Parkinsonism and Related Disorders 59 (2019) 117–124

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Tics and stereotypies: A comparative clinical review

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ARTICLE INFO

Keywords:
Tics
Stereotypies
Tourette syndrome
Autism
Phenomenology

ABSTRACT

Tics and stereotypies are the most common pathological repetitive complex motor behaviors occurring during the neurodevelopmental period. Although they may appear transiently during development without acquiring a pathological status, when they become chronic they may be distressing, socially impairing, or even, in the case of malignant tics, potentially physically harmful. Despite a certain similarity in their phenomenology, physicians should be able to distinguish them for their different variability over time, topographical distribution, association with sensory manifestations, and relationship with environmental triggers. The complex phenomenology of tics and stereotypies is constantly enriched by the characterization of novel variants, e.g. tics triggered by auditory stimuli in association with misophonia and stereotypies associated with intense imagery activity. Their pathophysiology remains partially elusive, but both animal model and brain imaging studies confirm the involvement of all the three major loops (sensorimotor, associative and limbic) within the cortico-basal ganglia circuitry. From a management perspective, the greatest advances witnessed in the last decade involve the diffusion of behavioral strategies (e.g. habit reversal training or response interruption and redirection), including the development of protocols for telehealth on online training in order to optimise access. In the context of severe tics, e.g. in refractory Tourette syndrome, there is increasing experience with deep brain stimulation of the intralaminar thalamic nuclei or the globus pallidus internus, although more research is needed to fine tune target choice and stimulation setting definition.

1. Introduction

Tics and stereotypies represent the two most common examples of non- or pseudo-purposeful motor behaviour exhibited in childhood. Tics are repetitive and patterned motor actions that are typically associated with preceding uncomfortable sensory experiences, known as premonitory urges (PU). Like tics, stereotypies are typically described as repetitive, patterned, distractible movements that are thought to lack purpose, although this latter, interesting feature can be challenged. Tics and stereotypies may co-exist in some individuals, and phenomenological differences between these two types of motor behaviour allow their distinction in clinical practice, as elaborated in the course of this review. Although in their milder version these movements may not require active intervention, typically reducing over time, in many cases they can cause distress to children and their families and even harm by inaccurate diagnosis and unnecessary investigation. There is uncertainty with regard to the origin and natural history of these movements. In their more intrusive presentation (i.e. severe chronic tics or complex stereotypies) they may persist through childhood and into adult life, representing a challenge to primary care practitioners and specialists for the elusive pathophysiology and for the complexity of the various management approaches. This article presents an overview of the current knowledge of pathophysiological, clinical aspects and techniques for therapeutic management of both tics and stereotypies.

2. A brief pathophysiological summary

The similarity of tics and stereotypies to voluntary behaviour and the presence of some volitional control raise the question of whether there is an overlap between these phenomena and voluntary motion [1,2]. Studies using event-related potentials have not entirely clarified this issue, as one recent study demonstrated a Bereitschaftspotential component (i.e. a pre-movement cortical potential associated with voluntary movements) in a minority of cases preceding motor tics in TS, albeit with a shorter duration in comparison with patients with functional jerks [3]. We have seen some children and adults with tics that have a 'functional' component to the movement pattern, and functional neurological symptoms (FNS) can co-exist with tics in some patients

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https://doi.org/10.1016/j.parkreldis.2019.02.005
Received 23 August 2018; Received in revised form 28 December 2018; Accepted 3 February 2019
1353-8020/

[4]. Unlike voluntary movements, stereotypies were found not to be preceded by movement-related cortical potentials in another study, suggesting that premotor areas are involved differently in the preparation of these complex movements [5]. With advancing development, children do sometimes report '*choosing* to engage in stereotypies' for example to reduce anxiety or when bored in order to gain stimulation. They can also usually choose to do the movements at certain times, for example when alone, allowing for the important management technique of 'promoting privatisation'.

