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Catatonia in children and adolescents: New perspectives

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ABSTRACT

Introduction: Catatonia is a rare and severe psychomotor condition in children and adolescents. In the current report, we aimed to review the recent literature.
Method: Using a PRISMA approach, we searched MEDLINE between 1982 and 2017 using the keywords 'CATATONIA' and 'CHILD' or 'ADOLESCENT'. In total, we reviewed 130 reports (controlled study, $N = 4$; clinical chart, $N = 23$; case report, $N = 54$; and editorial/review, $N = 42$).
Results: Several aspects seem to be age specific: (1) although the clinical presentation resembles that in adults, some symptoms are important in children and adolescents (e.g., psychomotor regression). (2) Associated disorders are similar to that found in adults; however, schizophrenia is more frequently observed than mood disorder. Additionally, a history of neurodevelopmental disorders maybe encountered. (3) Morbidity and mortality are among the worst in child psychiatry. (4) Underlying organic conditions are highly prevalent (>20% of the cases), and their search is warranted because some diagnoses may result in specific treatments (e.g., immune-suppressor therapy for autoimmune conditions). (5) Symptomatic approaches – high dose of benzodiazepines and electroconvulsive therapy (ECT) – are as efficient in children or adolescents as they are in adults, but this finding needs to be acknowledged because a resistance against the use of ECT or high-dose medication exists among child psychiatrists.
Discussion: Recent advances in child and adolescent catatonia research have offered major improvements in understanding catatonia and in new therapeutic opportunities. The syndrome is rare, but these advances need to be acknowledged in order to direct patients to centers that have developed a specific expertise.

1. Introduction

While catatonia has been described as an adult condition, catatonic symptoms have been reported in children or adolescents since the nineteenth century. In a series of 26 adults with catatonia, Kahlbaum noted that the majority had their first symptoms in childhood (Kahlbaum, 1874). Raecke (1909), who presented the first clinical series in youths ($n = 10$), observed that the presentation was comparable between children and adults. The first attempt to separate catatonia from other mental conditions in children was made by Karl Leonhard (1979), who listed the differences between "infant catatonia", autism and the "state of feeblemindedness" (Leonhard, 1979).

Leonhard's research on youths with neuro-developmental disorders helped distinguish catatonia from motor dysfunctions associated with autism (Ohta et al., 2006; Wachtel and Dhossche, 2010; Wing and Shah, 2000). In the same vein, the observations made by Cohen et al. (1999) and Dhossche et al. (2006) in cohorts of inpatient youths promoted a syndromic view of the condition. This perspective, which has progressively been internationally endorsed (American Psychiatric Association, 2000, 2013), has also contributed to the acceleration of evidence-based research development and helped in the recognition of catatonia in children and adolescents.

In this article, we provide a review on catatonia in children and adolescents. Section 3 presents the epidemiology and the phenomenology of the syndrome, including the differential diagnoses. Section 4 summarizes the etiological factors and disorders associated with catatonia in children and adolescents. Section 5 attempts to propose a comprehensive model for catatonia. Finally, Section 6 provides an overview of therapeutic approaches.

2. Methods

The systematic review was conducted following the recommendations outlined in the PRISMA guide (Moher et al., 2009). To take into account relevant papers that were written in English, MEDLINE databases between 1982 and 2017 were searched using key terms that included

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'CATATONIA' and 'CHILD' or 'ADOLESCENT' in addition to manual searches. Titles and abstracts were scanned for relevance. Full texts were ordered in case of uncertainty to maximize sensitivity. Reference lists of retrieved systematic reviews were checked. All full texts were checked for eligibility. Studies in which the onset age of every subject with catatonia was over 18 and those that did not specify the onset age as either over or under18 were excluded. Any controlled study, clinical chart, case report, review or editorial were eligible for inclusion in this review. Of the 130 studies obtained by this method, 4 were controlled studies, 23 were chart reviews without case presentations, 54 were case reports, and 42 were editorial/review articles on a specific issue. Seven articles were beyond the scope of this article, and thus, they were excluded (Fig. 1, for detailed research strategy see Table S1). In addition to the report of current evidence on pediatric catatonia, we also mention possible clinical strategies and research prospects that deserve more attention based on our experience in treating youths with catatonia.

3. Phenomenology and diagnosis of catatonia in children and adolescents

3.1. Epidemiology

A prevalence rate for the general population is not available, which indicates that catatonia is a rare clinical syndrome in children and adolescents. The prevalence of catatonia in inpatient youths varies from 0.6% to 17% (Cohen et al., 2005; Takaoka and Takata, 2003; Thakur et al., 2003; Wing and Shah, 2000). In the overwhelming majority of cases, catatonic episodes occur in patients at pubertal ages (Consoli et al., 2012) and exceptionally at pre-pubertal ages (e.g., Wachtel et al., 2008). Furthermore, although the phenomenology of catatonia in young people is similar to that reported in the adult literature (see below), the sex ratio is different, with more boys affected than girls (sex ratio approximately 2:1) (Cohen et al., 1999; Takaoka and Takata, 2003).

3.2. Clinical description and diagnosis

Catatonia is a syndrome of abnormal motor function. Catatonic symptoms can be classified into motor (e.g., posturing, catalepsy, waxy flexibility), behavioral (e.g., negativism, mutism), affective (e.g., uncontrollable emotional reactions, withdrawal), and regressive symptoms (e.g., enuresis). Isomorphism across ages is supported by empirical studies (Dhossche et al., 2010) and has been adopted in the international classification. The DSM-5 criteria for catatonia include the presence of three symptoms from the following list of twelve: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia and echopraxia (American Psychiatric Association, 2013) (Table 1). Other common symptoms are motor resistance to simple commands, posturing, rigidity, automatic obedience, and repetitive movements. While the DSM-IV uses different sets of criteria for the diagnosis of catatonia in schizophrenia and primary mood disorders versus neurological/medical conditions, the DSM-5 has adopted the syndromic approach promoted by most catatonia experts (Dhossche et al., 2010; Francis et al., 2010). In our own cohort, contributions to the classification of catatonia symptoms were limited, and no symptoms appeared pathognomonic of any psychiatric diagnoses, neuro-developmental histories or organic conditions (Benarous et al., 2016; Consoli et al., 2012). In addition to the DSM classification, we previously proposed a specific classification of catatonia in children and adolescents, as described in Table 2 (Cohen, 2006). This assumption was empirically derived from studies on the phenomenology of catatonia in youths (Benarous et al., 2016), the course of the disorder (Cornic et al., 2009), and its association with psychiatric and organic conditions (Consoli et al., 2012; Lahutte et al., 2008).

3.3. Clinical scales

One of the challenges in using rating scales is that catatonic symptoms fluctuate over time, and a longer period of observation may be required to obtain the full clinical picture. Several rating scales that were initially developed for adults were used in pediatric patients, such as

