Cognition in childhood dystonia: a systematic review

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This article is commented on by Adegboye on page 216 of this issue.

Dystonia is a hyperkinetic movement disorder characterized by involuntary contractions of opposing muscles resulting in deviating movement and/or postures. It can be classified into primary and secondary dystonia. Primary dystonia is defined as no neurological abnormalities visible on brain scans obtained through magnetic resonance imaging (MRI), including inherited and idiopathic forms of childhood dystonia. Secondary dystonia is defined as neurological abnormalities visible on brain MRI, including patients with focal lesions (e.g. patients with dyskinetic cerebral palsy [CP]) and patients with more diffuse lesions (e.g. patients with inborn errors of metabolism [IEM]).

Traditionally, dystonia has been considered a pure motor disorder resulting from basal ganglia dysfunction. However, similar to other basal ganglia syndromes as Parkinson’s and Huntington’s disease, non-motor features (e.g. cognitive deficits, pain, fatigue, sleep problems, and psychiatric problems) appear to be an integral component of the phenotype of dystonia and may contribute even more to the perceived burden of the disorder than motor symptoms. Specifically, the occurrence of cognitive deficits is supported by the basal ganglia’s dense connections to the prefrontal cortex, involved in the regulation of complex cognitive skills and behavior. Dysfunctional connections between the basal ganglia and the prefrontal cortex might explain cognitive deficits.

With regard to cognition in dystonia, previous studies have demonstrated mild cognitive deficits in adult patients with idiopathic dystonia in the domains of visuospatial functioning, verbal memory, and set shifting. Adult patients with dystonia in combination with other neurological disorders have been investigated, but because of vastly different methods no conclusions can be drawn so far.

Childhood dystonia often differs in its presentation from adult dystonia. For instance, childhood dystonia is prone to becoming generalized and is more often secondary to other neurological disorders. The question arises whether these differences between children and adults with dystonia also entail differences in non-motor symptoms. This might also shed a light over the question whether cognitive problems are part of the childhood dystonia phenotype and, if so, which cognitive problems are associated with the disorder. The answer to this question has potential implications for diagnosis and treatment. If cognitive deficits are part of the dystonia phenotype, patients might benefit from cognitive rehabilitation comparable to other neurological disorders. If these deficits develop as a consequence of the motor disorder, early intervention and treatment of the motor symptoms is important to prevent cognitive deficits later in life.
We aimed to conduct a systematic review that structures and evaluates existing literature on cognition in childhood dystonia.

With this systematic review we aim to provide an overview of the current state of research on cognitive deficits in children and adolescents with primary and secondary forms of dystonia, especially in the domains of memory, attention and processing speed, executive functioning, social cognition, and language. Herein we follow the advice of Jahan-shahi et al. who advised researchers to cover these cognitive domains and also measure intelligence. We also aim to evaluate the strength of the presented evidence by taking into account the sample size, method of assessment of cognitive functioning, and use of a control group.

METHOD

Search strategy
We conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. The population we were interested in consisted of patients with idiopathic dystonia, genetically defined dystonia (for an overview see Peall et al.), dystonia caused by IEM (for an overview see van Egmond et al.), or CP. We defined the interest as cognition and the context as early onset, that is, children and young adults. Our search terms can be found in Table I.

Inclusion criteria
We used PubMed and PsycInfo for our literature search. One of the authors (MAC) reviewed the titles and abstracts of the 527 initial results based on the following criteria that were discussed with all authors beforehand. The article had to be published in English before October 2017 and had to be available online. Studies about the effectiveness of treatment were included if baseline assessment of cognitive functioning was reported. Studies on secondary dystonia went through a two-stage process: these studies were included in the tables if they met our inclusion criteria but we only describe them in the text if they either exclusively concern patients with dystonia due to another neurological disorder or specify the test results for the group of patients with dystonia within their sample.

Extracted information
From the included articles, we extracted the following data: sample size, mean age of the sample, type of dystonia, type of assessment, results of the assessment of cognitive functioning, and use of a control group. The results were grouped according to the method used by Peall et al. into case reports, smaller case series (n<5), larger case series (n≥5), and case–control studies. Test scores are described as extremely low, borderline, low average, average, high average, superior, or very superior, according to the proposed classification by Wechsler (Wechsler Adult Intelligence Scale–III). Herein, we consider borderline scores and extremely low scores as an indication of an impairment.

