Child Neuropsychology, 2014
http://dx.doi.org/10.1080/09297049.2014.959480

Routledge
Taylor & Francis Group

Cognitive characterization of children with Dravet syndrome: A neurodevelopmental perspective

Joana Acha[1], Alejandro Pérez[2], Doug J. Davidson[2], and Manuel Carreiras[1,2,3]

[1]Department of Basic Cognitive Processes, University of the Basque Country Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), Donostia, Spain
[2]Basque Centre on Cognition, Brain and Language (BCBL), Donostia, Spain
[3]Ikerbasque, Basque Foundation for Science

Dravet syndrome (DS) is an epilepsy of infantile onset, usually related to a mutation in gene sodium channel alpha 1 subunit, that leads to different typological seizures before the first year of life. Although most research has focused on the clinical description of the syndrome, some recent studies have focused on its impact on cognitive development, identifying both motor disorders and visual-processing deficits as basic factors affected in adults and children with DS. In this article, we designed a cross-sectional study to examine the cognitive phenotype of children affected by DS from a neurodevelopmental perspective. We report measures for both basic (auditory perception, visual and phonological processing, motor coordination) and higher order cognitive processes (verbal production, categorization, and executive function) in two age groups of DS children (M = 8.8 and M = 14.1) and control children of the same chronological age. Results showed an important cognitive delay in DS children with respect to controls in both basic and higher order cognitive abilities, with a better general outcome in tasks that required processing visual material (visual memory and categorization) than in tasks involving verbal material. In addition, performance of DS children in certain basic tasks (visual memory) correlated with performance on complex ones (categorization). These findings encourage promoting an early identification of not only clinical but also cognitive features in DS children from very early stages of development in order to optimize their neurodevelopmental outcome.

Keywords: Dravet syndrome; Brain development; Working memory; Verbal production; Executive function.

Dravet Syndrome (DS) is a rare form of epilepsy characterized by recurrent seizures that appear in an apparently healthy child. The complex characterization of the syndrome onset during first year of life by febrile, afebrile, clonic, and tonic-clonic seizures, and further repetitive mainly myoclonic seizures (Dravet, 1978; Dravet, Bureau, Oguni,

The research reported in this article has been supported by the private funding from the Spanish Dravet Foundation.

We acknowledge the invaluable work of the Basque Centre on Cognition, Brain and Language lab coordinators Larraitz Lopez and Oihana Vadillo for the children assistance during the experimental sessions.

Address correspondence to Joana Acha, Department of Basic Cognitive Processes, University of the Basque Country UPV/EHU, Tolosa Hiribidea, 20018 Donostia, Spain. E-mail: joana.acha@ehu.es

Fukuyama, & Cokar, 2005) has led to an increasing interest in its clinical causes as well as in its neurological outcomes. Clinical evaluations have shown that the mutation of the sodium channel alpha 1 subunit (SCN1A) affects the phenotype in at least 80% of cases (Claes et al., 2009; Depienne et al., 2010). Although only one third of children show this mutation, it is one of the main markers used for diagnosis (Stenhouse, Ellis, & Zuberi, 2013). This mutation reduces sodium channel activity in inhibitory cortical and hippocampal interneurons, particularly in GABAergic (gamma-aminobutyric acid) interneurons involved in the regulated firing of neural patterns and neural excitability (Martin et al., 2010; Yu et al., 2006). The lack of regulated neural activity, together with an extreme sensitivity to temperature, seem to be the main underlying causes of seizures and epileptiform discharges in childhood (Hattori et al., 2008; Oakley, Kalume, Yu, Scheuer, & Catterall, 2009; Sánchez-Carpintero, 2011). During the last decade, most studies have focused on the clinical description of the syndrome to help identify prognosis factors and to prevent seizures with appropriate medical treatment. However, few studies have explored the neurodevelopmental cognitive pattern of children that experience such seizures (see Ragona et al., 2011) in order to clarify the impact of the syndrome on cognitive abilities that lag behind brain maturation during these critical years.

Much of the understanding of the underlying mechanisms of cognitive development and cognitive impairments comes from comparisons between impaired and normal developing children in different domains (Elman, 2005; Karmiloff-Smith, 1998). These comparisons rest on the assumption that the progressive development of brain connections lead to increasing and more sophisticated cognitive abilities (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Nagy, Westerberg, & Klingberg, 2004), and that delayed or impaired neurocognitive outcomes could be tied to disruptions or unusual patterns of connections during brain development (Fair, Posner, Nagel, Bathula, & Costa, 2010; Frith & Happe, 1998; Wang, Hesselink, Jernigan, Doherty, & Bellugi, 1992). Thus, the behavioral outcomes of a disrupted brain can be compared to the behaviors expected from a normal developing one. It is important to note that the earliest developmental stages seem to be crucial in this time course, since the functionality of the nervous system takes place with the myelination of oligodendrocytes even 1 or 2 months before birth and extends gradually to the frontal lobe by 9 months of postnatal age (Paus et al., 2001). The arborization of dendrites and axons during this period delimits the emergence of different functions. For instance, subcortical-somatosensory areas develop primarily during the first year of life (Huttenlocher, 2009), whereas connectivity to other brain areas increases from 12 months on, following a posterior-anterior direction. If higher order abilities are attributed to increased connectivity across medial and frontal cortical areas in the brain (Johnson, 2001; Levitt, 2003), the result of aberrant brain development could impact different aspects of perception, memory, and executive function with different manifestations across ages (see, for example, Frith, 2001). Epileptic syndromes can be addressed from this neurodevelopmental framework, taking into account that they are often extremely disruptive to development.

Several studies have previously examined the cognitive delay associated with epilepsy in young children (Aldenkamp et al., 1996; Mandelbaum & Burack, 1997), showing that epileptic syndromes lead to a general impairment in basic cognitive abilities like attention, speed of processing, and working memory (Aldenkamp & Arends, 2004). However, the special characterization of epileptiform discharges in DS does not allow the generalization of these previous results to this specific population, because seizure onset

before one year and the recurrent emergence and variability of seizures throughout early infancy in DS make it an exceptional case (Dravet 2011).

In fact, several studies have shown that children with DS typically exhibit manifestations such as ataxia, poor motor development, and visual function deficits (Brunklaus, Dorris, & Zuberi, 2011; Cassé-Perrot, Wolf, & Dravet, 2002; Chieffo, Ricci, et al., 2011), as well as to abnormal interictal encephalography (Korff et al., 2007). In addition, recurrent myoclonic seizures — extremely brief and barely discernible muscle contractions—that are typical from the second year of life seem to lead to more severe cognitive deficits. In view of the findings from longitudinal studies, the onset time of cognitive decline is approximately 2–3 years (Cassé-Perrot et al., 2002). For example, Chieffo et al. conducted an assessment of five cases. The age of infants ranged from 6 to 10 months, and the follow-up mean duration was 33.8 months. The authors observed that four of the evaluated kids showed impaired ocular activity (few fixations, low acuity, slow shifts) and low eye-hand coordination abilities (see also Dravet, 2011), and that these children were the ones showing cognitive decline throughout development. In another 6-year follow-up study of 12 children (age range 4–6) the same authors observed that the cognitive delay attained mainly hand-eye coordination, visual function, and language. Interestingly, the psychomotor delay was greater than the language delay, in which the deficit was manifested in production rather than comprehension. In addition, verbal working memory and executive function impairments were observed, as well as language production deficits. Using a larger cohort (age range 6–42), Brunklaus, Ellis, Reavey, Forbes, and Zuberi (2012) observed that, among the patients studied for a 5-year period, the most relevant developmental outcomes were motor disorders such as hypotonia, ataxia, spasticity, and dyskinesia (36%), behavioral problems (46%) as well as some autistic features (33% of the cohort). Noteworthy, the presence of a motor disorder (as well as abnormal interictial EEG in Year 1) was a strong predictor of a worse developmental outcome in this study. Two important conclusions can be drawn from these studies. First, early absences, myoclonic seizures, and early presence of subcortical (e.g., visual, motor) dysfunctions may be related to further cognitive decline in DS children (Brunklaus et al., 2012; Ragona et al., 2010). Second, these findings support the suggestion that the syndrome may involve greater cognitive impairment with increasing age (see also the cross-sectional assessment of Catarino et al., 2011), probably due to disrupted connectivity between posterior and anterior regions.

However, there is still an ongoing debate about the general cognitive pattern involved in DS (Ragona et al., 2011). In addition, most studies have focused on basic abilities reliant on subcortical areas. There is to date little evidence about the execution of complex cognitive abilities in DS children, such as verbal production, categorization, and inhibition—all dependent on interconnectivity between subcortical, temporo-parietal, and frontal regions. Stevens (2009) describes the delay of DS children with respect to normal developing children in such abilities and the relation between higher order and basic abilities. From a neurodevelopmental perspective, both basic and higher order processes should be examined at different chronological ages, when behaviors that lag behind such processes are expected to show up.