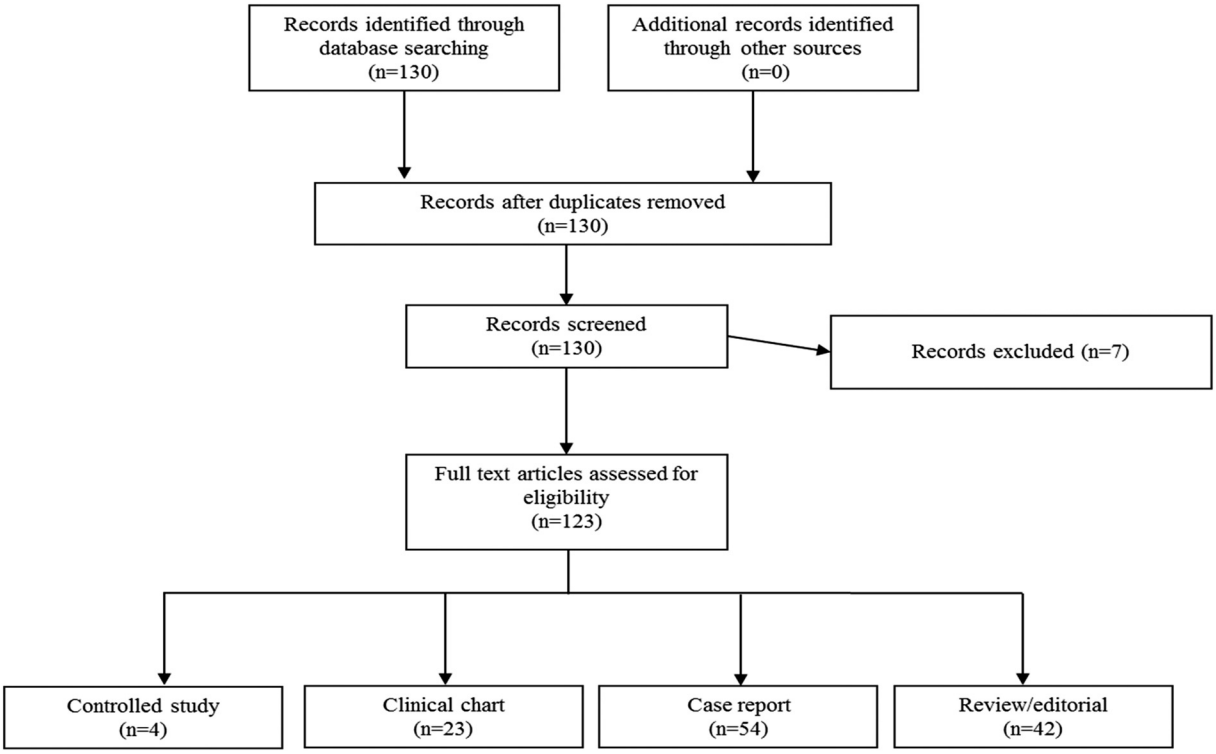

Fig. 1. PRISMA diagram flow of the study search.

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Table 1
Catatonic symptoms in children and adolescents.

Description of items of catatonia	DSM-5 criteria	BFCRS items	PCRS items
Motor symptoms			
Catalepsy (i.e., passive induction of a posture held against gravity)	X	**X**	X
Waxy flexibility (i.e., slight and even resistance to positioning by examiner)	X	**X**	X
Stupor (i.e., no psychomotor activity; not actively relating to environment)	X	**X**	X
Agitation(i.e., not influenced by external stimuli)	X		
Negativism (i.e., opposing or not responding to instructions or external stimuli)	X	**X**	X
Posturing (i.e., spontaneous and active maintenance of a posture against gravity)	X	**X**	X
Grasp reflex (i.e., per neurological exam)		X	
Stereotypes (i.e., repetitive, abnormally frequent, non-goal directed movements)	X	**X**	X
Excitement (i.e., extreme hyperactivity, constant motor unrest which is apparently non purposeful. Not to be attributed to akathisia or goal directed agitation)		**X**	X
Mannerisms (i.e., odd caricature of normal actions)	X	**X**	X
Grimacing (i.e., maintenance of odd facial expressions)	X	**X**	
Staring (i.e., fixed gaze, little or visual scanning of environment, decreased blinking)		**X**	X
Rigidity (i.e., maintenance of a rigid position despite efforts to be moved, exclude if cogwheeling or tremor present)		**X**	X
Impulsivity (i.e., patient suddenly engages in inappropriate behavior without provocation. Afterwards can give no, or only facile explanation)		X	
Mitgehen (i.e., "anglepoise lamp", arm raising in response to light pressure or finger, despite instruction to the contrary)		X	
Ambitendency (i.e., patient appears motorically "stuck" in indecisive hesitant movement)		X	
Perseveration (i.e., repeatedly returns to same topic or persists with movement)		X	
Automatic compulsive movements (i.e., involuntary muscle activity exhibited in posture, attitudes, mimic or gesture due to inhibition or forced motor action)			X
Automatic obedience (i.e., exaggerated cooperation with examiner's request or spontaneous continuation of movement requested)		X	
Gegenhalten (i.e., resistance to passive movement which is proportional to strength of the stimulus, appears automatic rather than willful)		X	
Non-motor symptoms (i.e., behavioral/emotional/autonomic)			
Mutism (i.e., no, or very little, verbal response, not applicable if there is an established aphasia)	X	**X**	X
Echolalia (i.e., mimicking another's speech)	X	**X**	X
Echopraxia (i.e., mimicking another's movements)	X	**X**	X
Verbigeration (i.e., repetition of phrases or sentences, like a scratched record)		**X**	X
Schizophasia (i.e. word salad)			X
Social withdrawal (i.e., refusal to make eye contact)		**X**	X
Refusal to eat/drink		**X**	X
Autonomic abnormality (i.e., circle temperature, BP, pulse, respiratory rate, diaphoresis)		X	X
Acrocyanosis (i.e., cyanosis of the extremities)			X
Combativeness (i.e., usually in an undirected manner, with no, or only a facile explanation afterwards)		X	
Incontinence (i.e., nocturnal enuresis, daytime urinary incontinence, or fecal incontinence)			X

the Bush-Francis Catatonia Rating Scale (BFCRS) and the Modified Rogers Scale (MRS) (Kinrys and Logan, 2001; Zaw and Bates, 1997). Cohen (2006) developed a modified version of the BFCRS for children and adolescents called the Pediatric Catatonic Rating Scale (PCRS). In addition to the 17-item of the BFCRS, six symptoms were added based on the analysis of 463 catatonic cases from seven studies and the review of historical descriptions of pediatric catatonia (Cohen, 2006): (i) *Withdrawal* was separated into *refusal to eat/drink* and *social withdrawal* to facilitate distinction with other pediatric psychiatric disorders such as eating disorders or autism. (ii) *Incontinence*, a symptom of general psychomotor regression, was reported at a high rate in children with catatonia and was added as a symptom (Dhossche et al., 2010). (iii) The criterion of *automatic compulsive movements* was proposed instead of *automatic obedience* and was regarded as a manifestation of psychomotor automatism (De Clérambault, 1927) that would predict a higher risk of associated psychotic disorder. (iv) *Schizophasia* and *acrocyanosis* were added as an indication of malignant catatonia in youths in addition to *autonomic abnormality*. And (v) *grimacing* was combined with *mannerism*. Similar to the BFCRS, each symptom could be rated from 0 (absent) to 3 (severe), leading to a maximum score of 60. Receiver operating characteristic analysis of the PCRS showed excellent discriminant validity with a threshold score of 9 in a sample of 138 inpatient youths with ($N = 88$) and without ($N = 50$) catatonia (Benarous et al., 2016).

Table 2
Proposed categories for diagnostic classification of catatonia in children and adolescents (modified from Cohen, 2006).

Classification element	Category
Catatonia	Stuporous catatonia
	Delirious catatonia (or excited catatonia)
	Malignant catatonia
	Psychomotor automatism (the main symptom is compulsive automatic movements)
Specifier for associated disorder	Secondary to a mood disorder
	Secondary to a medical condition (including toxic state and neurologic disorder)
	Secondary to a psychotic disorder
	Secondary to an acute non psychotic anxious state
Specifier for symptom course	Acute
	Chronic
Specifier for history of neuro-developmental disorder	With a history of ASD
	With a history of ID
	With a history of genetic syndrome

Adapted with permission from Taylor and Fink, American Journal of Psychiatry, 2003.

3.4. Clinical recognition and differential diagnoses

Patients with catatonia do not present impairments at the major items of the neurological examination (e.g., gross motor and sensory function, cranial nerves) (Cohen, 2006; Rosebush and Mazurek, 1999). Discrete neurological signs such as autonomic abnormalities (e.g., in case of malignant catatonia) or abnormalities in fine motor skills (e.g., motor coordination) can however exist. Differential diagnoses should be carefully assessed with regards to medical and obstetrical history, physical exam of other systems, and previous neurological examinations to help distinguishing between: soft signs in a context of developmental stressor (such as premature birth), signs of a comorbid developmental disorder, motor neurological signs due to an organic condition, or medication-induced motor symptoms (McKenna et al.,

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Table 3
Differential diagnosis of catatonia in children and adolescents.

