future research is still lacking
- A sensorimotor-integration impairment encompassing a visuo-dorsal-stream dysfunction and a coexistent cerebellar deficit can explain DS cognitive outcomes
- Future research should deeply inquire these aspects and disentangle their relative contribution to the disease

INTRODUCTION

Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy (SMEI), is a complex and rare developmental encephalopathy, with an estimated prevalence between 1/15.000 and 1/40.000 [1,2], first described by Charlotte Dravet in 1978 [3]. According to the International League against Epilepsy (ILAE) classification [4] Dravet syndrome manifests with drug resistant "febrile and afebrile generalized and unilateral, clonic or tonic–clonic seizures, that occur in the first year of life in an otherwise apparently normal infant" [5], later on associated with myoclonic and absence seizures and occurrence of epileptic status. Based on seizure semiology, two forms have currently been recognized: the typical SMEI and the borderline form (SMEIB), characterized by lack of myoclonic seizures and atypical absences [6].

At least 80% of subjects carry familial or de novo mutations of the sodium channel α1 subunit (SCN1A) gene [7].

From the second year of life, cognitive stagnation, associated with neurological signs and behavioral disorders, become evident, leading to a progressive pervasive developmental delay [8].

Many neuropsychological phenotypes are reported, ranging from mild specific deficits to extremely severe global impairment. Visual impairments and visuo-motor deficits in DS usually manifest precociously and anticipate higher order cognitive developmental abnormalities, such as visuo-constructive abilities, attention, language production and executive functions, in contrast with a better preservation of visual object recognition, memory and language comprehension [8–10] in line with a dorsal-ventral cognitive dissociation.

Behavioral disorders are common and often characterized by hyperactivity, attention deficits, autistic traits, as well as aggressiveness and opposition [11].

The pathophysiology underlying such a wide spectrum of neuropsychological features is not fully understood. Three main theoretical frameworks are independently assumed by authors to explain DS cognitive and behavioral profile: the dorsal stream vulnerability hypothesis [12] the cerebellar-like pattern [13] and the sensorimotor integration deficit [14,15].

According to DS dorsal stream vulnerability hypothesis, based on the cognitive dual stream hypothesis [16], an initial manifestation of visual deficits precedes the decline of visuo-motor dorsal pathway skills, which are more selectively and severely involved than ventral stream functions. The asymmetric involvement of the so called visual "dorsal pathway" functions, opposed to the "ventral" ones, is consistently reported in literature [8,12,15]. The dorsal pathway encompasses visually guided behaviors (fine and gross motor abilities), visual motion processing, sensorimotor integration functions, spatial coding and visual-attentive processes while ventral pathway is associated with object recognition, memory

functions and language comprehension abilites[16]. A similar asymmetry in the two cognitive pathways involvement was reported in other genetic syndromes (Williams, Prader Willi, fragile-X), leading to the concept of genetic involvement as crucial in the cognitive pattern besides the epilepsy [8,12]. A recent study found indeed an high degree of expression of some genes, including SCN1A, along the brain's visuo-motor integration network, connecting its malfunctioning with the genetic mutations [17].

The cerebellar-like pattern hypothesis has also been suggested to link the cognitive impairments and the genetic SCN1A mutations. Experimental studies on DS mice models showed decreased excitability of inhibitory cerebellar Purkinje neurons likely to explain many of the motor and cognitive deficits observed [13,18]: ataxia, poor motor coordination, impairment of executive functions, spatial cognition, language and autistic-like behaviors. [19]

Lastly, the sensorimotor integration hypothesis refers to the complex process at central nervous system level, which allows to accomplish specific motor responses based on the integration of multiple sources of sensory information [20].
These integrative processes, especially visuo-motor and auditory-motor integrations, are frequently impaired in DS, suggesting the sensorimotor integration deficit as a likely theoretical framework. According to this model, an integration deficit can explain the observed visuo-motor and visuo-constructive impairments as well as the productive language dysfunctions consequent an auditory-motor deficit [13–15]. Gait and postural abnormalities are interpreted as the result of abnormal proprioceptive and vestibular integration [15], while behavioral abnormalities are associated with precocious visuo-motor integration deficits limiting social learning abilities and communication efficacy [21,22].

The principal aim of this scoping review is to summarize literature' cognitive and behavioral findings on DS to collate evidences in favor or against the three main suggested rationales and propose a unified theoretical framework. Future researches, as well as clinical practice, could benefit from this understanding to design new effective rehabilitative approaches.
Toward this aim, the following research question was formulated: *What are the evidences in favor or against the main hypotheses to frame Dravet syndrome neurocognitive developmental phenotype?*

METHOD

We adopted the PRISMA-ScR checklist for Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews [23]. After data extraction and in light of the extreme heterogeneity of the assessed cognitive domains and neuropsychological test, we opted for a scoping review [24,25].

Eligibility Criteria

Inclusion criteria were: be full length papers, peer-reviewed, original research articles, written in English, and published between 1978, year of the first publication on Dravet syndrome [3] and March 15th 2020. Included papers involved human participants, meeting the ILAE diagnostic criteria for Dravet syndrome [4] and assessed behavioral disorders or at least one of the following cognitive functions: visual processing, phonological processing, visuo-motor processing, visuo-spatial abilities, visuo-attentive abilities, working memory, executive functions, language, measures of general development and/or intelligent quotients. Cognitive evaluations needed to be carried out by mean of standardized neuropsychological tests.
Single case studies, animal studies, and papers not meeting the inclusion criteria were excluded.
(See Appendix 1).

Information Sources

A systematic literature search on Dravet syndrome neuropsychological characterization was conducted by the first reviewer (MB). The electronic databases Scopus, PubMed, PsycInfo and MEDLINE, were consulted by adapting the following key words to better meet each database searching features: Dravet syndrome, severe myoclonic epilepsy in infancy, cognition, neuropsychology, neuropsychological phenotypes, autistic features, autism spectrum disorder. Detail search queries for PubMed are reported in **Appendix 1**.

The electronic database search was supplemented by screening

reference lists of each retrieved paper and scanning relevant reviews. Final search results were exported into MENDELEY bibliographic software package to keep track of the articles and apply deduplication procedure.

Selection of Sources of Evidence

To increase consistency in paper selection, three reviewers (MB, AH, KV) independently evaluated the identified articles. A fourth reviewer (ADF) revised papers in case of disagreement on data extraction and inclusion. A first screening based on titles and abstracts led to the identification of 36 papers, which underwent full text examination.

Of these, 15 were excluded for the following reasons: three were not full-lengths original research articles (editorials and internal progress reports); 7 were reviews that we used for screening potentially missing papers of interest; 2 didn't assess any of the outcomes of interest; 3 didn't utilize standardized neuropsychological assessment tools. See **Figure 1** for full selection procedure process.

Data Charting Process and Data Items

Reviewers jointly designed an *ad hoc* data charting form covering all relevant variables to answer research question by adapting the one proposed in Cochrane handbook for systematic review [26] (see **Appendix 1**).

The extraction form comprised a first part devoted to the identification of general article information and organizational aspects of the review: reviewer identity, date of reviewing, title of the paper, first author's name, publication year, country of origin, journal, publication type and a short article description.

The second part includes eligibility criteria and reasons for exclusion. Articles were selected as eligible based on type of publication, sample characteristics, assessment method, and outcomes of interest.

Eligible papers were eventually charted by extracting the variables of interest: sample characteristics (e.g., sample size, age of participants, diagnostic criteria, treatments), type of study design (e.g., longitudinal, cross-sectional, etc) cognitive domains assessed and assessment procedures (specific neuropsychological tests, test batteries, questionnaires, etc).

Cognitive and behavioral data were eventually summarized and discussed in light of the three hypotheses.

RESULTS

Synthesis of the results

Outcomes were grouped according to cognitive domain assessed : general intellectual/developmental quotient; lower order cognitive functions (visual processing, phonological processing, fine and gross motor functions); sensory-motor integration (visuo-motor and auditory-motor integration); higher order cognitive functions (visuospatial abilities, language comprehension, attention, executive functions), and behavioral outcomes. For each domain, we reported the assessment method and the main findings.

Study characteristics

Studies included were heterogeneous in terms of study design (7 cross-sectional, 3 longitudinal retrospective studies, 10 longitudinal prospective studies and 1 family cohort study), participants age (≥6 months- 60 years), cognitive assessment tools, and assessed domains (See table 1).

Table 1.

Assessed cognitive and behavioral domains and assessment tools

Cognitive Domains	N° studies	Assessment tools
Intellectual/Developmental quotient	17	Wechsler intelligence scales (WISC III; WISC IV; WISC-R; WPPSI; WAIS) [27–29] Griffiths mental developmental scales (GMDS) [30] Brunet-Lézine Developmental Scale (BL) [31] Raven's Colored Progressive Matrices (RCPM) [32] Bayley scales of infant and toddler (II and III editions) [33] Psychoeducational profile (PEP-3) [34] McCarthy Scales of Children's abilities (MSCA) [35] Gesell Developmental Schedules (GDS)[36]
Visual processing	6	Developmental Test of Visual perception (DTVP) [37] Fixation shift test [38] TNO random dots Stereogram Test [39] Teller acuity card procedure [40] Cambridge crowding cards [38] Form and motion coherence tests [38] Shape matching [38] Embedded figures [38] Frostig cats' silhouette task [38] Harris Test of lateral dominance [41]
Phonological processing	2	Same-different judgement paradigm [42] Phonological and morphosyntactic accuracy test [43]
Gross/Fine motor abilities	2	Movement ABC test [44] Peabody Developmental Motor Scales [45] Motor subscale of the Bayley Scales of Infant and toddler Development (III) [33] The Bruininks-Oseretsky Test of Motor Proficiency (BOT) [46] Harris Test of lateral dominance [41] Semi-quantitative psychomotor score (SQPS)[47] Early motor control scales [48]
Visuomotor integration	10	Motor tapping task [14] The Beery-Buktenica Developmental Test of Visual-Motor Integration [49] Trail-Making Test (TMT-A) [50]
Auditory-motor integration (language production)	9	Verbal language test (VLT) [51] Boston naming test [52] Batteria per l'analisi dei Deficit Afasici (BADA) [53] French scale for language (Épreuves pours l'examen du langage) [54] First Language test [43] Semi-quantitative psychomotor score (SQPS) [47] Dysarthria rating scale [55] Diagnostic Evaluation of Articulation and Phonology [56] Test for reception of grammar [57] Expressive vocabulary test [58]
Visuospatial abilities	5	Corsi Test [59] Trail-Making Test (TMT-A) [50] Block design [59] Rey Osterrieth Complex Figure copy [60]
Language comprehension	10	Verbal language test (VLT) [51] Peabody Picture Vocabulary Test – Revised (PPVT-R)[61] Batteria per l'analisi dei Deficit Afasici (BADA) [53] French scale for language (Épreuves pours l'examen du langage) [54] First Language test [43] Conversational speech sample [62]
Attention	5	Bell's Cancelation Test – Revised (BVN 5-11) [59] Teddy bear cancellation test [63]
Working memory	4	Phonological working memory task [64]

		Visual memory task [65] Semantic unrelated list [66] Digit span (from WPPSI/ WISC) [27,29]
Executive functions	4	Inhibition task [67] Category-to-sample match paradigm [42] Tower of London [68] Porteus Maze test (from WPPSI/ WISC) [27,29] Trail-Making Test (TMT-B) [50]
Behaviour and Autism traits	14	Pervasive developmental disorder in mental retardation (AVZ-R) [69] Maladaptive behavior scale for institutionalized individuals with ID (SGZ)[70] Temperamental scale for individuals with ID (TVZ) [71] Achenbach Child Behavior Checklist (CBCL)[72] Autism Behavior Checklist (ABC)[73] Childhood Autism Rating Scale (CARS) [74] The Autism Diagnostic Observation Schedule (ADOS) [75] the Autism Diagnostic Interview (ADI) [76] Diagnostic Interview for Social and Communication Disorders (DISCO) [77] Conners' Rating scale (CRS) [78] Vineland Adaptive Behavior Scales, Second Edition (VABS- II)[79]

Global cognitive assessment

General intellectual/developmental quotients were assessed in 18 out of 21 studies.

