Gilles de la Tourette syndrome

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Abstract | Gilles de la Tourette syndrome (GTS) is a childhood-onset neurodevelopmental disorder that is characterized by several motor and phonic tics. Tics usually develop before 10 years of age, exhibit a waxing and waning course and typically improve with increasing age. A prevalence of approximately 1% is estimated in children and adolescents. The condition can result in considerable social stigma and poor quality of life, especially when tics are severe (for example, with coprolalia (swearing tics) and self-injurious behaviours) or when GTS is accompanied by attention-deficit/hyperactivity disorder, obsessive–compulsive disorder or another neuropsychiatric disorder. The aetiology is complex and multifactorial. GTS is considered to be polygenic, involving multiple common risk variants combined with rare, inherited or *de novo* mutations. These as well as non-genetic factors (such as perinatal events and immunological factors) are likely to contribute to the heterogeneity of the clinical phenotype, the structural and functional brain anomalies and the neural circuitry involvement. Management usually includes psychoeducation and reassurance, behavioural methods, pharmacotherapy and, rarely, functional neurosurgery. Future research that integrates clinical and neurobiological data, including neuroimaging and genetics, is expected to reveal the pathogenesis of GTS at the neural circuit level, which may lead to targeted interventions.

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Gilles de la Tourette syndrome (GTS), also known as Tourette disorder or Tourette syndrome, is a childhood-onset disorder with a long, tortuous and somewhat controversial history (FIG. 1). The core diagnostic features are several motor and one or more phonic tics lasting >1 year. Pathognomonic features that are less common but are consistently described from early reports include coprolalia and echophenomena (BOX 1), as well as many comorbidities (which co-occur and have a shared or overlapping aetiology, for example, obsessive–compulsive disorder (OCD), obsessive–compulsive behaviour (OCB), attention-deficit/hyperactivity disorder (ADHD) and possibly autism spectrum disorder). Coexistent psychopathologies (which co-occur but without an evident shared aetiology) include depression, anxiety, oppositional defiant disorder, conduct disorder and/or personality disorders[1]. Although these features are characteristic for GTS, they are not essential for a diagnosis (BOX 2).

Several diagnostic criteria for GTS exist, the establishment of which (and resulting research worldwide) has led the scientific community to view GTS as a common disorder. The WHO criteria (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10; 1993); code F95.2) have remained reasonably constant over time and refer to GTS as a syndrome. Tics were first mentioned in the American Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria in 1952, but GTS was only included in DSM-III in 1980, resulting in a tranche of publications on the topic. In the DSM system, which is currently in its 5th edition[2], GTS is referred to as a disorder, as opposed to a syndrome. Aspects of the DSM criteria for GTS have changed over the years, including the specific age of onset, presence or absence of impairment, level of distress, and ability or inability to suppress tics. Impairment in this context implies that the tics hinder normal functioning, for example, not being able to sit still because of leg tics or being unable to participate in conversations because of tics involving the head, or repetitive and loud coprolalia interfering with conversations or speech. Other diagnostic systems exist, such as the Chinese diagnostic criteria[3,4] (stipulating impairment and distress), but the majority of clinicians, and researchers in particular, opt for the DSM criteria as comparison of data is important[5].

Although several motor and at least one phonic tic are the cardinal features of GTS, there is a spectrum of tic disorders[6], including provisional tic disorder, chronic (persistent) motor tic disorder, chronic (persistent) vocal tic disorder (together, chronic tic disorder)

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and GTS (BOX 2). Furthermore, most research suggests that GTS and chronic tic disorder are part of the same condition[7]; however, GTS is more commonly associated with the aforementioned comorbidities and coexistent psychopathologies.

Supportive therapy (including psychoeducation and reassurance) is often sufficient for most patients. If tics are severe or debilitating, behavioural therapy is the first-line option, followed by psychopharmacological treatment. Neuroleptics (also known as antipsychotics), such as haloperidol and pimozide, interfere with dopamine signalling pathways and are still used[8,9] despite the fact that these older drugs are associated with numerous adverse effects, including drowsiness, movement disorders and hyperprolactinaemia[10]. Indeed, haloperidol remains the only anti-tic medication that is prescribed on licence in many parts of the world. α_2-Adrenergic agonists[11] and second-generation 'atypical' neuroleptics, such as risperidone and aripiprazole, are currently gaining popularity, owing to improved adverse-effect profiles. Newer treatments that are under investigation include, among others, tetrabenazine[10,12], cannabinoids and deep brain stimulation (DBS) for refractory cases.

GTS is a complex neuropsychiatric disorder, with multiple phenotypic manifestations and limited, but evolving, treatment options. This disorder affects children, adolescents and adults worldwide, and, together with the disorders that are frequently comorbid with it, GTS has profound effects on quality of life (QOL) throughout the lifespan of the individual. In this Primer, we describe the epidemiology, pathophysiology, diagnosis and management of GTS in detail. We have chosen to review both historically important papers as well as the newest and exciting papers, which we hope will give the reader a broad and accurate understanding of GTS, its manifestations and therapies to help its myriad of symptoms.

Epidemiology

GTS was thought to be a rare condition for many years, until Comings *et al.*[13] somewhat controversially suggested in 1990 that GTS occurred in 0.66% of school children. If only boys were included, the prevalence was even estimated to be 1%, which is consistent with the finding that GTS is more common in boys than in girls with a male-to-female ratio of 3–4/1 (REFS 1,14,15). Importantly, tics typically have their onset at 4–6 years of age, reach their most severe level at 10–12 years of age and then decline in severity throughout adolescence (FIG. 2). Tics can persist into adulthood and many of the most severe and debilitating cases occur in adulthood. This explains why epidemiological studies are mainly conducted in children and why the age range has such an important affect when interpreting results.

Some controversy has prevailed since the early Comings paper[13], with a wide prevalence range being reported in many subsequent studies[1]. Studies on the basis of clinically diagnosed GTS (for example, those conducted by the US Centers for Disease Control and Prevention[16]) have reported rates ranging from 0.3% to 0.76%, whereas studies that have assessed GTS prevalence in the general population have reported rates ranging from 0.5% to 1%[1,17]. A meta-analysis of studies in children reported a prevalence rate of 0.77%, but the prevalence rose to 1.06% when only boys were accounted for[18]. Another meta-analysis reported a childhood prevalence of 0.52% when both boys and girls were included[19].

An explanation for this variation is that studies have varied enormously in methodology. For example, some studies included individuals who had been hospitalized for their GTS (that is, not measuring the 'true' prevalence), whereas in other studies, patients were not directly interviewed or assessed by the investigators (that is, cases were not directly confirmed) (4 out of 21 of the available studies)[16]. In addition, other investigations were conducted by telephone and included a wide age range of participants (4–17 years), different cohorts (birth cohort versus school pupils), assessment methods (1–3 stages) and/or assessment schedules, which further increases the heterogeneity between studies.

Although some studies point to geographical and ethnic differences in prevalence, the data are inconclusive. Global prevalence data are reported to be somewhat higher than those of many studies from the United States. Such differences in rates may partially reflect a sampling bias. For example, the low rates in an Israeli study could be because of the older ages of individuals examined (16–17 years versus <15 years in most other studies) and because participants were military recruits, who might have hidden their symptoms[20]. Studies conducted in schools in Colombia, Denmark, Iran, Israel,

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Italy, Poland, Spain, Sweden, the United States and the United Kingdom showed a somewhat higher prevalence than studies conducted in schools in the Far East. This potential difference may well be due to the different ages of individuals in the studies and the use of different diagnostic criteria[1], such as the Chinese classification system[3,4,21]. It should be noted that the figures from two studies from China, reporting rates of 0.43–0.55%[22,23], are not that dissimilar to some western data[16]. It has been suggested that GTS does not occur in sub-Saharan black African populations, potentially owing to genetic factors[17]. However, this hypothesis requires further assessment, both epidemiological and genetically, to be confirmed or refuted. GTS has indeed been shown to occur in individuals of African descent in the United States and Europe, but less frequently than in those of Caucasian European ancestry[16,17]. Finally, studies from Denmark[24] and Finland[25], based on national GTS registers, suggest that the incidence of GTS may be rising, although this finding might reflect increased awareness by patients wanting to be diagnosed and by physicians recognizing the disorder.