Motor symptoms of a psychiatric disorder
Obsessive-compulsive disorder (compulsive rituals involving repeating behaviors, indecision, slowness to complete tasks)
Autistic spectrum disorders (repetitive pattern of behaviors involving ritualistic and compulsive behaviors, mannerisms, grimacing)
Intellectual disability (stereotypies)
Acute stress disorder[a]
Conversion disorder
Complex motor symptoms of a neurologic disorder
Tic disorder (multiple motor and vocal tics)
Tourette's disorder(facial grimacing, phonic stereotypies, echopraxia and echolalia)
Stereotypic movement disorders
Developmental coordination disorders (bizarre sequencing of complex motor act)
Pharmacology-induced motor symptoms
Neurologic effects of antipsychotic (akathisia, parkinsonism, dyskinesia, and acute dystonia)
Serotonin syndrome

[a] Acute catatonia is possible in context of acute stress (e.g., catatonic stupor and posturing have been described in children after massive collective traumatic experiences, such as heartbreak) (Thakur et al., 2003; Dhossche et al., 2012). However, in this context, motor and emotional symptoms are usually transient (Dhossche et al., 2012).

1991; Raffin et al., 2015; Wing and Shah, 2000; Wong et al., 2007). From a clinical perspective, the distinction is important as inadequate treatment may worsen clinical signs and lead to malignant catatonia (Woodbury and Woodbury, 1992). Table 3 details the most frequent differential diagnoses of pediatric catatonia.

3.5. Course and prognosis of catatonia

Pediatric catatonia usually presents acutely but its onset can also be insidious. Duration can be transient or chronic for weeks or months. Similar to adults, children and adolescents with catatonia are at risk for severe complications due to akinesia, including pneumonia, decubitus ulcers, malnutrition, dehydration, contractures or thrombosis. If untreated, catatonia can progress to malignant catatonia, which is more frequent when antipsychotic medications are prescribed (Cornic et al., 2009). In this severe form, an exacerbation of motor (intense excitement, catalepsy, rigidity, stereotypies and posturing) and non-motor symptoms (e.g., mutism) are observed in addition to systemic symptoms such as delirium, marked autonomic instability and hyperthermia. At this stage, the risk of mortality increases dramatically. The life-threatening impact of catatonia is also evidenced in the only follow-up study found in the literature. Cornic et al. (2009) conducted a 3.9-yearfollow-up study to examine the course of inpatient youths who were admitted for catatonia ($N = 35$; mean age = 19.5 years; range 15–26). The authors found that subjects presented a 60-fold increased risk of premature death at follow-up, including suicide, when compared to the general population with the same sex and age using the Standardized Mortality Ratio. Delays in diagnosis and management were associated with increased morbidity. Additionally, a rare chronic form of catatonia that is associated with schizophrenia in males was identified.

4. Etiological factors and disorders associated with catatonia in children and adolescents

4.1. Psychiatric disorders associated with catatonia

Unlike adults, the most common underlying psychiatric disorders of catatonia in children and adolescents are schizophrenic disorders (Cohen et al., 2005; Takaoka and Takata, 2003). In our clinical cohort, 43 out of 89 youths (48.3%) presented schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, or a brief psychotic episode). The prevalence of catatonia among patients with early-onset schizophrenia is not known. Green et al. (1992) examined 38 children with schizophrenic disorder who were younger than 12 years of age and indicated that catatonia or other grossly disorganized behavior was present in 12 of them (32%). Catatonic episodes can also emerge after the prescription of antipsychotic drugs to patients already diagnosed with schizophrenia. Bonnot et al. (2008) examined youths with schizophrenia that was or was not associated with catatonia. Those who have experienced a catatonic episode presented more severe schizophrenic symptoms, possessed a poorer level of global functioning and required a longer duration of inpatient care to attain sufficient improvement for discharge compared to other subjects.

Mood disorder is the second most common psychiatric condition that is associated with catatonia. In our clinical cohorts, 37 out of 89 (41.6%) presented a mood disorder: 26 met the criteria for a major depressive episode while 11 had experienced a manic episode. Most of these youths presented both catatonic and psychotic features. In some severe cases, the diagnosis was feasible only after an improvement of the catatonic symptoms: Cotard syndrome was reported in an adolescent girl with malignant catatonia who presented with hypochondriac delusion only after the most severe catatonic symptoms were treated (Cohen et al., 1997a). Kinrys and Logan (2001) reported a case of periodic catatonia in a 16-year-old boy with bipolar disorder. Again, the underlying symptoms of the mood episode (i.e., mania with associated psychosis) became evident with the improvement of catatonia after benzodiazepine treatment and electroconvulsive therapy (ECT).

Traumatic factors play an important role in the onset of catatonic episodes in youths (Dhossche et al., 2012). Trauma-induced catatonic episodes are rarely reported in clinical charts. However, these studies rarely take into account situations observed in other settings (e.g., emergency department, consultation-liaison psychiatry, or disaster medical facility). Moreover, there is debate as to whether psychomotor syndromes described in youths under conditions of severe adversity should be considered as catatonia; for example, pervasive refusal syndrome that has been described among refugee children or the devitalization syndrome that has been described in Swedish children from ex-USSR countries (Nunn et al., 2014). In our cohort, nearly 25% of the patients reported a history of severe traumatic experiences (i.e., abuse or severe neglect). However, the nature and the frequencies of these experiences did not significantly differ from those of adolescent inpatients with bipolar disorder. In addition, those who reported a history of severe traumatic experiences exhibited a similar pattern of catatonic symptoms and response rate to treatment compared to other subjects (Benarous et al., 2016).

4.2. Catatonia in youths with developmental disorders

Wing and Shah (2000) were pioneers who studied the prevalence and burden associated with catatonic symptoms in patients with autism spectrum disorders (ASD). By assessing 506 patients that were referred to a specialist clinic for ASD, they were able to empirically demonstrate that catatonia can be distinguished from motor or behavioral manifestations of a developmental disorder. The assumption that a catatonic episode can complicate the course of a developmental disorder has been widespread ever since (Dhossche, 2004; Kakooza-Mwesige et al., 2008; Ohta et al., 2006).

In youths with developmental disorders, the diagnosis of catatonia can be more difficult due to the overlap in symptoms. Catatonia should be suspected when the patient presents a sharp and sustained increase of preexisting motor symptoms (psychomotor slowness or agitation) or when new symptoms are observed (extreme negativism or muteness, stereotypy, peculiarities of voluntary movement, echolalia, or echopraxia) (Taylor and Fink, 2003). As repetitive movements, posturing, and agitation are common symptoms in autism, Dhossche et al. (2006) suggested that a marked change in motor behavior should persist for at least days or weeks before considering a diagnosis of catatonia.

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Some severe forms of repetitive self-injurious behavior have been conceptualized as catatonic stereotypies (with bodily injury), which require specific treatments (Wachtel and Dhossche, 2010).

The prevalence of catatonia in neuro-developmental disorder is difficult to estimate because the existing studies pool youths and adults with ASD or Intellectual Disability (ID). Dhossche et al. (2006) found an incidence rate of 4–17% in adolescents and adults based on a review of six studies ($N = 811$). Catatonia seems to be more frequently observed during middle or late-adolescence (Wing and Shah, 2000), but case reports of prepubertal children have also been published (e.g., Wachtel et al., 2008). Various internal (e.g., epilepsy, pain) or external stressors (e.g., stressful life events) have been implicated in the onset of catatonic symptoms. A loss of routine and an inability to perform self-soothing ritualistic behaviors could lead to increased anxiety and, in turn, contribute to the maintenance of catatonic symptoms in ASD (DeJong et al., 2014; Shah and Wing, 2006). While the vast majority of the literature focuses on autistic youths, very little space was devoted to the recognition and treatment of catatonic syndrome in youths with intellectual disability. For example, the influence of the intellectual quotient score on the presentation of catatonic symptoms, especially motor, has not been examined.