To this aim, we designed a cross-sectional study in which we examined a broad set of cognitive processes and the relationship between early and late developing abilities in a sample of DS and control children of the same chronological age. Two age groups were selected to compare the developmental pattern in DS and controls through the following tasks: (a) auditory detection, visual memory, phonological working memory

and motor tapping to test earlier developing processes and (b) vocabulary production, categorization, and inhibitory control to test higher order processes that lag behind earlier developing ones.

GENERAL METHOD

Participants

We recruited 4 DS children from 8 to 10 years (M = 8.8) and 4 DS children from 11 to 16 years (M = 14.1), as well as 8 control children of the same chronological age for this study. The DS participants were selected from a larger pool of 27 children previously diagnosed by hospital physicians and recruited from the Spanish Dravet Foundation. All the parents from the foundation provided details about the clinical and cognitive history of the children as part of the recruitment. The neuropsychological examination at the hospital included information about motor skills, language, and general IQ, providing general information about the delay[1]. Our selection was based on the following criteria: (a) SCN1A mutation present, (b) seizure reported before the first year of age, and (c) EEG findings consistent with DS. Children who did not fit Criteria a, b, or c were excluded from the testing, and those who had severe motor impairments were also excluded from the analysis, since they were not able to complete the tasks, although they tried to do so. The clinical and neuropsychological characterization of the participants is described in Table 1. Both control and DS children came from the same region and socioeconomical background. All of them were native speakers of Spanish.

Tasks Designed to Measure Basic Processes: Materials and Procedure

Auditory Detection Task. This task was designed to test auditory perception and phonemic discrimination[2]. We focused on the early perceptual level since speech perception is based primarily on well-defined phonological representations that children will need to internalize and produce. Children of 7 months are already able to detect different phonemes as well as stress patterns in their language (Curtin, Mintz, & Christiansen, 2005) and a good ability to discriminate phonemes is related to language and reading development. We employed a very simple same-different judgment paradigm (Friedrich & Friederici, 2006) to test whether DS children were sensitive to different phonemic contrasts. To that aim, a list of 80 pairs of syllabic sounds was created. In 40 of the trials, both syllables in the pair were the same (20 bilabial: 10 *ba-ba* and 10 *pa-pa*; and 20 dental: 10 *da-da* and 10 *ta-ta*). In the

[1]As seen in Table 1, not all the children were run on the same neuropsychological batteries at the hospital. We tried to run the Kaufman brief intelligence test (Kaufman, 1990) in our lab to get a concrete measure of each child´s mental age. However, none of the children were able to complete the task, and they did not pay enough attention to do the logical section without the help of the experimenter. For this reason, it was estimated that all children had a mental age below 5 to 9 years of their chronological age (ranging from 2 to 3 years in the younger group and from 3 to 6 in the older group, approximately), although this was an approximate calculation. For this reason, it was impossible to create a proper mental-age control group and we decided to use the chronological-age control group only.

[2]Several tasks were discarded because of the at-chance error rate of DS kids. Children were unable to properly complete the following tasks: phoneme categorization and phoneme deletion (phonological level), auditory lexical decision, comprehension of causal events (linguistic level), and the Stroop task (automatic reading).

Table 1 Clinical and Educational Features in SCN1A Mutation-Positive Dravet Children Selected for the Experiments.

	Y4	Y11	Y14	Y22
Younger group clinical data				
Mutation type	Arg123Stop	truncating	change of c. 602 +1g>A	change of c. 302 g. axon 2
Age first seizure	5 months	3.5 months	6 months	4 months
EEG findings	decrease wave peaks multifocal left/ right hemis. mainly during sleep	slow wave discharges focal right frontal Fp2 and generalized 2–3 Hz	multifocal disch. diffused	Not reported
Photosensitivity	solar	solar, artificial	not reported	solar, artificial
Age at test time	8.1	8.2	8.9	9.2
Seizure freq.	8/year	1/month	3/year	2-5/month
Mean duration	5-20 min	30 sec	7 min	2 min
Treatment	Levetiracetam 700 Divalproex 450 Ethosuximide 500	Topiramate 250 Divalproex 300 Methyl phenidate 10/x2	Levetiracetam 200 D ivalproex 300	Ethosuximide 700 Divalproex 900
Most common type of seizure	Myoclonic focal typical/atypical	Tonic-clonic focal/typical absences	Myoclonic absences	Myoclonic focal/typical absences
Younger group educational data				
Age schooling	2 years	4 years	2 years	2 years
Type of school	Special	Special	Ordinary	Special
IQ reported	Mild delay Peabody 3 years	Mild delay MSCA 3 years Peabody 4 years	Mild delay	High delay WPPSI not completed
Damaged areas	Motor Language	Language Reasoning	Motor Language Reasoning	Memory Language Reasoning
Self-sufficiency	3/10	7/10	5/10	5/10
Symbolic Play	Yes	Yes	Yes	No

(*Continued*)

Table 1 (Continued).

	O13	O15	O17	O19
Older group clinical data				
Mutation Type	Stop c.1516 c>T Q516X	truncating	truncating	c.5132c>A Thr1711Asn
Age 1st seizure	5 months	10 months	5 months	11 months
EEG findings	slow waves generalized multifocal left hem altered sleep cycles	abnormal wave peaks multifocal decrease dischar.	Multifocal left/right	normalized
Photosensitivity	not reported	not reported	solar, artificial	not reported
Age at test time	11.2	13.8	15.3	16.1
Seizure freq.	1/week	irregular	1/week	1/month
Mean duration	1 min	5 min ap.	5-25min	1-2 min
Treatment/day	Levetiracetam 500	Topiramate 100	Topiramate 100	Levetiracetam 200
	Divalproex 450	Divalproex 300	Divalproex 300	Divalproex 300
Most common	Tonic-clonic	Myoclonic	Myoclonic	Myoclonic
type of seizure	focal/complex	focal/complex	focal	absences
		absences/atypical	absences/atypical	atypical
Older group educational data				
Age schooling	2 years	15 months	2 years	2 years
Type of school	Ordinary	Special	Special	Special
IQ reported	High delay	Mild delay	High delay	Mild delay
		Peabody around 5	WISC 4 years	
Damaged areas	Reasoning	Motor	All	Memory
	Language	Comprehension		Language
Self-sufficiency	7/10	6/10	3/10	10/10
Symbolic Play	Yes	Yes	Yes	Yes

Notes. The letter and the number of the code refer to the age group (Y = young, O = old), and the order of the experimental session, respectively. Data regarding frequency, duration, and most common type of seizure correspond to the evolution of patients from first seizure identified, until the report was filled out in 2010. EEG data and treatment correspond to the year in which the report was filled out. Self-sufficiency data correspond to the number of scores obtained from a survey with five questions that parents had to rate from 1 to 10 on a Likert scale. The questions were the following ones: "Is your child able to eat without help, to get dressed correctly, to wash up alone"; "What is the level of sphincter control," "Is the child able to ask for things when needed?"

other 40 trials, both syllables were different from each other, and the type of sound was counterbalanced across trials (five *ba* trials were matched to *pa*, and five to *da*, and so on) so that all possible combinations were constructed.

In all tasks, children were tested individually in a quiet room and the experiment was run using DMDX (software designed to run psycholinguistic experiments primarily but currently used to test different cognitive abilities behaviorally; Forster & Forster, 2003). Response times were measured from target onset until the participant's response. In this experiment, a fixation cross (+) was presented for 800 ms in the center of the screen on each trial. Next, the syllable pair was presented auditorily with the question "*Are these the same? "Ba –ba.*" No new stimulus was presented until a response was provided. The intersyllabic time was controlled across stimuli and was 30 ms. Participants were instructed to respond verbally "yes" or "no" to each question. The experiment was designed this way to avoid extra difficulties derived from having to press a button for "yes" and "no" responses, due to the motor control problems observed in DS children. Voice responses were recorded using a microphone connected to the computer. Trials were randomized in each experiment.

Visual Memory Task. This task examined the ability of children to retain visual information. Evidence shows that children before age 5 rely more on visual cues to retain information, and, from five years on, they start relying also on verbal information for recall (Conrad, 1971). This shift has been observed in several studies that have examined visual memory (Hitch, Halliday, Schaafstal, & Schraagen, 1988). Based on the paradigm of Hitch et al., we presented a set of 24 trials that each consisted of four pictures presented horizontally in a row. All pictures belonged to basic categories of medium frequency ($M = 29$). In half of the trials, one of the four pictures was a verbal distractor (phonologically overlapping, e.g., "oveja-oreja") and, in the other half, the distractor was visual (physically similar, e.g., "bomb-pineapple," see Figure 1). Targets and distractors were paired in frequency ($M = 29$ for both verbal and visual distractor condition).