Mechanisms/pathophysiology

Genetics

Several twin and family studies have demonstrated that GTS is one of the most heritable, non-Mendelian neuropsychiatric disorders. The population-based heritability estimate was found to be 0.77 (95% CI: 0.70–0.85), with a value of 1 suggesting 100% heritability; the risk of GTS in combination with chronic tic disorder (sometimes analysed together, as part of a broader tic spectrum) was increased by 15-fold in siblings of patients with GTS compared with the general population[26–28]. However, no definitive GTS-associated risk gene of major effect has been identified[29,30]. Instead, GTS seems to be highly polygenic, with a large proportion of disease heritability attributable to common risk variants that are distributed across the genome[31]. Inter-individual variation in polygenic burden, combined with rare, inherited or *de novo* mutations in a subset of patients, as well as environmental factors might account for the substantial heterogeneity of the phenotype and complex aetiology of GTS (FIG. 3). This genetic basis parallels that of other developmental neuropsychiatric disorders, such as schizophrenia and ADHD[32,33].

Candidate gene, genome-wide association and copy number variation studies. Although no individual genes have yet met statistical criteria as definitive GTS risk factors, several potential susceptibility genes, which might provide clues to the neurobiology of the disorder, have been identified. The implication of a member of the SLIT and NTRK family of proteins (SLITRK1) in GTS aetiology has spurred intense debate. The first mutation involving *SLITRK1* was a *de novo* chromosome 13 inversion with one of the breakpoints approximately 350 kb from *SLITRK1*; subsequently, two rare, functional *SLITRK1* mutations were identified: a truncating, frameshift mutation (varCDfs) and a missense variant (var321) in the 3′ untranslated region (3′ UTR). The var321 mutation altered a binding site for the microRNA hsa-miR-189 and impaired neurite outgrowth *in vitro*[34]. Subsequent sequencing and association studies have produced mixed results[35–38], supporting the notion that, if *SLITRK1* is involved in GTS aetiology, it might only account for a small fraction of cases, currently on the order of 1 per 1,000 patients if only exonic variants are considered.

The discovery of a deleterious premature termination codon (p.W317*, c.951G>A) mutation in the gene encoding L-histidine decarboxylase (*HDC*), which is the rate-limiting enzyme in histamine biosynthesis, in a GTS family with an affected father and eight affected children (out of eight) has raised the intriguing hypothesis of the involvement of neuronal histaminergic pathways in GTS pathophysiology[39]. Subsequently, a genome-wide analysis of *de novo* GTS copy number variation (CNV) found enrichment in genes encoding proteins in the histaminergic pathway in patients with GTS compared with the general population[40]. In addition, a targeted study of 520 families with GTS found a significant association between *HDC* tagging variants and GTS[41]. However, the largest GTS genome-wide association study to date did not confirm this association[42]. This genome-wide association study, which included 1,285 cases and 4,964 ancestry-matched controls, found no genetic variants that achieved genome-wide significance, although the strongest signal was located within an intron of *COL27A1*, the gene encoding collagen-α1 chain[42]. A subsequent targeted study of 42 of the top loci in 609 independent cases and 610 ancestry-matched controls revealed the most significant GTS association to date: a single-nucleotide polymorphism (SNP) close to *NTN4*, which encodes an axon guidance molecule that is expressed in the developing striatum[43].

Genome-wide investigations of CNVs in relation to GTS aetiopathogenesis have revealed multiple *de novo* or recurrent, rare and exon-affecting CNVs in several genes. The largest reported GTS CNV study to date (2,435 patients with GTS and 4,100 controls) identified two genome-wide significant loci: deletions in *NRXN1* (odds ratio (OR) = 20.3; $P = 6 \times 10^{-6}$), which encodes neurexin 1, and duplications of *CNTN6* (OR = 10.2; $P = 5.1 \times 10^{-5}$), which encodes contactin 6 (REF. 44). The implication of *NRXN1* deletions confirmed two earlier studies involving 111 and 210 individuals with GTS, respectively[45,46]. In addition, one of these studies also identified recurrent exon-affecting microdeletions in the gene encoding arylacetamide deacetylase (*AADAC*)[45], which was confirmed in a large meta-analysis that included a total of 1,181 patients with GTS and 118,730 controls from six European countries ($P = 4.4 \times 10^{-4}$)[47].

Shared genetic basis with other neuropsychiatric and neurological disorders. The high rates of comorbid and/or coexisting psychiatric disorders in patients with GTS lend support to the hypothesis of shared or overlapping neural circuitry alterations and genetic susceptibility[48–51]. Some of the rare CNVs identified in GTS were previously identified in other developmental

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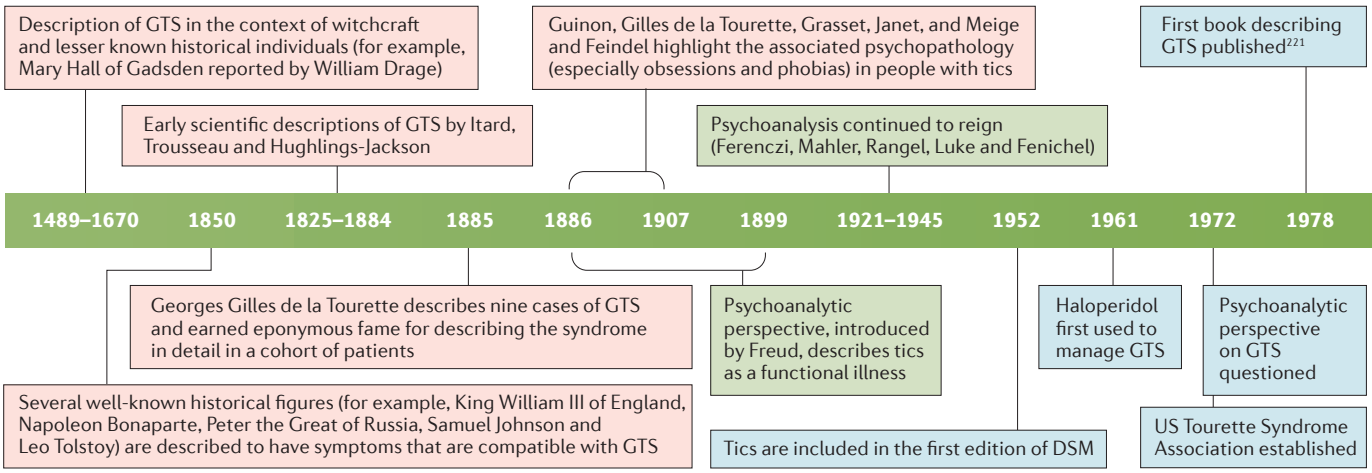

Figure 1 | **Key events in the history of Gilles de la Tourette syndrome.** Timeline depicting the key events in the history of Gilles de la Tourette syndrome (GTS), including events in the early description era, psychoanalytic era, early diagnostic era, and advanced diagnostic and research era. DSM, Diagnostic and Statistical Manual of Mental Disorders; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections; QOL, quality of life; YGTSS, Yale Global Tic Severity Scale.

neuropsychiatric disorders (such as autism spectrum disorder, schizophrenia and epilepsy), including deletions in 1q21, *NRXN1* and 16p13.11, as well as 22q11 duplications[45,52]. Another study independently identified an overall enrichment of CNVs in genes associated with autism spectrum disorder in GTS[40]. In addition, the top loci in the first reported epigenome-wide association study for GTS, although limited in size, were significantly enriched in genes that were previously found to be associated with other neuropsychiatric and neurological disorders[53]. Finally, genes encoding cell adhesion molecules, such as neurexins and neuroligins, were not only found to be associated with GTS but also with other neurodevelopmental phenotypes[54].