4.3. Catatonia due to general medical conditions

In > 20% of pediatric catatonia, an underlying organic condition could be identified (Consoli et al., 2012; Lahutte et al., 2008). For some of these conditions, specific treatments are available and can drastically improve catatonic symptoms. Table 4 presents the main etiologies that have been reported in youths with catatonia and the appropriate biological and non-biological assessments to confirm the diagnoses. Table 5 presents the clinical symptoms that are likely associated with an organic etiology.

4.3.1. Autoimmune disease

There are two separate classes of autoimmune disorders that are eventually associated with catatonia. Systemic autoimmune disorders should be suspected when youths exhibit extra-neurological symptoms such as polyarthritis, photosensitivity, malar rash, alopecia, proteinuria or hematuria. Systemic lupus erythematosus is the autoimmune disorder that is most frequently reported (Perisse et al., 2003). The pediatric form is known to be more aggressive than the adult form, and neuropsychiatric symptoms more frequent (80% vs 24%). Other systemic autoimmune diseases that are associated with catatonia in youths are less frequent (e.g., Hashimoto encephalopathy).

Auto-immune encephalitis are autoimmune disorders that are limited to brain tissues. The most common examples are anti-NMDA-receptor (anti-NMDAR) encephalitis (Consoli et al., 2011) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) (Elia et al., 2005). The large amount of studies that have focused on anti-NMDAR encephalitis in the last decade showed that the condition is more frequent than initially thought. Titulaer et al. (2013) found that 38% of the participants in the California Encephalitis Project (a cohort of 501 patients with confirmed diagnoses) were under 18. Approximately 70% of them developed a catatonic syndrome; other frequent symptoms were seizure, delirium, abnormal movements and autonomic instability that could lead to malignant catatonia (DeSena et al., 2014). Of note, approximately 38% of youths diagnosed with anti-NMDAR encephalitis also had a concurrent tumor (e.g., ovarian teratoma, extra ovarian teratoma, or testicular tumor) (Titulaer et al., 2013).

Autoimmune investigations should be conducted when caring for young patients with catatonia. In a few patients, inflammation markers in plasma and CSF as well as causal antibodies remained undetectable despite repetitive tests. We developed a score of causality for organic etiologies to guide therapeutic decision making (in particular, the use of immune-suppressors as a therapeutic challenge) in situations where an auto-immune etiology of catatonia is highly suspected (Ferrafiat et al., 2016).

4.3.2. Epilepsy

There is a complex relationship between catatonia and epilepsy, as catatonic syndrome can precede, occur with or continue after the ictus. Also, some of the organic (e.g., anti-NMDAR encephalitis) and psychiatric (e.g., ASD) etiologies described previously can manifest as seizures, making it difficult to differentiate between ictal catatonia and other organic catatonia that are comorbid with epilepsy. The therapeutic response to anticonvulsant drugs allows for the validation of the diagnosis of ictal catatonia. In youths, as in adults, only case reports are available (Consoli et al., 2012; Lahutte et al., 2008).

4.3.3. Intoxication and iatrogenic causes

Various drugs or toxic compounds can cause catatonia in youths, including steroids (Doherty et al., 1991; Sullivan and Dickerman, 1979), lithium (Desarkar et al., 2007), phencyclidine (an NMDA-receptor antagonist), chlorphenamine (an antihistaminic agent) (Baldridge and Bessen, 1990), antiretroviral agents (e.g., zidovudine, abacavir) (Lingeswaran, 2014), insulin (post-insulin coma encephalopathy) and cyclosporine (Consoli et al., 2012). A toxicity-induced catatonic state has been described in adolescents following cannabis overuse (Smith and Roberts, 2014) and after using ecstasy (Masi et al., 2002), gamma-hydroxybutyric acid (a weak agonist GABA-B receptor) (Constantinides and Vincent, 2009; Kuiper et al., 2009) and 4-methyl methcathinone (mephedrone or "bath salts") (Kolli et al., 2013). In ecstasy intoxication, a key issue is to treat the hyponatremia that frequently accompanies catatonia, as it can be life-threatening.

4.3.4. Metabolic and genetic conditions

In our cohort, we found that 25% of young patients with catatonia presented a potential metabolic and/or genetic condition associated with catatonia. Metabolic and/or genetic conditions should be suspected when the familial history is suggestive, when an aggravation of catatonic symptoms is observed with treatment or with conditions associated with catabolism (e.g., food intake, surgery and fever) and when clinical signs of intra-tissue storage are detected (e.g., hepatomegaly) (Sedel et al., 2007). Some patients have a history of developmental disorders or of cognitive regression. However, acute and recurrent attacks without preexisting symptoms can also be observed in the late-onset presentation of genetic and/or metabolic diseases (e.g., urea cycle defect, homocysteine remethylation defect and porphyria).

The main metabolic conditions that are associated with pediatric catatonia are Wilson's disease and porphyria. Single-gene conditions associated with pediatric catatonia that have been reported in the literature are Huntington's disease (Letort and Gonzalez-Alegre, 2013), fatal familial insomnia (Dimitri et al., 2006), PRODH mutations, Kleefstra syndrome, creatine deficiency and Sanfilippo syndrome (Consoli et al., 2012). Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) have also been reported (Ju Seok et al., 2009). Cytogenetic abnormalities or significant CNVs have also been described, including Down syndrome, 22q13.3 deletion including the SHANK 3 gene, and Prader-Willi syndrome (Dhossche and Bouman, 1997; Lahutte et al., 2008). A causal link between a specific CNV and the onset of catatonia in youths is difficult to determine, as the relationship could be mediated by a large variety of co-occurring neuro-developmental difficulties that contribute to increased catatonia risk (Consoli et al., 2012). However, it seems that converging findings exist regarding the possible implication of the SHANK3 gene as a vulnerability factor for pediatric catatonia (Leblond et al., 2014; Serret et al., 2015).

Paraclinical assessments of youths with catatonia should systematically involve ammoniemia, homocysteinemia, ceruloplasmin and urinary copper examination in addition to the standard investigations. If a metabolic condition is suspected, ophthalmologic examination and

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Table 4
Organic catatonia in children and adolescents.