The following scales were used: Wechsler intelligent scales, adapted to the age at testing (13 studies); Griffiths' mental scales (9 studies); Brunét-Lezine (BL) Developmental Scale (4 studies); Gesell Developmental Scales (1 study,[80]); McCarthy Scales of Children's abilities (1 study, [81]); Psychoeducational Profile, Third Edition (PEP- 3) (1 study,[82]). In two studies Raven's Colored Progressive Matrices were used as an alternative measure to test intelligence, when children were hardly collaborative [83,84].

All the 17 studies report variable degree of developmental delay/intellectual disability ranging from low average intellectual quotient to profound intellectual disability (see Table S1). In the study which report them, test's subitems analysis revealed greater contribution of the performance intellectual quotient (PIQ), compared to the verbal intellectual quotient (VIQ) in determining the global intellectual disability. Particularly, 11 out of 18 papers highlight severe impairment in visual, fine motor, gross motor, visuo-motor, visuospatial and receptive language functions. The remaining 7 studies don't clearly report single subitems scores.

Of 7 studies inquiring the relation between epilepsy features (semeiology and frequency of seizures) and intellectual disability, 3 highlighted the relation between myoclonic and/or absence seizures with a worse cognitive outcome [47,83,85]. Two studies found correlation between higher seizure frequency and worse cognitive outcome [10,86] whereas 2 did not found any clear association [12,87].

Two studies examining the relation between autism and IQ found significantly higher proportion of profound intellectual disability in those children additionally diagnosed with autism [80,82].

Behavioral assessment

Behavioral abnormalities have been evaluated in 14 out of 21 studies with the following scales:

Achenbach Child Behavior Checklist (8 studies); Vineland Adaptive behavioral scale (5 studies); Autism Diagnostic Interview (ADI) (2 studies); The Autism Diagnostic Observation Schedule (ADOS) (2 studies); Conner's Comprehensive Behavior Rating Scale (CBRS), Pervasive developmental disorder in mental retardation scale- revised (AVZ-R), Maladaptive behavior scale for individuals with ID (SGZ), Temperamental scale for individuals with ID (TVZ), Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), and Diagnostic Interview for Social and Communication Disorders (DISCO) in 1 study (see Table S2).

Among the 14 papers, 7 reported autistic-like traits, 6 attention deficits and 6 hyperactivity disorders. Externalizing behaviors, especially hyperactivity, impulsivity and aggressiveness are more often observed than internalizing behaviors

(anxiety, depressive-traits and overcontrolled behaviors), with the exceptions of two studies finding the opposite pattern [13,85].

Two studies reporting the longitudianl evolution of behvioral abnoramlities found a gradual decrese in behavioral disorders from adolescence to adulthood [83] and from the first evaluations (mean age: 21.7 months) to the last follow up (mean age: 6 years and 6 months) [87], especially releated to hyperactivity traits.

Three studies investigating comorbidity between DS and autism spectrum disorder (ASD) found resepectively 23.3%, 39.3% and 61.5% of people with DS additionaly diagnosed with ASD [80,82,88]. Other 8 studies reported the presence of pervasive autistic-like traits comprising poor eye contact, ritualistic behaviors, narrow interests, speech delay, adherence to routine and poor ability to express emotions. However, in some of these studies, authors underline a relative preservation of socialization capacity and excessive familiarity with strangers, which contrasts with the typical autistic pattern [9,88].

Specific cognitive functions assessment

1. Low level cognitive functions: (visual processing; phonological processing; gross/fine motor abilities)

Seven papers out of 21 clearly report evaluations of visual processing (4 studies), phonological processing (2 studies) and fine/gross motor abilities (2 studies) (see Table S3).

Two of the 4 papers assessing visual processing abilities highlight variable degrees of impairment in different sub-scores tested, ranging from abnormal to normal scores [12,89]. The other 2 report general pervasive visual perceptual impairment in all the assessed children [13,87].

Two studies examining phonological processing abilities underline impairments in both phonological perception and detection, specifically: near chance correctness (54%) in a same-different judgement paradigm, persistent with age, in contrast with 100% correctness of healthy age-matched controls [14] and abnormal scores in the phonological accuracy subitem of the First Language Testa (TPL) (5 out of 10 evaluated children, mean Z score = -2.53, SD= 0.45) [15].

The two studies assessing fine and gross motor abilities show delayed motor development in the majority of children older than 2 years. In the first study, gross and fine motor delay are reported respectively in 7 out of 7 patients and in 11 out of 13 patients [90] while in the other, abnormal fine and gross motor abilities are observed respectively in the 75% and 37.5% of cases [13].

2. Sensorimotor integration (visuo-motor integration; auditory-motor integration)

A total of seven papers analyze sensorimotor integration abilities in DS. Of these, 5 specifically examine visuo-motor integration abilities and 5 auditory-motor integration abilities (language production).

All the 5 papers inquiring visuo-motor integration abilities report extremely poor performances. Four papers assessing visuo-motor development through the Beery-Buktenica Developmental Test of Visual-Motor Integration report mean Z scores of – 2 standard deviations below the mean [12,13,87,90]. In a study, the execution of a finger tapping task showed fewer number of taps and higher inter-tap latencies, compared to healthy age-matched controls [14].

All the 5 studies assessing language production abilities report dysfunctions in naming and repetition, reported to oral sensorimotor impairment rather than semantic dysfunctions, resulting in imprecise articulation, omission errors and poor phonological and morphosyntactic accuracy [13–15,87,91] (see Table S4).

3. High level cognitive functions (language comprehension; attention; working memory; executive functions)

Seven studies report results on the assessment of language comprehension, attention, memory and executive functions. Language comprehension abilities tested in 3 studies [15,87,91] resulted mainly in the range of normality with few exceptions

showing borderline level of impairment. Visual attention abilities, assessed in 4 studies [12,13,87,89], as well as executive functions [12–14,87], resulted defective. More in detail, the Teddy Bear Cancellation test and the Bell's cancellation Test scores resulted on average lower than 2 standard deviations under the mean, with few borderline scores exceptions.

Significantly worst performance is reported in DS compared to controls in a go/no-go task both in terms of correct action execution (% of correct responses in DS Group: M= 30.1, SD= 13.2, vs. Control group: M = 94.6, SD = 4.6) and inhibitory capacity ($p<.001$) [14]. The performance on the Tower of London test, as assessed by 3 studies [13,87], resulted impaired as well.

Verbal working memory (digit/word span, forward and backward) and spatial working memory (Corsi test, forward and backward) tasks appeared to be impaired [13,87], while a visual memory task [14] did not found any significant differences between controls and DS group (see Table S5).

DISCUSSION

This review highlights the paucity of literature within this topic, characterized by methodological and clinical heterogeneity and small cohort sample size.

Variable degrees of global cognitive impairment, ranging from mild (IQ = 50-69) to profound (IQ<20) as assessed by general developmental/ intelligent scales, emerged. No unequivocal relation between the degree of global cognitive impairment and seizure type or frequency could be recognized [10,47,83,85,86]. Therefore, the assumption of a purely epileptic etiology of cognitive deterioration in DS should be re-discussed [47,83].

The 11 papers analyzing the relative contribution of the tests' subitems in determining the global intellectual retardation revealed significantly worse scores in performance Wechsler's subscales (picture completion, block design, matrix reasoning, digit symbol coding, symbol search) and in the hand-eye coordination and gross-motor subscales of the Griffiths' and Brunet Lézine developmental scales. Verbal comprehension and memory scores (VIQ of the Wechsler scales, hearing-language and personal-social subitems of Griffiths' and Brunet Lézine developmental scales) appear less compromised. However, these findings need to be interpreted with caution when referred to infants [9,84,91] whose IQ scores, assessed by Griffiths scales, rely primarily on performance subitems and motor abilities.

The verbal-performance cognitive asymmetry is confirmed also by the assessment of specific cognitive function. Low level cognitive functions comprising visual processing, phonological detection/discrimination as well as fine and gross motor abilities, resulted impaired from very young age [12–14,89,90] and often herald a progressive abnormal development of higher order cognitive functions [14,89], such as visual attention, motor inhibition and executive functions [12–15,87,91].

Visuo-motor and auditory-motor integration abilities resulted extremely poor and characterized by average Z scores of - 2 SD below the mean [12,13,87,90].

In 14 papers pervasive behavioural abnormalities, slightly improving with age, are reported [83,87], mainly comprising autistic-like traits, attention deficits and hyperactivity disorders.

This complex picture fits with all the three proposed hypotheses. According to the sensorimotor integration model, DS cognitive outcomes may be explained by a deficient integration process across various sensory modalities, such as vision, hearing and proprioception, which in turn, prevents correct motor programming and execution. Among the brain structures involved in these processes are the ones constituting the dorsal stream pathway (occipital-parieto-frontal circuits),whose function is linked to the integration of multiple sensorimotor experiences into a unified model of the outside world and of the body in the world [94]. The progressive deterioration of early visual processing abilities in DS, gradually spreading to visuo-motor integration, spatial information processing, visuo-attentive abilities, and executive functions follows the dorsal stream vulnerability hypothesis. However, the observed sensorimotor integration deficits are not limited to the visual dorsal stream. The same pattern emerges in the language domain [95], in which the motor aspects

of the speech production (dorsal-temporo-frontal sensorimotor mapping of sound into articulation) are significantly more affected than the semantic processing (ventral-temporo-frontal-lexical semantic pathway) [8,14]. These poor performances in visuo-motor and auditory-motor integration manifest from the first developmental stages, rather than maturing later as a consequence of an abnormal developmental process, and seem responsible for both cognitive and motor disharmonic development [15].

Abnormalities in visual and language sensorimotor systems were observed in other genetically based clinical pictures, such as Williams syndrome, Fragile-X syndrome and Prader-Willi syndrome, leading to the hypothesis of a genetic role in the determination of the cognitive outcome [13,15]. Indeed, a family study investigating the contribution of SCN1A mutation to DS neuropsychological phenotype revealed variable involvement of visuo-motor abilities among three generations of mutation carriers, despite the great heterogeneity in seizure severity and global neuropsychological functioning observed [96].