Rodents and primate models suggest commonalities between the generation of tic-like behaviours and stereotypies. Repetitive axial and limb movements highly resembling human tics are generated through the microinfusion of $GABA_A$ receptor antagonists in the sensorimotor portion of the striatum or in the sensorimotor cortex of these animals (striatal disinhibition model) [6–8]. These movements co-occur with phasic activation of the different regions forming the sensorimotor loop of the cortico-basal ganglia (CBG) circuitry (motor cortex, striatum, globus pallidus internus and externus, and thalamus) [9]. A somatotopic correspondence between the region of the striatum that is disinhibited and the body location of the tic-like movements is also observed: the *location* and the *type* of tic-like movements probably depend primarily on which neuronal populations in the striatum are variably active. Interestingly, another study that used the same striatal disinhibition model in monkeys showed that the unilateral disinhibition of the nucleus accumbens generates vocal tics, associated with coupling of alpha oscillations between this nucleus, and the anterior cingulate and primary motor cortical regions [10]. The timing of the same tic-like movements probably depends on the interaction between corticostriatal excitatory inputs and the intrinsic activity state of the striatum, suggesting that this *timing* is modulated by the motor cortical regions [11].

In line with this functional anatomical framework of spatial and temporal encoding, event-related functional magnetic resonance imaging (fMRI) studies on patients with chronic tic disorders demonstrated that the supplementary motor area relays preparatory signals related to tics to the primary motor area and other regions involved in action monitoring, subsequently activating the CBG circuits and leading to tic release [12]. MR spectroscopy and positron emission tomography studies suggest a complex interaction of different neurotransmitters (dopamine, noradrenaline, GABA and glutamate) in association with tic generation [13–17]. The functional anatomy of the premonitory urge (PU) characterized by volumetric, cortical thickness and fMRI studies highlights the involvement of somatosensory areas and of the insula, in line with their contribution to interoceptive awareness and interoceptive stimuli processing [18,19].

The pathophysiological mechanisms of motor stereotypies have been investigated primarily in pharmacological rodent models using cocaine and other stimulants. Earlier reports indicate that the probability of developing motor stereotypies was predicted by the amount of activation induced by dopaminergic overstimulation in the striosomal compartment of the striatum and whether this exceeded the activation in the matrix compartment [20]. A subsequent model of strong cocaine-induced motor stereotypy suggested that the severity of motor stereotypies was modulated by the degree of inhibition of acetylcholine release in the dorsal striatum (caused by the local excess of dopamine release) and the restoration of acetylcholine activity was associated with the arrest of stereotypies [21,22]. Studies on children with complex motor stereotypies support a potential role for the habitual pathway within cortico-basal ganglia circuits, with reported reduction in putamen volume and decrease in size and grey matter density of the caudate [23,24]. A more recent 7T MR spectroscopy study in young people with complex motor stereotypies demonstrated decreased GABA levels in anterior cingulate cortex and striatum [25], although the limited spatial resolution of spectroscopy did not allow differentiation between the specific loops affected within the CBG.

3. Clinical phenomenology and clinimetric aspects

Tics vary in *complexity* across and within individuals, ranging from simple brief movements engaging one or two muscles, to complex motor sequences that may look similar to normal voluntary behaviours. Just like tics, stereotypies may vary across a broad continuum of complexity. The terms *simple* and *complex* are also applied to stereotypies by some authors in a similar way to how these terms are applied to tics, although this distinction does not rest on defined criteria and appears rather arbitrary. Prevalence figures for tics in childhood –including cumulatively both provisional and chronic tics-range from 4 to 24% [26]. Prevalence estimates for primary complex motor stereotypies are more approximate and reported to range between 3 and 8% [27,28].

Tics and stereotypies are seen as a discrete motor behaviour. This appears different from some other hyperkinesias like chorea and dystonia, in which it is extremely difficult to separate individual fragments of involuntary motion from the overall hyperkinetic condition. The examiner can analyze each type of tic or stereotypy independently with the patient or caregiver. This has important implications in the setting of any proposed behavioral treatment, as indicated below.

The frequency of individual tics is variable, with tic-free intervals of different duration over time. Stereotypies cluster in longer periods compared to tics, with a tendency to involve the same muscle groups in a consistent, repetitive pattern that often gives the impression of rhythmicity of movement.

The list of possible movements included in the repertoire of human tics is long, and practically any body muscle may be involved, although the majority of tics involve the head, neck and upper body. Moreover, the observation of large clinical samples of youth with chronic tic disorders indicates a rostro-caudal progression in the topographic distribution of tics, with the ocular and facial regions being the ones affected earlier [29,30]. Developmental stereotypies, on the other hand, are considerably more represented in the distal upper extremities, together with the trunk, and very often mouth stretching phenomena. Typical childhood examples of complex motor stereotypies include hand/arm flapping and out stretching, hand rotating, and finger wiggling [31]. These movements can be confused for complex seizures by some physicians [31], but they are distractible (sometimes with marked annoyance) unlike most epileptic phenomena.