Two studies analysed genome-wide association study data to examine the unique and shared components of heritability for GTS and OCD, which is the neuropsychiatric disorder most strongly aetiologically associated with GTS[31,55]. Davis *et al.*[31] observed a significant proportion of shared heritability between the two disorders ($r = 0.41$; SE = 0.15), although the overall genetic architecture (for example, the specific proportion of heritability attributed to each chromosome and the relative contribution of common and rare variants) differed. Yu *et al.*[55] used polygenic risk scores to identify distinct differences between polygenic risk burden of OCD with or without co-occurring GTS and chronic tic disorder; while OCD polygenic risk scores predicted OCD case status when examined in cases without co-occurring GTS or chronic tic disorder, these risk scores were less strongly associated with case status among individuals with OCD plus co-occurring tic disorders. Similarly, in one study involving 222 patients with pure GTS (that is, GTS with only tics and without comorbidities, such as OCD), no family history of OCD was found, which suggests that additional genes or environmental factors may be at play when GTS is associated with OCD and perhaps also with other comorbidities[5].

A large-scale cross-disorder study using genome-wide association study data from 23 different neurological and psychiatric disorders demonstrated that a significant proportion of GTS polygenic heritability is shared with OCD, ADHD and migraine[56]. Although OCD and ADHD have long been known to share heritability with GTS[48], the shared genetic relationship between migraine and GTS is new. GTS and migraine have been observed to co-occur more frequently than control rates[57]. Interestingly, a cross-disorder meta-analysis of top loci from genome-wide association studies of GTS and ADHD[58] reported *TBC1D7* (which encodes a protein involved in the tuberous sclerosis protein complex) as the top signal; *TBC1D7* was also identified to be associated with migraine[59].

Immune and environmental factors

Increasing evidence links the crosstalk between neural and immune pathways to the pathogenesis of GTS, which is consistent with observations in other neurodevelopmental disorders. Recapitulating a model previously proposed for psychosis[60], prenatal and perinatal factors (for example, infections, maternal stress during pregnancy and gestational smoking)[61] could, on a background of increased genetic susceptibility, trigger the priming of microglia (which are glial cells belonging to the monocytic/macrophagic lineage that are involved in synapse formation and elimination). Subsequent hits (for example, psychosocial stressors or infections) could, at a central level, activate microglia, thereby influencing synaptic plasticity close to symptom onset, and enhance peripheral immune or inflammatory responses[62,63]. Initial evidence suggests that these secondary hits might contribute to the waxing and waning course of tics in an interactive manner. For example, the predictive effect of psychosocial stressors on tic and obsessive–compulsive severity becomes three-times stronger when an infection (such as a group A streptococcal

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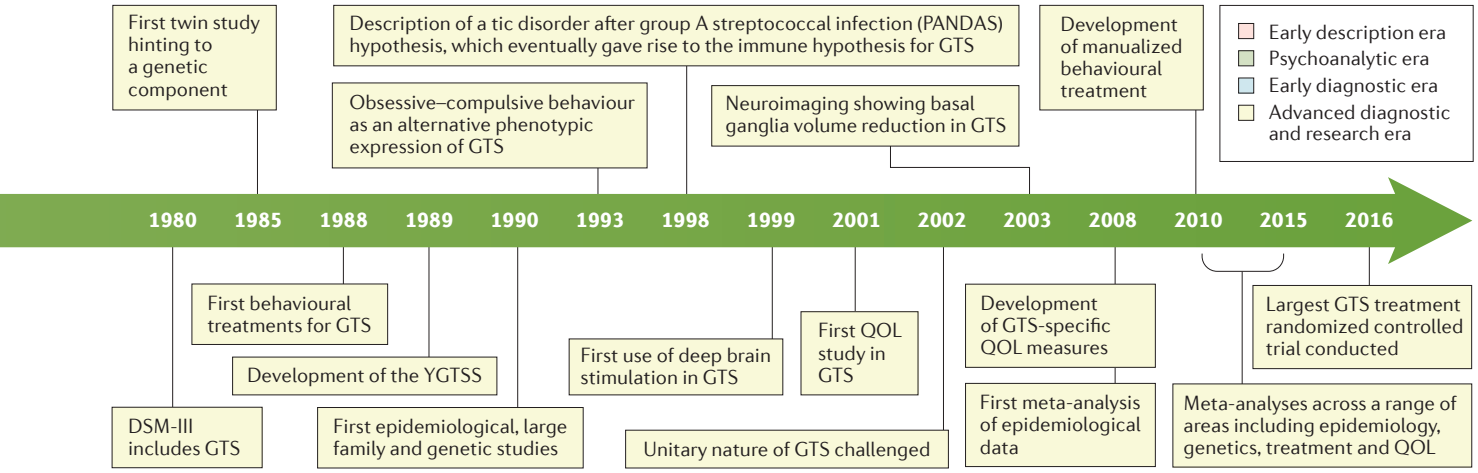

pharyngitis) co-occurs with raised psychosocial stress levels[64]. Exploring the effect of *in utero* versus postnatal environmental influences in the context of valid animal models of tic generation would add to our understanding of their complex aetiology[65].

The genetic basis of the dysregulation of immune-mediated mechanisms in GTS is poorly understood. A study using a Danish health care population registry has shown that a maternal history of autoimmune disorders is associated with a 29% higher risk of GTS in the male offspring but not in female offspring[66]. However, this finding does not clarify whether this association depends on inherited genetic factors, whether it involves transplacental transfer of antibodies or other immune effector molecules or whether it is merely epiphenomenal. Likewise, the interesting observed association between tics in the context of ADHD and common allergies is still unexplained[67].

Direct evidence of altered function of immune cells located in the central nervous system in GTS is limited, but intriguing. The post-mortem analysis of the striatal transcriptome of nine adult patients with GTS and nine closely matched control individuals showed a widespread upregulation of inflammatory response transcripts related to the activity of microglia[68]. Some of these transcripts reflect the expression of 'hub' genes (genes that are present in the highly connected hub nodes according to pathway analysis) that are crucial in the regulation of both innate and adaptive immune mechanisms. In addition, preliminary *in vivo* evidence shows activated microglia in the caudate nucleus of children with GTS[69]. These findings support the hypothesis that immune-competent neural cells play an important part in the pathophysiology of GTS across different age periods, which is sustained by functional interactions with cortico–basal ganglia circuits ranging from early influences on synaptogenesis and circuit formation to post-developmental influences on circuit activity.

The analysis of peripheral lymphoid and myeloid immune cells of children and adolescents with GTS also indicates upregulation of genes encoding proteins that are involved in pathogen recognition and cell-mediated innate and adaptive response, compared with controls[70]. Interestingly, some of these transcripts also encode proteins that are involved in cholinergic and noradrenergic signalling (which is relevant for pathogen recognition), as well as γ-aminobutyric acid (GABA) signalling (which is relevant for its immunosuppressant properties at both a central and a peripheral level)[71,72]. In addition, clinical studies have reported several peripheral immunological changes (for example, dysgammaglobulinaemia, a decreased number of regulatory T cells and an increased antibody response to pathogens) in patients with GTS, which point to chronically hyperactive innate and adaptive mechanisms[63,73].

CSTC circuits and neurotransmitters

Parallel, interacting cortico–striato–thalamo–cortical (CSTC) circuits, which link specific regions in the frontal cortex to subcortical structures (including the basal ganglia and thalamus), provide the framework for understanding GTS (FIG. 4a). Three CSTC circuits are potentially involved in GTS: the habitual behavioural circuit (the premotor cortex–putamen circuit), the goal-directed circuit (the ventral medial prefrontal cortex–caudate nucleus circuit) and the emotion-related limbic circuit (inputs from the hippocampus, amygdala, prefrontal cortex and anterior cingulate gyrus to the ventral striatum)[74–77]. Which neurotransmitter, or combination of neurotransmitters, located within these pathways is relevant in GTS pathogenesis remains to be determined. Likely neurotransmitter candidate abnormalities in GTS, which are probably the end result of more-proximal developmental abnormalities related to the organization or maintenance of CSTC circuits, include dopamine, glutamate, serotonin and acetylcholine.

Dopamine. The strongest neurochemical evidence continues to favour a major role for dopamine in GTS (FIG. 4b). Dopaminergic inputs from the ventral tegmental area innervate the frontal cortex and ventral striatum. In addition, in the striatum, dopaminergic outputs from the substantia nigra pars compacta synapse presynaptically on glutamatergic cortical projections and on direct and indirect GABAergic striatal projections.