Disorder	Clinical contribution to diagnosis	Paraclinical contribution to diagnosis	Specific treatment
Infectious diseases			
Toxoplasmosis	*Congenital*: intracranial calcifications, mental retardation, seizures, retinal damage *Later*: cognitive regression, psychosis, confusion, seizures.	Brain CT scan or MRI (calcifications); serologic analysis of blood or CSF (IgM and IgG)	Specific antibiotic therapy
Typhoid fever	*Acute*: high fever, headache, fatigue, muscle aches, sweating, rash, weight loss, digestive symptoms (abdominal pain, diarrhea or constipation, swollen abdomen) *Later*: confusion, delusions idea, hallucinations	Isolation of *Salmonella enterica* serotype Typhi from blood, urine, or stool	Specific antibiotic therapy
Viral encephalitis	*Acute*: fever, seizures, dysesthesia, paresthesia, speech or hearing dysfunctions, double vision, muscle weakness, partial paralysis, seizures, memory loss *Later*: confusion, behavioral and cognitive changes, hallucinations	Brain CT scan and/or MRI; serologic analysis of blood or CSF, followed by PCR	Antiviral therapy appropriate for the specific virus; corticosteroids and antiepileptic treatment in some cases
Autoimmune diseases			
Anti-NMDA receptor encephalitis	*Prodromal phase*: fever, headache, nausea, vomiting, diarrhea, and upper respiratory signs *Onset*: Acute behavioral changes, acute psychosis and multiple hallucinations, manic symptoms, major anxiety and agitation *Neurologic phase*: Seizures, abnormal movements, aphasia/other language disorders, cognitive dysfunction, cognitive regression and confusion Evolution towards dysautonomic activity	Inflammatory/autoimmune markers in CSF: high IgG index, oligoclonal bands, pleocytosis, ab anti-NMDA (NR1 sub-unit) in CSF EEG: delta brush, focal and diffuse slow activity	Immunosuppressive treatments: – First line: plasma exchange (adjunctive to corticoids or alone) – Second line: rituximab (pulses then oral) – Tumor removal (if found)
Neuro-psychiatric systemic lupus erythematosus	*Neuro-psychiatric symptoms*: acute psychosis, delusions ideas, hallucinations, manic or depressive symptoms, cognitive regression. *Other symptoms*: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis), seizure, hematologic manifestations (leukopenia, lymphopenia, hemolytic anemia, thrombocytopenia), renal involvement with proteinuria	Ab in plasma: ANA (anti-Sm; anti-SSA; anti-SSB; anti-RNP); anti-dsDNAAb; antiphospholipid Ab; anticardiolipin Ab. Low complement (C3, C4, CH50)	Immunosuppressive treatments: – First line: high dosage corticoids, plasma exchange, IV Immunoglobulin – Second line: azathioprine, mycophenolate mofetil, methotrexate
Encephalopathy associated with autoimmune thyroid diseases	*Neuro-psychiatric symptoms*: acute or chronic psychosis, hallucinations (visual), manic or depressive symptoms, hypersexuality, cognitive regression, seizures, stroke-like episodes, optic neuritis, atypical headaches, ataxia, lack of coordination, dysarthria, tremors, restlessness *Other symptoms*: weight gain, mix edema, changes in hair and skin	Ab anti-TPO, anti-TSH receptor, anti-TG, anti-alpha-enolase, antinuclear, antigliadin, antineuronal in plasma Inflammatory/autoimmune markers in CSF: high IgG index, oligoclonal bands, pleocytosis Ab anti-TPO and anti-TG in CSF	Immunosuppressive treatments: – First line: high dosage corticoids, plasma exchange – Second line: rituximab, aziathropine
PANDAS	*Neuro-psychiatric symptoms*: prepubertal acute onset of OCD, tics, separation anxiety, school issues with deterioration in school performance, sleep disruptions *Other symptoms*: history of GAS infections, choreiform movements, enuresis	Plasma explorations: Positive GAS culture b ASLO and Ab anti-DNAse B titer	Immunosuppressive treatments: – First line: plasma exchange, IVIg
Epilepsy			
Epileptic encephalopathy	General or partial complex seizures, cognitive regression, movement disorders, ataxia, dystonia, isolated hallucinations	Brain CT scan and/or MRI EEG	Intravenously antiepileptic treatment
Toxic induced states			
Lithium	Gastrointestinal symptoms: nausea, vomiting, cramping, and sometimes diarrhea Neurologic symptoms: confusion, seizures, coma, tremulousness, dystonia, hyperreflexia, and ataxia Cardiac dysrhythmias	ECG: T-wave flattening Plasma lithium dosage	– Hydration to maximize lithium clearance – Gastrointestinal decontamination – Dialysis
Ecstasy	Psychomotor excitation, delusion ideas (paranoid or megalomaniac), visual hallucinations, major anxiety Nausea, swearing, hypertension, dehydration, tachycardia, dilated pupils, seizures, confusion	MDMA plasma and urine dosage	Symptomatic treatment – Hyponatremia treatment – Hypertension treatment – Activated charcoal
Metabolic and genetic conditions			
Huntington disease	Academic difficulties, subtle changes in handwriting, clumsiness, choreic movements, aggression/disinhibition), apathy, suicide Subsequent: speech difficulties, seizures, rigidity, tremor, myoclonus, cognitive decline, severe generalized motor disturbance, physical dependence	Elongated CAG repeat (>36) in *huntingtin* gene (*4p16.3*)	No
Nieman-Pick type C	Chronic psychosis, persecutory delusions, hallucinations (auditory), learning disabilities, cognitive regression Abnormal movements, ataxia, seizures, vertical supranuclear ophtalmoplegia, hepatosplenomegaly	Skin biopsy (Filipin test) Cholestanol Gene *NPC1*, *NPC2*	Miglustat
Wilson disease	Schizophrenia, manic symptoms, learning disabilities, ADHD Abnormal movements, dysarthria, tremor, rigidity, drooling and swallowing problems, jaundice	Plasma and urine copper Gene *ATP7B*	Chelating agents: zinc acetate and penicillamine
Mucopolysaccharidoses type III a–d	Developmental delay (especially affecting speech), hyperactivity, severe sleep disturbances, slow cognitive deterioration after 10 years old Seizures, retinitis pigmentosa	High level of heparan sulfate in urine Gene *SGSH*, *NAGLU*, *HGSNAT*, *GNS*	Hematopoietic stem cell transplantation

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Table 4 (*continued*)

Disorder	Clinical contribution to diagnosis	Paraclinical contribution to diagnosis	Specific treatment
Acute porphyria	Acute attacks with neurovisceral symptoms (abdominal pain, neuropathy), anemia, hypertension, tachycardia, fine tremors, nausea, vomiting, constipation or diarrhea	High level of porphyrins in plasma, urine (porphobilinogen and delta-aminolevulinic) and stool samples Gene *HMBS*, *PPOX*, *CPOX*, *PBGS*	Glucose and other carbohydrates/intravenous heme
Cerebro-tendinous xanthomatosis (CTX)	ADHD, learning disabilities, cognitive regression, psychosis Chronic diarrhea, ataxia, spastic paraparesis, peripheral neuropathy, parkinsonism, bilateral juvenile cataracts, Achilles (or other) tendon xanthomas	Cholestanol Gene *CYP27A1*	Chenodeoxycholic acid
Vitamin B_{12} deficiency	Depression, psychosis, cognitive regression, early dementia Anemia, pancytopenia, glossitis, mouth ulcers, paresthesia	Low level of cyanacobalamin	Vitamin B12 and folates supplementation
Tay-Sachs	Chronic psychosis, hallucinations, cognitive regression Hypotonia, ataxia, retina "cherry red spot" (loss of vision), seizures	Hexoaminidase type A deficit	No
Prader-Willi syndrome	ID, ASD, behavioral problems, ADHD; psychosis Hypotonia, seizures, global developmental delay, morbid obesity	Duplication *15q11-q13*	No
22q11.2 deletion syndrome	Developmental delay (motor and language), learning problems (verbal; mathematic skills), ASD, rarely ID, ADHD, anxiety, schizophrenia in 20–30% Conotruncal anomalies, palatal anomalies, feeding/swallowing difficulties, hypoparathyroidism (±hypocalcemia), mild facial dysmorphia	Deletion *22q11.2*	No
Fatal familial insomnia	Depression, acute psychosis Insomnia, dysautonomia, dysarthria, ataxia, myoclonus	Polysomnography EEG *PNRPD178N/129* mutation	No
ProDH mutation	Chronic psychosis, schizophrenia	Hyperprolinemia *PRODH* gene mutation	No
Kleefstra syndrome	ASD, ID Dysmorphia, heart defects, renal/urologic defects, genital defects in males, severe respiratory infections, epilepsy/febrile seizures	Heterozygous microdeletion chromosome *9q34.3*	No
Down syndrome	ASD, ID Dysmorphia	Karyotype	No
Hyperhomocysteinemia	Acute psychosis, hallucinations Seizures, ataxia, pyramidal signs, strokes, peripheral neuropathy, cerebral atrophy, megaloblastic anemia, thromboembolic events (lens dislocation and Marfan-like appearance in Cystathionine β-synthase deficiency)	High level of plasma homocysteinemia Gene: *MMACHC*, *MMADHC*, *MTRR*, *LMBRD1*, *MTR*	Hydroxycobalamin (or cyanocobalamin, or methylcobalamin), oral betaine
Creatine deficiency	ID, ADHD, ASD, irritability Hypotonia, movement disorder: dystonia, extrapyramidal	Creatine deficiency detected by proton magnetic resonance spectroscopy	Oral supplementation of creatine
Intracerebral serotonin deficit	Schizophrenia, ASD, depression Frontal and extrapyramidal syndrome, headache, facial paralysis, cerebellum syndrome, tremor, extrapyramidal syndrome, seizures	5-HT deficit in CSF	Possible benefits of levotonine and levodopa