The sensorimotor integration hypothesis can thus account for the majority of the reported cognitive alterations but also for some behavioural and gait motor abnormalities [97].

Sensorimotor impairment is reported as a causative factor in the development and maintenance of autistic-like traits [21,22]. Particularly, an early deficit in visuo-motor integration can limit social learning abilities and communication efficacy, leading to unusual motor processing and poor coordination of eye contact with speech and gesture [21,98].

Accumulating evidence suggests the fundamental role of sensory integration process in determining the final gait output [99], whereas others authors define gait a sensorimotor function *per se* [100]. One of the reviewed papers directly suggests the disruption of the sensorimotor integration of vision, proprioception, and vestibular inputs as the core process leading to later emergence of DS gait abnormalities and postural instability [15].

Papers advocating a cerebellar involvement as causative factor of DS cognitive and behavioural outcome are not in contrast with a sensorimotor integration deficit. A cerebellar involvement is likely to coexist [13,87] as highlighted by the similarities observed between DS cognitive outcomes and the cerebellar-like cognitive dysfunctions, characterized by language production and visuo-spatial organization abnormalities as well as attention, working memory and executive functions deficits. Some neurological cerebellar signs, as ataxia and hypotonia, are frequently reported and linked with the SCN1A genetic mutation thought to affect Purkinje cerebellar neurons excitability [87].

DS neuropsychological pattern mimicking cerebellar cognitive affective syndrome alone cannot explain the whole picture: the early visual deficits are not fully compatible with a pure cerebellar deficit neither can explain all the variety of motor and behavioral abnormalities observed. Moreover, given the complexity of the epileptic and clinical manifestations we cannot exclude the involvement of neocortical and subcortical areas other than the cerebellum.

CONCLUSION

In light of existing evidence, the sensorimotor integration deficit hypothesis, enclosing dorsal stream vulnerability hypothesis, can account for the majority of the cognitive/behavioral disability in DS, but also of autistic-like traits and gait abnormalities development. The cerebellar involvement is likely to contribute as well but cannot account alone for the global picture. Figure 2 summarizes the final unified theoretical framework we propose.

Future research should specifically address the sensorimotor integration deficit and the cerebellar signs to disentangle their relative contribution in determining the final cognitive/behavioural phenotype and planning new rehabilitation approaches targeting both motor and cognitive domains.

LIMITATIONS

The methodological heterogeneity of the included studies, and the small amount of literature within this topic, prevented

a clear DS cognitive profile extraction. In addition, as the majority of studies reported just global intelligence scores, we couldn't clearly analysis single sub-item contribution in all the included papers.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR STATEMENT

No undisclosed groups or persons have had a primary role in the study or in manuscript preparation. All coauthors have seen and approved the final submission of the paper and accept responsibility for its content.

BIBLIOGRAPHY

1. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain. 2012;135(8):2329–36.
2. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of dravet syndrome in a US population. Pediatrics. 2015;136(5):e1310–5.
3. Dravet C. Les epilepsies graves de l'enfant. Vie Medicale [Internet]. 1978 [cited 2020 Mar 23];8:543–8. Available from: https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=PASCAL7850407561
4. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia [Internet]. 2017 Apr 1 [cited 2020 Jul 9];58(4):512–21. Available from: https://pubmed.ncbi.nlm.nih.gov/28276062/
5. Dravet C, Oguni H. Dravet syndrome (severe myoclonic epilepsy in infancy) [Internet]. 1st ed. Vol. 111, Handbook of Clinical Neurology. Elsevier B.V.; 2013. 627–633 p. Available from: http://dx.doi.org/10.1016/B978-0-444-52891-9.00065-8
6. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011 Apr;52(SUPPL. 2):3–9.
7. Jiang TJ, Shen Y, Chen H, Yuan Z, Mao S, Gao F. Clinical and molecular analysis of epilepsy-related genes in patients with Dravet syndrome. Med (United States) [Internet]. 2018 Dec 1 [cited 2020 Sep 4];97(50). Available from: /pmc/articles/PMC6320057/?report=abstract
8. Battaglia D, Ricci D, Chieffo D, Guzzetta F. Outlining a core neuropsychological phenotype for Dravet syndrome. Vol. 120, Epilepsy Research. Elsevier B.V.; 2016. p. 91–7.
9. Villeneuve N, Laguitton V, Viellard M, Lépine A, Chabrol B, Dravet C, et al. Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome. Epilepsy Behav. 2014;31:143–8.
10. Wolff M, Cassé-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): Natural history and neuropsychological findings. Epilepsia [Internet]. 2006 Nov [cited 2020 Mar 18];47(SUPPL. 2):45–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17105460
11. Guzzetta F. Cognitive and behavioral characteristics of children with Dravet syndrome: An overview. Vol. 52, Epilepsia. 2011. p. 35–8.
12. Ricci D, Chieffo D, Battaglia D, Brogna C, Contaldo I, De Clemente V, et al. A prospective longitudinal study on visuo-cognitive development in Dravet syndrome: Is there a "dorsal stream vulnerability"? Epilepsy Res. 2015;109(1):57–64.
13. Battaglia D, Chieffo D, Siracusano R, Waure C de, Brogna C, Ranalli D, et al. Cognitive decline in Dravet

syndrome: Is there a cerebellar role? Epilepsy Res. 2013 Sep;106(1–2):211–21.

14. Acha J, Pérez A, Davidson DJ, Carreiras M. Cognitive characterization of children with Dravet syndrome: A neurodevelopmental perspective. Child Neuropsychol. 2015 Sep 3;21(5):693–715.
15. Chieffo D, Battaglia D, Lucibello S, Gambardella MLMLML, Moriconi F, Ferrantini G, et al. Disorders of early language development in Dravet syndrome. Epilepsy Behav [Internet]. 2016 Jan 1 [cited 2020 Mar 4];54:30–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26630186
16. Milner AD, Goodale MA. Two visual systems re-viewed. Neuropsychologia. 2008;46(3):774–85.
17. Bueichekú E, Aznárez-Sanado M, Diez I, Uquillas F d. O, Ortiz-Terán L, Qureshi AY, et al. Central neurogenetic signatures of the visuomotor integration system. Proc Natl Acad Sci U S A. 2020;117(12):6836–43.
18. Genton P, Velizarova R, Dravet C. Dravet syndrome: The long-term outcome. Epilepsia [Internet]. 2011 Apr [cited 2020 Mar 16];52(SUPPL. 2):44–9. Available from: http://doi.wiley.com/10.1111/j.1528-1167.2011.03001.x
19. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain [Internet]. 1998 Apr [cited 2020 Aug 24];121(4):561–79. Available from: https://pubmed.ncbi.nlm.nih.gov/9577385/
20. Machado S, Cunha M, Bruna Velasques, Daniel Minc, Silmar Teixeira CAD, Julio G. Silva, Victor H. Bastos, Henning Budde, Mauricio Cagy, Luis Basile, Roberto Piedade PR. The neural bases of sensorimotor integration process [Internet]. Vol. 51, www.neurologia.com Rev Neurol. 2010 [cited 2020 Apr 27]. Available from: www.neurologia.com
21. Hannant P, Tavassoli T, Cassidy S. The role of sensorimotor difficulties in autism spectrum conditions. Front Neurol [Internet]. 2016 Aug 10 [cited 2020 Jul 6];7(AUG):124. Available from: /pmc/articles/PMC4978940/?report=abstract
22. Coll SM, Foster NEV, Meilleur A, Brambati SM, Hyde KL. Sensorimotor skills in autism spectrum disorder: A meta-analysis. Res Autism Spectr Disord. 2020 Aug 1;76:101570.
23. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med. 2018;169(7):467–73.
24. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theory Pract. 2005;8(1):19–32.
25. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. Implement Sci. 2010;5(1):1–9.
26. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions | The Cochrane Collaboration [Internet]. The Cochrane Collaboration. 2011 [cited 2020 Aug 24]. Available from: http://www.cochrane.org/training/cochrane-handbook
27. Wechsler D. Wechsler Intelligence Scale for Children [Internet]. 1992 [cited 2020 Jul 1]. Available from: https://psycnet.apa.org/record/1950-02930-000
28. Wechsler D. Manual for the Wechsler Adult Intelligence Scale. [Internet]. Manual for the Wechsler Adult Intelligence Scale. 1955 [cited 2020 Jul 8]. vi, 110–vi, 110. Available from: https://psycnet.apa.org/record/1955-07334-000
29. Wechsler D. WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence-Revised. 1989 [cited 2020 Jul 8]; Available from: https://www.uv.uio.no/isp/english/about/oslo-assessment-intervention-and-learning-lab-%28O-AILL%29/tests/ability-tests/wippsy-r.pdf
30. Griffiths R. The Griffiths Mental Development Scale (babies) from birth to 2 years (Manual). Public Health

[Internet]. 1997 [cited 2020 Jul 8];111(5):347–8. Available from: https://ci.nii.ac.jp/naid/10029561297/