A fixation cross (+) was presented for 500 ms in the center of the screen, and then a target image was presented for 1000 ms. Then the screen remained blank for 6000 ms. Afterwards, the image with the four pictures was presented. The experiment was conducted with a tactile screen, so that the child was instructed to touch the image that had been presented previously. The position of the target was counterbalanced across both conditions, and to that aim four lists were created, so that children could see the same target in the four different positions. Trials were randomized for each experiment. The time from the appearance of the four candidates until participant's response and the response position on the screen were recorded.

Phonological Working Memory Task. The number of items that can be retained in phonological memory over a period of time is said to provide a measure of an individual´s memory span. This capacity is related to IQ measures and increases with age (Ellis & Hennelly, 1980). Based on the classical paradigm of Hulme, Thomson, Muir, and Lawrence (1984; see also Hulme & Tordoff, 1989), we examined the verbal memory span presenting sets of words auditorily that had to be repeated by the child in the same order. For this purpose, six high-frequency words were selected ($M = 230$). The words were *casa, luna, gato, agua, mesa,* and *niño.*

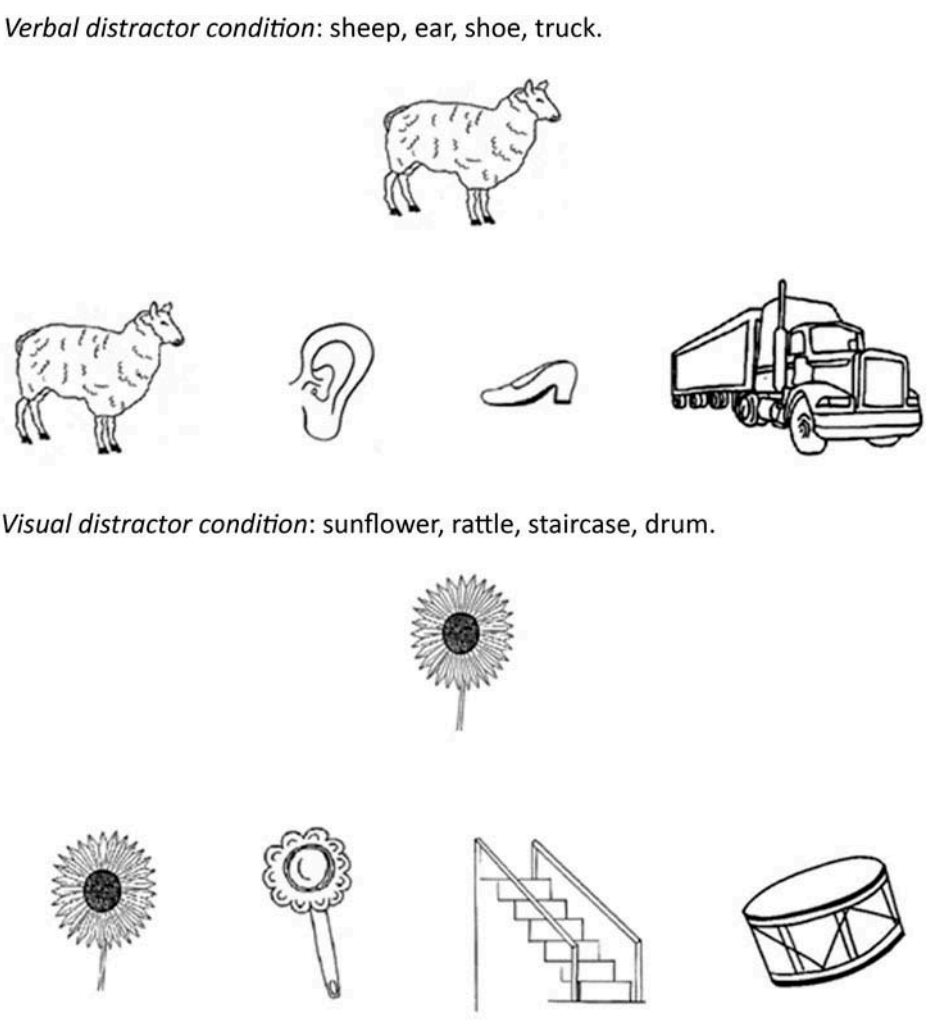

Figure 1 Examples of trials in the Visual Memory task.

A fixation cross was presented on the screen for 500 ms. Afterwards, the child would listen to a set of words ranging from two to six items. After four correct trials with two items, the child passed to the next level with three items and so on. If one of the four trials was not correctly recalled, the task was finished and the assigned memory span was the previous one. The time elapsed from word to word was always 1000 ms, and from trial to trial 10,000 ms.

Motor Tapping Task. We examined motor coordination with a simple tapping standardized task that consisted of pressing a button on the keyboard as many times as possible for 15 ms. In this task, a fixation cross was presented on the center of the screen for 800 ms. Afterwards, a 110 Hz tone sounded. The child was instructed to press a key

on the computer as fast and as many times as possible until hearing the same tone again. The second tone was presented after 15 seconds. The number of taps and the intertap rate were measured.

Tasks Designed to Measure Higher Order Processes: Materials and Procedure

Executive Function. Executive function refers to the ability to plan, to monitor, and to coordinate both action and cognitive processes. The development of working memory is highly dependent on executive function as it implies the maintenance of certain information in memory while being handled and processed (Barkley, 1997). It can be measured by simple tasks that account for control of action—giving a response after a certain stimulus— and inhibition—avoiding a response after a certain stimulus (Durston et al., 2002). More complex tasks can also examine cognitive flexibility and the ability to change response criteria using rule-shifting tasks (see Zelazo, Muller, Frye, & Marcovitch, 2003). In this experiment, we only examined the first ability, adapting the task of Durston et al. Specifically, we used characters of the "Sponge Bob" cartoon, which are familiar to Spanish children, instead of the characters from the "Pokemon" series used in the original study. Four characters of the cartoon were presented as targets, each repeated 12 times. The child was asked to give a response to these four characters. The character of Sponge Bob appeared 48 times and under this condition the child had to withold a response. Due to the motor problems observed in the DS children, instead of pressing a key, they were asked to give a vocal response.

The children were instructed to name the characters appearing on the screen, but to be quiet when the character was Sponge Bob. Each character appeared on the screen after a cross signal of 800 ms, and the character remained for 3000 ms. Voice responses were recorded using a microphone connected to the computer.

Verbal Production Task. There is no experimental evidence about the abilities of DS children in language tasks. Of particular interest is language production, taking into account the observed poor motor execution. We examined verbal production ability in a picture-naming task, in which 28 concrete medium frequency pictures (M = 36) were selected from the Pérez and Navalón (2003) picture database. From these pictures, 14 began with a simple consonant-vowel (CV) syllable, and 14 began with a complex consonant-consonant-vowel (CCV) syllable cluster. Word frequency was paired in both conditions (M = 36). Subsets of pictures were also paired with respect to the initial phoneme (for a word with a simple cluster "*barco*," there was a complex cluster pair "*brazo*"). The phonemes used were b, c, d, f, g, p, and t (two words for each phoneme per subset).

The pictures were displayed on the screen for 5000 ms after a 500 ms fixation cross (+). Voice responses were recorded using a microphone connected to the computer. Experimenters were instructed to transcript each response and to categorize it as correct or incorrect.

Categorization Task. Categorizing is a complex ability that implies making inferences from perceptual and functional properties of objects. It is said to be one of the major constraints of learning, since it implies attending to similarities of different objects, treating them as somehow equivalent or labeling them with the same name

(Neisser, 1987). Finding similarities is a rapid and holistic way to understand the world. This categorization —grouping recurrent evens to form a unique prototype—involves other basic processes such as visual perception, discrimination, and inference. According to recent evidence, children start creating basic categories (e.g., *car*) attending to physical properties and physical similarities because the rely more on visual cues before 15 months (Mandler & Bauer, 1988), but, from this age on, they start categorizing by attending to functional aspects so that they can start creating supra-categories like "*vehicle*" (Mandler & McDonough, 1993; Pauen, 2002). We examined whether this was also the case for DS children using a simple category-to-sample match paradigm (Friedrich & Friederici, 2006; Mandler, Bauer, & McDonough, 1991). In this task, children listened to a supra-category name while four pictures were presented linearly on the screen. The category could be high frequency (e.g., *bird*), medium frequency (e.g., *vegetable*) or low frequency (e.g., *tool*). There were six trials for each supra-category. From the four pictures presented, one was a basic exemplar of this supra-category, and, in half of the trials (three out of six trials), one was a visually similar distractor, whereas, in the other half, one was a distractor that shared a property (another animal for bird, sharing the "living" property; a fruit for vegetable, sharing the "edible" property; and a toy for tools, sharing the "utilitary" property). This way, 24 pictures were selected for the category "bird," 24 for the category "vegetable," and 24 for the category "tool." Picture frequencies were paired across categories (M = 15, M = 15, and M = 16 for the pictures belonging to the condition bird, vegetable, and tool, respectively). Pictures were rotated across the four positions so that position could not be the factor explaining the results. Four counterbalanced lists were created for this purpose.

