Deconstructing Dravet Syndrome neurocognitive development: a scoping review

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Abstract

Dravet syndrome (DS) is a rare severe epilepsy syndrome associated with slowed psychomotor development and behavioural disorders from the second year onwards in a previously seemingly normal child.

Among cognitive impairments, visuo-spatial, sensorimotor integration and expressive language deficits are consistently reported. There have been independent hypotheses to deconstruct the typical cognitive development in DS (dorsal stream vulnerability, cerebellar-like pattern, sensorimotor integration deficit), but an encompassing framework is still lacking.

We performed a scoping review of existing evidence to map DS cognitive and behavioural developmental profiles' current understanding and summarize the evidence on suggested frameworks.

We searched PubMed, Scopus, PsycInfo and MEDLINE to identify reports focusing on cognitive deficits and/or behavioural 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 was followed. Twenty-one reports were selected and tabulated by three independent reviewers based on predefined data extraction and eligibility forms.

Eighteen reports provided assessments of global intelligence quotients with variable degrees of cognitive impairment. Eleven of these single analyzed sub-item, contributing to global cognitive scores, showed consistently higher performance impairment than in verbal scales. Studies assessing specific cognitive functions demonstrated 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.

Behavioural abnormalities, reported from 14 studies, highlighted autistic-like traits, attention and hyperactivity disorders, slightly improving with age.

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

Key Points Box

- DS is a complex developmental encephalopathy characterized, among other symptoms, by cognitive stagnation and behavioral disorders
- A comprehensive framework facilitating the understanding of cognitive/behavioral issues in DS to guide future research is still lacking
- A sensorimotor-integration impairment encompassing a visuo-dorsal-stream dysfunction and a coexistent cerebellar deficit may explain DS cognitive outcomes
- Future work should concentrate on these aspects and disentangle their relative contributions to the disease

INTRODUCTION

Dravet syndrome (DS), is a complex and rare epileptic developmental encephalopathy, with an estimated prevalence between 1/15.000 and 1/40.000 [1,2], first described by Dravet in 1978 [3]. DS manifests with drug-resistant "febrile and afebrile generalized and unilateral, clonic or tonic-clonic seizures, occurring in the first year of life in an otherwise apparently normal infant" [4], later on, associated with myoclonic and absence seizures and the occurrence of status epilepticus. Based on seizure semiology, two forms are currently recognized: typical DS and atypical DS, characterized by the lack of myoclonic seizures [5].

At least 80% of people with DS carry familial or de novo mutations of the sodium channel α1 subunit (SCN1A) gene [6]. From the second year of life, cognitive stagnation, associated with neurological signs, gait abnormalities[7] and behavioural disorders, becomes evident, leading to a progressive ubiquitous developmental delay [8].

Several neuropsychological phenotypes are reported, ranging from mild specific deficits to severe global impairment. Visual impairments and visuo-motor deficits in DS usually manifest early. They may anticipate higher-order cognitive-developmental abnormalities, such as impaired visuo-constructive abilities, attention, language production and executive functions. This contrasts with better preservation of visual object recognition, memory and language comprehension [8–10] in line with a dorsal-ventral cognitive dissociation, suggesting an involvement of the dorsal stream pathway (see Table 1).

Behavioural disorders are common and often characterized by hyperactivity, attention deficit, autistic traits, aggressiveness, and opposition [11].

The pathophysiology underlying such a broad spectrum of neuropsychological features is not fully understood. Three main theoretical frameworks have been independently proposed to explain the DS cognitive and behavioural profile: the dorsal stream vulnerability hypothesis [12] the cerebellar-like pattern [13] and the sensorimotor integration deficit [14,15] (see Table 2).

According to the dorsal stream vulnerability hypothesis (based on the cognitive dual-stream hypothesis[16]), slight visual deficits precede the decline of visuo-motor dorsal pathway skills. The asymmetric involvement of the so-called visual "dorsal pathway" functions, opposed to the "ventral" ones, is consistently reported. A similar asymmetry in the involvement of the two cognitive pathways has been described in other genetic syndromes (Williams, Prader Willi, fragile-X), leading to the concept of genetic involvement as the determinant for the cognitive pattern as well as for the seizures [8,12]. A recent study found a high degree of expression of some genes, including SCN1A, along with the brain's visuo-motor integration network, connecting its malfunctioning with the genetic mutations [17].