31. Brunet O, Lézine I. Le développement psychologique de la première enfance. 1951 [cited 2020 Jul 10]; Available from: https://psycnet.apa.org/record/1951-07964-000
32. Raven JC, Court JH, Raven J. Manual for Raven's Standard Progressive Matrices and vocabulary scales [Internet]. 1996. 1996 [cited 2020 Jul 8]. Available from: https://ci.nii.ac.jp/naid/10008039872/
33. Bayley N. Bayley scales of infant development. 2013;
34. Schopler E, Lansing M, Reichler R, Marcus L. PEP-3: Psychoeducational profile [Internet]. 2005 [cited 2020 Jul 8]. Available from: https://edipsico.pt/files/PEP-3.pdf
35. Kaufman AS, Kaufman NL. Sex differences on the Mccarthy Scales of Children's Abilities. J Clin Psychol [Internet]. 1973 [cited 2020 Jul 8];29(3):362–5. Available from: https://psycnet.apa.org/record/1979-00092-001
36. Gesell A. Monthly increments of development in infancy. Pedagog Semin J Genet Psychol [Internet]. 1925 [cited 2020 Jul 13];32(2):203–8. Available from: https://www.tandfonline.com/doi/abs/10.1080/08856559.1925.10534063
37. Voress J.K., Pearson N.A. HDD. Developmental Test of Visual Perception (DTVP) [Internet]. 2004 [cited 2020 Jul 8]. Available from: https://www.sig-net.be/uploads/werkgroepen/een_kijk_op_het_oog/dtvp2.pdf
38. Atkinson J, Anker S, Rae S, Hughes C, Braddick O. A test battery of child development for examining functional vision (ABCDEFV). Strabismus. 2002 Dec;10(4):245–69.
39. Okuda FC, Apt L, Wanter BS. Evaluation of the TNO random-dot stereogram test. Am Orthopt J. 1977;Vol.27:124–30.
40. Mohn G, Duin J van H, Fetter WPF, de Groot L, Hage M. ACUITY ASSESSMENT OF NON-VERBAL INFANTS AND CHILDREN: CLINICAL EXPERIENCE WITH THE ACUITY CARD PROCEDURE. Dev Med Child Neurol. 1988;30(2):232–44.
41. Harris AJ. Lateral Dominance, Directional Confusion, and Reading Disability. J Psychol Interdiscip Appl. 1957;44(2):283–94.
42. Friedrich M, Friederici AD. Early N400 development and later language acquisition. Psychophysiology [Internet]. 2006 Jan [cited 2020 Jul 8];43(1):1–12. Available from: https://pubmed.ncbi.nlm.nih.gov/16629680/
43. Axia G. Test del primo linguaggio. 1995. Firenze: Organizzazioni Speciali.
44. Hutchins T, Vivanti G, Mateljevic N, Jou RJ, Shic F, Cornew L, et al. Movement Assessment Battery for Children: 2nd Edition (MABC-2). In: Encyclopedia of Autism Spectrum Disorders [Internet]. Springer New York; 2013 [cited 2020 Jul 8]. p. 1925–39. Available from: https://link.springer.com/referenceworkentry/10.1007/978-1-4419-1698-3_1922
45. van Hartingsveldt MJ, Cup EHC, Oostendorp RAB. Reliability and validity of the fine motor scale of the Peabody Developmental Motor Scales-2. Occup Ther Int. 2005;12(1):1–13.
46. Bruininks R. Bruininks-Oseretsky test of motor proficiency. 1978;
47. Nabbout R, Chemaly N, Chipaux M, Barcia G, Bouis C, Dubouch C, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis. 2013;8(1):1–8.
48. Hayden D, Wetherby A, Cleary J, Prizant B. Early Motor Control Scales: Prepublication Version. Baltimore: Paul H. 2011;
49. Ryckman DB, Rentfrow RK. The Beery Developmental Test of Visual-Motor Integration: An Investigation of Reliability. J Learn Disabil. 1971 Jun;4(6):333–4.
50. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. Percept Mot Skills [Internet]. 1958 Dec 31 [cited 2020 Mar 13];8(3):271–6. Available from:

http://journals.sagepub.com/doi/10.2466/pms.1958.8.3.271

51. Cianchetti C., and Sannio Fancello G. TVL/ Test di valutazione del linguaggio [Internet]. 1997 [cited 2020 Jul 12]. Available from: https://books.google.com/books?hl=it&lr=&id=VK3JW9IK3egC&oi=fnd&pg=PA17&dq=Cianchetti+and+Sannio+Fancello,+1997)&ots=orqZOv5aA7&sig=iWEYgqINDcjN6mMeerQJMTnN14s
52. Kaplan E, Goodglass H, Weintraub S. Boston naming test. 2001;
53. Miceli G. Batteria per l'analisi dei deficit afasici B.A.D.A. 1994. 419 p.
54. Chevrie-Muller C. Épreuves pour l'examen du langage. psycnet.apa.org [Internet]. 1981 [cited 2020 Jul 12]; Available from: https://psycnet.apa.org/record/1983-20093-001
55. Murdoch BE. Dysarthria: A Physiological Approach to Assessment and Treatment [Internet]. 1998 [cited 2020 Jul 12]. 431 p. Available from: https://books.google.com/books?hl=it&lr=&id=aoiVaVokj2sC&oi=fnd&pg=PR9&dq=+Murdoch+BE.+Dysarthria:+A+Physiological+Approach+to+Assessment+and+Treatment.+Cheltenham,+UK:+Stanley+Thornes%3B+1998.&ots=IrKcYpdyAi&sig=afeX77bI9UXIhI0xWY6_4F8PiaA
56. Dodd B. Diagnostic evaluation of articulation and phonology (DEAP) / Barbara Dodd ... [et al]. [Internet]. DEAP Phonology assessment. 2002 [cited 2020 Jul 12]. Available from: http://eprints.bbk.ac.uk/5547/
57. Bishop DV. Test for Reception of Grammar - Second Edition. 1982.
58. Williams KT. Expressive Vocabulary Test Second Edition (EVT ™ 2). J Child Lang J Am Acad Child Adolesc Psychiatry. 2000;27(42):255–66.
59. Bisiacchi PS, Cendron M, Gugliotta M, Tressoldi P, Vio C. BVN. Batteria di Valutazione Neuropsicologica per l'Età Evolutiva [Internet]. 2005 [cited 2020 Jul 12]. 324 p. Available from: http://www.sebastianolupo.it/wordpress/wp-content/uploads/2011/01/Copia-di-Profilo-Individuale-BVN.pdf
60. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Rey-Osterrieth complex figure: Normative values in an Italian population sample. Neurol Sci [Internet]. 2002 Mar [cited 2020 Mar 13];22(6):443–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11976975
61. Bracken B. Peabody Picture Vocabulary Test-Revised: An Appraisal and Review. School Psych Rev [Internet]. 1984 [cited 2020 Jul 12];13(1):49–60. Available from: https://www.tandfonline.com/doi/abs/10.1080/02796015.1984.12085079
62. Brady NC, Fleming K, Thiemann-Bourque K, Olswang L, Dowden P, Saunders MD, et al. Development of the Communication Complexity Scale. Am J Speech-Language Pathol [Internet]. 2012 [cited 2020 Jul 12];21(1):16–28. Available from: https://pubs.asha.org/doi/full/10.1044/1058-0360%282011/10-0099%29
63. Laurent-Vannier A, Chevignard M, Pradat-Diehl P, Abada G, De Agostini M. Assessment of unilateral spatial neglect in children using the Teddy Bear Cancellation Test. Dev Med Child Neurol. 2006;48(2):120–5.
64. Hulme C, Tordoff V. Working memory development: The effects of speech rate, word length, and acoustic similarity on serial recall. J Exp Child Psychol [Internet]. 1989 [cited 2020 Jul 12];47(1):72–87. Available from: https://www.sciencedirect.com/science/article/pii/0022096589900635
65. Hitch GJ, Halliday S, Schaafstal AM, Schraagen JMC. Visual working memory in young children. Mem Cognit. 1988 Mar;16(2):120–32.
66. Vicari S, Pasqualetti P, Marotta L, Carlesimo GA, Vicari S, Marotta L. Word-list learning in normally developing children: Effects of semantic organization and retention interval. Ital J Neurol Sci. 1999;20(2):119–28.
67. Durston S, Thomas KM, Yang Y, Uluğ AM, Zimmerman RD, Casey BJ. A neural basis for the development of

inhibitory control. Dev Sci. 2002 Nov;5(4).

68. Krikorian R, Bartok J, Gay N. Tower of London Procedure: A Standard Method and Developmental Data. J Clin Exp Neuropsychol. 1994 Dec 1;16(6):840–50.
69. Kraijer D, De Bildt A. The PDD-MRS: An instrument for identification of autism spectrum disorders in persons with mental retardation. J Autism Dev Disord [Internet]. 2005 Aug [cited 2020 Jul 21];35(4):499–513. Available from: https://link.springer.com/article/10.1007/s10803-005-5040-0
70. Kraijer DW. Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder. J Autism Dev Disord [Internet]. 2000 [cited 2020 Jul 21];30(1):39–47. Available from: https://link.springer.com/article/10.1023/A:1005460027636
71. Blok J, Berg P Van den, Feij J. Temperamentschaal voor zwakzinnigen/TVZ: Handleiding. 1990;
72. Achenbach T. Child behavior checklist. In: books.google.com [Internet]. 1991 [cited 2020 Jul 21]. Available from: https://books.google.it/books?hl=it&lr=&id=YxCXh5ZvTksC&oi=fnd&pg=PA372&dq=CBCL+CHILD+BEHAVIOR+CHECKLIST+di+T.+M.+Achenbach+(2001)&ots=uHfVdM09Ut&sig=_k8zKP0Zo_hPN03fWivrQ33Wxho
73. Krug DA, Arick J, Almond P. BEHAVIOR CHECKLIST FOR IDENTIFYING SEVERELY HANDICAPPED INDIVIDUALS WITH HIGH LEVELS OF AUTISTIC BEHAVIOR. J Child Psychol Psychiatry [Internet]. 1980 [cited 2020 Jul 21];21(3):221–9. Available from: https://acamh.onlinelibrary.wiley.com/doi/abs/10.1111/j.1469-7610.1980.tb01797.x
74. Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). J Autism Dev Disord [Internet]. 1980 Mar [cited 2020 Jul 21];10(1):91–103. Available from: /record/1980-22500-001
75. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, Dilavore PC, et al. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord [Internet]. 2000 [cited 2020 Jul 21];30(3):205–23. Available from: https://link.springer.com/article/10.1023/A:1005592401947
76. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord [Internet]. 1994 Oct [cited 2020 Jul 21];24(5):659–85. Available from: https://link.springer.com/article/10.1007/BF02172145
77. Stabel A, Kroeger-Geoppinger K, McCullagh J, Weiss D, McCullagh J, Schneider N, et al. Diagnostic Interview for Social and Communication Disorders. In: Encyclopedia of Autism Spectrum Disorders [Internet]. Springer New York; 2013 [cited 2020 Jul 21]. p. 926–31. Available from: https://link.springer.com/referenceworkentry/10.1007/978-1-4419-1698-3_876
78. Mueller F, Brozovich R, Johnson CB. Conners' Rating Scales-Revised (CRS-R). Diagnostique. 1999 Mar;24(1–4):83–97.
79. Sparrow S, Cicchetti D, Balla D. Vineland adaptive behavior scales. 1984 [cited 2020 Jul 21]; Available from: https://psycnet.apa.org/doiLanding?doi=10.1037/t15164-000
80. Li BM, Liu XR, Yi YH, Deng YH, Su T, Zou X, et al. Autism in Dravet syndrome: prevalence, features, and relationship to the clinical characteristics of epilepsy and mental retardation. Epilepsy Behav. 2011/05/31. 2011;21(3):291–5.
81. Cassé-Perrot C, Wolff M, Dravet C. Neuropsychological Aspects of Severe Myoclonic Epilepsy in Infancy.

Neuropsychol Child Epilepsy,. 2001;131–40.