The ability to suppress tics usually develops with advancing age, being better in adults than younger children, although this ability varies enormously across patients and the reasons for this are unclear [30]. The voluntary active suppression of tics can generate a build-up of the intensity of the associated PU, but, conversely, in some this exacerbation of tension or urge does not occur [32]. The ability to suppress tics can be related to the distribution of tics: the body parts that exhibit the fewest tics (e.g. limbs or trunk) seem to be the ones for which tic inhibition is most effective [30]. In line with the susceptibility of tics to environmental contingencies, high levels of stress and anxiety may reduce one's ability to suppress tics voluntarily, whereas engaging in an attention-demanding task may diminish their severity temporarily.

PU for tics are similar to the general construct of urge-for-action, defined as a physical need to respond to a sensory stimulus with a motor action [33]. PU are often difficult to describe for the subject (especially if younger than 8 years), are temporarily abolished by the performance of the related tic, and typically become more intense (at least for a period) if the related tic is voluntarily inhibited. Often the most rapid tics are urge-free. Interoceptive awareness needs further study and this may be increased in subjects reporting greater PU intensity [34,35]. Given the association between stereotypies and various neuro-developmental phenotypes, sensory phenomena associated with stereotypies are poorly defined. When patients verbalise the sensory correlate to their stereotypies, sometimes they report a need to perform them until it feels "just right" [36]. Similar "just right" phenomena are common also in patients with tics with associated obsessive-compulsive

features [37].

The ability to voluntarily control or suppress stereotypies is also variable across subjects, but this is usually due to motivational issues and whether the child is socially aware of their movements. Older children (after 6–7 years) and adults usually acquire the ability to suppress stereotypies, but unlike tics, which are unpleasant, stereotypies are usually enjoyable (at least when alone) and can be very gratifying [38]. It is more usual for individuals to learn to camouflage them as semi-purposeful movements or to engage in the movements in private. However, subjects at times may feel 'compelled' to engage in prolonged bouts of motor stereotypies rather than in tasks necessary for school, for work, or daily functioning, which can then result in distress and impairment. Distraction often has a very powerful and immediate suppressive effect on stereotypies.

Some complex repetitive behaviours may co-occur with tics, especially in the setting of Tourette syndrome (TS). These appear phenomenologically different from both tics and stereotypies in that they neither respond to an unpleasant urge nor aim at generating a pleasant, "just right" feeling, but can be induced by the surrounding stimuli. Echophenomena (copying others' gestures or words) is a physiological behaviour occurring during specific developmental stages that has a key relevance for motor and social adaptive learning [39]. If persisting beyond the first two years of life, it becomes intrusive and disabling. Other stimulus-bound repetitive behaviours occurring in TS are socially disinhibited behaviours that can have an obscene content, as in coprolalia and copropraxia, or be non-obscene yet still socially inappropriate. Socially disinhibited tic behaviours are a highly heritable sub-phenotype within the Tourette spectrum [40].

Misophonia has recently been described as a hatred of a specific sound that acts as a sensory trigger for tics in some people [41]. The specific sounds vary widely across subjects and even include certain everyday words or voices of family members. It is key to identify and differentiate these phenomena when considering management. A recent challenging case of a young boy refractory to many pharmacological and behavioral treatments made significant improvement with exposure response prevention treatment targeting the misophonic stimuli [41].

Stereotypies are sometimes associated with sensory deprivation, such as blindness, hence leading to their interpretation as motor responses aiming to increase the level of sensory stimulation, arousal and interaction with the environment. Stereotypies can increase at times of boredom and conversely during extreme excitement or enjoyment with activities.

A recent subgroup of motor stereotypies has been characterized by our group in the context of episodes of intense imagery (IIM) [36]. During these, children with stereotypies from a very young age (less than 3 years) develop the ability later to semi-consciously engage in acts of intense imagery together with simultaneous, highly patterned complex movements, usually of all four limbs, in relation to computer games, cartoons/films, and fantasy scenes. These children are usually able to verbalise and discuss the imagery phenomena complex movements. This ability to enter imaginary and fantasy worlds is remarkably consistent within the IIM group and does not appear to be a learned response but more of an innate ability. If unrecognized, IIM-related stereotyped movements may lead to intensive, unnecessary investigative work-up. Table 1 summarizes relevant clinical features distingushing tics from stereotypies, as well as diagnostic criteria for tic and stereotypic movement disorders.