Grouping of results
In the text we will only discuss primary sources that are case–control studies and larger case series as these studies provide

Table I: Search terms used in the literature search

<table>
<thead>
<tr>
<th>Primary dystonia</th>
<th>Diffuse lesions</th>
<th>Focal lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia OR idiopathic-dystonia OR DYT1 OR DYT2 OR DYT3 OR x-linked-dystonia-parkinsonism OR DYT4 OR whispering-dysphonia OR DYT5 OR dopa-responsive-dystonia OR segawa-syndrome OR segawa-disease OR DYT6 OR DYT7 OR DYT8 OR paroxysmal-dystonia OR non-kinesigenic-dyskinesia OR DYT10 OR PRRT2 OR episodic-kinesigenic-dyskinesia OR DYT11 OR myoclonus-dystonia OR DYT12 OR rapid-onset-dystonia-parkinsonism OR DYT13 OR DYT15 OR DYT16 OR DYT17 OR DYT18 OR glut1-deficiency-syndrome OR DYT20 OR DYT21 OR DYT23 OR DYT24 OR DYT25 OR hereditary-dystonia OR primary-dystonia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cerebral-palsy AND Dystonia</td>
</tr>
</tbody>
</table>

Specify cognitive deficits
Cognitive-functioning OR Cognition OR Neuropsychology OR Neurocognition OR Intelligence OR Memory OR Attention OR Information-processing-speed OR Executive-functions OR Social-cognition OR Language OR Non-motor-symptom

Early-Onset OR Young-Onset OR Children OR Adolescent OR Young-adult

What this paper adds
- There is limited data on cognition in childhood dystonia.
- Primary dystonia showed intact cognition and IQ, but mild working memory and processing speed deficits.
- Secondary dystonia showed more pronounced deficits and lower IQ, with frequent intellectual disability.
- There is a strong need for case–control studies assessing cognition using standardized neuropsychological tests.
stronger evidence. We will structure the results according to
the type of assessment: (1) standardized neuropsychological
assessments, (2) intelligence measurement (usually IQ), (3)
experimental designs. Within each of these sections, evidence
is structured according to two etiological groups, namely
patients with primary and secondary dystonia. We are aware of
the recent classification system by Albanese et al.1 However,
as most of the existing literature uses the older classification of
primary and secondary dystonia, and in order to increase clarity
and readability, we decided to also use the old classification.

RESULTS
Our literature search yielded 665 initial results and the
subsequent steps are illustrated in Figure 1. After removal
of 138 duplicates, the title and abstract of the remaining
527 articles were screened leading to 34 articles that met
our inclusion criteria. A schematic summary of our findings
can be found in Figure 2.

Standardized neuropsychological assessments
Primary dystonia
Table II shows the included studies that used standardized
neuropsychological assessments. An extensive neuropsycho-
logical assessment was performed in a retrospective larger
case series with 13 children (mean age=11y 6mo, range 6–
18; 7 males) with primary dystonia as part of a screening
before deep brain stimulation (DBS) treatment.10 Four of
these children had a DYT1 mutation, three had a dystonia
plus syndrome, and the etiology was unknown in six chil-
dren. No control group was involved in this study. Individual
scores varied greatly, but mean scores showed that
working memory is on a low average level and processing
speed a low average to borderline level, indicating mild
impairments in these functions. Verbal comprehension,
perceptual organization, and verbal and visual memory
were found to be intact. However, the data set contains
many missing values and the patients with dystonia plus
syndromes especially, could not complete all tasks.

Secondary dystonia
Owen et al. also investigated children with secondary dys-
tonia using a neuropsychological test battery in a retro-
spective longitudinal study.11 Their sample consisted of 40
children (mean age=12y 6mo, range 5–18; 19 males) with
different forms of secondary dystonia, including dyskinetic
CP (n=22) and dystonia caused by IEM (n=12). All patients
underwent DBS surgery. Verbal comprehension and working memory were found to be average, perceptual reasoning and visual and verbal memory were low average. Falkman et al.\textsuperscript{12} investigated theory of mind in a prospective longitudinal case–control study with three patients with dyskinetic CP (mean age = 6y 1 mo, range 5–7; 1 male). Their results showed a delayed yet normally patterned development of theory of mind.