Note: NMDA, *N*-methyl-D-aspartate; Ab, antibody; ANA, anti-nuclear antibody; GAS, group A streptococcal; ASLO, anti-streptolysin O; DNAse B, antideoxyribonuclease B; ECG, electrocardiogram; EEG, electroencephalogram; IVIg, intravenous immunoglobulin; MDMA, 4-methylenedioxymeth-amphetamine; 5-HT, 5-hydroxytryptamine; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; ID, intellectual disabilities; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CSF, cerebral spinal fluid; TPO, thyroperoxydase; TG, thyroglobulin; PCR, polymerase chain reaction.

abdominal ultrasonography can help to document the infraclinical signs. Genetic testing is not systematic. When available, specific treatments such as alimentary restrictions, vitamins, or chelators can be provided in addition to the usual treatment for catatonic episodes.

5. Proposed integrative model for catatonia

5.1. Subjective experiences of catatonic patients

The subjective feelings experienced by catatonic patients can be examined through retrospective investigations with patients in remission from an acute form of catatonia (Cohen et al., 1999). Northoff et al. (1998) and Rosebush and Mazurek (1999) have largely improved in adult patients our understanding of the specific experience associated with catatonia by comparing them with those reported by patients with neurological symptoms. Unlike patients with motor neurological disorder (e.g., Parkinson disease), patients with catatonia appear unaware of the objective position of their body or of the consequences of their movements. Despite prolonged posture they appear unable to experience pain or fatigue that can result in skin injury lesions. Movement dysfunction is reported in different modalities by catatonic patients (Cohen, 2006, see Fig. S1). Some of them reported a rush of contradictory and ambivalent thoughts associated with disorganization of timing and planning. Other ones described intense and uncontrollable emotions associated with a suspension of their will. Some of them described an adherence to delusional ideas that leads to a psychomotor automatism. Finally other ones described a resistance to delusional thinking or conviction. Unlike patients with impairments in general cognitive function (e.g., delirium) no major deficit in memory and/or general awareness are reported in catatonic patients (Northoff et al., 1998; Rosebush and Mazurek, 1999). Hence, patients, even younger ones, usually remembered well the persons who treated them on admission (Cohen, 2006). These findings shed light on the problem of locomotion and voluntary movement at the level of the subjects' experience in catatonic patients. The psychopathological model for catatonia presented in Fig. S1 (Supplementary material) stresses how subjective experiences affecting emotions, flow and content of thoughts linked with psychopathology can alter the process involves in locomotion and finally result in catatonic symptoms.

5.2. Dysfunction of motor selection/planning

Assuming an intact gross motor system, voluntary movement results from intentionality (or will), behavioral planning in both movement

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Table 5
Psychiatric and physical features of selected medical causes of catatonia in childhood.

	Acute psych onset	Isolated psych onset	Intellectual disability	Regression	Confusion	Hypotonia	Seizure	Gastro-intestinal	Hepatomegaly	EPS	Ataxia	Neuropathy	Stroke	Eye	Skin	Kidney	Heart
Autoimmune diseases																	
Anti-NMDA receptor encephalitis		+		+	+		+	+									
EAATD				+	+		+	+		±	+			+			
NPSLE	±	±		+	+									±	+		
Metabolic and genetic conditions																	
Acute porphyrias	+				+			+				+			+		
CTX		+	+	±				+			+	+		+	+		
Huntington's disease		+	+	+			+			+							
Hyperhomocysteinemia		+	+	+	+					+			+	+		+	
JCNL	+						+							+		+	
Metachromatic leukodystrophia				+			+		+		+	+		+			
– late onset																	
MPS III (a–d)	±	+	+	+					+						+		
Niacin deficiency				+				+				+					
NPC		+		+			+		+		+			+			
OTC deficiency		+	+		+	+									+		
Tay-Sachs	+			±			+	+	+	+	+			+			
Vitamin B_{12} deficiency				+			+				+	+			+		
Wilson disease	+	+	±	+					+	+							±
X-ALD		+	+	+								+		+			+

Note: ALD, adrenoleukodystrophy; CTX, cerebrotendinousxanthomatosis; EAATD, encephalopathy associated with autoimmune thyroid disease; EPS, extrapyramidal syndrome; JNCL, juvenile neuronal ceroid lipofuscinosis; MPS, mucopolysaccharidosis; NPC, Niemann-Pick type C; NPSLE, neuropsychiatric systemic lupus erythematosus; OTC, ornithinetranscarbamylase; Psych, psychiatric (isolated – psychiatric symptoms can predominate at onset).

control/execution and timing, and emotional context. The integrity and timely linkage between cognitive (attention, motivation, memory schemes), motor (motor control, timing and computing) and emotional systems are required to enable the execution of an intentional motor act (Bloulac et al., 2004).

A preponderance of glutamate excitatory system over the GABAergic inhibitory system in cortical regions would be a primary mechanism by which catatonic symptoms emerge (Parenti et al., 2016). This model is based on the quick and drastic anti-catatonic effect of GABA-A agonists (Dhossche and Wachtel, 2013; Escobar et al., 2000; Raffin et al., 2015; Sharma et al., 2014) and, on a lesser extent, of NMDA-receptor antagonists that decrease glutamatergic activity (Goetz et al., 2013; Mukai et al., 2011). Functional neuroimaging studies have confirmed the reduced GABAergic activities in cortical regions in catatonic patients, with for example, a lower GABA-A radioligand binding in the right lateral orbitofrontal cortex (OFC) and in the dorsolateral prefrontal cortex (DLPFC) found in 10 akinetic catatonic patients compared to non-catatonic patients in a SPECT study (Northoff et al., 1999).

An imbalance between hypofunctional GABAergic and hyperfunctional glutamatergic cortical activities would secondarily affect subcortical regions involved in motor control. Basal ganglia is a group of subcortical nuclei involved, among other things, in the selection of motor action, in particular the striatum arbitrates among different actions and to allow for the activation of the winner by disinhibiting the corresponding motor circuits according to the input received from cortical regions. A dysregulation of GABA/glutamatergic cortical tone to the striatum would interfere with the filtering between different motor actions programs and impact cortico-striatal loops. A full inability to arbitrate between different motor sequences would result in a complete motor inactivity (e.g., observed in patients with stupor or akinesia), while a partial inability to filter motor sequences would lead to the execution of contradictory behaviors and induce bizarre motor activity (e.g., as observed in patients with ambitendency).

The fact that catatonic patients seem unaware of their own body, described as "a motor anosognosia" (Northoff, 2002b), was associated with posturing, this symptom was linked with deficits in visual-constructive abilities and abnormalities in the activity of the right posterior parietal cortex reported in adults (Northoff et al., 1999). Such findings support the view that the treatment of spatial information from the somatosensory cortex (e.g., muscular tone) to control the execution motor action is poorly effective in catatonic patients resulting in strange or unfinished movements.

The range of catatonic symptoms due to a lack of motor action inhibition of either internally initiated (e.g., perseveration and stereotypies) or externally observed (e.g., mitmachen/gehen and automatic obedience) was linked to a hyperactivity of the prefrontal regions (Northoff et al., 2004) that disappears after the administration of lorazepam (Richter et al., 2010). In catatonia, frontal disinhibition not only increases the general responsiveness to the environment but also emotional hyperexcitability, which results from the loss of the inhibitory modulation of cortical areas on limbic regions (Northoff, 2002b).