Four scales have been recommended to rate tic severity (Yale Global Tic Severity Scale [YGTSS], TS Clinical Global Impression, Tourette's Disorder Scale, Shapiro TS Severity Scale) and one was recommended for PU above age 10 (Premonitory Urges for Tics Scale) [42]. Of these, the YGTSS, which has undergone slight revision recently [43], remains the most widespread, reliable and valid. Most of these scales assess tic severity across different domains based on symptoms related to the previous week. The Rush Video-based Tic Rating Scale is the only validated instrument measuring tic number, frequency and inhibition potency in real time [44]. Caregiver-based instruments to rate stereotypies include the Repetitive Behaviour Scale (6 subscales: Stereotyped, Self-injurious, Compulsive, Ritualistic, Sameness, Restricted) [45], the Stereotypy Severity Scale (assessing Number, Frequency, Intensity and Global Impairment) [46], and the Behaviour Problems Inventory (3 subscales: self-injurious, stereotyped, and aggressive or destructive behaviors) [47]. Quality of life measures are key in our clinical experience and it is enlightening when children with apparently severe tics rate their life quality as high and yet those with an apparently minor simple tic are severely affected. This is usually due to the comorbidities seen in association.

4. Clinical syndromes and etiology

Tic disorders are common and represent a spectrum of neurodevelopmental disorders usually beginning in the first decade (Fig. 1). Tics are, however, not uncommon in autism spectrum disorder (ASD) or in people with learning difficulties (LD), displaying a similar topographical rostro-caudal gradient to the one observed in TS, although often with a reduced self-awareness of tics and therefore may be perceived with less severity [48]. It is interestingly also possible to see the coexistence of tics and stereotypies in the same patient. The phenomenology of tics associated with other medical conditions is not well known (e.g. following toxic, neurodegenerative or post-infectious, e.g. Sydenham's chorea) and has not been widely investigated to date.

So-called 'primary' stereotypies may present as isolated manifestations in otherwise normal young children, or in association with a spectrum of behavioral and cognitive comorbidities that are not etiologically linked to stereotypies. So-called secondary stereotypies are seen in association with autistic traits and/or clinically relevant learning or intellectual disabilities (Fig. 1). A very long list of genetic disorders may cause secondary stereotypies, including chromosomal aberrations like Down syndrome, Williams syndrome, cri-du-chat syndrome, fragile X syndrome, Smith-Magenis syndrome and others, as well as inborn errors of metabolism e.g. phenylketonuria and adenylsuccinate lyase deficiency. 'Deprivation' stereotypies have been linked to deprivation or confinement, for example with neglect, and also with sensory loss as in congenital blindness. A peculiar phenomenological subtype of stereotypies is seen in Rett syndrome, classically diagnosed in young but also adult women with concurrent learning disabilities, in whom stereotypies are located to the hands (less commonly involving fingers), mouth and axial region, are more continuous and often involve object manipulation [49]. Motor stereotypies in the distal upper extremities are also seen in childhood narcolepsy associated with cataplexy, where they become enhanced by emotional stimulation with time [50], and seem to occur more often following a recent group A streptococcal infection [51].

Even in the absence of a well defined genetic origin, attention deficit and hyperactivity disorder (ADHD) is a common comorbidity for both tics and complex motor stereotypies, and is likely to have a relevant impact on the burden of coexisting executive dysfunction (Fig. 2) [31,37]. Inhibitory control deficits might have an impact on the ability to suppress tics on demand, although there is still large heterogeneity of data from the existing literature on this particular aspect [52,53]. Children with complex motor stereotypies without co-existing severe autistic features or learning difficulties may exhibit developmental motor coordination problems in about one third of cases, alongside motor speed problems and motor overflow [54]. A comprehensive assessment encompassing screening for obsessive-compulsive features, mood problems, attentional difficulties, impulse control problems, motor coordination and learning difficulties is crucial for both patients with tics and with complex motor stereotypies to identify all the relevant therapeutic targets and tailor active interventions accordingly.

The term "stereotypies" is frequently used, and in some occasions probably mis-used [55], in the realm of adult-onset movement

Table 1
Summary of the most relevant clinical characteristics that differentiate tics and stereotypies, and of diagnostic criteria for tic and stereotypic movement disorders.