82. Ouss L, Leunen D, Laschet J, Chemaly N, Barcia G, Losito EM, et al. Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype. Epilepsia Open. 2019 Mar 1;4(1):40–53.
83. Darra F, Battaglia D, Dravet C, Patrini M, Offredi F, Chieffo D, et al. Dravet syndrome: Early electroclinical findings and long-term outcome in adolescents and adults. Epilepsia [Internet]. 2019 Dec 1 [cited 2020 Mar 18];60 Suppl 3(S3):S49–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31904122
84. Olivieri G, Battaglia D, Chieffo D, Rubbino R, Ranalli D, Contaldo I, et al. Cognitive-behavioral profiles in teenagers with Dravet syndrome. Brain Dev. 2016;38(6):554–62.
85. Ragona F. Cognitive development in children with Dravet syndrome. Epilepsia. 2011 Apr;52(SUPPL. 2):39–43.
86. Ragona F, Brazzo D, De Giorgi I, Morbi M, Freri E, Teutonico F, et al. Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients. Brain Dev [Internet]. 2010 Jan [cited 2020 Mar 18];32(1):71–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19854600
87. Chieffo D, Battaglia D, Lettori D, Del Re M, Brogna C, Dravet C, et al. Neuropsychological development in children with Dravet syndrome. Epilepsy Res. 2011 Jun;95(1–2):86–93.
88. Berkvens JJL, Veugen I, Veendrick-Meekes MJBM, Snoeijen-Schouwenaars FM, Schelhaas HJ, Willemsen MH, et al. Autism and behavior in adult patients with Dravet syndrome (DS). Epilepsy Behav [Internet]. 2015;47:11–6. Available from: http://dx.doi.org/10.1016/j.yebeh.2015.04.057
89. Chieffo D, Ricci D, Baranello G, Martinelli D, Veredice C, Lettori D, et al. Early development in Dravet syndrome; visual function impairment precedes cognitive decline. Epilepsy Res. 2011 Jan;93(1):73–9.
90. Verheyen K, Verbecque E, Ceulemans B, Schoonjans AS, Van De Walle P, Hallemans A. Motor development in children with Dravet syndrome. Dev Med Child Neurol. 2019 Aug 1;61(8):950–6.
91. Turner SJ, Brown A, Arpone M, Anderson V, Morgan AT, Scheffer IE. Dysarthria and broader motor speech deficits in Dravet syndrome. Neurology. 2017;88(8):743–9.
92. Ragona F, Granata T, Bernardina BD, Offredi F, Darra F, Battaglia D, et al. Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients. Epilepsia [Internet]. 2011 Feb [cited 2020 Mar 4];52(2):386–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21269283
93. Riva D, Vago C, Pantaleoni C, Bulgheroni S, Mantegazza M, Franceschetti S. Progressive neurocognitive decline in two children with Dravet syndrome, de novo SCN1A truncations and different epileptic phenotypes. Vol. 149, American Journal of Medical Genetics, Part A. 2009. p. 2339–45.
94. Rauschecker JP. Where, When, and How: Are they all sensorimotor? Towards a unified view of the dorsal pathway in vision and audition. Cortex [Internet]. 2018;98:262–8. Available from: https://doi.org/10.1016/j.cortex.2017.10.020
95. Fridriksson J, Yourganov G, Bonilha L, Basilakos A, Den Ouden DB, Rorden C. Revealing the dual streams of speech processing. Proc Natl Acad Sci U S A [Internet]. 2016 [cited 2020 Jul 3];113(52):15108–13. Available from: https://www.pnas.org/content/113/52/15108.short
96. Passamonti C, Petrelli C, Mei D, Foschi N, Guerrini R, Provinciali L, et al. A novel inherited SCN1A mutation associated with different neuropsychological phenotypes: Is there a common core deficit? Epilepsy Behav. 2015 Feb 1;43:89–92.
97. Di Marco R, Hallemans A, Bellon G, Ragona F, Piazza E, Granata T, et al. Gait abnormalities in people with Dravet syndrome: A cross-sectional multi-center study. Eur J Paediatr Neurol [Internet]. 2019;23(6):808–18.

Available from: https://doi.org/10.1016/j.ejpn.2019.09.010

98. Foster N. Sensorimotor learning and control in autism spectrum disorders: The role of sensorimotor integration. [Internet]. 2019 [cited 2020 Jul 6]. Available from: http://researchonline.ljmu.ac.uk/id/eprint/10122/

99. Mitchell T, Starrs F, Soucy JP, Thiel A, Paquette C. Impaired Sensorimotor Processing During Complex Gait Precedes Behavioral Changes in Middle-aged Adults. Journals Gerontol - Ser A Biol Sci Med Sci [Internet]. 2019 [cited 2020 Jul 10];74(12):1861–9. Available from: https://academic.oup.com/biomedgerontology/article-abstract/74/12/1861/5104862

100. Nutt JG. Higher-level gait disorders: An open frontier. Mov Disord. 2013;28(11):1560–5.

Figure

1. Flow chart of the systematic literature search
2. Unified theoretical framework

Table

1. Assessed cognitive and behavioral domains and assessment tools

Supplementary Material

Table S1. Global cognitive outcomes

Table S2. Behavioral outcomes

Table S3. Low level cognitive functions

Table S4. Sensorimotor integration functions

Table S5. High level cognitive functions

Appendix 1

1. PubMed search strategy

Queries Pubmed		
Search	Query	Items found
#6	#4 OR #5	68
#5	#1 AND #3 Filters: Humans, English	46
#4	#1 AND #2 Filters: Humans, English	28
#3	("cognition"[MeSH Terms]) OR "neuropsychology"[MeSH Terms]	143187
#2	("autism spectrum disorder"[MeSH Terms]) OR "autistic features"[MeSH Terms]	27489
#1	("epilepsies, myoclonic" [MeSH Terms] OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("dravet" [All Fields] AND "syndrome" [All Fields]) OR "dravet syndrome" [All Fields]) OR (severe[All Fields] AND ("epilepsies, myoclonic" [MeSH Terms]OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("myoclonic" [All Fields] AND "epilepsy" [All Fields]) OR "myoclonic epilepsy" [All Fields]))))	4585

2. Data extraction form

ORGANISATIONAL ASPECTS				**EX**		**IN**	
REF ID		Reviewer, Date		Checked by			
Author, Year							
Journal/Source				Study ID		NR /	
Title							
Country of origin							
Publication type	Full text / Abstract / B o o k chapter / other (please specify)						
Fate	Decision pending / Check references / Use for discussion /Excluded / Other (please specify)						
Notes / Short description							
CURRENT STATUS: *(NAME OF REVIEWER + DATE)*							
Question to author **Status verified with study investigators or sponsors: Yes** / N o Enter name of the source (e.g. PI, sponsor, etc.) _____							
Contact address:							

ELIGIBILITY FORM		
Factors	**Assessment**	**Comments**
Article characteristics		
1. Did the study undergo a full peer review?	YES NO UNCLEAR	If NO → exclude
2. Is it a single case study?	YES NO UNCLEAR	If YES → exclude

3. Is it an animal study?	YES NO UNCLEAR	If YES → exclude
4. Is it written in English?	YES NO UNCLEAR	If NO → exclude
Participants		
Were participants diagnosed with Dravet syndrome?	YES NO UNCLEAR	If NO → exclude
Methodology		
Were participants tested with standardized neuropsychological tests?	YES NO UNCLEAR	If NO → exclude
Outcomes		
Did the study report cognitive outcomes and/ or sensory-motor integration abilities assessment?	YES NO UNCLEAR	If NO → exclude
FINAL DECISION	YES NO	

REASONS FOR EXCLUSION FROM REVIEW	
Article type	No full-length article/ Animal study/ Single case study/Review/ Language
Methods	Observational evaluations / Questionnaires / Not standardized neuropsychological tests
Patients	Syndromes other than Dravet / Diagnosis not meeting ILAE criteria
Outcomes	No relevant outcomes assessed/ Just QI measurements
Other	
None	INCLUDED

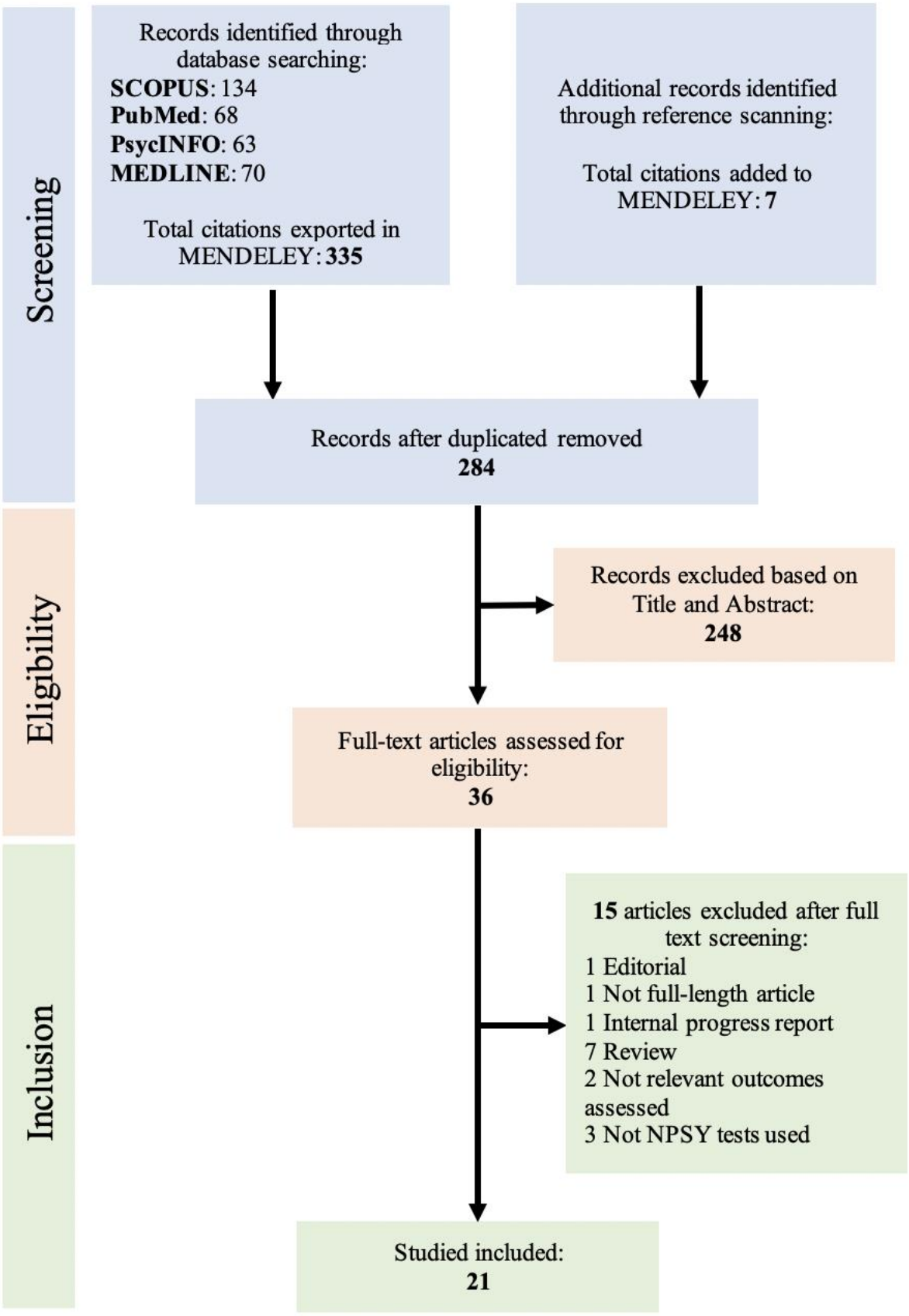
STUDY CHARACTERISTICS	
Disease(s)	
Author's inclusion criteria	