The cerebellar-like pattern hypothesis also links the cognitive impairments and SCN1A mutations. Experimental studies on a DS model in mice [18] showed decreased excitability of inhibitory cerebellar Purkinje neurons likely to explain some of the motor and cognitive deficits observed [13,19]: ataxia, poor motor coordination, impairment of executive functions, spatial cognition, language and autistic-like behaviours. [20]

Lastly, the sensorimotor integration hypothesis refers to the complex process at the central nervous system level that allows the accomplishment of specific motor responses based on integrating multiple sensory information sources [21]. These integrative processes, especially visuo-motor and auditory-motor integrations, are frequently impaired in children with DS, suggesting the sensorimotor integration deficit as a likely framework. According to this model, an integration deficit can explain the observed visuo-motor and visuo-constructive impairments and the productive language dysfunctions consequent to an auditory-motor deficit [13–15]. Conversely, the frequently observed gait and postural abnormalities, [7] may be interpreted as the result of abnormal proprioceptive and vestibular integration [15]. Behavioural

abnormalities are associated with earlier visuo-motor integration deficits limiting social learning abilities and communication efficacy [22,23].

We aim to summarize cognitive and behavioural findings in DS to collate evidence in favour or against the three proposed hypothesis and propose a unified theoretical framework. Future research and clinical practice could benefit from this understanding to aid new practical rehabilitative approaches.

Toward this aim, the following research question was formulated: Is *the evidence favouring or contradicting the main hypotheses to deconstruct DS neurocognitive developmental phenotype?*

METHOD

We used the PRISMA-ScR checklist for Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews [24]. After data extraction and in light of the extreme heterogeneity of the assessed cognitive domains and neuropsychological test, we opted for a scoping review [25,26].

Eligibility Criteria

Inclusion criteria were: full-length items, peer-reviewed, original research articles in English, and published between 1978 (when DS was initially described) [3] and 15 March 2020. Included items reported on individuals meeting the ILAE diagnostic criteria for DS [27] and assessed to have behavioural disorders or at least one of the following cognitive dysfunctions: visual processing, phonological processing, visuo-motor processing, visuo-spatial abilities, visuo-attentive abilities, working memory, executive functions, language, measures of general development besides intelligent quotients. Cognitive evaluations had to be carried out using standardized neuropsychological tests. Single case studies, animal studies, and articles not meeting the inclusion criteria were excluded.

(See Appendix 1).

Information Sources

A systematic search on DS neuropsychological characterization was conducted by one author (MB). The databases Scopus, PubMed, PsycInfo and MEDLINE were searched by adapting the following keywords to meet each database's search features: Dravet syndrome, severe myoclonic epilepsy in infancy, cognition, neuropsychology, neuropsychological phenotypes, autistic features, autism spectrum disorder. Detailed search queries for PubMed are provided in **Appendix 1**.

The electronic database search was supplemented by screening the reference lists of retrieved articles and scanning relevant reviews. Final search results were exported into the MENDELEY bibliographic software package to keep and organize finding and apply deduplication procedures.

Selection of Sources of Evidence

To increase consistency in the selection, three reviewers (MB, AH, KV) independently evaluated the identified articles. A fourth reviewer (ADF) revised articles in cases of disagreement on data extraction or inclusion. See Figure 1 for the full selection procedure.

Data Charting Process and Data Items

Reviewers jointly designed an *ad hoc* data extraction form covering relevant variables to address the research question by adapting one proposed in the Cochrane handbook for systematic reviews [28] (see **Appendix 1)**.

The first part of the extraction form identifies general article information and organizational aspects: reviewer identity, day of review, article title, 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 the type of publication, sample characteristics, assessment method, and outcomes of interest.

Eligible items were eventually tabulated 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) cognitive domains assessed and assessment procedures (specific neuropsychological tests, test batteries, questionnaires).

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

RESULTS

Synthesis of the results

A first screening based on titles and abstracts led to identifying 36 articles, which underwent full-text examination.

Of these, 15 were excluded: three were not full-lengths original research articles (editorials and internal progress reports); seven were reviews used to screen for missing items of potential interest; two did not assess outcomes of interest; 3 did not use standardized neuropsychological assessment tools.

Lastly, the outcomes of the 21 included articles were grouped according to cognitive domain assessed (see Table S1): 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 behavioural outcomes. For each domain, we reported the assessment method and the main findings.

Study characteristics

Studies included were heterogeneous in study design (seven cross-sectional, three longitudinal retrospective studies, ten prospective longitudinal studies and one family cohort study), participants age (≥6 months - 60 years), assessment tools, and assessed domains. Multiple tests were administered in the same study (See Table S2).