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The direct projections contain excitatory dopamine D1 receptors, whereas the indirect pathway expresses inhibitory dopamine D2 receptors. Hypotheses involving dopamine abnormalities in GTS have included presynaptic, intrasynaptic and postsynaptic dysfunctions[78]. Presynaptic alterations include a developmental hypofunction of dopaminergic neurons, hyperinnervation and an increased number of dopamine transporters. Postsynaptic changes include variable increases in the number of striatal and cortical dopamine receptors. Furthermore, a proposed intrasynaptic hypothesis involves the phasic (stimulus-induced) release of dopamine. This suggestion is based on observations such as an increased release of dopamine following amphetamine stimulation[78], tic exacerbation by environmental stimuli and tic suppression with very low doses of dopamine agonists. The positive therapeutic effect of dopamine antagonists in GTS and the multiple interactions between the dopaminergic system and both glutamatergic and GABAergic systems within CSTC pathways further support the role of dopamine as the primary neurotransmitter abnormality[78].

Glutamate. Glutamate, which is an excitatory agent, is the neurotransmitter of cortical and thalamic projection neurons and the subthalamic nucleus (FIG. 4b). Arguments in favour of a role of the glutamatergic system in GTS include its essential role in CSTC pathways, extensive interaction between the glutamatergic and dopaminergic systems and a possible beneficial therapeutic effect of glutamate-altering medications on OCD symptoms[78]. Reduced levels of glutamate have been identified in post-mortem globus pallidus interna, globus pallidus externa and substantia nigra pars reticulata in patients with GTS compared with controls[78]. By contrast, glutamate levels measured by 7T magnetic resonance spectroscopy in children with GTS were higher within the striatum and premotor cortex than for controls[79]. Animal models support a role for cortico–striatal glutamatergic afferents in the generation of tic-like movements[80]. However, therapeutically, tic suppression did not exceed that of a placebo control group following treatment with either a glutamate agonist (D-serine) or a glutamate antagonist (riluzole) in a small study[78].

GABA. GABA is the primary neurotransmitter of striatal synaptic projection neurons and interneurons located in both the striatum and the cortex (FIG. 4b). Alterations of GABAergic function in GTS are supported by post-mortem, PET and magnetic resonance spectroscopy studies[78]. In the striatum, post-mortem studies have identified a reduction in the number of GABAergic parvalbumin-containing interneurons. By contrast, measurements of striatal GABA in children 5–12 years of age with GTS showed increased concentrations of GABA within the striatum[79]. The increased quantities probably represent tonic extrasynaptic levels of GABA and greater inhibitory tone. PET imaging of GABA receptors showed decreased binding bilaterally in the ventral striatum, globus pallidus, thalamus, amygdala and right insula[78]. In the cortex, a deficiency of inhibitory interneurons is suggested based on a reduction of short-interval intracortical inhibition measured by transcranial magnetic stimulation[81] and a reduction in the levels of GABA in the primary sensorimotor cortex[82]. By contrast, increased concentrations of GABA were observed within the supplementary motor area[83]. In rodent and primate models, disruption of striatal and cortical GABAergic connectivity by local injections of GABA type A receptor antagonists has produced tic-like behaviours[80,83,84]. Other supporting evidence for GABA involvement includes the beneficial therapeutic effect of benzodiazepines (which enhance the effects of GABA) and an association between mutations in GABA-related genes and tic severity[78].

Acetylcholine. Large aspiny cholinergic striatal interneurons influence striatal projection neurons and local interneurons. Results of pharmacological studies in GTS using agents that affect cortical nicotinic and muscarinic receptors (for example, transdermal nicotine, mecamylamine and donepezil) have been variable. Post-mortem studies have shown a decrease in the number of choline acetyltransferase-containing interneurons in the striatum, supporting reports of an anatomical reduction of cholinergic interneurons in the region[78]. In mice, ablation of 50% of cholinergic interneurons in the dorsomedial striatum caused no effect, whereas ablation in the dorsolateral striatum plus a stressful stimuli or amphetamine challenge caused tic-like stereotypical behaviours[85]. Striatal cholinergic interneurons may co-opt dopamine terminals and drive GABA release[86].

Box 1 | **Definitions**

- Bereitschaftspotential: a measure of activity in the motor cortex and supplementary motor area of the brain, leading up to voluntary muscle movement
- Blepharospasm: abnormal twitching of the eye lid, which results in the eyes being shut tight or closed for a sustained period of time
- Coprolalia: a type of complex phonic tic that involves the uttering of obscene words or phrases
- Coprophenomena: complex motor and phonic tics with obscene connotations
- Copropraxia: movements or gestures of an obscene nature
- Echolalia: copying someone else's words or phrases
- Echophenomena: copying behaviours or sounds made by others
- Echopraxia: the need to mimic a movement made by someone else in the immediate environment
- Non-obscene socially inappropriate behaviours: behaviours that are non-obscene but are very inappropriate (for example, shouting out 'bomb' in an airport), which can have serious social consequences, and are related to impulsivity and disinhibition
- Palilalia: repetition of one's own utterances
- Palipraxia: repetition of one's own movements (for example, repetitive buttoning and unbuttoning of coat buttons)
- Psychogenic tics: tics that are psychological, rather than neurological, in origin (also known as functional tics)
- Self-injurious behaviours: behaviours that, when milder, are associated with obsessive–compulsive behaviour or obsessive–compulsive disorder, and when more severe are associated with impulsivity
- Suicidality: thoughts or behaviours that involve deliberate self-harm
- Torticollis: abnormal sustained twisting of the neck

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Box 2 | **Spectrum of tic disorders**

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), tic disorders are classified according to the type (motor or phonic) and duration of tics. DSM-5 classifies the spectrum of tic disorders as follows:

Provisional tic disorder
Replaces transient tic disorders in the DSM-IV-TR definition (ICD-9 code 307.21; ICD-10 code F95.0).

- Single or multiple motor and/or vocal tics
- Tics have been present for <1 year since first tic onset
- Age of onset is before 18 years
- The disturbance is not attributable to the physiological effects of a substance (for example, cocaine) or another medical condition (for example, Huntington disease or post-viral encephalitis)
- Criteria have not been met for Gilles de la Tourette syndrome (GTS) or persistent (chronic) motor or vocal tic disorder

Chronic (persistent) tic disorder
Single or multiple motor or vocal tics have been present for >1 year during the illness, but not both motor and vocal tics (ICD-9 code 307.22; ICD-10 code F95.1).

GTS
A combination of both motor tics (more than one) and phonic tics (one or more) for >1 year, with an age of onset before 18 years (ICD-9 code 307.23; ICD-10 code F95.2). In 90% of patients, GTS is accompanied by comorbid or coexisting conditions. GTS and the other chronic (persistent) tic disorders have the same typical comorbid conditions, but they are more frequent in GTS. Comorbid conditions are conditions that co-occur and have a shared or overlapping aetiology. Examples are obsessive–compulsive disorder (OCD), obsessive–compulsive behaviour, attention-deficit/hyperactivity disorder and there is some evidence for autism spectrum disorder. Migraine is significantly more common in GTS than in the general population and various control populations; there has been one exciting documentation of a shared genetic aetiology[59]. Coexistent conditions co-occur without a shared aetiology. Examples are depression, non-OCD anxiety, separation anxiety, impulsive anger outbursts, hair-pulling and skin-picking disorders, substance abuse, conduct disorder, oppositional defiant disorder, personality disorders and learning disorders.

Serotonin. Axons from serotonergic neurons within the median raphe nucleus project to the striatum, substantia nigra pars compacta, ventral tegmental area, nucleus accumbens and prefrontal cortex. Evidence supporting serotonergic involvement in GTS includes reduced serum and cerebrospinal fluid levels of serotonin and tryptophan (the serotonin precursor) in patients with GTS compared with healthy controls, and PET imaging showing diminished serotonin transporter binding capacity in the midbrain and thalamus[78]. However, these findings may be associated with the presence of comorbid OCD. PET imaging of tryptophan demonstrated decreased uptake in the dorsolateral prefrontal cortical regions and increased uptake in the caudate nucleus and thalamus[87].