Tics	**Stereotypies**
Tics Key clinical features	**Stereotypies Key clinical features**
DSM5 definition: sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations Mean onset 5–7 years Distressing, uncomfortable Typically migrate over months to years to different body parts Premonitory urges precede them and are relieved by tic performance Intense imagery not a reported feature Common location: eyes, face, head, shoulders	DSM5 definition: repetitive, seemingly driven and apparently purposeless motor behaviours Typical onset < 3 years Comforting, enjoyable, gratifying Typically remain relatively stable in the same body part over time Presence of urge uncertain Often occur with associated intense imagery Involve mouth, hands, arms, or, when more complex, frequently the entire body
DSM5 Diagnostic criteria	**DSM5 Diagnostic criteria**
Tourette's Disorder A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset. C. Onset is before age 18 years. D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis). Persistent (Chronic) motor or vocal tic disorder A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal. B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset. C. Onset is before age 18 years. D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis). E. Criteria have never been met for Tourette's disorder. Provisional tic disorder A. Single or multiple motor and/or vocal tics. B. The tics have been present for less than 1 year since first tic onset. C. Onset is before age 18 years. D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis). E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.	Stereotypic Movement Disorder A. Repetitive, seemingly driven and apparently purposeless motor behaviours. B. Repetitive motor behaviours interfere with social, academic, or other activities, may result in self-injury. C. Onset in early developmental period. D. Not attributable to physiological effects of substance or neurologic condition or better explained by another neurodevelopmental disorder or mental condition.

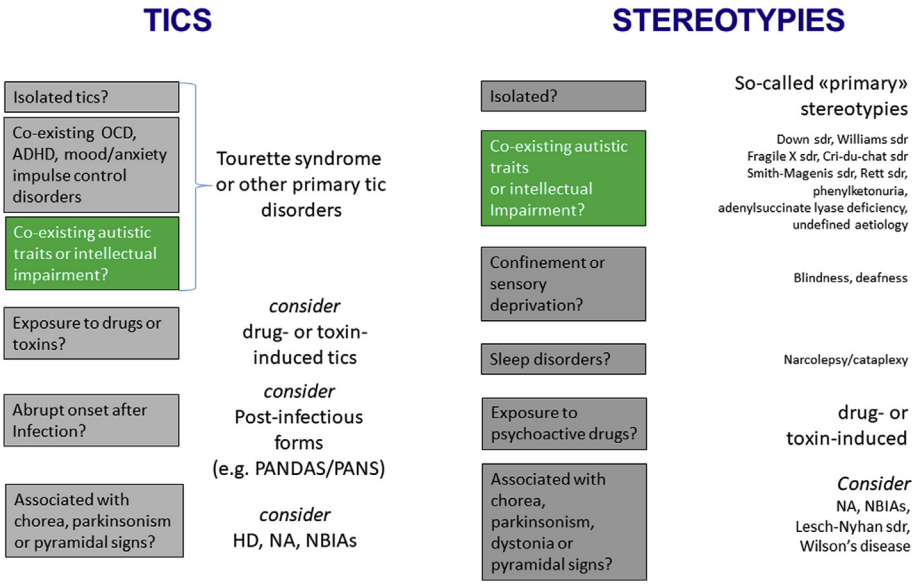

Fig. 1. Schematic diagram of the etiology of tics and stereotypies. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. PANS: pediatric acute neuropsychiatric syndromes. HD: Huntington's disease. NA: Neuroacanthocytosis syndromes. NBIAs: Neurodegeneration with brain iron accumulation syndromes (modified from D. Martino, A.J. Espay, A. Fasano, F. Morgante, Unvoluntary Motor Behaviours, in Disorders of Movement, Springer-Verlag Berlin Heidelberg 2016, p.107 and p.123).

disorders. Often, tardive dyskinesia is also labeled as stereotypy on the basis of its relatively patterned character, but not everything which is relatively patterned is predictable and distractible as stereotypies. A good proportion of orobuccolingual dyskinesia are indeed unpredictable in their succession, fulfilling more the phenomenological labels of chorea or dystonia. It is nevertheless acceptable that some D2-blockers or stimulant-induced hyperkinesias are phenomenologically stereotypies, especially when they involve the distal limbs. The differential diagnosis with motor hyperactivity, restlessness or akathisia may be difficult, especially if a sensory discomfort preceding the movements