The experiment was conducted using DMDX and a tactile screen. A fixation cross signal (+) was presented for 500 ms in the center of the screen, and then a category name was heard through headphones while four images were presented. These remained on the screen for 10,000 ms. The children were instructed to touch the exemplar that corresponded to the name they were hearing through the headphones.

RESULTS

Auditory Detection Task

Analyses of variance (ANOVAs) were conducted based on the subjects' error rate based on a 2 (Group: DS, control) × 2 (Age: young, old), × 2 (Type Of Contrast: same, different) on the percent of correct responses[3]. A significant group effect was found, $F(1, 8) = 5.88$, $p = .04$, $MSE = 915.2$. Nonetheless, it should be taken into account that the proportion of errors in DS children was near chance: DS children were correct in the 54% of trials (SD = 4.1) with no differences across ages or conditions. Control children were correct in 100% of trials (SD = 0.0) showing a ceiling effect. Percentages of correct detection per group are included in Table 2. No interaction was found with age or with type of contrast. These results imply that perception and detection of phonemes were severely disrupted in DS children and that this disruption persisted with age. Interestingly, none of the groups showed greater

[3]Due to the nature of the sample, we conducted a Kruskal-Wallis analysis first. As the results mimic the ones obtained with the parametric tests, we decided to report the standard and commonly used ANOVA results.

Table 2 Percentage of Correct Detection of Sound Pairs for DS and Control Children of Both Age Groups.

	Auditory Detection			
	% Correct Same Sound Pair		% Correct Different Sound Pair	
Dravet				
Young	53.0	(3.1)	55.0	(4.8)
Old	55.1	(5.2)	51.0	(3.2)
Control				
Young	100.0	(0.0)	100.0	(0.0)
Old	100.0	(0.0)	100.0	(0.0)

sensitivity for sound discrimination of the same phonetic group (*ba-pa*, both bilabials) or different phonetic group (*ba-da*, bilabial-dental).

Visual Memory Task

ANOVAs were conducted based on the subjects' median correct response latencies and error rates based on a 2 (Group: DS, control) × 2 (Age: young, old) × 2 (Type of Distractor: verbal, visual) × 4 (List: 1, 2, 3, 4). List was included as a dummy variable in the ANOVAs to model the variance due to the lists (Pollatsek & Well, 1995).

Reaction times showed that DS children were slower than control children both in the visual distractor condition (M = 2847 ms, SD = 744; M = 1872 ms, SD = 609, respectively) and in the verbal distractor condition (M = 2887 ms, SD = 1108; M = 1773 ms, SD = 572, respectively). However, the group difference between DS and controls did not reach significance, $F(1,8) = 0.52$, $p = .65$. The same pattern was found with the error rates ($p = .38$). DS children committed more errors than controls in the visual (M = 23%, SD = 19.0; M = 14%, SD = 2.4, respectively) and in the verbal distractor condition (M = 20%, SD = 9.7; M = 16%, SD = 2.4) but the difference was not significant.

These results show that there was no strong evidence for a difference between the groups. In fact, DS children were not at chance, since the error rates in this group were within 10% of the controls. In addition, the lack of interaction between group (DS, control) and age implies that DS children were executing the task as expected for a child older than 5, and that the execution of the task was probably mediated by the preferred processing modality of each child rather than by a general cognitive mechanism (visual or verbal) that constrains decisions differently in DS or control children. Further observations are described in the Discussion section.

Phonological Working Memory Task

ANOVAs were conducted based on number of words remembered based on a 2 (Group: DS, control) × 2 (Age: young, old) design. Results showed a main group difference, $F(1, 12) = 29.82$, $p < .001$, $MSE = 4.2$, DS children had a lower span than control children (M = 2.0, SD = 0.7; M = 3.25, SD = 0.5, respectively). This effect did not interact with age. Values for visual memory and phonological working memory are presented in Table 3.

Table 3 Results on the Visual Memory Task (Mean and Standard Deviations for reaction times in milliseconds and percentage correct response), and on the Verbal Working Memory Task (number of words remembered).

	Visual Memory		Phonological Working Memory		
	RT		% Correct		
	Visual	*Verbal*	*Visual*	*Verbal*	Word Span
Dravet					
Young	2592 (999)	2877 (1170)	75.0 (23.5)	75.0 (15.2)	2.0 (0.8)
Old	3101 (490)	2896 (1046)	79.2 (14.4)	85.4 (4.2)	1.8 (0.5)
Control					
Young	2164 (608)	1808 (272)	79.2 (4.2)	77.1 (4.8)	3.0 (0.5)
Old	1580 (610)	1737 (870)	93.8 (4.2)	91.7 (0.2)	3.8 (0.5)

Table 4 Tapping Rate (in ms) and Number of Taps in the Motor Tapping Task.

	Motor Tapping Task	
	Tapping Rate	No. of Taps
Dravet		
Young	551.3 (507.9)	32 (17.4)
Old	557.0 (204.4)	31 (17.7)
Control		
Young	245.6 (52.4)	65 (4.6)
Old	174.0 (4.5)	84 (1.0)

Motor Tapping Task

ANOVAs were conducted based on the subjects median number of taps and intertap latencies based on a 2 (Group: DS, control) × 2 (Age: young, old) design. DS children pressed the key fewer times than controls (M = 30.1, SD = 17.6; M = 73.8, SD = 2.8, respectively), $F(1, 12) = 47.70$, $p < .01$, MSE = 1914.7, and with a greater intertap timing (M = 553 ms, SD = 356; M = 220 ms, SD = 28), $F(1, 12) = 6.28$, $p = .028$, MSE = 75,622.3. There was no interaction with age. These results —summarized in Table 4—show that basic abilities, such as visual memory, working memory, and motor development, are significantly impaired in Dravet children compared to children of the same chronological age. This is in line with other studies that reported similar impairment in DS samples (Brunklaus et al., 2011). In addition, we showed that working memory was also significantly impaired. Due to the implication of working memory in most higher order cognitive skills (Barkley, 1997; Klingberg, 2010; Schweitzer et al., 2000), we believe that the observed perceptual, motor, and memory impairment in DS children are key factors in understanding the cognitive pattern in this population.

Executive Function

ANOVAs were conducted based on the participants' positive action and negative inhibition responses based on a 2 (Group: DS, control) × 2 (Age: young, old) design. For positive responses (giving a naming response to all the characters that were not Sponge Bob), there was a significant difference between DS and controls, $F(1, 12) = 168.51$, $p <$

Table 5 Percentage of Correct Action (yes response) and Inhibition (avoiding response) Response in the Go-No/Go Task.

	Executive Function Task	
	Action *% correct*	Inhibition *% correct*
Dravet		
Young	26.0 (12.3)	54.8 (5.5)
Old	34.3 (14.1)	71.8 (14.8)
Control		
Young	91.6 (4.2)	97.0 (4.8)
Old	97.5 (5.0)	97.5 (5.2)

.001, *MSE* = 98.4. The percentage of correct responses was lower in Dravets ($M = 30.1$, $SD = 13.2$) than in controls ($M = 94.6$, $SD = 4.6$). Also inhibitory capacity was smaller in DS children as compared to controls, $F(1, 12) = 61.93$, $p < .001$, $MSE = 74.4$. DS children inhibited responses in a lower percentage of trials ($M = 63.3\%$, $SD = 10.2\%$) compared to controls ($M = 97.2\%$, $SD = 4.9\%$). In addition, this inhibitory capacity interacted with age $F(1, 8) = 5.15$, $p = .040$, $MSE = 893.6$. The inhibitory capacity in control children was similar in the 8 to 10 age range group and in the older age range group of 11 to 16, $p = .87$; whereas in the DS group the percentage of correctly inhibited responses was lower in the younger than in the older group ($M = 54.8\%$, $SD = 5.5\%$; $M = 71.8\%$, $SD = 14.8\%$), $F(1, 8) = 8.41$, $p = .028$, $MSE = 101.7$. These results are summarized in Table 5.

The results show that DS children have a lower control of action than normal developing children of the same chronological age. Interestingly a significant difference is observed between young and old DS children's capacity to inhibit a response. Whereas control children show a great inhibitory capacity by the age of 8 and maintain it at the age of 14, older DS children show a low but better inhibitory capacity than young DS children.