Noradrenaline. Evidence for the involvement of noradrenaline in GTS is limited and partly based on the therapeutic tic-suppressing effect of α_2-adrenergic agonists (such as clonidine and guanfacine)[78]. However, clonidine also decreases the release of glutamate and regulates spontaneous and glutamate-modulated firing activity in medial frontal cortical pyramidal neurons, and its activity can, therefore, not be solely attributed to the modulation of the adrenergic pathway. Measurements of noradrenaline are normal in post-mortem cerebral cortex, basal ganglia and plasma in patients with GTS, and the levels of its metabolite, 3-methoxy-4-hydroxyphenylethylene glycol, are normal in plasma and cerebrospinal fluid, but variable in urine. α_2-Adrengerigc receptor densities have been variable in post-mortem cortex studies, and either normal or increased in Brodmann area 10 and area 11 (REF. 78). Increased α_2-adrenergic receptor densities, if confirmed, could lead to a reduction in the basal release of dopamine, given that activation of α_2-adrenergic receptors has been shown to inhibit dopamine release in the prefrontal cortex.

Histamine. G protein-coupled histamine H_3 receptors are located postsynaptically on striatal projection neurons and modulate dopamine neurotransmission. Results in several animal models, including an *Hdc*-knockout mouse, and mutations in patients with GTS support a role for histamine deficiency in GTS[39,40,88,89].

Endogenous cannabinoid and opioids system. The two most relevant cannabinoid receptors are CB1, which is primarily located in areas of the brain that are associated with reward, appetite regulation and nociception, and CB2, which was initially thought to be solely peripheral, but has been identified in the striatum, ventral tegmental area, hippocampus and thalamus. The endocannabinoid system interacts with the opioid system[90,91]. Several reports and two small placebo-controlled studies have suggested that cannabinoids (smoking marijuana or using oral δ-9-tetrahydrocannabinol (THC)) have a beneficial effect on tics in patients with GTS[92].

Neuroimaging studies

Neuroimaging studies in GTS have shown somewhat diverse findings. Functionally, it has been shown that patients with GTS have significantly increased cerebral blood flow and tic-related hyperperfusion to the left caudate nucleus and anterior cingulate and hypoperfusion to the left dorsolateral prefrontal cortex, which were related to mood. Hypoperfusion in striatal, frontal and temporal areas has also been observed; however, identification of an endophenotype has not been possible, as there are no observed differences between individuals within families with different phenotypes, namely, tics, GTS and/or OCB or OCD[93,94]. Structural imaging studies have also shown cortical thinning in frontal and sensorimotor areas, as well as diminished sulcal depth and reduced sulcal cortical thickness[95]. Furthermore, smaller caudate nucleus volume in children with GTS is associated with more severe tic symptoms in adulthood[96]. Overall, most neuroimaging studies have been limited due to small sample size and motion artefacts; further studies are required to overcome these issues.

Diagnosis, screening and prevention

Tics

Tics are sudden, repetitive and disinhibited movements (motor tics) or noises (phonic tics) that typically mimic some fragment of normal behaviour (for example, repetitive brief eye blinking)[93,97]. Diagnosis of GTS requires the occurrence of both multiple motor and one or more

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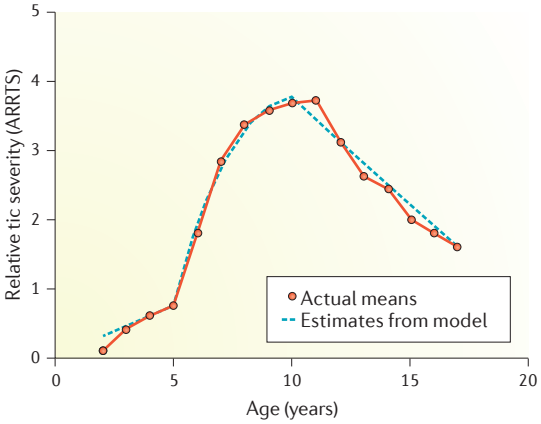

Figure 2 | **Course of tic severity in Gilles de la Tourette syndrome.** Plot of average tic severity in a cohort of 36 children 1–18 years of age with Gilles de la Tourette syndrome (GTS). The Annual Rating of Relative Tic Severity (ARRTS) is a scale that is rated by the parent, which uses a six-point ordinal scale ranging from the absence of tics (0 points) to most severe tics (6 points). Similar data are also available from an independent cohort[128]. From REF. 129; reproduced with permission from Pediatrics, Vol. 102, Pages 14–19, Copyright © 1998 by the AAP.

phonic tics, whereas chronic (persistent) motor or vocal tic disorder requires only one or the other type of tic, but not both (BOX 2). This distinction has been suggested to be arbitrary, as phonic tics are actually motor tics that involve oral, nasal, pharyngeal, laryngeal and respiratory musculature; in some cases, air passing through makes the sounds (for example, sniffing), whereas others (for example, palatal tics) do not require air movement[14].

Tic characteristics. A single tic typically lasts <1–2 seconds and typically occurs in bouts, whereby the same tic occurs repetitively with short inter-tic intervals[98]. Intriguingly, bouts of tics also recur throughout the day.

Tics are classified as simple or complex. Simple motor tics, such as blinking and head jerking, involve only one group of muscles causing brief jerk-like movements and are usually abrupt and rapid (clonic). Slow movements are also possible, resulting in a briefly sustained abnormal posture (dystonic tics, such as blepharospasm and torticollis; BOX 1) or an isometric contraction (tonic tics, such as abdominal tensing). Complex motor tics consist of coordinated sequenced movements resembling motor acts or gestures that are inappropriately timed and intense (for example, repetitive touching, jumping and bending)[14]. These tics may involve the need for the individual to maintain a specific abnormal distorted posture for a few seconds to >1 minute[99]. Very rarely (<5%), associated gestural echopraxia presents or complex motor tics of an obscene nature (copropraxia) occur (BOX 1).

Simple phonic tics include sniffing, throat clearing, coughing and belching. Complex phonic tics are of longer duration than simple phonic tics and include linguistically meaningful verbalizations and utterances, such as words and phrases, as well as echolalia and palilalia[14] (BOX 1). Although coprolalia is commonly associated with GTS, only 20–35% of adult patients with GTS who seek specialist treatment have coprolalia[100–102]. In large pedigrees[103,104] (for example, multiple affected GTS families) or epidemiological studies[105–108], coprolalia almost never occurs. Thus, the Tourette Syndrome Association of America has concluded that, overall, only a small minority (<10%) of individuals with GTS actually have coprolalia.

The severity and intensity of tics vary. They can be unobtrusive and go almost unnoticed, or they can be extremely frequent, forceful and intrusive. Many patients report that their tics can be exacerbated by stress, tiredness and high temperatures[109,110]. In very severe cases (4–5%), the tics can be self-injurious and extremely serious[14,111,112]. Importantly, when individuals with GTS engage in behaviours that require focused attention and motor control, such as playing the piano, reciting a poem or participating in sport, their tics often completely disappear.

Premonitory urges and tic suppression. By 8–10 years of age, the majority of individuals with tics are acutely aware of premonitory urges, such as feelings of tightness, tension or itching that are accompanied by a mounting sense of discomfort or distress that can be relieved only by the performance of a specific tic[113,114]. These premonitory urges are similar to the sensation that precedes an itch or a sneeze. The majority of patients also report a momentary and fleeting sense of relief after a tic or bout of tics has occurred.

Of note, most individuals are able to suppress their tics, but only for a limited period of time and only with mounting discomfort. Enhancing an individual's awareness of their premonitory urges followed by a competing response (that is, the selection and subsequent implementation of a physically incompatible behaviour to the emerging tic) is at the core of behavioural treatments that have proven to be the most effective[115]. In the majority of patients, there is rebound after suppression of a tic[1], although this might not always occur in adults[116]. Although tics have historically been considered to be involuntary, this may not always be so, with some patients describing tics as semi-voluntary with some degree of control and others describing tics as voluntary in response to the premonitory urges[117–119].