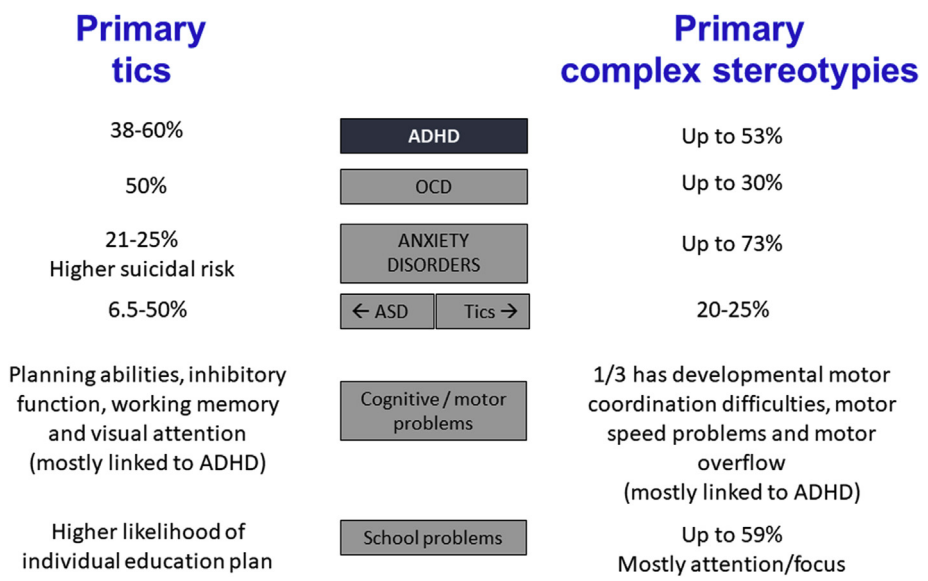

Fig. 2. Summary of the most common behavioral and cognitive problems associated with primary tics and complex stereotypies. ADHD: attention deficit hyperactivity disorder. OCD: obsessive-compulsive disorder. ASD: autistic spectrum disorder.

is not reported. Punding in the context of dopaminergic drugs in PD or stimulant abuse can be considered a "habit transformed in stereotypy", in that it often arises from idiosyncratic habits or pastimes, and consists of an intense fascination with repetitive manipulations of equipment (examining, handling, sorting, hoarding, hypergraphia) [56]. Patients with frontotemporal dementia exhibit different stereotyped repetitive movements, which are phenomenologically heterogeneous and include, alongside 'new onset' stereotypies, also the stereotypic transformation of ritualistic behaviours, perseverative behaviours and compulsive behaviours [57]. A leg stereotypy syndrome has been recently characterized, which consists of repetitive, rhythmical leg movements, mostly present when sitting and in the majority of cases with family history of similar disorder [58].

5. Management

5.1. Tics

After diagnosis and comprehensive assessment, a more active intervention for tics is necessary when tics impact on social and academic functioning, are stigmatising, or potentially physically uncomfortable or harmful. Therapeutic algorithms prompt to a beneficial trade-off between efficacy and invasiveness [59,60]. An important starting point is psychoeducation and this should be provided to all those seeking a consultation. A clear understanding of the etiology, precipitating factors, personal coping strategies, management options and natural history is essential in order to achieve patients' and families' acceptance of the diagnosis and to optimise awareness of tics and urges. Moreover, specific issues related to peer acceptance, academic, family and work-related difficulties can also be targeted by educational or counselling interventions. A clinician should remind patients that treatments for tics typically do not lead to complete cessation of tics. The first therapeutic decision to make when approaching active tic management is about goals of management, motivation and a formulation of the current difficulties, not assuming the motor aspect is the most bothersome. If tics themselves are to be targeted for treatment, behavioral and pharmacological options can be tried together or one or another approach may be preferred, although research on the most effective treatment sequencing approach is warranted. Behavioral techniques are unfortunately still relatively less available and probably slower in producing results, whereas the main drawback of medication is usually tolerability. There is little available evidence on the efficacy of combined approaches, or with the newer available therapies such as cannabinoids. In the adult group there is an increasing experience with deep brain stimulation for highly severe and disabling tics.