Verbal Production Task

After the task was completed, we checked that all of the children knew the name of the pictures and that errors were due to the production of the word —retrieval failure at the beginning or producing the first sound and stopping before continuing—rather than to the fact that they did not know the name. A preliminary analysis showed that there were no differences between CV- and CCV-cluster production. Hence, ANOVAs were conducted based on correct production rate on a 2 (Group: DS, control) × 2 (Age: young, old) design. Correct responses were considered when the name was pronounced without error. The percentage of errors in DS children was 46% ($SD = 20.5$), whereas in controls it was 17% ($SD = 12.2$), $F(1, 12) = 4.86$, $p = .040$, $MSE = 1273.1$. In addition, this percentage was similar for complex ($M = 56\%$, $SD = 29.5$; $M = 18\%$, $SD = 17.5$, in DS and controls, respectively) and simple clusters ($M = 42\%$, $SD = 20.5$; $M = 15\ \%$, $SD = 12.2$, see Table 6).

Due to the fact that children actually reported the correct name of the pictures afterwards, these errors might be attributed to articulatory difficulties related to their lack of motor abilities, rather than a poor knowledge of the objects in their environment, at least of those that belong to the basic exemplars they usually interact with. The observed poor production could be due to two reasons: (a) a poor motor coordination that leads to a

Table 6 Percentage of Correct Word Production for Dravet and Control Children of Both Age Groups.

	Verbal Production Task	
	CV *% Correct*	CVV *% Correct*
Dravet		
Young	69.0 (17.3)	51.5 (34.3)
Old	46.6 (23.6)	35.2 (24.8)
Control		
Young	78.0 (40.3)	78.6 (24.7)
Old	93.6 (4.4)	87.1 (5.3)

poor articulation and (b) a poor working memory that leads to a difficult access to the word in the lexicon and, consequently, to an impaired vocal production.

Categorization Task

ANOVAs were conducted based on the correct detection rate for a 2 (Group: DS, control) × 2 (Age: young, old) × list (1, 2, 3, 4) design. The results showed that, in general, DS children showed poorer categorizing ability, $F(1, 8) = 20.2$, $p = .009$, $MSE = 928.5$. For the low-frequency category "*tool*," the percentage of correct responses in DS and controls was 62.5% and 90%, respectively ($SD = 17.7$; $SD = 13.3$), $F(1, 8) = 3.02$, $p = .09$. For the high-frequency category "*bird*," these percentages were 79.4% and 100%, respectively ($SD = 8.9$; $SD = 0.0$), $F(1, 8) = 16.2$, $p = .007$, $MSE = 426.2$, and 47.9% and 89.5%, ($SD = 8.9$; $SD = 0.0$) for the medium-frequency category "*vegetable*," $F(1, 8) = 22.5$, $p = .003$, $MSE = 305.8$. In addition, group interacted with age in this category, $F(1, 8) = 8.1$, $p = .029$, $MSE = 1227.1$. DS in the younger group showed better performance than in the older group, $F(1, 8) = 8.1$, $p = .029$, $MSE = 1111.1$ ($M = 16.6$, $SD = 19.4$, and $M = 16.6$, $SD = 19.4$, respectively), whereas controls showed the same proportion of correct responses in both groups ($M = 83.36$, $SD = 0.0$, and $M = 83.3$, $SD = 0.2$, respectively). There was no interaction with type of distractor.

As observed in Table 7, control children showed stable categorization abilities across ages and types of categories, with performance reaching a ceiling effect of the

Table 7 Percentage of Correct Selection of Exemplar for Low-, Medium-, and High- Frequency Basic Categories in the Categorization Task.

	Categorization Task		
	High-frequency Bird *% Correct*	Medium-Frequency Vegetable *% Correct*	Low-Frequency Tool *% Correct*
Dravet			
Young	80.0 (9.3)	16.6 (25.2)	58.3 (11.8)
Old	75.0 (8.5)	66.7 (13.7)	66.7 (23.6)
Control			
Young	100.0 (0.0)	83.3 (0.0)	68.3 (2.4)
Old	100.0 (0.0)	83.3 (0.2)	80.0 (11.8)

exemplars in the high-frequency category. Again, Dravet children showed a big delay with respect to controls. A significant difference between the two age groups indicated (as with inhibitory abilities) that categorization abilities were better in the older Dravet group than in the younger Dravet group with respect to controls. However, results in the older Dravet group showed a big variability, particularly in tasks that involved higher order abilities. This issue will be further considered in the "Discussion" section.

Correlational Analysis

Finally, we carried out a correlational analysis to test whether the outcomes observed in DS fit the pattern assumed from the neurodevelopmental framework. Thus, correlations between basic cognitive functions (auditory detection, visual memory, verbal working memory, motor tapping) and higher order functions (verbal production, executive control, categorization for vegetables) were examined based on mean % correct responses for each measure, in both DS and control children. In DS children, the highest correlation was found between visual memory and categorization, $r = .901$, $p = .032$, and between motor tapping and executive control, $r = .67$, $p = .049$. Also, the correlation between phonological memory and production was near significance, $r = .68$, $p = .052$. Correlations in the control group were not significant.

DISCUSSION

Early onset and recurring seizures during childhood are critical features in DS, a syndrome that can lead to a broad and severe cognitive impairment throughout development. Previous studies have reported an important cognitive decline on basic processes, such as perception, memory, and motor development (Caraballo & Fejerman, 2006; Ragona et al., 2011; Wolff, Cassé-Perrot, & Dravet, 2006). In our study, we tried to provide a broad picture of the cognitive impairment involved in DS taking the nature and time course of cognitive development into account. Our aim was to compare the neurocognitive pattern of DS children in two age ranges with that of control children of the same chronological age. Thus, we examined a large range of skills in a small cohort of DS children to assess their performance in basic (early developed) and higher order (later developed) cognitive abilities. Our study provides three major findings. First, the cognitive delay in Dravet children with respect to control children of the same chronological age involved both basic and higher order processes. Second, there seemed to be a relation between early acquisition of basic abilities and subsequent development of complex skills. Third, DS children showed greater outcome variability with respect to controls, particularly in the older group.

Regarding the general neurocognitive pattern, our results confirm and extend previous findings about the delay involved in DS. When it came to basic abilities, control children showed a ceiling effect in the perceptual task and performed significantly better than DS children in almost all of the rest of the tasks. Perceptual auditory detection was near chance in both DS age groups. The same occurred with motor tapping. In line with previous studies, these seemed to be the most damaged functions, presumably because they rely mainly on early developed brain regions. However, this should also be true for the visual function (see Doria et al., 2010) and, interestingly, the measure for visual memory in Dravet children was closer to that of controls. In addition, the old DS group showed lower interference in the verbal distractor condition than in the visual distractor

condition (although this difference was only numerical). This sign of cognitive load in the visual domain can suggest that DS children in the older group were more sensitive to visual information when dealing with iconic material and that their processing mode was visual rather than verbal. This was in line with the poor execution in the verbal processing tasks: auditory detection, phonological working memory, and word production. Concretely, in the word-production task, the gap between DS and controls was particularly evident in the older group. This could be due to two difficulties, namely, word access before production and accurate articulation of the retrieved lexical item, which could be more evident once children have acquired control and monitoring abilities. These findings support language dysfunctions observed in other studies both at the coding (omissions, distortions, and altered sequencing of phonemes reported by Chieffo, Battaglia, et al., 2011) and output levels (disartria, phonemic production and spontaneous language difficulties reported by Cassé-Perrot et al., 2002). These errors have been attributed to a poor integration of auditory-motor information, probably due to a cerebellar dysfunction (Battaglia et al., 2013). This lack of integration might therefore explain the poorest performance of the DS group in the verbal domain.

One reason why our DS sample showed a better performance in tasks pertaining visual processing—note, for example, that in the work of Battaglia et al. (2013) visual abilities were more impaired than verbal ones—might be that synapse density in the visual cortex reaches its peak mainly in the first 8 months. Thus, good visual abilities could be either a sign of a preserved connectivity in the visual region (Huttenlocher, de Courten, Garey, & Van der Loos, 1982), a compensatory effect of an early disrupted verbal system (Sloutsky & Napolitano, 2003), or evidence for appropriate integration of perceptual information to resolve tasks involving higher order abilities, as long as they were domain specific. Another possibility is that the most impaired perceptual modality might be related to the hemispheric location of the epileptic discharges. Some authors (Binnie, Channon, & Marston, 1990; Wolff et al., 2005) have found that left-sided spiking might involve greater impairment in the verbal than in the visual domain. Yet, no such relation has been properly examined in DS. Concretely in our DS sample, most EEGs showed multifocal bilateral discharges. This fact does not allow extracting any conclusion about this relation in our cognitive pattern.

As to the higher order abilities, a large difference between DS and controls was found in measures of executive function, production, and categorization abilities. This gap was particularly evident in the executive function and categorization tasks in the old group, due to the good performance of control children at this age. Note also that the discrepancy between cognitive performance and chronological age on DS children has been reported in previous studies (Chieffo, Battaglia, et al., 2011; Ragona et al., 2010). Some authors argue that the increasing cognitive gap between Dravet children and controls could be a result of the discrepancy between a stable mental age and an increasing chronological age in the DS population (Chieffo, Battaglia, et al., 2011; see Hermann, Seidenberg, & Jones, 2008; for this debate in other types of epilepsy). Taking this fact into consideration, we believe that DS children could experience difficulties in mastering complex skills due to the impaired basic abilities, a pattern that should be more evident when they grow up.