5.3. Limitations and future research

Dysfunction in basal ganglia activities was first suspected in the development of catatonic symptoms since the pioneer work of the neurologist Karl Kleist (1927). A model of the putative dysfunction in basal ganglia associated with catatonia is presented in Fig. 2 and detailed in Supplementary material. This exploratory model is derived from the few clinical and neuroimaging available on catatonia. Most of them are uncontrolled observational studies, such as case-reports, for which causality cannot be inferred and subjects to various biases (e.g., publication bias and over-interpretation). This work can be regarded as a first step paving the way to the development of hypothesis-driven research. In particular, dysfunction of motor selection/planning with a focus on the activities of cortico-striatal loops would be worth testing in animal

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models (as the selective electrical stimulation of the globus pallidus monkeys cited by Bari and Robbins (2013), in pharmacological studies that would combine clinical and neuroimaging studies in the vein of Northoff's works or finally in computational models.

6. Treatments

6.1. Benzodiazepines

Lorazepam represents the first line of treatment for pediatric catatonia (Sharma et al., 2014). In most cases, symptoms are drastically reduced within three hours after receiving 1 to 3 mg of lorazepam. When a positive response is observed, a titration should be completed to maintain the dose that achieves a complete resolution of symptoms. This symptomatic treatment should be maintained until the underlying cause of catatonia is found and appropriately treated. In a naturalistic study of 66 children and adolescents with catatonia (Raffin et al., 2015), the response rate for benzodiazepines was approximately 65%.The mean daily dose of lorazepam was 5.35 ± 3.64 mg/day and reached 15 mg/day in some patients. The need for higher doses of benzodiazepines for catatonia patients than that which is usually prescribed for anxiety symptoms is particularly true for ASD patients, where a response can be observed with lorazepam doses as high as 30 mg/day (DeJong et al., 2014). Benzodiazepines are generally well tolerated in youths, and excessive sedation is the most frequent side-effect that is reported (Raffin et al., 2015). In our clinical cohort we reported positive responses with clonazepam, clorazepate, and prazepam (Raffin et al., 2015). Successful use of diazepam and oxazepam were reported in adults but not in pediatric population up till now. No controlled studies or pharmacological findings support the preferential use of one benzodiazepine on the other for pediatric catatonia.

6.2. Other agents

Zolpidem, a non-benzodiazepine GABA agonist, leads to transitory improvements of catatonic symptoms. It has been reported to be effective in the treatment of catatonia in adults. A case report showed a positive response in a 14-year-old boy with ASD (Zaw and Bates, 1997). However, zolpidem is mainly used as a therapeutic test because of its very low half-life (Thomas et al., 1997). Because of their NMDA antagonist properties, amantadine (100–500 mg three times a day) and its derivative memantine (5–20 mg/day) have been tested as a potential treatment for catatonia in youths. Catatonia in an adolescent girl that was resistant to ECT improved after the addition of amantadine (Goetz et al., 2013). Memantine at 10 mg/day with benzodiazepine was also effective on catatonia in a young girl with severe Obsessive-Compulsive Disorder (Mukai et al., 2011).

6.3. Electroconvulsive therapy

ECT should be considered in youths with catatonia that is resistant to benzodiazepines or when a decisive and rapid response is required in severe cases with life-threatening conditions, such as malignant catatonia (Cohen et al., 1997b). The benefit of ECT in youths with lorazepam-refractory catatonia has been supported by case reports (Rey and Walter, 1997; Yeung et al., 1996), retrospective chart reviews (Grover et al., 2013) and prospective cohort studies (Consoli et al., 2010a; Raffin et al., 2015). The response rate for ECT in the treatment of catatonic symptoms in youths is 76–92% (Consoli et al., 2010a; Grover et al., 2013), with remission or a marked improvement observed in 75% of patients (Rey and Walter, 1997). The most common adverse effects immediately following ECT are headache, confusion, memory loss, nausea and vertigo (Cohen et al., 1997b). ECT is effective and safe for treating catatonia in youths with ASD, based on case series and reports (Consoli et al., 2010a; Dhossche and Wachtel, 2013; Wachtel and Dhossche, 2010; Wachtel et al., 2008).

6.4. Supportive measures

Concurrent care may include adequate hydration by IV fluids, prevention of aspiration, and consideration of thrombophlebitis prophylaxis. The most common serious complication is pulmonary aspiration, which can result in pneumonitis and/or pneumonia. Reduction of oral intake leads to dehydration and malnutrition, which promote other complications, especially infection and skin breakdown (risk of decubitus ulcers). When the refusal to eat is observed, enteral feeding may be necessary.

A complete immobility and a lack of reaction to stimuli can be seen by the family as the signs of an imminent death. At referral, certain families may communicate their fear of losing the child; sometimes, it can result in concerns and mistrust of the medical team. At this stage, frequent contact with the family is extremely important to help the family handle the situation. Explanations about catatonic symptoms (for example, that awareness can be preserved despite the lack of social response) and about the treatment provided by the medical team are of major importance.

Psychomotor therapy by occupational therapists or nurses can be regarded as a valuable adjunct treatment. Bodily mediation (such as massages or therapeutic body wrap) has been empirically used as a non-specific treatment to relieve anxiety and restore sensori-motor integrity (Cohen et al., 2009; Consoli et al., 2010b). In ASD, behavioral interventions, especially routine, repetitive, and structured activity, seem to be beneficial (Dhossche et al., 2006). Indeed, the loss of predictability and routine due to hospitalization can cause major anxiety and stress, which in turn could exacerbate psychomotor regression (DeJong et al., 2014; Shah and Wing, 2006).

6.5. The antipsychotics debate

Antipsychotics have been found to worsen catatonia and cause the progression to malignant form (Cohen, 2006; Woodbury and Woodbury, 1992). This is particularly, but not exclusively, true for the first-generation of antipsychotics with higher affinity for dopaminergic receptor. Conversely, there is limited evidence for a possible benefit of second-generation of antipsychotics during the acute phase of catatonic symptoms: two case reports published for aripiprazole (Roberto et al., 2014; Strawn and Delgado, 2007) and one for quetiapine (Ishitobi et al., 2014). The lack of repeated assessment and the concomitant prescription of benzodiazepine in these studies make virtually impossible to establish the real benefit of these molecules on catatonic symptoms. Regarding the paucity of data and the higher-sensibility of the youngest to neuroleptic-induced motor symptoms (Cohen et al., 2012), we recommend that antipsychotics should be discontinue at the acute phase of catatonic episode and should be used with caution to treat the underlying psychiatric disorders when catatonic symptoms are stabilized, with regular clinical assessment for motor side effects.

6.6. Etiological treatments

While the patient is treated for catatonic symptoms, the underlying etiological cause must be found and treated without delay. For the ease of presentation, we have distinguished between psychiatric and organic conditions.

In patients without a history of psychiatric disorders, at least partial remission of catatonic symptoms is often needed to unmask psychiatric symptoms and establish the final diagnosis. Treatment of the associated psychiatric condition should be provided in addition to treatment of the catatonic syndrome. It should be noted that for patients with schizophrenia spectrum disorder or mania, antipsychotics can worsen catatonic symptoms and precipitate malignant catatonia (Woodbury and Woodbury, 1992). Atypical antipsychotics with the fewer D2 antagonist activity (aripiprazole, clozapine, olanzapine, quetiapine and risperidone) would be better tolerated. Additionally, despite lacking formal