Author's exclusion criteria	
Neuropsychological test used	
Outcomes assessed (mean/median/range)	Autistic features General developmental quotient (+ subitems) General intelligent quotient (+ subitems) Visual processing Phonological processing Visuomotor abilities Visuo-attentional abilities Visuo-spatial abilities Working Memory Executive Functions Language
Confounders	
Sample size	
Number of excluded patients	
Recruitment method	
Setting	in-patient / o u t -patient / unclear / N R
Trial Design	Cross-sectional Longitudinal Prospective Longitudinal Retrospective Family study
Length of follow-up	From _____ till_____
Conflict of interest statement	Yes / No / NR

Number of groups/subgroups (DS vs. control group)	

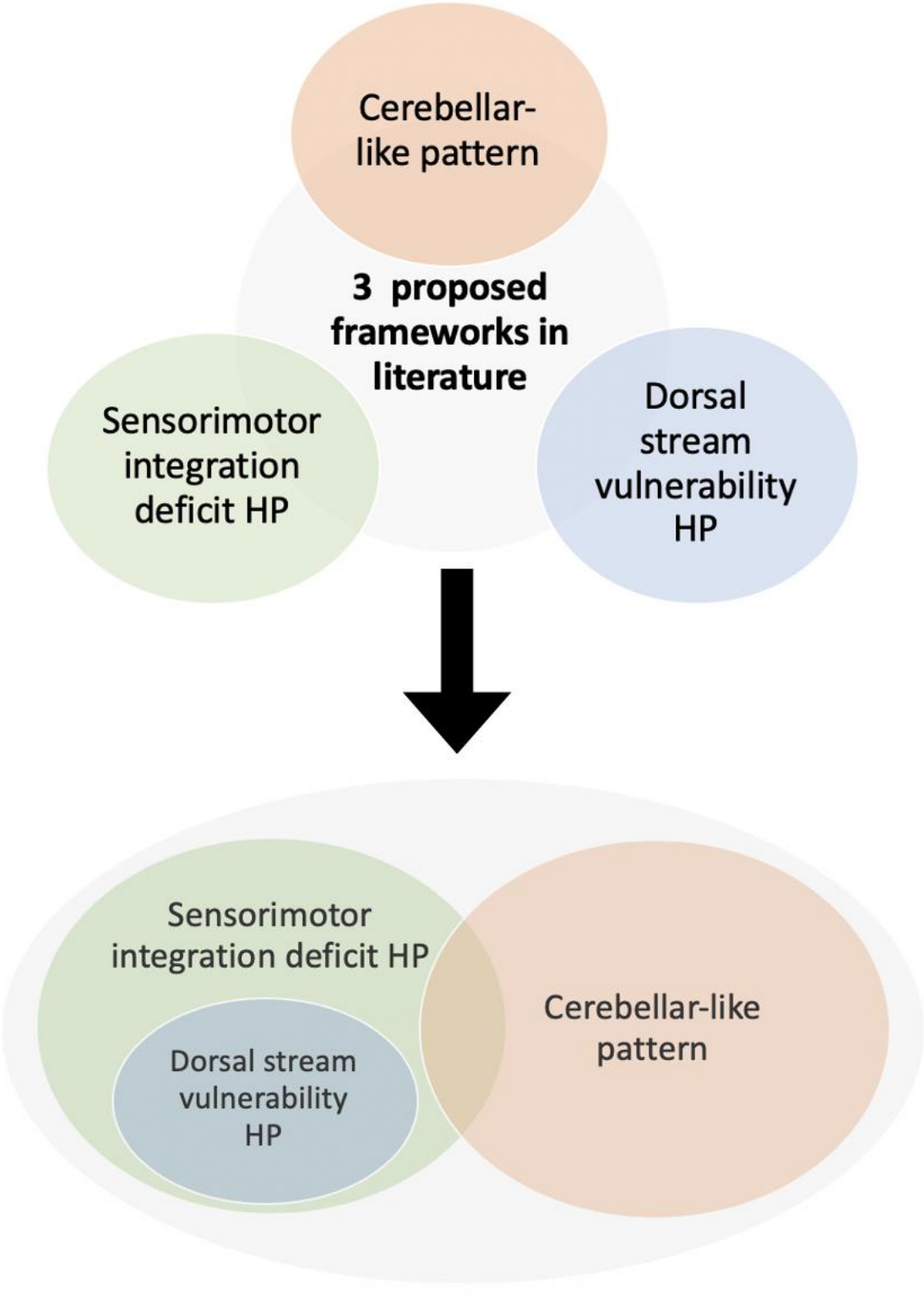
BASELINE CHARACTERISTICS OF PATIENTS	
Age	
mean/±	
median/±	
Ethnicity No. %	
Gender No. %	
Definition of Diagnosis	
Group stratifications (complete/ incomplete forms …)	
Additional diagnoses in group	
Treatment	

Figure 1. Flow chart of the systematic literature search



Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) flow chart showing the process of systematic article search and selection.

Figure 2. Unified theoretical framework



Three main theoretical frameworks have independently been proposed by authors to explain DS cognitive and behavioural profile. This review aims to propose a unified literature-based theoretical framework, to better understand DS cognitive characterization and guide future researches.
HP=hypothesis

Supplementary material

Table S1

Global cognitive outcomes

First author	Year	N° subjects	Age	Developmental/intelligent quotient assessment (tests)	Outcomes
Battaglia, Domenica	2013	9	From 4 years 6 months to 13 years	WPPSI WISC III Griffiths' mental scales (in 1 child)	**TIQ**: mean=63.3; SD=12,1; median=61.5; range=48-78 **VIQ**: mean=77.5, SD= 11.28, median=61.5 range 59-91 **PIQ**: mean=56.37, SD=11.10, median=52.5; range=44-72
Cassé-Perrot, Catherine (*)	2011	20	From 11 months to 16 years and 7 months	Wechsler scales revised Brunét-Lezine (BL) Developmental Scale McCarthy Scales of Children's abilities	**DQ range:** 11-21 months: 60-100 2 years 4 months-5 years 10 months: 32-70 6-16 years: 20-40
Chieffo, Daniela (*)	2011a	12	First NPSY: 9 months to 42 months Follow up end: 4 years to 10 years	WIPPSI WISC-R Griffiths' mental scales	VIQ and Griffiths language items > PIQ and hand eye coordination/ performance items
Chieffo, Daniela	2011b	5	First NPSY: from 6 months to 24 months Follow up-end: from 30 to 51months	Griffiths' mental scales	**case 1**: GQ from 105 (6 months) to 88 (30 months) **case 2**: GQ from 92 (10 months) to 79 (45 months) **case 3**: GQ from 95 (12 months) to 51 (39 months) **case 4**: GQ from 110 (24 months) to 80 (51 months) **case 5**: GQ from 102 (10 months) to 94 (51 months)
Chieffo, Daniela	2016	13	From 2 years to 7 years and 8 months	WISC III Griffiths' mental scales	**30 months ±6 months :** GQ: mean=87.5; SD=16.28; median=90; range=58-108 **5 years and 8 months to 7.8 months:** TIQ: mean=69.75; SD=18,13; median=68; range=45-105; VIQ: mean=79.12; SD=20,68; median=80; range=46-110; PIQ: mean=62.25; SD=19,79; median=59; range=41-96;
Darra, Francesca (*)	2019	84	Adults mean age: 29 years // Adolescents mean age: 16 years and 3 months	Wechsler scales Griffiths' mental scales Raven's Colored Progressive Matrices	**ID (% number of adolescent subjects**): Mild ID: 26,5% Moderate ID: 41,2% Severe ID: 29,4% **ID (% number of adult subjects**): Mild ID: 14% Moderate ID: 36% Severe ID: 22%
Li, Bing Mei (*)	2011	37	From 4.1 years to 15.8 years	Chinese Wechsler Intelligence Scale for Children (C-WISC) Gesell Developmental Scales	**ID (% number of subjects):** Mild to moderate MR: 43.2% Severe MR: 37.8% Profound MR: 13,5%
Nabbout, Rima	2013	67	From 9 months to 24 years	WPPSI WISC IV Brunét-Lezine (BL) Developmental Scale	**Up to 2 years** DQ/IQ: mean=79.5, SD=12.0, range=64-105 **Age 2- 3 years** DQ/IQ: mean=73.3, SD=15.0, range=36-105 **After 3 years** DQ/IQ: mean=48.0, SD=18.9, range=30-69 **BL subitems (age < 6):** Hand-eye coordination: mean = 62.0, SD = 16.8 Language: mean = 72.3, SD = 17.6 Socialization: mean=73.4, SD = 15.8 Posture: mean = 76.5, SD = 16.9

Olivieri, Giorgia	2016	20	From 10 years 6 months to 19 years 11 months	WISC-III WAIS Raven's Colored Progressive Matrices	**TIQ:** mean= 54.08; SD=9.89; median= 53; range= 39-69 (7 not tested; 1 RCPM= 41) **VIQ:** mean= 60.42; SD=10.51; median= 62.5; range= 39-78 (8 not tested) **PIQ:** mean= 54.58; SD=13.32; median= 52.5; range= 36-76 (8 not tested)
Ouss, Lisa	2019	35	From 2 to 7 years	Psychoeducational Profile, Third Edition; PEP- 3	**% number of subjects (PEP-3):** No risk of delay: 3.3% High risk of delay: 20% Very high risk of delay: 23% **Subitems:** **FM moderate-severe level:** 90%; mean=56; range=36-92 **GM moderate-severe level:** 90%; mean=52; range=29-89 **VMI moderate-severe level:** 70%; mean=57; range=32-114 **EL moderate-severe level:** 63%; mean=48; range=18-80 **RL:** mean=57; range= 16-90 **CVPV moderate-severe level:**80%; mean= 60; range=26-97 **AE moderate-severe level:** 43.3%
Passamonti, Claudia [(*)]	2015	8 family members carrying SCN1 A mutation	From 5 to 73 years	WPPSI WAIS	**WAIS average IQ:** 4 subjects carriers of the SCN1A mutation without seizures manifestation: mean= 95; range= 90-102 1 subject diagnosed with GEFS+: 90 1 subject diagnosed with FS: 92 1 subject diagnosed with DS: 45 **WPPSI:** 1 subject diagnosed with PEFS+: 95
Ragona, Francesca [(*)]	2010	37	From 4 months to 28 years	Wechsler scales Griffiths' mental scales	**ID (% number of subjects):** **6 months- 6 years** Mild delay: 33.33% Moderate: 20% Severe:13.33% **7years-10years** Mild: 50% Moderate: 33.33% Severe:16.66% **Older than 10 years** Mild:12.5% Moderate: 12.5% Severe: 75%
Ragona, Francesca [(*)]	2011	26	From 1 year to 5 years	Griffiths' Mental Scale Brunét-Lezine Developmental scales	**dGQ (12 months-60 months)** mean= 32.31; median=30.5; range=6-77 **GQ at 12 months:** mean= 88.46; SD=14.56; median=84.5; range=56-113 **GQ at 60 months:** mean= 56.15; SD=22.09; median=55.5; range=16-102
Ricci, Daniela	2015	5	First evaluation: 4 years Last evaluation: from 6 years 10 months to 8 years	Griffiths' Mental Scale WPPSI WISC III	**Griffiths' Mental scales:** **GD:** Mean=79; median=80; range=52-104 **Locomotor:** mean= 76; median= 80; range= 44-97 **Personal-social:** mean= 85.45; median= 94; range= 49-117 **Hearing and language:** mean= 80.91; median= 86; range= 41-115 **Eye and hand coordination:** mean= 75.27; median= 71; range= 41-100 **Performance**: mean= 75.91; median= 81; range= 36-96 **Practical reasoning:** mean= 76; median= 82; range= 53-93 **WPPSI /WISC III:** **TIQ**: mean=64.71; SD=10.73; median=64; range=48-81; **VIQ**: mean=76, SD= 10.85, median=74; range