Thus, an early impairment of earlier acquired abilities might have a detrimental effect on the acquisition of new skills. For example, in our sample, a good phonological memory was related to better production abilities (supporting the planning + articulation difficulty explanation; Battaglia et al., 2013). Likewise, a good visual memory was linked

to better categorization skills, particularly if the verbal system was mostly impaired (note the detrimental effect of the visual distractor in the old DS group). Especially interesting was the relation observed between motor control and executive function—a good index of brain maturation and cognitive development. This reflects the key role of motor control on the enhancement of complex skills as reported in the literature (Brunklaus et al., 2012; Cassé-Perrot et al., 2002; Chieffo, Battaglia, et al., 2011; Dravet 2011) and supports an interactive view of brain development (Friston & Price, 2001; Uddin, Supekar, Ryali, & Menon, 2011) according to which the emergence of cognitive functions relies on a complex and increasing interaction of different brain structures.

Evidence of this complexity was the great intragroup variability, reflected in the large standard deviations. In other words, some children in the DS sample were much closer to their chronological-age counterparts than others. In the light of this finding, we further considered several possible causes of this variability.

Although there is still an ongoing debate about the variables affecting phenotype in DS children, evidence from different epileptic syndromes suggest that seizure frequency and early age at onset could be crucial for cognitive delay. One of the reasons argued for this is that brains in these conditions are less able to develop a functional reserve capacity to cope with subsequent decline (Hermann, Seidenberg, & Bell, 2002). We examined this possibility by illustrating the outcomes of all Dravet participants in each task (see Figure 2). This figure gives account of the inconsistent cognitive outcomes among DS participants with respect to controls. We considered the measures of each child across the tasks, to check whether general outcomes could be related to typological characteristics of the syndrome in each child. According to the clinical description in our young DS group, Subject Y4 reported greater seizure duration, whereas Y11 and Y22 reported earlier onset and greater seizure frequency during childhood. As seen in Figure 2, Y11 and Y22 showed the poorest inhibition, word production, motor tapping, and categorization outcomes. With respect to the older group, O17 reported the greatest seizure durations, and O13 and O17 showed the worse characterization regarding early onset and seizure frequency. Again, these two children showed the poorest outcome in inhibition, word production, motor tapping, and categorization. Additionally, children with later seizure onset and small seizure frequency (Y4, Y14, O19) showed the most preserved phenotype. These observations are in line with the findings of Wolff et al. (2006). In their sample of DS children aged 11 months to 12.5 years, these authors found a correlation between cognitive impairment and seizure frequency. Concretely, children that showed more than five seizures per month showed the worse cognitive and behavioral outcome (see also Rodin, Schmaltz, & Twitty, 1986; Thompson & Duncan, 2005; for evidence in epileptic syndromes). Following this rationale, Y22, O13, and O17, should show the worst performance in our sample. Indeed, this was actually the case, particularly in tasks that require cognitive and motor control (inhibition, tapping) or processes that tackle diffuse brain abilities (word production, categorization; see also Cassé-Perrot et al., 2002).

The same factors might play a role on the greater gap between DS and controls in the older group. Although at first sight the characterization of severity might seem greater in the younger than in the older DS group (earlier onset, greater mean seizure duration, reported self-sufficiency score), the combination of onset and frequency in the old group might have modulated the phenotype expression during development so that children who met these criteria were more prone to manifest difficulties during the time course of cognitive development. Yet, there is still a debate about the causes of cognitive deterioration in the course of epilepsy (Pitkänen & Sutula, 2002) and about a possible

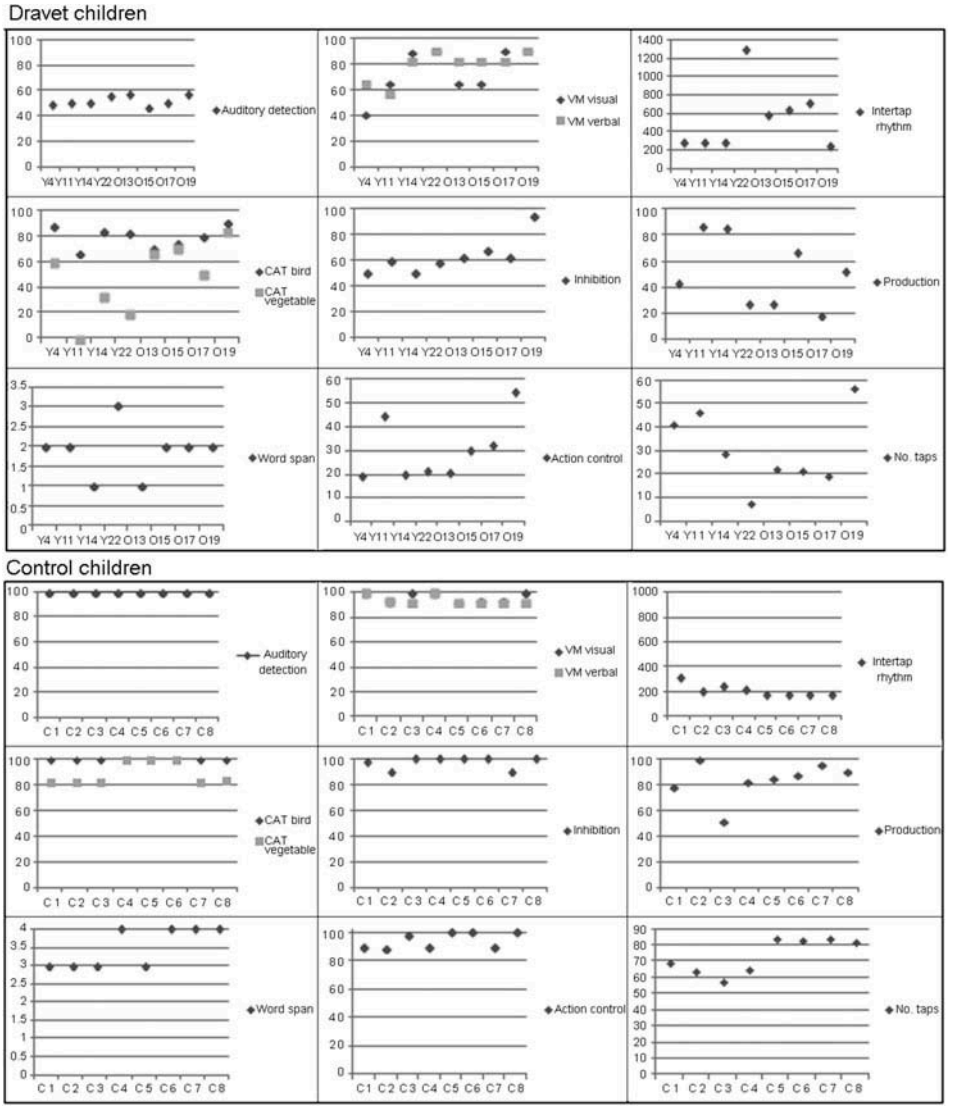

Figure 2 Illustration of measure variability in Dravet and control participants across tasks. Participants are represented in *X*-axis, while *Y*-axis represents % correct responses in all tasks but Intertap rhythm (time in milliseconds), word span (number of words remembered from 1 to 4), and number of taps (amount of taps given in 15 seconds). The remaining measures are presented in percentage of correct answers.

decline with increasing age as a result of a greater total number of seizures (Dodrill, 2004). It has been argued that this deterioration seems to be slower after 20, due to the fact that the amount of seizures decreases and seizure type (prevalently tonic-clonic) tends to be less severe at this age (Genton, Velizarova, & Dravet, 2011). Overall, these findings shed some light onto the possible key roles of seizure onset and frequency in cognitive decline and phenotype variability also in DS (Catarino et al., 2011), although there is still a debate about the impact of other factors such as medical treatment (see Loring & Meador, 2004; but also Wolff et al., 2006) or idiopathic dysfunctions derived

from the expression of the SCN1A mutation on the observed maturational phenotype (Brunklaus & Zuberi, 2014).

Taking all these factors into account, the potential limitations of our study (small sample size and variability of the sample in terms of clinical characterization, see Table 1) do not allow us to extract straightforward conclusions. However, our findings address the importance of evaluating both basic and higher order abilities in DS children from a neurodevelopmental perspective. On the one hand, all evaluated Dravet children showed a general impairment in early and late developed skills, and this seems to be a common cognitive marker for DS. On the other hand, the progressive manifestation of the cognitive phenotype might be unique depending on clinical features of the syndrome and external factors. To date, the complexity of the syndrome has made it difficult to establish an explanatory model of the cognitive decline and variability observed in DS. Further long-term studies with a larger population are needed to highlight this question in order to provide a more comprehensive framework of the neurocognitive profile and a better therapeutic management of DS children.