Clinical rating scales. The severity of tics can vary dramatically according to the setting and activity, and, because many individuals with GTS can suppress their symptoms for brief periods of time, objective measure is important. To this end, direct observational methods are the most objective measure of tic severity; indeed, a range of clinical rating scales have been developed (TABLE 1). The Yale Global Tic Severity Scale (YGTSS) is the most widely used assessment tool that records an individual's current repertoire of tics[120,121]. The Modified Rush Video-based Rating Scale (MRVS)[122] is an excellent method to objectively record tics; compared with the original version, only the scoring was changed in the modified rating scale[121,123]. The Premonitory Urge for Tics Scale (PUTS) is a validated instrument to characterize and quantify the premonitory urges[114].

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Psychogenic tics. Psychogenic tics or functional tic disorders (BOX 1) are rare (5% of patients with psychogenic movement disorders have tics[124], as opposed to the 95% of patients who have tremor, weakness and sensory loss, among others), but it can be difficult to distinguish from tics that are associated with GTS. Clues for functional tics include acute onset, precipitation by a physical event, incongruous symptoms, inconsistent phenomenology, distractibility, entrainment of symptoms, no premonitory sensations, not being able to suppress the tic, the presence of a Bereitschaftspotential (BOX 1) preceding the movement and also a lack of response to otherwise effective pharmacological therapies used in GTS[124]. It is also important to emphasize that functional tics do not follow the typical neurological patterns and, notably, they can also be seen as an overlay in the presence of a true tic disorder (such as GTS). Although psychogenic tics can arise in children, it is more commonly encountered in adults (average age of onset: 34–50 years)[125,126] and in female patients[124,125,127].

Clinical course

Tics usually have their onset in the first decade of life, with a median onset of simple motor tics at 5–7 years of age[1,97]. The first symptoms usually occur in the head and neck area and might progress to include muscles of the trunk and extremities. Motor tics generally precede the development of phonic tics and simple tics often precede complex tics. Once present, individual tics can remain part of an individual's tic repertoire for weeks to months, but an individual's tic repertoire typically evolves over time. Some tics persist, others disappear and new tics emerge. Most patients experience peak tic severity at 10–12 years of age, following which there is a gradual decline in severity[128,129] (FIG. 2).

A complete remission of both motor and phonic symptoms can occur by adulthood, but estimates vary considerably[15,97,128], with some studies reporting rates of remission of 30–50%[128,129]. If tics resolve by adulthood, the legacy of GTS in adult life is most closely associated with the affect the disorder has had during childhood. For example, a patient who was misunderstood and punished will fare worse than a child whose immediate interpersonal environment was more understanding and supportive[130]. Intriguingly, in a study in which patients were videoed when they were young and then at >20 years of age at follow-up[131], adult patients said they were tic free, but on video, 90% of the adults still had tics. However, the tics no longer caused distress and the need for medication was much less[131].

However, in a minority of patients, adulthood is the period when the most severe and debilitating forms of tic disorder are encountered, possibly following on from childhood severity or a re-emergence of tics later in life. In approximately 4–5% of patients, severe, self-injurious tics[14,112] (referred to by some as 'malignant' tics[111]) can persist or re-emerge with considerable intensity. These treatment-refractory, severe tics can lead to permanent disability and injury, for example, severe and forceful head-snapping tics that lead to permanent injury to the cervical spinal cord, hitting one-self or persistent eye-poking tics that lead to blindness[111,112], and head banging with resultant ventricular enlargement and cavum septum pellucidum cavities detected by neuroimaging (which is similar to the pathology seen in boxers) or even death resulting from a subdural haematoma[112]. Compared with patients with 'non-malignant' GTS, those with 'malignant' GTS are considerably more likely to have greater severity of motor symptoms, comorbid OCD, complex phonic tics, coprolalia, copropraxia, self-injurious behaviours, mood disorders, suicidal ideation and poor response to medications[111,112] (BOX 1). A study reported differences between those whose tics had started before 18 years of age and those after 19 years of age; the latter group had fewer phonic tics and lower rates of ADHD and oppositional behaviour than the former group. From an aetiological perspective, older-onset patients with GTS might largely represent re-emergence or exacerbation of childhood-onset GTS; the adult phenotype is dominated by facial, neck and truncal tics, and a greater prevalence of substance abuse and mood disorders[132].

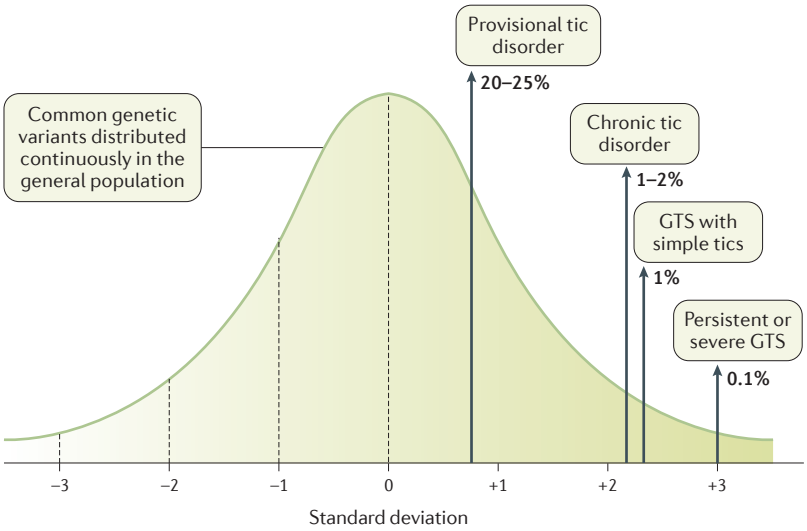

Figure 3 | **Genetic architecture of Gilles de la Tourette syndrome and related developmental tic disorders.** In the polygenic risk model, in which genetic risk arises from a cumulative burden of hundreds of small effect size risk variants, every individual in the general population has some degree of genetic risk, but only develops symptoms when a threshold of risk is surpassed. Under this hypothesis, the same genetic risk factors might contribute to each of the developmental tic disorders, with a higher burden of disease causing more severe or persistent disease. Gilles de la Tourette syndrome (GTS) disease severity and/or comorbidity could arise from high levels of polygenic risk, low polygenic risk in combination with a detrimental, large effect size variant (that is, copy number variation, gene-disrupting coding mutations or deleterious chromosomal rearrangement), low-to-moderate polygenic risk in combination with non-genetic, environmental risk factors or all of the above. Standard deviation represents the theoretical normal distribution of underlying disease risk.

Comorbidity and coexistent conditions

The majority of patients (90%) with GTS do not have 'pure GTS' (that is, tics only), but have additional comorbid and/or coexistent disorders that contribute to the GTS phenotype: this pattern is seen in both community and clinical settings[1]. Comorbid conditions are those that are not only more common in patients with

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GTS than in the general population but also have clinical similarities and definite or purported genetic links with GTS[133]. Comorbid disorders that meet these criteria are OCD (40–60% of patients), OCB (60–90% of patients)[7,26,31,34,55,133] and ADHD (about 60% of patients)[134]. There have also been early possible hints for autism spectrum disorder[135,136] but was not substantiated in later studies[56,137] (BOX 2). Migraine has been documented to occur in 25–26% of cohorts of patients with GTS[57,138] and the percentages are significantly higher than in the control populations (8–13%); it is thus exciting that a recent report indicates a shared genetic vulnerability to GTS and migraine[139].

By contrast, coexistent conditions co-occur in patients with GTS, but a genetic or other aetiological overlap has not (yet) been identified[31,55]. Coexistent conditions include depression, non-OCD anxiety, separation anxiety, substance abuse, conduct disorder, personality disorders and learning disorders[1,101,140] (BOX 2). Depression affects 13–76% of all patients with GTS[141], which is more than observed in the general population[141]. Echophenomena and coprophenomena, premonitory sensations, sleep disturbances, self-injurious behaviours, childhood conduct disorder, OCD, OCB and ADHD are all correlated with depression. The aetiology of the depression in the context of GTS has been suggested to be multifactorial[141], but not involving genetic factors[142], and may be related to the OCD[48]. Other behavioural or emotional problems, such as aggression, difficulties with anger control, sleep disturbances, self-injurious behaviours and non-obscene socially inappropriate behaviours (NOSIs) occur at higher rates than expected in people with GTS than in people with tic disorders who also have ADHD or OCD. High rates of mood disorders associated with GTS may be accounted for by OCD, whereas mood, anxiety and disruptive behaviours may be accounted for by ADHD[48].