					60-91 **PIQ**: mean=58.14, SD=11.26, median=56; range=41-73
Riva, Daria	2009	2	From 11months to 7 years From 23 months to 8 years	Griffiths' Mental Scale	**Patient 1 DQ:** T1 (11 months) = 66; T2 (24 months) =50 T3 (36 months) =56,70 T4 (47 months) =46 T5(7 years and 6 months)=30 **Patient 2 DQ:** T1 (23 months) = 66,8 T2 (31 months) =62,3 T3(39 months) =59 T4 (63 months) =48,2 T5 (80 months) =41,4 T6 (8 years and 6 months) = 33 **Subitems:** **A. locomotor** Patient 1: 65 – 60 – 61.10 – 47.9 – 27.2 Patient 2: 74 – 63.3 – 56.4 – 38 – 32.5 – 28 **B. personal-social** Patient 1: 53 – 66 – 54.20 – 47.9 – 27.8 Patient 2: 66 – 56.7 – 55.1 – 49.2 – 43.8 – 32 **C. hearing and language** Patient 1: 78 – 52 – 51.40 – 42.6 – 22.8 Patient 2: 32 – 48.3 – 47.4 – 37.3 – 30 – 26 **D. eye-hand coordination** Patient 1: 62 – 50 – 52.80 – 42.6 – 30.5 Patient 2: 70 – 68.3 – 53.8 – 54 – 47.5 – 36 **E. performance** Patient 1: 76 – 50 – 63.90 – 48.9 – 40 Patient 2: 92 – 76.7 – 82.1 – 63.5 – 52.5 – 42 **F. practical reasoning** Patient 2: 47.6 – 40 – 34
Turner, Samantha J. (*)	2017	26	From 15 months to 28 years	WISC IV, Wechsler Abbreviated Scale of Intelligence–II	**TIQ:** mean= 64.83; SD=18.74; median=63.5; range=40-95 **Severe ID:** 8 participants not able to complete the battery (IQ<40)
Villeneuve, Nathalie	2014	21	From 6 to 10 years	WISC III and IV	**TIQ:** mean=46.87; SD=10.23; median=42; range= 40-73 **VIQ:** mean=54.47; SD=10.93; median=51; range= 45-74 **PIQ:** mean=53.87; SD=11.76; median=46; range= 41-82
Wolff, Markus	2006	20	From 11 months to 16 years	Brunét-Lezine Developmental scales	**Global DQ** 1 year to 3 years: DQ range 60-95% 3-6 years: DQ significantly lower >6 years: DQ range 25-40% **Subitems** Poor visuomotor skills: DQ range=15-35% Results of language subtest more heterogeneous

TIQ= total intelligent quotient; VIQ= verbal intelligent quotient; PIQ= performance intelligent quotient; DQ= developmental quotient; GQ= Griffith's global quotient; ID= intellectual disability; IQ= intelligent quotient; MR= mental retardation; FM=fine motor; GM= gross motor; VMI= visual motor imitation; EL= expressive language; RL= receptive language; CVPV= cognitive verbal/preverbal; AE= affective expression; (*) Global scores and subitems scores are not clearly reported;

Table S2

Behavioral outcomes

First author	Year	N° subjects	Age	Developmental/intelligent quotient assessment (tests)	Outcomes
Battaglia, Domenica	2013	9	From 4 years 6 months to 13 years	Achenbach Child Behaviour Checklist (CBC)	**CBC (% number of subjects)** Behavioural abnormalities (66,7%): Internalization=abnormal (22,2%) Externalization=abnormal (44,4%)
Berkvens, Jessica, J.L.	2015	13	From 18 years to 60 years	**AVZ-R** (Pervasive developmental disorder in mental retardation) **SGZ** (maladaptive behaviour scale for individuals with ID) **TVZ** (temperamental scale for individuals with ID)	**ASD in 61.5% patients** **AVZ-R (PDD):** 46.15% PDD; 7.7% uncertain; 46.15% no PDD **SGZ:** 38.46% maladaptive behaviour; 30.77% average score; 30.77 lower scores than other institutionalized patients **TVZ:** 46.15% difficult temperament; 46.15% average score; 7.69% above average
Chieffo, Daniela	2011, a	12	First NPSY: 9 months to 42 months Follow up end: 4 years to 10 years	Achenbach Child Behaviour Checklist (CBC)	**Scores not clearly reported:** Attention and Hyperactivity problems at earlier ages becoming negative at outcome; Withdrawn scale Z scores < -2
Chieffo, Daniela	2011, b	5	First NPSY: from 6 months to 24 months Follow up-end: from 30 to 51months	Achenbach Child Behaviour Checklist (CBC)	**Scores not clearly reported:** Abnormalities found in 3 out of 5 patients starting from 30 months of age in the following CBC subscales: withdrawn sleep attention
Darra, Francesca	2019	84	Adults mean age: 29 years // Adolescents mean age: 16 years and 3 months	Achenbach Child Behaviour Checklist (CBC) Vineland Adaptive Behaviour Scale (VABS-II)	**Adolescents group** CBC: 73% of patients show behavioural or psychiatric disorders; **Behavioural disorders mild or moderate in:** attention; anxiety; perseveration; rule breaking; aggressiveness **Severe:** obsessive compulsive behaviours (13 patients) autistic features and psychosis (5 patients) **Adult group** CBC: 52% severe behavioural disorders; **Behavioural disorders:** Attention deficit, obsessive, and oppositional disorder (12 patients) Marked autistic traits (11 patients) Psychosis (2 patients) **VABS-II:** 58% of patients show abnormal scores in: communication (median age equivalent: 5.3 years); Daily living (median age equivalent: 5.9 years); Socialization (median age equivalent: 4.9 years).

Li, Bing Mei	2011	37	From 4 years 1 month to 15 years 8 months	**ABC** Autism Behaviour Checklist **CARS** (Childhood Autism Rating Scale) **ADOS** (The Autism Diagnostic Observation Schedule) **ADI** (the Autism Diagnostic Interview) **DISCO** (Diagnostic Interview for Social and Communication Disorders)	**24.3% of patients diagnosed with ASD:** Average ABC scores: 81.1 Average CARS scores: 36.4 **autistic features:** Speech delay, narrow interests, and no emotional reciprocity in 100% of patients; Adherence to routine in 88.9% of patients; Short temper in 77.8% of patients; Language regression (44.4%); **No ASD patients**: average ABC scores: 35.0 average CARS scores: 19.9 **autistic features:** speech delay in 89.3% patients
Nabbout, Rima	2013	67	From 9 months to 24 years	Achenbach Child Behaviour Checklist (CBC) Conner's scale	**CBC:** Abnormal sub scores (T-score between 60-70) in: Attention Hyperactivity **Conner's scale:** Abnormal learning abilities (>70) Hyperactivity
Olivieri, Giorgia	2016	20	From 10 years 6 months to 19 years 11 months	Achenbach Child Behaviour Checklist (CBC)	**Abnormal sub scores in:** Withdrawn (100%) Somatic complains (83.33%) Internalizing (100%)
Ouss, Lisa	2019	35	From 2 to 7 years	**ADOS** (The Autism Diagnostic Observation Schedule) **ADI** (Autism Diagnostic Interview-Revised) Vineland Adaptive Behaviour Scale	**Autistic features according to DSM-5, ADI-R and ADOS-2:** ASD in 39.3%; SCD (social communication disorder) in 7.1%; neither ASD nor SCD in 53.6% **VABS-II:** adaptive behaviour mean=75 (range= 56-105)
Ragona, Francesca	2010	37	From 4 months to 28 years	Observational/qualitative evaluation	Behaviour problems observed in 21/37 patients, mainly attention deficit, hyperactivity and opposition
Ragona, Francesca	2011	26	From 1 year to 5 years	Achenbach Child Behaviour Checklist (CBC) Vineland Adaptive Behaviour Scale (VABS-II)	Attention deficit in 69.2% hyperactivity 58% autistic-like behaviour 15.4%
Riva, Daria	2009	2	From 11months to 7 years From 23 months to 8 years	Achenbach Child Behaviour Checklist (CBC)	**Scores not clearly reported:** Patient one: severely hyperactive Patient two: autistic-like traits; hyperactive
Turner, Samantha J.	2017	26	From 15 months to 28 years	Vineland Adaptive behavioural scale (VABS-II)	**Scores not clearly reported**
Villeneuve, Nathalie	2014	21	From 6 to 10 years	Vineland Adaptive behavioural scale (VABS-II)	**Low adaptive and behavioural DQ in all the children:** DQ=50 ± 3; range: 28– 76 **Socialization skills were significantly higher than autonomy:** 59 ± 3 vs. 43 ± 4; p = 0.002, t-test, n = 20 **Socialization skills were significantly higher than communication:** 59 ± 3 vs. 50 ± 3; p = 0.04; n = 20

ASD= autism spectrum disorder; PDD= pervasive developmental disorder; SCD= social communication disorder; DQ= developmental quotient