Global cognitive assessment

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

The following scales were used: Wechsler intelligent scales, adapted to the age at testing (13 studies); Griffiths' mental scales (nine studies); Brunét-Lezine (BL) Developmental Scale (four studies); Gesell Developmental Scales (one study); McCarthy Scales of Children's abilities (one study); Psychoeducational Profile, Third Edition (PEP- 3) (one study). In two studies, Raven's Coloured Progressive Matrices were used as an alternative measure of intelligence when children were not fully-cooperative. (See Table S3).

All 18 studies reported a variable degree of developmental delay/intellectual disability, ranging from low average intelligent quotient to profound intellectual disability. In the studies which reported them, the tests' sub-items analysis showed a more significant contribution of the performance intellectual quotient (PIQ), than the verbal intellectual quotient (VIQ) in determining the global intellectual disability. In particular, 11 of 18 reports highlighted severe impairment in visual, fine motor, gross motor, visuo-motor, visuospatial and receptive language functions. The remaining seven studies did not report single sub-item scores.

Of seven studies investigating the relationship between epilepsy features (semiology and frequency of seizures) and intellectual disability, three highlighted the relationship between myoclonic plus absence seizures with a worse cognitive

outcome [29–31]. Two studies found a correlation between higher seizure frequency and worse cognitive development [10,32], whereas another two did not find any clear association [12,33].

Two studies examining the relationship between autism and IQ found a significantly higher proportion of profound intellectual disability in children who were also diagnosed with autism [34,35].

Behavioural assessment

Behavioural abnormalities were evaluated in 14 of 21 included studies using the following scales:
Achenbach Child Behaviour Checklist (eight studies); Vineland Adaptive behavioural scale (five studies); Autism Diagnostic Interview (ADI) (two studies); The Autism Diagnostic Observation Schedule (ADOS) (two studies); Conner's Comprehensive Behaviour Rating Scale (CBRS), Pervasive developmental disorder in mental retardation scale-revised (AVZ-R), Maladaptive behaviour scale for individuals with ID (SGZ), Temperamental scale for individuals with ID (TVZ), Autism Behaviour Checklist (ABC), Childhood Autism Rating Scale (CARS), and Diagnostic Interview for Social and Communication Disorders (DISCO), each in one study (see Table S4).

Of the 14 articles, seven reported autistic-like traits, six attention deficits and six hyperactivity disorders. Externalizing behaviours, especially hyperactivity, impulsivity and aggressiveness, were more often observed than internalizing behaviours (anxiety, depressive-traits and over-controlled behaviours), with the exceptions of two studies finding the opposite pattern [13,31].

Two studies reporting the longitudinal evolution of behavioural abnormalities found a gradual decrease in behavioural disorders from adolescence to adulthood [29] and from the first evaluation (mean age: 21.7 months) to the last follow up (mean age: 6 years 6 months) [33], especially related to hyperactivity traits.

Three studies investigating comorbidity between DS and autism spectrum disorder (ASD) found between 23% and 62% of people with DS additionally diagnosed with ASD [34–36]. Another eight studies reported the presence of pervasive autistic-like traits such as poor eye contact, ritualistic behaviours, narrow interests, speech delay, adherence to routine and low ability to express emotions. In some of these studies, however, authors emphasized relative preservation of socialization capacity and excessive familiarity with strangers, which contrasts with the typical autistic pattern [9,36].

Specific perceptual and cognitive functions assessment

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

Seven of 21 articles reported evaluations of visual processing (four studies), phonological processing (two studies) and fine/gross motor abilities (two studies) (see Table S5).

Two of the four articles assessing visual processing abilities emphasized variable degrees of impairment in the different sub-scores tested, ranging from abnormal to average scores [12,37]. Two items reported general pervasive visual perceptual impairment in all assessed children [13,33].

Two studies examining phonological processing abilities emphasized impairments in phonological perception and detection, particularly: 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 sub-item of the Testa (TPL) (5 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 most children older than two-years. In the first study, gross motor delay was reported in 7 of 7 and fine motor delay in 11 of 13 individuals [38] while in the other, abnormal fine motor abilities were observed in 75% and abnormal gross motor abnormalities in 37.5%[13].

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

Seven articles analyzed sensorimotor integration abilities in DS. Of these, five examined visuo-motor integration abilities and five auditory-motor integration abilities (see Table S6)

All five articles investigating visuo-motor integration abilities reported inferior performances. Four reports assessing visuo-motor development using the Beery-Buktenica Developmental Test of Visual-Motor Integration reported mean Z scores of 2 SD below the mean [12,13,33,38]. In one study, a finger tapping task's performance showed fewer taps and higher inter-tap latencies than healthy age-matched controls [14].

All five studies assessing language production abilities reported dysfunctions in naming and repetition, related to oral sensorimotor impairment rather than semantic dysfunctions, resulting in imprecise articulation, omission errors and low phonological and morphosyntactic accuracy [13–15,33,39].