NOSIs are seen in about 30–60% of patients with GTS, which often reduces the QOL, are often socially disabling and can have serious consequences[143,144]; NOSIs occur at higher rates in people with tic disorders who also have ADHD or OCD. NOSIs are also related to ADHD and conduct disorder independent of tic severity, suggesting the possibility that it is fundamentally a problem of impulse control[144]. This is particularly important in the light of recent genetic findings that social disinhibition is a heritable sub-phenotype of tics in GTS[145,146].

Phenotype

When discussing phenotype of GTS, we first acknowledge that there are many tic phenotypes (as described above), but it is to be noted that in all somewhat similar

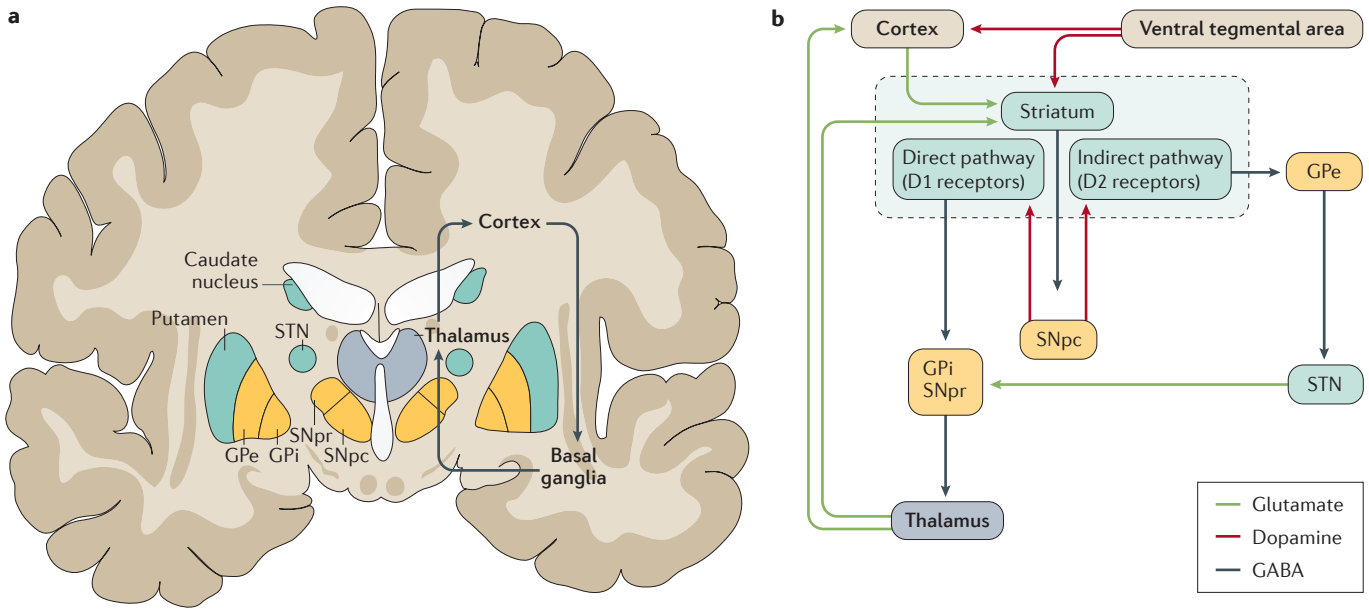

Figure 4 | **CSTC circuit. a** | The cortico–striato–thalamo–cortical (CSTC) circuit is a complex interconnection between the cortex, basal ganglia and thalamus, which regulates complex behaviours and involves many neurotransmitters (including dopamine, glutamate and γ-aminobutyric acid (GABA)). An imbalance in one or more of these neurotransmitters might explain some of the characteristics of Gilles de la Tourette syndrome (GTS). **b** | A simplified CSTC circuit includes projections from excitatory glutamatergic pyramidal neurons located in the frontal cortex to GABAergic medium spiny neurons (MSNs) in the striatum. Striatal output pathways include a direct pathway that transmits striatal information monosynaptically to the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNpr) and an indirect pathway that conveys information to these same regions via a disynaptic relay from the globus pallidus externa (GPe) to the subthalamic nucleus (STN). Direct pathway MSNs express dopamine D1 receptors, muscarinic M1 and M4 acetylcholine receptors and the neuropeptide substance P. Indirect pathway MSNs express dopamine D2 receptors, muscarinic M1 receptors, adenosine A_{2A} receptors and enkephalin. Each pathway has an opposing effect on GABAergic GPi and SNpr output neurons: the direct pathway inhibits and the indirect pathway stimulates. Consequently, these pathways have a reverse effect on excitatory projections from thalamic neurons to the frontal cortex and striatum, and, in turn, the facilitation of motor activity. Specifically, activation of the direct pathway facilitates motor activity, whereas activation of the indirect pathway reduces motor activity. The dopaminergic pathway, which is likely to be involved in GTS, is also indicated. SNpc, substantia nigra pars compacta.

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eight investigations to date — despite using differing methods (for example, using cluster analysis, latent class analysis, hierarchical cluster analysis and principal component factor analysis) — have reported several classes (phenotypes) based on tics. The resulting phenotypes have included variously OCD or OCB, ADHD, depression, phobias and panic attacks[147]. However, the only phenotype that has been consistently replicated in all studies that examined for it is pure GTS. Interestingly, coprolalia does not seem to be class specific, other than not arising in pure GTS[5]. It is also noteworthy that less-severe tic phenotypes (for example, persistent motor or vocal tic disorder) have lower rates of comorbidity than does GTS[148]. Clearly, with regard to psychopathology, more research is required. A recent similar study was performed across multiple symptom dimensions. The exploratory factor analysis revealed a five factor structure: tic/aggression/symmetry symptoms; obsessive–compulsive symptoms associated with compulsive tics and a preoccupation with numbers and patterns; ADHD symptoms; autism symptoms; and hoarding/inattention symptoms[49]. Another study showed that the mean number of lifetime comorbid diagnoses in patients with GTS was 2.1; if OCD and ADHD were excluded, the mean number was 0.9 (REF. 48). GTS was also associated with an increased risk of anxiety and a decreased risk of substance abuse disorders. High rates of mood disorders may be accounted for by OCD, whereas mood, anxiety and disruptive behaviours may be accounted for by ADHD[48]. However, another study showed no associations of specific symptom clusters to either the presence of coexisting psychiatric conditions or to treatment outcomes[149]. A further study reported that social disinhibition is a heritable sub-phenotype[146]. These examples illustrate that the GTS phenotype is more complex than was initially thought, and, importantly, all challenge the unitary nature suggested by the main diagnostic criteria (both ICD and DSM).

Finally, suicidality (ideation and attempts) (BOX 1) shows a higher prevalence in GTS (9.7%) than in healthy controls (3%)[150]. Associated factors include tic-related factors (such as severity, coprophenomena, complex phonic tics and self-injurious behaviours), poor response to medication and the presence of comorbidities and coexistent psychopathologies[111,151–153].

The comorbid and coexisting conditions might complicate the diagnosis of GTS, especially to the non-expert. Many of these disorders are more common in patients with GTS than in the general population, and contribute substantially to the functional impairment of GTS and reduction of QOL, occur early in childhood, and should be assessed for at first interview and subsequently screened for on a regular and recurring basis. Future collaborative research, using uniform methods, will be used to ascertain the longitudinal course and predictors of long-term outcome, including a focus on individual variability in tic symptoms, which are important considerations along with risk and resilience factors for successful long-term outcomes. Ideally, the clinical research could be conducted with basic science (as is being undertaken, for example, in Europe, in the EMTICS study), examining onset, course, peaks and simultaneous measures of prenatal and postnatal insults, immune status and other factors in both patients with GTS and those at risk for GTS.