One larger prospective longitudinal case series investigated cognitive functioning in children with more diffuse neurological lesions caused by IEM. Seven children with dystonia secondary to pantothenate kinase–associated neurodegeneration (mean age = 11y 7mo, range 8–17; 2 males) were included in a study on the effectiveness of DBS by Mahoney et al.\textsuperscript{13} Four of these children completed a neuropsychological assessment; severe motor impairment prevented neuropsychological assessment in the other patients. The results showed impairments in verbal and non-verbal reasoning as well as memory. Other cognitive domains were not assessed. These data again concern patients eligible for DBS surgery, which might imply that these patients represent a more severely affected group of patients.

**Conclusion**

We can conclude that patients with primary dystonia (mainly DYT1 mutation) show intact verbal comprehension, perceptual organization, and memory while there are mild impairments in working memory and processing speed. Patients with secondary dystonia caused by focal lesions show more serious impairments concerning perceptual reasoning, verbal, and visual memory. No firm conclusions can be drawn about theory of mind as the available data were obtained from a sample of only three children. Most pronounced deficits, problems concerning verbal and non-verbal reasoning as well as memory, are reported in patients with secondary dystonia caused by more diffuse lesions due to pantothenate kinase–associated neurodegeneration.

**Intelligence measurement**

**Primary dystonia**

Table III shows the included studies concerning intelligence or school performance. This includes one larger retrospective case series with a sample of 14 primary dystonia children (mean age = 9y 8mo, range 6–16; 5 males) from 11 families with torsion dystonia.\textsuperscript{14} The authors compared intelligence tests between the patient group, their siblings without clinical symptoms, and an age, sex, and religion–matched healthy control group. The exact tests used were not reported. The authors reported a significantly higher IQ in the patients with dystonia in comparison to healthy controls, where there was no difference in IQ between unaffected siblings and healthy controls.

A retrospective larger case series was conducted on 18 patients with focal hand dystonia caused by a duplication of the *aristaless-related homeobox* gene. Demographic characteristics are available for only 10 of the 18 patients (mean age = 16y 6mo, range 5–35; 18 males).\textsuperscript{15} Unfortunately, the methods of this study are reported incoherently, so conclusions are difficult to draw.

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**Figure 2:** Simplified graphical representation of the results for each group. Missing crosses in a row indicate lack of data. CP, cerebral palsy; IEM, inborn errors of metabolism.
<table>
<thead>
<tr>
<th>Author (y)</th>
<th>Patient group (n)</th>
<th>Mean age y:mo (range)</th>
<th>Sex</th>
<th>Study design</th>
<th>Cognitive function</th>
<th>Instruments</th>
<th>Results of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary dystonia</strong></td>
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</tr>
<tr>
<td>Owen et al. (2015)10</td>
<td>Primary dystonia (13)</td>
<td>11:6 (6-18)</td>
<td>7 males, 6 females</td>
<td>Retrospective larger case series on the effect of DBS</td>
<td>Verbal comprehension Perceptual organization Working memory Processing speed Visual memory Verbal memory</td>
<td>WISC-IV WISC-IV</td>
<td>Borderline to high average Borderline to high average</td>
</tr>
<tr>
<td>Falkman et al. (2005)12</td>
<td>CP (6; 3 dystonic CP)</td>
<td>6:1 (5-7)a</td>
<td>1 male, 2 females</td>
<td>Prospective longitudinal case-control study</td>
<td>Verbal comprehension and working memory Perceptual reasoning and memory ToM</td>
<td>WISC-IV &amp; WASI CMS &amp; WMS</td>
<td>Average</td>
</tr>
<tr>
<td>Adegboye et al. (2017)28</td>
<td>CP (22; 19 dystonic CP)</td>
<td>13:0 (8-17)</td>
<td>12 males, 10 females</td>
<td>Cross-sectional study</td>
<td>Test for ToM, emotion, behavior and social difficulties, Non-verbal reasoning, perceptual reasoning</td>
<td>WISC-IV &amp; WASI CMS &amp; WMS Pretend play Perception Part-whole Desire First &amp; Second order false belief tasks RMET Emotion regulation Checklist, SDQ RSPM</td>
<td>WISC-IV</td>
</tr>
<tr>
<td>Dahlgren Sandberg (2006)19</td>
<td>CP (6; 3 dystonic CP)</td>
<td>6:5 (5-7)</td>
<td>1 male, 5 females</td>
<td>Prospective longitudinal study</td>
<td>Working memory tests</td>
<td>Digit Span Corsi Blocks WPPSI, WISC-R, &amp; WAIS-R</td>
<td>WISC-IV</td>
</tr>
<tr>
<td>Gagliardi et al. (2011)18</td>
<td>CP (64; 2 dystonic CP)</td>
<td>8:10 (4-14)</td>
<td>38 males, 26 females</td>
<td>Observational case-control study</td>
<td>Visuoperceptual skills, Visualspatial skills, Sequence learning</td>
<td>Corsi blocks WPPSI, WISC-R, &amp; WAIS-R</td>
<td>WISC-IV, WISC-III, WASI, &amp; WPPSI, BPVS-II, CMS, &amp; Nepsy – II</td>
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<tr>
<td>Mahoney et al. (2011)13</td>
<td>Dystonia secondary to PKAN (7)</td>
<td>11:7 (8-17)</td>
<td>2 males, 5 females</td>
<td>Prospective longitudinal case series</td>
<td>Verbal reasoning and non-verbal reasoning &amp; memory</td>
<td>WISC-IV, WISC-III, WASI, &amp; WPPSI, BPVS-II, CMS, &amp; Nepsy – II</td>
<td>WISC-IV</td>
</tr>
<tr>
<td>Isaac et al. (2008)32</td>
<td>PKAN (1)</td>
<td>16:0</td>
<td>Male</td>
<td>Case report</td>
<td>Visual perception, receptive language skills, non-verbal reasoning</td>
<td>Visual Object and Space perception Test, BPVS, &amp; Matrix reasoning WASI</td>
<td>Visual perception average non-verbal reasoning borderline delay in development of receptive language</td>
</tr>
</tbody>
</table>