Different behavioral interventions for tics have been proposed and tried over the past two decades. The most commonly used methods exploit the strategy of facilitating habituation to the urges, either through repeated exposure, e.g. in exposure-response prevention (ERP), or through the implementation of competing motor strategies, e.g. in habit reversal training. There is, however, limited evidence comparing the efficacy of these two approaches. Based on trial evidence, comprehensive behavioral intervention for tics (CBIT) is to date the most effective behavioral intervention for tics, as well as the intervention for tics with the best efficacy/safety trade-off [61,62]. CBIT is a manualized treatment program encompassing HRT administered through 8 weekly sessions, relaxation training, and functional interventions acting of modifiable tic-triggering settings. It produces an effect comparable to antipsychotics, demonstrated for patients aged 9 years or older, although greater tic severity, lower motivation and greater comorbidity burden might require longer treatment courses. CBIT is very well tolerated, with durable improvements at 6-months follow-up and benefit also on some disruptive behaviours, obsessive-compulsive symptoms, anxiety and familial distress. Specific motor (eye blinking, head jerks/nods, complex motor combinations) and vocal (sniffing, throat clearing) tics appear to respond better to CBIT than other types of tics, and baseline urge presence was found to be associated with tic remission with this treatment [63]. The duration of the treatment and the relative paucity of trained therapists in the program foster research on alternative administration formats using telemedicine. However, its efficacy when delivered using a telehealth format is still being investigated [64]. Alternative online treatment programs for patients and parents are becoming available, e.g. the interactive TicHelper.com, which combines education and active intervention. This website is easily navigable and presents different treatment modules that parallel core CBIT procedures, including interactive exercises, teaching video material, and self-report ratings. Finally, an alternative approach focused on changing the underlying physiological process leading to tic behaviour has also been proposed and tested in an open label study [65].

Antipsychotics and alpha-2 adrenergic agonists are the two classes of medications bearing the strongest evidence of efficacy in the treatment of tics [66,67]. The selection of the antipsychotic agent depends primarily on the patient's general medical profile in relation to the

Table 2
Summary of pharmacological agents for which there is sufficient evidence of efficacy compared to placebo on tic severity, demonstrated by at least one randomized controlled trial.

Pharmacological agent	Pharmacological class	Number of published randomized controlled trials	Most common side effects
Clonidine	Alpha agonist	3 [72–74]	Sedation, hypotension, bradycardia
Guanfacine	Alpha agonist	3 [75–77]	Drowsiness, sedation, hypotension, bradycardia, QTc prolongation (extended release formulation)
Haloperidol	Antipsychotic	2 [78,79]	Movement disorders, metabolic side effects
Risperidone	Antipsychotic	2 [80,81]	Movement disorders, weight gain and metabolic side effects, somnolence, hyperprolactinemia
Aripiprazole	Antipsychotic	2 [82,83]	Weight gain and metabolic side effects, somnolence
Tiapride	Antipsychotic	1 [84]	Somnolence, metabolic side effects
Pimozide	Antipsychotic	3 [78,85]	Movement disorders, QTc prolongation, hyperprolactinemia, metabolic side effects
Ziprasidone	Antipsychotic	1 [86]	QTc prolongation, metabolic side effects
Metoclopramide	Anti-hemetic	1 [87]	Hyperprolactinemia, movement disorders
Ecopipam	D1-dopamine receptor antagonist	1 [69]	Headache, sleep disruption, nausea
Onabotulinum toxin A	Chemodenervating agents	1 [88]	Weakness, hypophonia (when injected in laryngeal muscles)
Topiramate	Anti-epileptic	1 [89]	Cognitive and language problems, somnolence, weight loss, increased risk of renal stones
5-Ling granule	Traditional Chinese Medicine product	1 [84]	None specific reported
Δ-9-tetrahydrocannabinol	Cannabinoid receptor agonist	1	Dizziness, dry mouth, fatigue (only short-term side effects are reported confidently)

specific agent propensity for metabolic and cardiac adverse effects, and to a lesser extent hormonal and motor. In this view, aripiprazole offers a more favourable efficacy-safety balance compared to risperidone, haloperidol and pimozide. Fluphenazine (used more in adults) has a favourable side effect profile and its efficacy is supported by large uncontrolled case series [68]. Regional differences in licensed indication and availability also intervene in the selection of the antipsychotic agent. Ecopipam, a selective D1 receptor antagonist, has recently shown small efficacy, but significantly greater than placebo, in decreasing tic severity at 1 month, with acceptable tolerability, and should be investigate further [69]. Among alpha-2 adrenergic agents, clonidine demonstrated efficacy in several RCTs (Table 2), but may induce bradycardia, hypotension, and sleepiness [70]. The evidence of efficacy for guanfacine extended release is less strong, but tolerability is better despite more cautious monitoring is required in the presence of higher cardiac risk at baseline. Botulinum neurotoxins are often beneficial in focal cranial, cervical and vocal tics in adolescents and adults. Newer agents currently under investigation are selective vesicular monoamine transporter inhibitors (e.g. deutetrabenazine), exogenous cannabinoids, and monoaminoacylglycerol lipase inhibitors potentiating endogenous cannabinoid release [66,71]. Table 2 provides a summary of the medications for which evidence of efficacy on tic severity has been demonstrated, and their side effect profile.