Original manuscript received March 27, 2014
Revised manuscript accepted August 17, 2014
First published online October 3, 2014

REFERENCES

Aldenkamp, A. P., & Arends, J. (2004). The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function. *Epilepsia, 45*, 54–63. doi:10.1111/j.0013-9580.2004.33403.x

Aldenkamp, A. P., Overweg, J., Gutter, T. H., Beun, A. M., Diepman, L., & Mulder, O. G. (1996). Effect of epilepsy, seizures and epileptiform EEG discharges on cognitive function. *Acta Neurologica Scandinavica, 93*(4), 253–259. doi:10.1111/j.1600-0404.1996.tb00516.x

Barkley, R. A. (1997). Behavioral inhibition, sustained attention and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65–94. doi:10.1037/0033-2909.121.1.65

Battaglia, D., Chieffo, D., Siracusano, R., Waure, C. D., Brogna, C., Ranalli, D., … Guzzeta, F. (2013). Cognitive decline in Dravet syndrome: Is there a cerebellar role? *Epilepsy Research, 106*, 211–221. doi:10.1016/j.eplepsyres.2013.03.012

Binnie, C. D., Channon, S., & Marston, D. (1990). Learning disabilities in epilepsy: Neurophysiological aspects. *Epilepsia, 31*(s4), SS2-SS8. doi:10.1111/j.1528-1157.1990.tb05864.x

Brunklaus, A., Dorris, L., & Zuberi, S. M. (2011). Comorbidities and predictors of health related quality of life in Dravet syndrome. *Epilepsia, 52*, 1476–1482. doi:10.1111/j.1528-1167.2011.03129.x

Brunklaus, A., Ellis, R., Reavey, E., Forbes, G. H., & Zuberi, S. M. (2012). Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain, 135*, 2329–2336. doi:10.1093/brain/aws151

Brunklaus, A., & Zuberi, S. M. (2014). Dravet syndrome-From epileptic encephalopathy to channelopathy. *Epilepsia*. Advance online publication. doi:10.1111/epi.12652

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. E. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron, 33*, 301–311. doi:10.1016/S0896-6273(01)00583-9

Caraballo, R. H., & Fejerman, N. (2006). Dravet syndrome: A study of 53 patients. *Epilepsy Research, 70*, 231–238. doi:10.1016/j.eplepsyres.2005.11.026

Cassé-Perrot, C., Wolf, M., & Dravet, C. (2002). Neuropsychological aspects of severe myoclonic epilepsy in infancy. In I. Jambaque, M. Lassonde, & O. Dulac (Eds.), *Neuropsychology of childhood epilepsy* (pp. 131–140). New York, NY: Springer. doi:10.1007/0-306-47612-6_14

Catarino, C. B., Liu, J. Y. W., Liagkouras, I., Gibbons, V. S., Labrum, R. W., Ellis, R., … Sisodiya, M. S. (2011). Dravet syndrome as epileptic encephalopathy: Evidence from long-term course and neuropathology. *Brain, 134*, 2982–3010. doi:10.1093/brain/awr129

Chieffo, D., Battaglia, D., Lettori, D., Del Re, M., Brogna, C., Dravet, C., … Guzzetta, F. (2011). Neuropsychological development in children with Dravet syndrome. *Epilepsy Research, 95*, 86–93. doi:10.1016/j.eplepsyres.2011.03.005

Chieffo, D., Ricci, D., Baranello, G., Martinelli, D., Veredice, C., Lettori, D., … Guzzeta, F. (2011). Early development in Dravet syndrome; visual function impairment precedes cognitive decline. *Epilepsy Research, 93*, 73–79. doi:10.1016/j.eplepsyres.2010.10.015

Claes, L. R., Deprez, L., Suls, A., Baets, J., Smets, K., Van Dyck, T., … De Jonghe, P. (2009). The SCN1A variant database: A novel research and diagnostic tool. *Human Mutation, 30*(10), E904-E920. doi:10.1002/humu.21083

Conrad, R. (1971). The chronology of the development of covert speech in children. *Developmental Psychology, 5*, 398–405. doi:10.1037/h0031595

Curtin, S., Mintz, T. H., & Christiansen, M. H. (2005). Stress changes the representational landscape: Evidence from word segmentation. *Cognition, 96*, 233–262. doi:10.1016/j.cognition.2004.08.005

Depienne, C., Trouillard, O., Gourfinkel-An, I., Saint-Martin, C., Bouteiller, D., Graber, D., … LeGuern, E. (2010). Mechanisms for variable expressivity of inherited SCN1A mutations causing Dravet syndrome. *Journal of Medical Genetics, 47*(6), 404–410. doi:10.1136/jmg.2009.074328

Dodrill, C. B. (2004). Neuropsychological effects of seizures. *Epilepsy & Behavior, 5*, 21–24. doi:10.1016/j.yebeh.2003.11.004

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., … Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences, 107*(46), 20015–20020. doi:10.1073/pnas.1007921107

Dravet, C. (1978). Les epilepsies graves de l′enfant. *Vie Med, 8*, 543–548.

Dravet, C. (2011). The core Dravet syndrome phenotype. *Epilepsia, 52*, 3–9. doi:10.1111/j.1528-1167.2011.02994.x

Dravet, C., Bureau, M., Oguni, H., Fukuyama, Y., & Cokar, O. (2005). Severe Myoclonic epilepsy in infancy (Dravet syndrome). In J. Roger, M. Bureau, C. Dravet, P. Genton, C. A. Tassinari, & P. Wolff (Eds.), *Epileptic syndromes in infancy, childhood and adolescence* (4th ed., pp. 89–113). Montrouge: John Libbey Eurotext. doi:10.1016/B978-0-444-52891-9.00065-8

Durston, S., Thomas, K. M., Yan, Y., Ulug, A. M., Zimmerman, R. D., & Casey, B. J. (2002). A neural basis for the development of inhibitory control. *Developmental Science, 5*(4), F9–F16. doi:10.1111/1467-7687.00235

Ellis, H. D., & Hennelly, R. A. (1980). A bilingual word length effect: Implications for intelligence testing and the relative ease of mental calculation in Welsh and English. *British Journal of Psychology, 71*, 43–51. doi:10.1111/j.2044-8295.1980.tb02728.x

Elman, J. L. (2005). Connectionist models of cognitive development: Where next? *Trends in Cognitive Sciences, 9*(3), 111–117. doi:10.1016/j.tics.2005.01.005

Fair, D. A., Posner, J., Nagel, B. J., Bathula, D., & Costa, T. G. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 68* (12), 1084–1091. doi:10.1016/j.biopsych.2010.07.003

Forster, K. I., & Forster, J. C. (2003). DMDX: A Windows display program with millisecond accuracy. *Behavior Research Methods, Instruments, & Computers, 35*, 116–124. doi:10.3758/BF03195503

Friedrich, M., & Friederici, A. D. (2006). Early N400 development and later language acquisition. *Psychophysiology, 43*, 1–12. doi:10.1111/j.1469-8986.2006.00381.x

Friston, K. J., & Price, C. J. (2001). Dynamic representations and generative models of brain function. *Brain Research Bulletin, 54*(3), 275–285. doi:10.1016/S0361-9230(00)00436-6

Frith, U. (2001). Mind blindness and the brain in autism. *Neuron, 32*, 969–979. doi:10.1016/S0896-6273(01)00552-9

Frith, U., & Happe, F. (1998). Why specific developmental disorders are not specific: On-line and developmental effects in autism and dyslexia. *Developmental Science, 1*, 267–272. doi:10.1111/1467-7687.00041

Genton, P., Velizarova, R., & Dravet, C. (2011). Dravet syndrome: The long-term outcome. *Epilepsia, 52*(s2), 44–49. doi:10.1111/j.1528-1167.2011.03001.x

Hattori, J., Ouchida, M., Ono, J., Miyake, S., Maniwa, S., Mimaki, N., … Ohmori, I. (2008). A screening test for the prediction of Dravet syndrome before one year of age. *Epilepsia, 49*(4), 626–633. doi:10.1111/j.1528-1167.2007.01475.x

Hermann, B., Seidenberg, M., & Jones, J. (2008). The neurobehavioural comorbidities of epilepsy: Can a natural history be developed? *The Lancet Neurology, 7*(2), 151–160. doi:10.1016/S1474-4422(08)70018-8

Hermann, B. P., Seidenberg, M., & Bell, B. (2002). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research,* 135, 429–438. doi:10.1016/S0079-6123(02)35040-4

Hitch, G. J., Halliday, S., Schaafstal, A. M., & Schraagen, J. M. (1988). Visual working memory in young children. *Memory & Cognition, 16*(2), 120–132. doi:10.3758/BF03213479

Hulme, C., Thomson, N., Muir, C., & Lawrence, A. (1984). Speech rate and the development of short-term memory span. *Journal of Experimental Child Psychology, 38*, 241–253. doi:10.1016/0022-0965(84)90124-3

Hulme, C., & Tordoff, V. (1989). Working memory development: The effects of speech rate, word length, and acoustic similarity on serial recall. *Journal of Experimental Child Psychology, 47*, 72–87. doi:10.1016/0022-0965(89)90063-5

Huttenlocher, P. R. (2009). *Neural plasticity: The Effects of environment on the development of the cerebral cortex*. Cambridge, MA: Harvard University Press.