aAge and sex calculated for patients with dystonia only. DBS, deep brain stimulation; WISC-R/-III/-IV, Wechsler Intelligence Scale for Children – Revised/-Third edition/-Fourth edition; CMS, Children’s Memory Scale; WMS, Wechsler Memory Scale; CP, cerebral palsy; IEM, inborn errors of metabolism; WASI, Wechsler Abbreviated Scale of Intelligence; ToM, theory of mind; RMET, Reading the Mind in the Eyes Test; SDQ, Strength and Difficulties Questionnaire; RSPM, Raven’s Standard Progressive Matrices; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WAIS-R, Wechsler Adult Intelligence Scale – revised; PKAN, pantothenate kinase-associated neurodegeneration; BPVS-II, British Picture Vocabulary Scale – Second edition; Nepsy-II, A Developmental Neuropsychological Assessment – Second edition.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patient group (n)</th>
<th>Mean age y:mo (range)</th>
<th>Sex</th>
<th>Study design</th>
<th>Type of assessment</th>
<th>Results of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary dystonia</strong></td>
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<tr>
<td>Eldridge et al. (1970)</td>
<td>Torsion dystonia (101; 14 with psychological assessment)</td>
<td>9:8 (6–16)</td>
<td>5 males, 9 females</td>
<td>Retrospective case series</td>
<td>Intelligence based on patient history</td>
<td>Higher IQ in the patient group compared to healthy controls (p &lt; 0.030) Borderline</td>
</tr>
<tr>
<td>Szczaluba et al. (2006)</td>
<td>Focal hand dystonia in patients with ARX gene duplication (18; 10 with demographic data)</td>
<td>16:6 (5–35)</td>
<td>18 males</td>
<td>Retrospective larger case series</td>
<td>WISC-IV &amp; WAIS-III, Terman-Merrill scales</td>
<td></td>
</tr>
<tr>
<td>Dale et al. (2011)</td>
<td>Myoclonus dystonia (6; one family, one child)</td>
<td>17:0*</td>
<td>Female*</td>
<td>Case reports</td>
<td>WISC-III</td>
<td>Borderline</td>
</tr>
<tr>
<td>Szymanska et al. (2014)</td>
<td>Different forms of IEM and neurodevelopmental disorders (7; 2 patients with dystonia: DYT-1 and idiopathic)</td>
<td>23:0 (21–26)*</td>
<td>1 male, 1 female*</td>
<td>Case reports</td>
<td>Intelligence based on patient history</td>
<td>Average</td>
</tr>
<tr>
<td>Labate et al. (2012)</td>
<td>Paroxysmal kinesigenic dystonia (2)</td>
<td>11:6 (7–16)*</td>
<td>2 males*</td>
<td>Case reports</td>
<td>WISC (unclear which version)</td>
<td>Intellectual disability in both cases</td>
</tr>
<tr>
<td>Crosiers et al. (2011)</td>
<td>Juvenile dystonia-parkinsonism (1)</td>
<td>12:0</td>
<td>Male</td>
<td>Case report</td>
<td>WISC-III</td>
<td>Intellectual disability</td>
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<tr>
<td><strong>Secondary dystonia</strong></td>
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<tr>
<td>Broggi et al. (1983)</td>
<td>CP (33; 11 with dyskinetic CP)</td>
<td>15:10 (12–21)*</td>
<td>6 males, 5 females*</td>
<td>Prospective longitudinal case series on effect of thalamotomy</td>
<td>WISC (unclear which version) or if motor impairment was too severe Raven test Neuropsychological tests covering memory, visual perception and language Rorschach test Intelligence estimated based on school type</td>
<td>Results for patients with dyskinetic CP: Borderline to high average</td>
</tr>
<tr>
<td>Ben-Pazi (2011)</td>
<td>Dyskinetic CP (35)</td>
<td>8:10 (6mo–19y)</td>
<td>21 males, 14 females</td>
<td>Retrospective larger case series on effect of anticholinergic medication</td>
<td>WPPSI, WISC, WAIS</td>
<td>34/35 patients assumed borderline</td>
</tr>
<tr>
<td>Gagliardi et al. (2011)</td>
<td>CP (64; 2 with dyskinetic CP)</td>
<td>8:10 (4–14)</td>
<td>38 males, 26 females</td>
<td>Observational case–control study</td>
<td></td>
<td>Lower IQ in patients than controls (p &lt; 0.010) Patients distribute over two groups: high functioning group with intact sequencing learning and low functioning group with impaired sequencing learning, lower IQ and worse visuoperceptual and visuospatial skills</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Patient group (n)</td>
<td>Mean age y:mo (range)</td>
<td>Sex</td>
<td>Study design</td>
<td>Type of assessment</td>
<td>Results of assessment</td>
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<tr>