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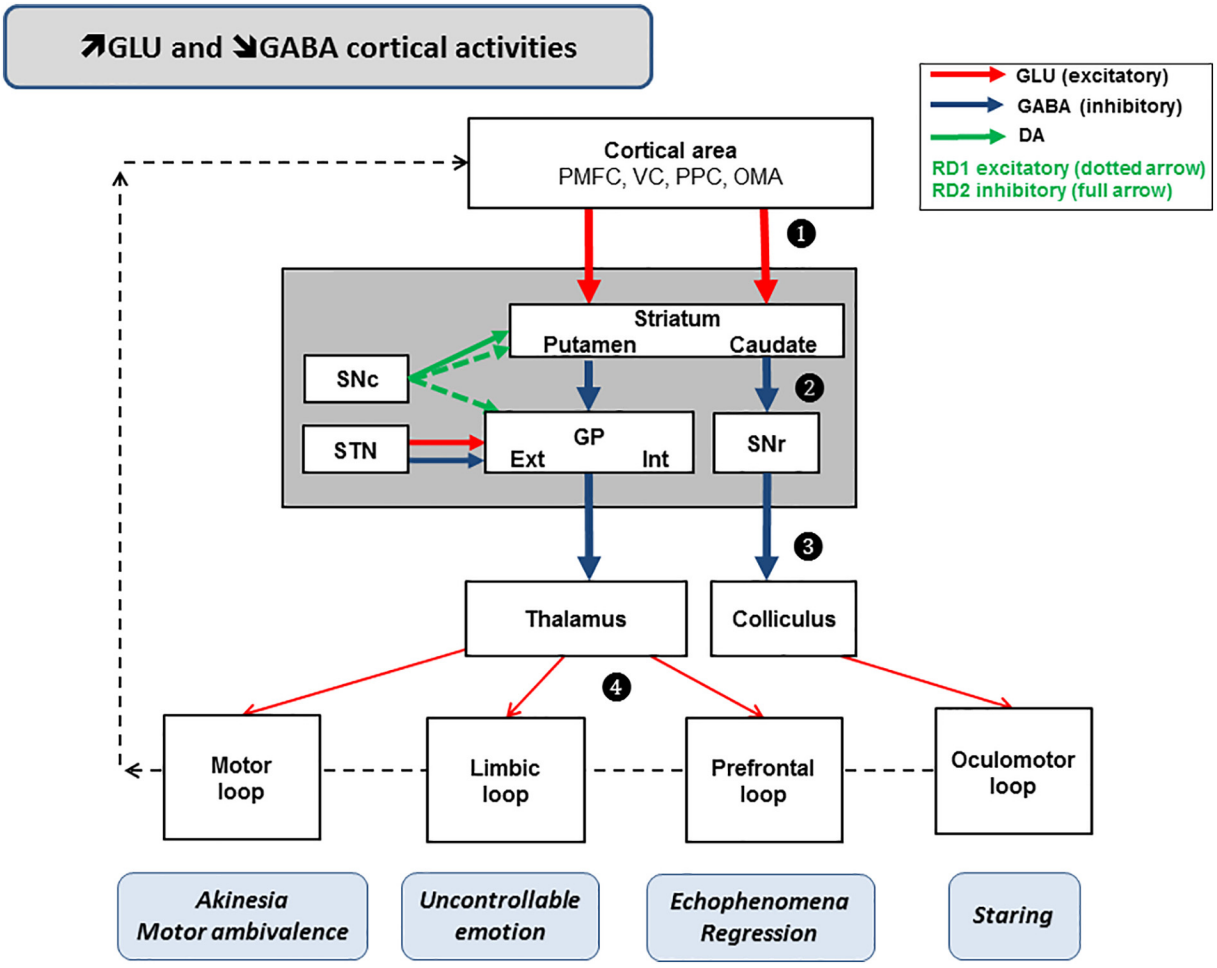

Fig. 2. A neurobiological model of catatonia. ❶ Decreased activation of GABAergic neurons in the striatum; ❷ Decreased disinhibiting of a specific competing channels; ❸ Increased tonic inhibition of the colliculus and thalamus resulting in difficulties in choosing a specific motor or non-motor executive programs; ❹ Interferences with cortico-striatal circuits involving action selection. These circuits originate in cortex project to the striatum followed by the globus pallidus and the substantia nigra and finally to the thalamus with feedback loops back to PFC.
GP: Globus Pallidus; SNc: Substantia Nigra compacta; STN: Subthalamic nucleus; PMFC: Premotor frontal cortex; VC: Visual cortex; PPC: Posterior parietal cortex; OMA: Oculomotor areas; GLU: Glutamate; GABA = γ amino-butyric acid; DA = Dopamine.

empirical evidence, we suggest waiting for the acquisition of a therapeutic dose of benzodiazepines and some improvement in catatonia before introducing antipsychotics.

Organic conditions may have specific treatments as well. For example, some metabolic diseases have been treated with regimens, supplementation (creatine deficit), B12 vitamin and folates (deficit in MTHFR) or anti-storage drugs (Wilson's disease) (Sedel et al., 2007). Autoimmune modulators and suppressors have been successfully used to treat catatonia in neuropsychiatric systemic lupus erythematosus (Ferrafiat et al., 2016; Lanham et al., 1985; Marra et al., 2008; Perisse et al., 2003), PANDAS (Elia et al., 2005; Kovacevic et al., 2015) and anti-NMDA-receptor encephalitis (Consoli et al., 2011; Ferrafiat et al., 2016; Florance et al., 2009; Schimmel et al., 2009; Wilson et al., 2013). Autoimmune catatonia appears to drastically improve with first-line (i.e., corticoid bolus, immunoglobulin and plasma exchange) and second line immune-suppressive treatments (e.g., rituximab and azathioprine). The diagnosis of autoimmune encephalitis is based on a set of clinical and biological arguments; however, a positive diagnosis may not be possible when causal antibodies cannot be identified or are missed despite systematic and repetitive paraclinical assessments. In such situations, the challenge exists during the early use of immunosuppressive treatment, as drastic improvements in the prognosis appear to be time-related to the introduction of drug treatment (Florance et al., 2009; Hacohen et al., 2015; Titulaer et al., 2013). A causality assessment score (CAUS) has been developed to facilitate diagnosis and treatment (if available) decision-making in organic catatonia (Consoli et al., 2012). For auto-immune catatonia, we suggest the inclusion of an immune-suppressive challenge (Ferrafiat et al., 2016).

7. Conclusion

Catatonia is an infrequent but potentially lethal condition in children and adolescents. While clinical presentation and associated disorders are broadly comparable to that found in adults, the presence of an associated developmental disorder or an underlying organic condition should be carefully investigated in children and adolescents in order to tailor the therapies to the patients. Recent advances in childhood and adolescent catatonia have majorly improved our understanding and may finally help to reduce the morbidity of this syndrome. In particular, the identification of organic etiologies has offered new therapeutic opportunities among the youngest patients. A lot of work remains to be done to better understand the mechanisms behind catatonic symptoms; however, we believe that a focus on motor planning/execution provides a valuable research framework for the integration of disparate perspectives. The lack of controlled studies on the therapeutic of pediatric catatonia represents a limitation. The preliminary findings on the benefits of new medication such as NMDA antagonist, presented in few case-reports, have now to be confirmed in controlled studies.

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Note: Distinction between motor and non-motor symptoms was developed by Bush et al. (1996) and further operationalized to facilitate identification of catatonia in pediatric sample by Cohen et al. (1999). DSM-5 criteria for catatonia encompass 12 symptoms. Subjects have to present a minimum of three of the 12 catatonic symptoms (APA 2013). The Bush-Francis Catatonia Rating Scale (BFCRS) encompasses 23 catatonic symptoms, 14 items are used for screening (in bold) (Bush et al., 1996). Compared to DSM-5 criteria some of these items are merged (e.g., Posturing/catalepsy, Echopraxia/echolalia, Social withdrawal/refusal to eat and drink, and Immobility/stupor). The Pediatric Catatonic Rating Scale (PCRS) encompasses 20 items. In addition to the 14-item of the BFCRS, six symptoms were added based on the analysis of 463 catatonic cases pooled from seven studies and review of historical description of pediatric catatonia (Cohen, 2006; Benarous et al., 2016).

Contributors

Study concept and design: DC, XB, and VF.
Acquisition of data: DC, AC, MR, XB, and VF.
Interpretation of data: DC, AC, MR, XB, and VF.
Drafting the manuscript: DC, XB, and VF.
Critical revision of the manuscript for important intellectual content: DC, AC, and MR.
Final draft: All authors.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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