Huttenlocher, P. R., de Courten, C., Garey, L. J., & Van der Loos, H. (1982). Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. *Neuroscience Letters, 33*(3), 247–252. doi:10.1016/0304-3940(82)90379-2

Johnson, M. H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience, 2*(7), 475–483. doi:10.1038/35081509

Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences, 2*, 389–398. doi:10.1016/S1364-6613(98)01230-3

Kaufman, A. S. (1990). *K-BIT: Kaufman brief intelligence test*. Circle Pines, MN: American Guidance Service.

Klingberg, T. (2010). Training and plasticity of working memory. *Trends in Cognitive Sciences, 14*(7), 317–324. doi:10.1016/j.tics.2010.05.002

Korff, C., Laux, L., Kelley, K., Goldstein, J., Koh, S., & Nordli, D. (2007). Dravet syndrome (severe myoclonic epilepsy in infancy): A retrospective study of 16 patients. *Journal of Child Neurology, 22*(2), 185–194. doi:10.1177/0883073807300294

Levitt, P. (2003). Structural and functional maturation of the developing primate brain. *The Journal of Pediatrics, 143*, 35–45. doi:10.1067/S0022-3476(03)00400-1

Loring, D. W., & Meador, K. J. (2004). Cognitive side effects of antiepileptic drugs in children. *Neurology, 62*(6), 872–877. doi:10.1212/01.WNL.0000115653.82763.07

Mandelbaum, D. E., & Burack, G. D. (1997). The effect of seizure type and medication on cognitive and behavioral functioning in children with idiopathic epilepsy. *Developmental Medicine & Child Neurology, 39*(11), 731–735. doi:10.1111/j.1469-8749.1997.tb07374.x

Mandler, J. M., & Bauer, P. J. (1988). The cradle of categorization: Is the basic level basic? *Cognitive Development, 3*, 247–264. doi:10.1016/0885-2014(88)90011-1

Mandler, J. M., & McDonough, L. (1993). Concept formation in infancy. *Cognitive Development, 8*, 291–318. doi:10.1016/S0885-2014(93)80003-C

Mandler, J. M., Bauer, P. J., & McDonough, L. (1991). Separating the sheep from the goats: Differentiating global categories. *Cognitive Psychology, 23*, 263–298. doi:10.1016/0010-0285(91)90011-C

Martin, M. S., Dutt, K., Papale, L. A., Dubé, C. M., Dutton, S. B., De Haan, G., … Escayg, A. (2010). Altered function of the SCN1A voltage-gated sodium channel Leads to -aminobutyric acid-ergic (GABAergic) interneuron abnormalities. *Journal of Biological Chemistry, 285*(13), 9823–9834. doi:10.1074/jbc.M109.078568

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience, 16*, 1227–1233. doi:10.1162/0898929041920441

Neisser, U. (1987). *Concepts and conceptual development: Ecological and intellectual factors in categorization*. Cambridge: Cambridge University Press.

Oakley, J. C., Kalume, F., Yu, F. H., Scheuer, T., & Catterall, W. A. (2009). Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy. *Proceedings of the National Academy of Sciences,* 106, 3994–3999. doi:10.1073/pnas.0813330106

Pauen, S. (2002). Evidence for knowledge-based category discrimination in infancy. *Child Development, 73*, 1016–1033. doi:10.1111/1467-8624.00454

Paus, T., Collins, D. L., Evans, A. C., Leonard, G., Pike, B., & Zijdenbos, A. (2001). Maturation of white matter in the human brain: A review of magnetic resonance studies. *Brain Research Bulletin, 54*(3), 255–266. doi:10.1016/S0361-9230(00)00434-2

Pérez, M. A., & Navalón, C. (2003). Spanish norms for 290 new pictures: Name agreement, image agreement, familiarity, visual complexity and image variability. *Psicológica, 24*, 215–241.

Pitkänen, A., & Sutula, T. P. (2002). Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. *The Lancet Neurology, 1*(3), 173–181. doi:10.1016/S1474-4422(02)00073-X

Pollatsek, A., & Well, A. D. (1995). On the use of counterbalanced designs in cognitive research: A suggestion for a better and more powerful analysis. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21*(3), 785. doi:10.1037//0278-7393.21.3.785

Ragona, F., Brazzo, D., Giorgi, I. D., Morbi, M., Freri, E., Teutonico, F., … Granata, T. (2010). Dravet syndrome: Early clinical manifestations and cognitive outcome in 37 Italian patients. *Brain and Development, 32*(1), 71–77. doi:10.1016/j.braindev.2009.09.014

Ragona, F., Granata, T., Bernardina, B. D., Offredi, F., Darra, F., Battaglia, D., … Dravet, C. (2011). Cognitive development in Dravet syndrome: A retrospective multicenter study of 26 patients. *Epilepsia, 52*, 386–392. doi:10.1111/j.1528-1167.2010.02925.x

Rodin, E. A., Schmaltz, S., & Twitty, G. (1986). Intellectual functions of patients with Childhood-onset epilepsy. *Developmental Medicine & Child Neurology, 28*(1), 25–33. doi:10.1111/j.1469-8749.1986.tb03826.x

Sánchez-Carpintero, R. (2011). Diagnóstico temprano del síndrome de Dravet: Aportaciones de la clínica y la biología molecular. *Revista De Neurología, 52*, 681–688.

Schweitzer, J. B., Faber, T. L., Grafton, S. T., Tune, L. E., Hoffman, J. M., & Kilts, C. D. (2000). Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *American Journal of Psychiatry, 157*, 278–280. doi:10.1176/appi.ajp.157.2.278

Sloutsky, V. M., & Napolitano, A. C. (2003). Is a picture worth a thousand words? Preference for auditory modality in young children. *Child Development, 74*(3), 822–833. doi:10.1111/1467-8624.00570

Stenhouse, S. A., Ellis, R., & Zuberi, S. (2013). SCN1A genetic test for dravet syndrome (Severe myoclonic epilepsy of infancy and its clinical subtypes) for use in the diagnosis, prognosis, treatment and management of dravet syndrome. *PLoS Currents, 5*, doi:10.1371/currents.eogt.c553b83d745dd79bfb61eaf35e522b0b

Stevens, M. C. (2009). The developmental cognitive neuroscience of functional connectivity. *Brain and Cognition, 70*, 1–2. doi:10.1016/j.bandc.2008.12.009

Thompson, P. J., & Duncan, J. S. (2005). Cognitive decline in severe intractable epilepsy. *Epilepsia, 46*(11), 1780–1787. doi:10.1111/j.1528-1167.2005.00279.x

Uddin, L. Q., Supekar, K. S., Ryali, S., & Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *The Journal of Neuroscience, 31*(50), 18578–18589. doi:10.1523/JNEUROSCI.4465-11.2011

Wang, P. P., Hesselink, J. R., Jernigan, T. L., Doherty, S., & Bellugi, U. (1992). Specific neurobehavioral profile of Williams' syndrome is associated with neocerebellar hemispheric preservation. *Neurology, 42*, 1999. doi:10.1212/WNL.42.10.1999

Wolff, M., Cassé-Perrot, C., & Dravet, C. (2006). Severe myoclonic epilepsy of infants (Dravet syndrome): Natural history and neuropsychological findings. *Epilepsia, 47*(s2), 45–48. doi:10.1111/j.1528-1167.2006.00688.x

Wolff, M., Weiskopf, N., Serra, E., Preissl, H., Birbaumer, N., & Kraegeloh-Mann, I. (2005). Benign partial epilepsy in childhood: Selective cognitive deficits are related to the location of focal spikes determined by combined EEG/MEG. *Epilepsia, 46*(10), 1661–1667. doi:10.1111/j.1528-1167.2005.00255.x

Yu, F. H., Mantegazza, M., Westenbroek, R. E., Robbins, C. A., Kalume, F., Burton, K. A., … Catterall, W. A. (2006). Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nature Neuroscience, 9*(9), 1142–1149. doi:10.1038/nn1754

Zelazo, P. D., Muller, U., Frye, D., & Marcovitch, S. (2003). I. The development of executive function. *Monographs of the Society for Research in Child Development, 68*(3), 1–27. doi:10.1111/j.0037-976X.2003.00261.x