<td>Dahlgren Sandberg (2006)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>CP (6; 3 with dyskinetic CP)</td>
<td>6.5 (5–7)</td>
<td>1 male, 5 females</td>
<td>Prospective longitudinal study</td>
<td>Experimental task: Linguistic capabilities Working memory tests</td>
<td>Decreased reading, spelling and working memory abilities in comparison with the control group (no p-values reported), yet development over time</td>
</tr>
<tr>
<td>Falkman et al. (2005)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>CP (6; 3 dyskinetic CP)</td>
<td>6.1 (5–7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 male, 2 females&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Prospective longitudinal case-control study</td>
<td>Raven’s Progressive Matrices Coloured version</td>
<td>IQ used as matching criterion (borderline to average), no difference with control group (p=0.656)</td>
</tr>
<tr>
<td>Bodensteiner &amp; Johnsen (2004)&lt;sup&gt;37&lt;/sup&gt;</td>
<td>CP (10; 4 with dyskinetic CP)</td>
<td>Unknown (7 m–18y)</td>
<td>Unknown</td>
<td>Retrospective observational study</td>
<td>Intelligence based on patient history</td>
<td>9/10 patients assumed borderline</td>
</tr>
<tr>
<td>Bottos et al. (2001)&lt;sup&gt;38&lt;/sup&gt;</td>
<td>CP (29; 3 with dyskinetic CP)</td>
<td>6.2 (3–8)</td>
<td>12 males, 17 females</td>
<td>Intervention study on the effect of powered wheelchairs</td>
<td>Leitner International Performance Scale and Peabody Developmental Verbal Scale</td>
<td>Mean IQ borderline before treatment</td>
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<tr>
<td>Marlow (2004)&lt;sup&gt;39&lt;/sup&gt; Vogels et al. (1994)&lt;sup&gt;40&lt;/sup&gt;</td>
<td>CP (review) Left-sided thalamic lesion (1)</td>
<td>Unknown</td>
<td>Unknown Female</td>
<td>Review Case report</td>
<td>Review IQ measurement</td>
<td>Development borderline</td>
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<tr>
<td>López-Laso et al. (2010)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Dopa-responsive dystonia (14; two families, 7 children)</td>
<td>10.7 (4–16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 males, 6 females&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Larger prospective observational case series</td>
<td>WISC-R, WAIS-III, WPPSI</td>
<td>IQ average, receptive language skills average, expressive language borderline</td>
</tr>
<tr>
<td>Neville et al. (2005)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Dopa-responsive dystonia (7)</td>
<td>7.5 (11 m-14y)</td>
<td>4 males, 3 females</td>
<td>Observational case study</td>
<td>Unknown</td>
<td>Borderline</td>
</tr>
<tr>
<td>Ebrahimi-Fakhari et al. (2015)&lt;sup&gt;41&lt;/sup&gt; Kylleman et al. (1994)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Glutaric aciduria type I (12; 10 with dystonia)</td>
<td>15:0</td>
<td>Male</td>
<td>Case report</td>
<td>IQ measurement</td>
<td>Low average</td>
</tr>
<tr>
<td>Nicolaides et al. (1998)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Methylmalonic aciduria (35; 5 with dystonia all of whom did not respond to cobalamin)</td>
<td>11.9 (5–16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 males, 6 females</td>
<td>Cross-sectional study</td>
<td>Unknown</td>
<td>Coloured Progressive Matrices, Peabody Picture Vocabulary Test, WISC-III, British Ability Scales, Bayley Scales of Infant Development, Ruth Griffiths Developmental Scales</td>
</tr>
<tr>
<td>Shevell et al. (1993)&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Methylmalonic aciduria (20; 1 with dystonia; data on psychological assessment only for other patients)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Observational study</td>
<td>Intelligence based on patient history</td>
<td>No results available for dystonia patient</td>
</tr>
<tr>
<td>Jinnah et al. (2010)&lt;sup&gt;23&lt;/sup&gt; Mengel et al. (2013)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Lesch-Nyhan disease (46; 21 with dystonia)</td>
<td>21:2 (3–45)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21 males&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Prospective larger case series Review</td>
<td>IQ unclear method Review</td>
<td>IQ scores for 13 patients with dystonia low average In children delay of cognitive development and later cognitive decline</td>
</tr>
</tbody>
</table>
Secondary dystonia