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

Seven studies reported the assessment of language comprehension, attention, memory and executive functions. Language comprehension abilities investigated in three studies showed results mainly in the normal range with few exceptions showing a borderline impairment level. Visual attention abilities as well as executive functions, assessed in four studies, showed impaired skills. In detail, the results of the Teddy Bear Cancellation test and the Bell's cancellation Test showed scores on average lower than 2 SD below the mean, with a few borderline scores (see Table S7).

Significantly worst performance was reported in DS than in controls in a go/no-go task, 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 three studies, also showed impairments.

Verbal working memory (digit/word span, forward and backward) and spatial working memory (Corsi test, forward and backwards) tasks appeared to be impaired [13,33]. In contrast, a visual memory task [14] did not find any significant differences between controls and the DS group.

DISCUSSION

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

We associated each of our finding with the three main hypotheses to deconstruct DS neurocognitive developmental phenotype: the dorsal stream vulnerability premise, the sensorimotor integration deficit theory and the cerebellar-like configuration (see Table 3). We discuss our findings accordingly.

Findings fitting with all three hypotheses

Variable degrees of global cognitive impairment, ranging from mild to profound as assessed by general developmental/ intelligence scales, emerged. No unequivocal relationship between the degree of global cognitive impairment and seizure type or frequency could be recognized [10,29–32]. Therefore, the assumption of a purely epileptic aetiology of cognitive deterioration in DS should be re-considered [29,30].

The relative contribution of the tests' sub-items in determining the global intellectual retardation displayed significantly worse scores in Wechsler's performance subscales and the hand-eye coordination and gross-motor subscales of the (Griffiths' and Brunet Lézine developmental scales) compared to verbal comprehension and memory abilities.

The assessment of specific cognitive function also confirms the verbal-performance cognitive asymmetry. Low-level cognitive functions including visual processing and fine and gross motor abilities, showed impairment from a young age

[12–14,37,38,42] and often heralded a progressively abnormal development of higher order cognitive functions [14,37], motor inhibition, planning, set-shifting, verbal fluency and working memory [12–15,33,39]. These findings seamlessly match the dorsal stream vulnerability model and the sensorimotor integration deficit hypothesis, suggesting an early visual deficit preceding the decline of visuo-motor dorsal pathway skills leaving the ventral ones relatively preserved.

The cerebellar-like pattern may also account for this: low fine and gross motor abilities, impairment of executive functions including poor planning, set-shifting, verbal fluency and spatial working memory, are often referred as part of the so-called "cerebellar cognitive-affective syndrome" [43].

Dissociation between the three hypotheses

Sensorimotor integration abilities showed inferior results [12,13,33,38], which are not limited to the visual dorsal stream functions.

In the language domain [45] the motor aspects of 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]. Functional abnormalities of this sensory-motor loop in the dorsal stream may also account for observed verbal working memory deficits [14]. According to Baddeley's model of working memory[46], keeping an active trace of auditory-based representation relays on the continuous rehearsal of information through articulatory-based processes [46].

These poor performances in visuo-motor and auditory-motor integration manifest from the first developmental stages, rather than maturing later due to an abnormal developmental process, and seem responsible for cognitive and motor disharmonic development [15].

Abnormalities in visual and language sensorimotor systems have been observed in other genetically based clinical pictures, such as Williams syndrome, Fragile-X syndrome and Prader-Willi syndrome, leading to a genetic hypothesis in the determination of the cognitive outcome [13,15]. A study investigating the contribution of the SCN1A mutation to the DS neuropsychological phenotype in a family showed variable involvement of visuo-motor abilities among three generations of mutation carriers, despite the great heterogeneity in seizure severity and global neuropsychological functioning observed [47].

Some reported language production abnormalities such as dysarthric speech characterized by imprecise articulation, abnormal nasal resonance, voice and pitch, fit better with the cerebellar-like pattern than with the sensorimotor model [43]. Thus, a cerebellar parallel contribution to the language profile should be taken into account.

Sensorimotor impairment is reported as a causative factor in the development and maintenance of autistic-like traits [22,23]. In particular, 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 [22,48]. Conversely, anatomical, clinical and neuroimaging studies strongly claim a vital role of the cerebellum as one of the neural underpinnings of autism spectrum disorder and ADHD [43]. The affective component of the cerebellar cognitive, affective syndrome comprises impairment in attentional and emotional control, psychosis, autism spectrum signs and social impairment [20]. This has been interpreted in light of the cerebellar interconnections with limbic structures. Its function in error-driven automatic and implicit learning processes is at the base of social cognition development [49].