Table S3

Low level cognitive functions

First Author	Year	N° subjects	Age	Visual processing/ Phonological processing/ Fine-Gross motor abilities
Acha, Joana	2015	8	Dravet Young: From 8 to 10 years Dravet Old: From 11 to 16 years	**Phonological processing (%correct):** Same sound pair (8-10 years): 53% (SD=3.1); Same sound pair (11-16 years): 55.1% (SD=5.2) Different sound pair (8-10 years): 55% (SD=4.8); Different sound pair (11-16 years): 51.0% (SD=3.2)
Battaglia, Domenica	2013	9	From 4 years 6 months to 13 years	**Visual processing (Z scores):** VPI= -2.02 (SD=0.61) **Fine motor abilities (ABC movement test)** Abnormal 75% **Gross motor abilities (ABC movement test)** Abnormal in 37.5%
Chieffo, Daniela	2011a	12	First NPSY: 9 months to 42 months Follow up end: 4 years to 10 years	**Visual processing (Z scores):** visual perception test (form completion, figure ground) = -2 **Visual perception longitudinal data (Z scores):** age 4-5 years: -2.6 (SD=0.57) age 6 years: -2 (SD=0) age 7 years: -2 (SD=0) age 8 years: -1.83 (SD=0.24) age 9 years: -1.77 (SD=0.38)
Chieffo, Daniela	2011b	5	First NPSY: from 6 months to 24 months Follow up-end: from 30 to 51months	**Visual processing:** **Ocular motility** Case 1: asymmetric at 18/24/30 months Case 2: borderline at 24/32/39 months; abnormal at 45 months Case 3: borderline at 12 months; abnormal at 32/39 months Case 4: abnormal at 30/51 months Case 5: normal at 10/30/42 months **Attention over distance:** Case 1: abnormal at 18/24/30 months Case 2: abnormal at 24/32/39/45 months Case 3: abnormal at 12/32/39 months Case 4: abnormal at 30/51 months Case 5: normal at 10/30/42 months **Acuity:** Case 1: abnormal at 18/24/30 months Case 2: abnormal at 24/32/39/45 months Case 3: 12/32/39 months Case 4: abnormal at 30/51 months Case 5: normal at 10/30/42 months **Visual fields:** Case 1: asymmetric at 18/24/30 months; borderline at 6/8 months Case 2: abnormal at 32/39/45 months Case 3: asymmetric at 32 months; abnormal at 39 months Case 4: borderline at 30 months; abnormal at 51 months Case 5: normal at 10/30/42 months **Fixation shift:** Case 1: abnormal at 6/8/18/24/30 months Case 2: abnormal at 24/32/39/45 months Case 3: 12/32/39 months Case 4: abnormal at 30/51 months Case 5: normal at 10/30/42 months **Stereopsis:** Case 1: not evaluated Case 2: abnormal at 32/39/45 months Case 3: not evaluated Case 4: not evaluated Case 5: not evaluated
Chieffo, Daniela	2016	13	From 24 – 36 months to 4.3 – 7.8 years	Phonological processing (phonological accuracy subitem of the First Language Test (TPL): abnormal in 5/10 (mean Z score = -2.53, SD= 0.45) borderline in 4/10 (mean Z score= -1.5, SD= 0,19) normal 1/10 (Z score= -0.33)
Ricci, Daniela	2015	5	From 4 to 8 years	**Visual Processing:** Visual total score: abnormal in 3/ 5 at the age of 2years; became normal in all cases but 1 EF (Atkinson): 6 normal, 4 abnormal (10 results of 5 children) SM (Atkinson): 9 normal, 1 abnormal (10 results of 5 children) CD(Atkinson): 5 normal, 5 abnormal (10 results of 5 children)

				VPI: 1 normal, 3 borderlines (4 results of 4 children)
Verheyen, Karen	2019	43	From 9 months to 13 year 11 months	**Fine motor development:** mean motor age equivalent= 52.4; median= 65; range= 9-110 mean chronological age= 87.9; median= 100; range= 19-167 **Gross motor development:** mean motor age equivalent= 46.7; median= 48; range= 12-92

VPI=visual perception test; EF=embedded figures; SM=shape matching; CD=contrast discrimination of the frosting cats

Table S4

Sensorimotor integration functions

First Author	Year	N° subjects	Age	Visuomotor integration/ Auditory motor integration
Acha, Joana	2015	8	Young Dravet group: From 8 to 10 years Old Dravet group: From 11 to 16 years	**Visuomotor integration:** Median number of taps (8-10 years): M= 32, SD = 17.4 Median number of taps (11-16 years): M= 31, SD = 17.7 Median Inter-tap latencies (8-10 years): M= 551.3, SD=507.9 Median Inter-tap latencies (11-16 years): M= 557.0, SD=204.4) **Language production** % correct word production CV (8-10 years): 69.0 %17.3) CV (11-16 years): 46.6% (23.6) CVV (8-10 years): 51.5% (34.3) CVV (11-16 years): 35.2% (24.8)
Battaglia, Domenica	2013	9	From 4 years 6 months to 13 years	**Visuomotor integration:** Beery VMI z-score: -2.18, SD=0.50 **Language production** Naming (z scores): -2.03, SD= 0,99
Chieffo, Daniela	2011a	12	First NPSY: 9 months to 42 months Follow up end: 4 years to 10 years	**Visuomotor integration:** Beery VMI z-scores at 3 years: mean=-2.38, SD=0.40 Beery VMI z-scores at 4-5 years: mean=-2.47, SD=0.58 Beery VMI z-scores at 6 years: mean=-2.19, SD=0.33 (evaluated in 3 subjects) **Language production** Lexical naming z-scores at 3 years: mean=-1.68, SD=0.95 z-scores at 4-5 years: mean=-1.71, SD=0.74 z-scores at 6 years: mean=-0.96, SD=0.62 (evaluated in 3 subjects)
Chieffo, Daniela	2016	13	From 24 – 36 months to 4.3 – 7.8 years	**Language production** **First assessment** Naming z scores: mean= -1.71, SD= 1.18 **Outcome** Naming z scores: mean= -1.63, SD= 0.62 (2 children not tested) Repetition z scores: mean= -1.56, SD= 0.81(2 children not tested) Phonological accuracy: mean=-2.07, SD=0.64 (3 children not tested) Morphosyntactic accuracy: mean=-2.29, SD=0.71 (3 children not tested)
Ricci, Daniela	2015	5	From 4 to 8 years	**Visuomotor abilities** Beery VMI: 1 borderline, 8 abnormal (9 results of 4 children) Block design (subtest WISC): 3 borderline, 1 abnormal (4 results of 4 children) Rey-Osterrieth Complex Figure copy: 1 borderline, 3 abnormal (4 results of 4 children)
Turner, Samantha J	2017	26	From 15 months to 28 years	**Language production** 7 patients: not able to cooperate 13 patient's performance in the expressive vocabulary test: mean= 59.77; median= 59; range= 20-105 (Normative data—mean 100, SD 15; scores 70 and below: ,2 SD below the mean)
Verheyen, Karen	2019	43	From 9 months to 13 year 11 months	**Visuomotor abilities** Beery VMI: mean motor age equivalent= 48.7; median= 31; range= 9-110 (17/22 results delayed in 16 children) mean chronological age (months)= 79.6; median= 58; range= 11-167

CCV= consonant-consonant-vowel syllable cluster; CV= consonant-vowel syllable cluster; VMI= visuo-motor integration

Table S5

High level cognitive functions

First Author	Year	N° subjects	Age	Language comprehension; Attention; Memory; Executive functions
Acha, Joana	2015	8	Young Dravet group: From 8 to 10 years Old Dravet group: From 11 to 16 years	**Visual Memory task** Mean reaction times with visual distractors (8-10 years): 2592ms, SD=999// error rate=75.0% (23.5) Mean reaction times with visual distractors (11-16 years): 3101ms, SD= 490// error rate=79.2% (14.4) Mean reaction times with verbal distractors (8-10 years): 2877 ms, SD=1170// error rate=75.0% (15.2) Mean reaction times with verbal distractors (11-16 years): 2896 ms, SD=1046// error rate= 85.4% (4.2) **Working Memory:** number of items that can be retained in phonological memory (PWMT): Word span (8-10 years): mean=2.0, SD= 0.8 Word span (11-16 years): mean=1.8, SD= 0.5 **Executive Functions:** **%correct control of action:** 8-10 years= 26.0 (12.3) 11-16 years= 34.3 (14.1) **%correct control of inhibition:** 8-10 years= 54.8 (5.5) 11-16 years= 71.8 (14.8) **% correct categorization:** High frequency word= 79.4% (8.9) medium frequency word= 47.9% (8.9) low frequency word= 62.5% (17.7)
Battaglia, Domenica	2013	9	From 4 years 6 months to 13 years	**Memory (short/long term):** **Learning lists** Short term=4/9 abnormal Long term= 5/8 abnormal (1 not performed) **Working Memory:** digit span forward= 6/9 abnormal digit span backward= 2/9 abnormal **Visuo-spatial abilities** Corsi test forward=3/9 abnormal Corsi test backward= 3/9 abnormal Block design (z scores) = -2.04 (0.41) Rey copy (z scores) = -2.49 (0.48) **Visuo-attentional abilities**: Bell's Cancellation test-revised (z-scores) = -2.22 (0.83) **Executive Functions**: Tower of London (z scores) = -2.22 (0.52); (5 not performed)
Chieffo, Daniela	2011a	12	First NPSY: 9 months to 42 months Follow up end: 4 years to 10 years	**Working Memory:** Digit span (z scores) = < -2 **Visuo-attentional abilities:** Teddy bear and selective visual attention from LEITER-R scale revised (z scores) = < - 2 **Executive Functions (only 3 subjects)** **Word fluency (z scores):** At 6 years = -0.83 (0.24) 2 children At 7 years = -1.66 (1,42) 2 children At 8 years = -2,11 (0,96) 3 children At 9 years = -1.88 (0.84) 3 children **Tower of London (z scores):** At 6 years = -2.33 (0.94) 2 children At 7 years = -2.33 (0.94) 2 children At 8 years = -1.83 (1.18) 2 children At 9 years = -2.12 (1.02) 3 children **Language**: Lexical comprehension (z scores): At 3 years = -0.96 (1.05) At 4-5 years= -1.71 (0.74) At 6 years = -1,18 (0.54) At 7 years = -0,93 (0,30) 3 children At 8 years = -0,88 (0,19) 3 children

Chieffo, Daniela	2011b	5	First NPSY: from 6 months to 24 months Follow up-end: from 30 to 51months	**Visuo-attentional abilities**: age 6 – 12 months: normal (3/5), abnormal (1/5); age 30 – 51 months: normal (1/5), abnormal (4/5) **Visuo-spatial abilities**: age 6-12 months: normal (3/5), borderline or immature (1/5); age 30 – 51 months: normal (1/5), asymmetric (1/5), abnormal (3/5)
Chieffo, Daniela	2016	13	From 24 – 36 months to 4.3 – 7.8 years	**Pragmatic comprehension** normal 8/13), borderline (1/13), abnormal (2/13); **Word comprehension**: normal 8/13, borderline 1/13, abnormal 3/13 **Receptive language** Sentence comprehension= normal (6/13), borderline (3/13), abnormal (1/13), 3 children not tested Global comprehension= normal (8/13), borderline (3/13), 2 children not tested
Ricci, Daniela	2015	5	From 4 to 8 years	**Visuo-attentional abilities** **Teddy bears cancellation test**: 6 normal, 4 abnormal (10 results of 5 children) **The Bells Test** 1 borderline, 3 abnormal (4 results of 4 children) **Visuo-spatial abilities** **Shape matching (Atkinson)**: 9 normal, 1 abnormal (10 results of 5 children) **Executive Functions** Porteus (subtest WISC III): 2 borderline, 1 abnormal (3 results of 3 children)
Turner, Samantha J	2017	26	From 15 months to 28 years	**Receptive Language** 7 patients: not able to cooperate 12 patients: mean= 59.17; median= 56.5; range= 20-100 1 patient: PPVT 76; TROG 71

VMT=visual memory task; PPVT= Peabody Picture Vocabulary Test; TROG= Test for Reception Of Grammar