Only one larger prospective longitudinal case series that reported the test results for patients with dystonia: borderline intellectual disability showed probable intellectual disability in children with dystonia based on IEM. Intelligence of patients with dopa-responsive dystonia was investigated in one larger prospective case series (14 patients, mean age $10y 7mo$, range 4–16; 4 males) and an observational study (mean age 5–14y, range 11mo–14; 4 males). Intelligence of patients with methylmalonic aciduria, two groups can be distinguished based on whether or not they respond positively to treatment with cobalamin. In this cross-sectional study, none of the patients with dystonia (mean age 5–14y, range 1–19) responded to cobalamin and showed a borderline IQ. One prospective larger case series included 55 patients with dystonia and showed a borderline IQ. One prospective larger case series included 55 patients with dystonia and showed a borderline IQ. One prospective larger case series included 55 patients with dystonia and showed a borderline IQ.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patient group (n)</th>
<th>Mean age y:mo (range)</th>
<th>Sex</th>
<th>Study design</th>
<th>Type of assessment</th>
<th>Results of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ito et al. (2011)24</td>
<td>Glut-1 deficiency (6; 5 with dystonia)</td>
<td>15:1 (10–19)$^a$</td>
<td>5 males$^a$</td>
<td>Prospective larger case series on effect of modified Atkins diet</td>
<td>Tanaka-Binet Scale, Tsumori-Inage Scale, WISC-III</td>
<td>IQ scores for 4 patients with dystonia: borderline</td>
</tr>
<tr>
<td>Gumus et al. (2015)25</td>
<td>Glut-1 deficiency (6; 2 with dystonia)</td>
<td>7:0 (2–11)$^a$</td>
<td>2 males$^a$</td>
<td>Prospective larger case series</td>
<td>WISC-IV, Stanford-Binet Intelligence Scale for Children younger than 6 years of age</td>
<td>IQ score for one patient with dystonia: borderline</td>
</tr>
<tr>
<td>Klepper et al. (2003)45</td>
<td>PKAN (1)</td>
<td>12:0</td>
<td>Male</td>
<td>Case report</td>
<td></td>
<td>Difficulties in emotional control and academic skills, cognitive decline</td>
</tr>
</tbody>
</table>