Between 5% and 30% of adult TS patients followed by a specialist clinic manifest disabling tics, in some cases violent and associated with involuntary self-harm, which are refractory to behavioral or pharmacological treatments. This subgroup of adult patients, defined by some authors as 'malignant' TS [90], may be considered for deep brain stimulation treatment, if adherence to long-term follow-up can be guaranteed and comorbidities are stable. This can be considered when there has been an adequate trial of the behavioral treatments and when refractory to pharmacological methods [91]. The evidence of DBS efficacy for tics still relies, to date, on two larger RCTs targeting the globus pallidus pars interna (more frequently the anteromedial or limbic portion) [92,93] and four smaller trials targeting either the GPi or the thalamic intralaminar nuclei [66]. Although the effect of GPi-DBS observed during the randomized period remains uncertain after the two larger trials, tic severity improved in most patients during the post-randomization open label phase. An international registry recently published data on DBS response from 171 patients, reporting similar efficacy across the thalamic and pallidal targets, with persisting improvement of mean tic severity at 1 year [94]. Future studies should compare the efficacy of the different targets, improve our knowledge of the most beneficial stimulation settings, and explore the application of adaptive DBS strategies for the treatment of tics.

5.2. Stereotypies

The mainstay of management of stereotypies remains recognition of the subtypes, assessment for co-occurring conditions and psychoeducation. Patients' and families' education play a crucial role for acceptance of the diagnosis, similar to tics. The identification of intense imagery can be helpful and an assessment for social awareness and motivation to privatise. Stereotypies can be considered in a positive framework and not necessarily considered as a disorder unless they are interfering with daily functioning and being compulsive in nature. As with tics, behavioral treatment can be offered. Habit reversal therapy has been implemented with some success in a proportion of patients, especially those with minimal or mild intellectual disabilities [95]. Recently, a DVD-based parent-delivered behavioral therapy program supplemented by telephone contact with a therapist has shown efficacy in reducing complex motor stereotypies in children [96]. Regularity and consistency are crucial requirements for an effective administration of behavioral therapies for stereotypies. The first stage in any intervention is naming the movement and promoting awareness of when this is occurring. A distraction method can be used and we recommend gentle interruption and redirection [97]. Reward strategies if a child is successful can be very effective. Some children 'use the imagery' to feel more creative and focused and so an individualised approach is key. This can only occur with a detailed psychological formulation and, in our experience, it is crucial to involve an experienced psychologist in the management. The aim is to provide the support to teach a child or adult the skill to privatise the movement (i.e. have control of the stereotypies and be able to limit the movements or IIM to a private space). In a small proportion of patients with disabling stereotypies not caused by medications or toxic substances that do not respond to behavioral interventions, pharmacological treatment can be attempted. However, the quality of evidence of pharmacological trials for stereotypies is considerably lower than for tics. There is some evidence supporting the efficacy of risperidone, aripiprazole and serotonin reuptake inhibitors (clomipramine and fluoxetine) [98,99].

6. Important questions for future research

1. What are the key molecular pathways responsible of the neurodevelopmental abnormalities underlying tics and stereotypies? What is the exact role of non-neuronal cell types (e.g. microglia) in these abnormalities?
2. What are the key differences in cortico-basal ganglia dysfunction between tics and stereotypies?
3. Is enhanced interoceptive or exteroceptive awareness (e.g. in misophonia) a predisposing trait to the occurrence of premonitory urges and tics, or are these merely concurrent epiphenomena?
4. What are the main phenomenological and pathophysiological features differentiating intense imagery-associated movements and 'garden variety' complex motor stereotypies?
5. What is the most effective behavioral approach to treat tics and stereotypies?
6. What is the most effective combination of behavioral and pharmacological strategies for tics, when monotherapies are not sufficiently effective?
7. What is the role of non-invasive neuromodulation (e.g. transcranial magnetic or current stimulation) for the treatment of tics and stereotypies?
8. How should we select target and stimulation settings for deep brain stimulation in patients with severe, disabling tics?

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