Another feature characterizing DS neurocognitive development concerns fine and gross motor abilities abnormalities. Some neurological cerebellar signs, such as ataxia and hypotonia, are frequently reported and linked with the SCN1A genetic mutation thought to affect Purkinje cerebellar neurons' excitability [33].

Accumulating evidence suggests the sensory integration process's fundamental role in determining the final gait output [50], whereas other define gait as a sensorimotor function *per se* [51]. One of the reports reviewed 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].

Even if the sensorimotor integration deficit hypothesis and the cerebellar-like pattern may account for motor deficits, it clear that they may explain complementary but not overlapping aspects of the final motor profile. The two systems have different roles in motor control. While parietal lobes integrate information of other sensory modalities to build an internal model of the outside world and the body to set proper motor programs, the cerebellar system provides additional control over the incoming sensory information quality and movements' accuracy.

None of the three hypotheses alone can account for the heterogeneity of the described symptoms affecting motor, cognitive and behavioural domains. We believe that a unified sensorimotor-cerebellar framework may explain the coexistence of most of the signs and symptoms. This model may promote a syndrome-specific assessment tool, which addresses domains prevalent in DS rather than testing all of them.

We stress the need and potential advantage of designing new assessment tools sensitive enough to detect the different contribution of sensorimotor integration deficits and cerebellar ones.

LIMITATIONS

Our review has limitations. The overall number of reports on this subject was small. The reports' methodological heterogeneity and the small amount of evidence within this topic prevent a precise DS cognitive profile extraction. As most studies also reported just global intelligence scores, we could not analyze single sub-item contribution in the included material. These limitations, however, do not detract our view of a unifying framework for the cognitive profile of people with DS.

CONCLUSION

The sensorimotor integration deficit hypothesis supports the dorsal stream vulnerability hypothesis. It may account for most of the cognitive/behavioural disabilities in DS and the autistic-like traits and gait abnormalities.

The cerebellar disorder is likely to play a role in determining impairments that are different and complementary to the ones explained by the sensorimotor integration deficit. In fact, given the clinical manifestations' complexity, we cannot exclude neocortical and subcortical areas other than the cerebellum.

A unified sensorimotor-cerebellar framework may explain most of the behavioural, motor and language disorders seen, which if taken in isolation provide only a fragmentary picture of the complex signs and symptoms in DS. Figure 2 summarizes the unified framework we propose.

Future work should specifically address the sensorimotor integration deficit and the cerebellar signs to disentangle their relative contribution in determining the final cognitive/behavioural phenotype. People with DS mainly present a set of sensorimotor integration deficits or more cerebellar signs. Conversely, one set of symptoms may be more predominant in a specific developmental period or precede the other's onset. Future research should focus on developing new screening tools able to grasp and distinguish these aspects during the diagnostic phase. This, in turn, will lead to cognitive and motor rehabilitation programs targeting each subject' specific pool of symptom.

CONFLICT OF INTEREST

None of the authors has conflicts of interest to disclose concerning this work. We confirm that we have read the Journal's position on ethical publication issues 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 manuscript preparation. All co-authors have seen and approved the final submission of the manuscript and accept responsibility for its content.

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Tables

1. Cognitive dual stream theory

2. Three theoretical frameworks for Dravet syndrome

3. Evidence in favour of the main hypotheses

Figures

1. Flow chart of the systematic search

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

2. Unified theoretical framework

Three main theoretical frameworks to explain DS cognitive and behavioural profile have been independently suggested. This review offers a unified literature-based theoretical framework to understand DS cognitive characterization better and guide future research.

Supplementary Material

Table S1. Number of articles and the articles assessing each outcome of interest

Table S2. Assessed perceptual, cognitive and behavioural domains and assessment tools

Table S3. Global cognitive outcomes

Table S4. Behavioural outcomes

Table S5. Low level cognitive and perceptual functions

Table S6. Sensorimotor integration functions

Table S7. High level cognitive functions

Table S8. Research teams and main sustained hypotheses

PRISMA-ScR Checklist: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

Appendix 1

1. PubMed search strategy

Queries Pubmed		
Search	Query	Items found
#6	#4 OR #5	46
#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

ORGANIZATIONAL 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 / Book 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** / No Enter name of the source (e.g. PI, sponsor, etc.) _____	
Contact address:	

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

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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 / out-patient / unclear / NR
Trial Design	Cross-sectional Longitudinal Prospective Longitudinal Retrospective Family study
Length of follow-up	From _____ until_____
Conflict of interest statement	Yes / No / NR
Number of groups/subgroups (DS vs. control group)	

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

Treatment	

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