Table III: Continued

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$^a$Age and sex calculated for patients with dystonia only. ARX, aristaless-related homeobox; WISC-R/-III/-IV, Wechsler Intelligence Scale for Children – Revised/–Third edition/–Fourth edition; WASI, Wechsler Abbreviated Scale of Intelligence; CP, cerebral palsy; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; PKAN, pantothenate kinase-associated neurodegeneration.
**Table IV**: Included studies using experimental designs

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patient group (n)</th>
<th>Mean age y:mo (range)</th>
<th>Sex</th>
<th>Study design</th>
<th>Cognitive domain</th>
<th>Results of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary dystonia</strong></td>
<td></td>
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<tr>
<td>Mayor-Dubois et al. (2010)</td>
<td>Basal ganglia pathology (18; 2 with idiopathic dystonia)</td>
<td>8:0 (7–9)*</td>
<td>1 male, 1 female*</td>
<td>Experiment</td>
<td>Memory</td>
<td>Patients with idiopathic dystonia: procedural learning difficulties</td>
</tr>
<tr>
<td><strong>Secondary dystonia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Boy et al. (2015)</td>
<td>Glutaric aciduria type I (30; 13 with dystonia)</td>
<td>Unknown (5–29)</td>
<td>18 males, 12 females</td>
<td>Prospective case–control study</td>
<td>Attention and working memory</td>
<td>Preserved information processing if no demand on motor speed</td>
</tr>
</tbody>
</table>

*Age and sex calculated for patients with dystonia only.

**Experimental tasks**

**Primary dystonia**

Table IV shows the studies using experimental tasks that were included in this systematic review. Mayor-Dubois et al. conducted an experiment on procedural learning in children with basal ganglia pathology. They used a task focusing on visuomotor sequence learning and classification skills in 18 children (mean age=11y 6mo, range 8–15; 9 males) with varying basal ganglia pathology and normal cognitive functioning (i.e. an IQ in the average range). Two patients had idiopathic progressive dystonia (mean age=8y, range 7–9; 1 male), and showed more problems with the motor aspects (procedural learning) than with the cognitive aspects (classification) of the task. The authors speculate that their results suggest a highly specific dysfunction of motor pathways in the cortex-basal ganglia-cortex circuits as opposed to other disorders with basal ganglia involvement.

**Secondary dystonia**

Boy et al. investigated information processing of 30 children and young adults with glutaric aciduria type I (mean age=unknown, range 5–29y; 18 males) in comparison to a healthy control group (n=196, age range 5–28y, 103 males) in a prospective case–control study. In the patient group, 13 children were diagnosed with dystonia secondary to glutaric aciduria type I but the paper does not specify the results for this subgroup, therefore no conclusion can be drawn here.

**Conclusion**

Concerning patients with primary dystonia, existing literature points towards procedural learning difficulties and intact information processing speed.

**DISCUSSION**

This systematic review aimed to provide an overview of the current knowledge about cognition in childhood dystonia. We showed that the available data on cognitive functioning in patients with childhood dystonia are very limited. In particular, studies on specific cognitive functions are scarce as the majority of the studies solely focus on IQ. For primary dystonia, we can at the most say that intelligence and most cognitive functions are intact except for mild deficits in working memory and verbal memory. Only one study used standardized neuropsychological tests in this patient group. 

In patients with secondary dystonia, mild cognitive deficits as well as cognitive impairments and frequent intellectual disability have been found (see Fig. 2). Mild deficits in memory, information processing speed, and social cognition have been shown in patients with CP. Visuospatial functions were found to be impaired in this group. Patients with secondary dystonia based on IEM were found to have impaired memory functions. However, these results have to be interpreted with caution, as only parts of the described samples consisted of patients with dystonia. Furthermore, not all domains of cognitive functioning have been investigated yet. In three out of four cases, data on neuropsychological functioning were obtained from children who underwent DBS surgery, which implies that their dystonia is not treatable with medication. It is possible that this creates a bias in the samples, in the sense that these patients represent the more severely affected patients with dystonia. It is unclear whether more severe motor impairments are associated with more severe cognitive problems in patients with dystonia.

Memory has been investigated and results show mild working memory deficits in patients with primary dystonia. In patients with secondary dystonia, memory deficits are more pronounced and occur in visual- and verbal- as well as working memory. Here, patients with diffuse neurological lesions show the most pronounced memory deficits compared to patients with primary dystonia and dystonia secondary to CP. Overall, the results on memory match the results found in adult patients. Other domains of cognitive functioning have been investigated less consequently. Visuospatial functions have been assessed in patients with dyskinetic CP only and the results point to an impairment of these functions. Slow information processing has been found in patients with primary dystonia and dystonia caused by CP.
Social cognition was investigated in two studies with children with CP. One study has shown that social cognition is not intact in this patient group.28 This sample also contained children with dyskinetic CP but as the results were not specified for this subgroup, no conclusion can be drawn considering social cognition in children with dystonia. Still, the results are in line with the results of the other study, a case–control study12 on social cognition of children with CP. This study suggests a delayed yet normally patterned development of social cognition in children with dyskinetic CP. This conclusion is based on three children and therefore cannot be generalized. No results for the domains of attention, language, and executive functioning have been reported in the literature for any of the patient groups described here, leaving a gap in our knowledge of the cognitive functioning of these patients.

We have discussed intelligence measurements separately, because the resulting IQ may only partially reflect functioning in daily life.29 Intelligence is a psychological construct that is difficult to define. Generally, the discussion revolves around the question of whether intelligence should be considered one single concept (g-factor) or several related factors. Today, most intelligence tests are a representation of the former idea (g-factor).30 Commonly used intelligence tests for children are not developed to measure specific cognitive domains and several aspects of cognitive functioning are missing from these tests, for example executive functioning and social cognition. The manuals of intelligence tests require a strongly structured testing environment which is necessary to achieve reliable results but at the same time does not match situations in daily life.

Concerning intelligence, the limited results (14 children) in primary childhood dystonia show a higher IQ compared to healthy controls. Unfortunately, the intelligence test used is not reported, which prevents an evaluation of the reliability of the results. In addition, this finding has not been replicated since 1970 and the findings cannot be generalized as the sample size was small. Intelligence is mostly average in patients with primary dystonia, but patients with secondary dystonia caused by CP often have an IQ below average. In patients with secondary dystonia caused by IEM, intellectual disability frequently occurs.

Of the studies included, 17 were larger case series or case–control studies presenting relatively stronger evidence than single case studies. However, the assessment tools differ greatly between the studies and not all studies assess the same domains of cognitive functioning. Furthermore, not all cognitive domains have been investigated yet. Data are missing on attention, language, and executive functioning. The domain of social cognition has not yet been sufficiently investigated in young patients with dystonia.

As we have stated above, knowing more about the cognitive profile of young patients with dystonia enables clinicians to adapt their treatment strategies to the individual patients. Additionally, identifying cognitive problems is important for the detection of possible impairments and initiation of support in order to enable a positive course of development. With this systematic review, we have sought to describe the cognitive profile of childhood dystonia. More research is needed to complete this profile and enable clinicians to make full use of it for clinical practice.

The scarcity of the available data can reflect three things: (1) the low prevalence of dystonia, which makes it difficult to find homogeneous patient groups big enough to draw sound conclusions; (2) the difficulties of diagnosing dystonia which becomes particularly evident in the studies with patients with secondary dystonia where it is not always clear how many patients were also diagnosed with dystonia; (3) the difficulties that arise when conducting a neuropsychological assessment with patients with severe motor impairments. Neuropsychological tests are not designed to be used in this patient group and necessary adjustments in the testing procedure can invalidate the results. This makes the use of a control group obligatory. In this systematic review, we have identified only five case–control studies in the 34 included studies. This small number of case–control studies underlines the need for further research using standardized neuropsychological testing and control groups. In the five presented case–control studies, test results of patients were compared to results of a healthy control group. Following Macerollo et al.,31 it is possible that there are cognitive deficits inherent to movement disorders in general. Therefore, additional control groups consisting of patients with other movement disorders would help to further elucidate the neuropsychological profile of patients with childhood dystonia.

In addition to the limitations at study level, the current systematic review also has limitations. The naming of dystonia and cognitive problems differs vastly between studies. We have tried to include the most commonly used terms in our key words, but we cannot rule out the possibility that we have missed studies that have used different key words.

CONCLUSION
In summary, there is a strong need for studies assessing cognitive functioning in patients with varying forms of childhood dystonia using standardized neuropsychological methods. So far we know that memory functions are impaired especially in patients with secondary dystonia and that these patients also show lower IQ scores. Other domains of cognitive functioning have been investigated insufficiently. Research should focus on the following domains: memory, attention and processing speed, language, executive functioning, visuospatial skills, and social cognition. Measures or estimations of intelligence are useful to match the patient group to a control group. Future studies need to assess cognitive functioning in young patients more consequently in order to find out if the deficits seen in adults2 are also present in young patients, how they develop during brain maturation, and which factors
are associated with these deficits. Knowing more about these deficits will help us to tailor treatment plans to the specific needs of individual patients.

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