Management

The optimal treatment strategy for individuals with GTS must take the severity of tics and their effect on daily functioning and QOL into consideration, in addition to determining which symptoms are the most prominent, disabling and causing the patient the most difficulty (FIG. 5). Indeed, comorbidities and coexisting conditions (BOX 2) may be more problematic than the motor and phonic tics per se[11]. For most individuals with GTS whose tics are mild to moderate and do not impair social functioning, the provision of psychoeducation to parents, teachers and peers and the exploration of associated coping strategies are typically sufficient.

If motor and phonic tics are severe enough to warrant treatment, where resources permit, behavioural interventions are currently considered the first-line treatment for tics[154–157]. However, the limited number of trained therapists, inconveniences (for example, travel distance) and willingness to engage can serve as barriers. Pharmacological interventions are typical second-line options, whereas experimental approaches include DBS (for severe and treatment-refractory cases). Although combining tic-reducing medication and behavioural therapy may theoretically seem to have a synergistic effect, the data are currently conflicting and additional research into this topic is needed to provide supporting data.

Behavioural treatments

Habit reversal therapy (HRT) was the first behavioural treatment for tics with a significant evidence base[158] (BOX 3). HRT involves three primary components: awareness training, competing response training and social support. Awareness training is aimed at noticing the premonitory urge or tic onset. In competing response training, the patient learns to do an action that is incompatible with the target tic. Social support is important to praise the proper use of the competing response and to remind the patients. In HRT, tics are treated one at a time, at a rate of one per week. Function-based treatment elements have been added to traditional HRT procedures. These therapeutic strategies are aimed at reducing tic frequency and/or severity and are based on the assessment of contextual factors that reliably increase tics and reactions to tics that may inadvertently reinforce tics.

Comprehensive behavioural intervention for tics (CBIT), a combination of HRT, function-based interventions, relaxation training, psychoeducation about GTS and a reward procedure to enhance treatment compliance[159], has been recommended as a first-line treatment for those with GTS in multiple practice guidelines[154,155,160]. Two large randomized controlled trials[115,161] compared CBIT (eight structured 60–90 minute sessions over 10 weeks) with a control group receiving supportive therapy (comprising broad psychoeducation about GTS and nonspecific therapy and emotional support

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Table 1 | **Clinical rating systems used in Gilles de la Tourette syndrome**

Symptoms	Measurements	Comments
Tics and characteristic features of GTS		
Yale Global Tic Severity Rating Scale (YGTSS)	Tic severity (50 points out of 100) and impairment (50 points out of 100) in the preceding week	Gold standard for tic severity and the most widely used scale. Estimates tic severity based on the number, frequency, intensity, complexity and interference associated with their motor and phonic tics viewed in separate aggregates. Total score from 0–100 points rated by the clinician
Hopkins Motor and Vocal Tic Scale (HMVTS)	Tic presence, type and severity using visual analogue scales (0–10 score)	Simple, accurate and comprehensive rating system that is accessible and can be used by a clinician or parent
Parent Tic Questionnaire (PTQ)	Devised for use in children and adolescents. Parents are asked to assess the number of tics from a list of 14 common tics, each of them rated for tic presence in the past week. Frequency and intensity are rated on a four-point scale and these are added for each tic to produce scores ranging from 0 (tic not present) to 8 (constant and intense tics)	Rating system for the parents to assess tics in young children. Mainly used in the United States
National Hospital Interview Schedule (NHIS)	Data on tics, OCB, OCD, ADHD, family history, physical and psychological health and substance abuse	Too long and detailed for regular use in clinics; requires a trained medical professional. Developed at the National Hospital for Neurology and Neurosurgery and University College London, UK
Motor tic, Obsessions and compulsions, Vocal tic Evaluation Scale (MOVES)	Motor and vocal tics, obsessions and compulsions. Self-reporting based on 16 statements, which generate five subscales (scored 0–3)	Good correlation with YGTSS and suggested to be used in epidemiological studies
Diagnostic Confidence Index	Scoring system from 0–100 based on the presence of positive symptoms (for example, coprolalia, echophenomena, complex tics, waxing and waning course, suppressibility, suggestibility, rebound, premonitory sensations and relief after tic) and also negative symptoms (for example, the absence of medical problems that might cause tics, such as stimulants or a history of encephalitis)	Performed by the clinician. Developed at the National Hospital for Neurology and Neurosurgery and University College London
Modified Rush Video-based Rating Scale	The original scale and video protocol were retained but a new (and better) scoring system was added	Tic ratings of values 0–4 on five categories are the new (modified) form, with tic disability currently scored from 0 to 20
Premonitory urges*		
Premonitory Urge for Tics Scale	Premonitory urges. The scale is quite brief, containing 10 descriptions of somatic sensations. The severity of the urges is rated on a four-point scale ranging from 1 (not at all true) to 4 (very much true)	Self-reporting in young and adult patients; translated in Hebrew and Italian
University of São Paulo Sensory Phenomena Scale	Sensory phenomena. The externally triggered sensory experiences (tactile, auditory and visual) and the inner 'just right' perceptions are measured. Severity is rated on a six-point scale, which indicates the frequency, distress and interference of the phenomena (with a maximum severity score of 15)	Rated by the clinician; good correlation with the Premonitory Urge for Tics Scale
Comorbidities and symptomatology		
Y-BOCS (Yale-Brown Obsessive–Compulsive Scale) or C Y-BOCS (Children's Yale Brown Obsessive–Compulsive Scale)	Past or present OCBs	Performed by the clinician
Leyton Obsessional Inventory (LOI) short questionnaire form	Obsessive–compulsive symptomatology	Self-reporting
Maudsley Obsessive Compulsive Inventory (MOCI)	Obsessive–compulsive symptomatology	Self-rating of 30 items in four subgroups
The Obsessive–Compulsive Inventory (OCI)	OCBs (the short version (the OCI-R) consists of 18 items)	The original OCI is a self-report scale consisting of 42 items, for which patients are asked to rate the presence of their symptoms during the previous month on a five-point scale
Swanson, Noland and Pelham-IV (MTA SNAP-IV) Scale	ADHD symptoms and oppositional defiant disorder	Self-reporting or performed by the parent or teacher

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Table 1 (cont.) | **Clinical rating systems used in Gilles de la Tourette syndrome**

Symptoms	Measurements	Comments
Comorbidities and symptomatology		
Conners ADHD Rating Scales	ADHD symptoms in young people and adults	Self-reporting or performed by the parent or teacher

The assessment and psychometric properties of some of the instruments used in patients with Gilles de la Tourette syndrome (GTS) and their associated comorbidities and psychopathology (modified, adapted and updated from REFS 93,121,222–224). ADHD, attention-deficit/hyperactivity disorder; OCB, obsessive–compulsive behaviour; OCD, obsessive–compulsive disorder. *Premonitory urges are the sensory phenomena associated with tics in GTS (they are sometimes called sensory tics). They are usually difficult to describe: most patients will frequently refer to them as unpleasant somatic phenomena that build up prior to the tic (or upon attempts to resist the tic) and are momentarily alleviated by performance of the tic; they are bodily sensations[113]. Another type of sensory phenomena frequently encountered in patients with GTS involves a need for things to feel, look or sound 'just right' (REF. 225), and most patients can readily distinguish these from premonitory urges or sensations. The 'just right' phenomenon is often more of a 'mental phenomenon' rather than a bodily sensation; the 'just right' awareness is usually visual or tactile and the patients with GTS with these often have comorbid OCD[225]. There may also be inner 'just right' perceptions[224].

for the difficulties experienced when living with tics). Children with GTS who received CBIT showed significant improvements in tics and tic-related impairment, defined as clinical response, at the end of acute-phase treatment compared with the control group (53% of the CBIT group versus 19% of the control group). Furthermore, 6-month follow-up data of treatment responders showed that gains were maintained and associated with significant decreases in anxiety and disruptive behaviours relative to baseline (before treatment) compared with non-responders[115]. Similar findings were observed in adults[161]. No adverse events associated with CBIT were observed. CBIT delivered via teleconferencing devices[162], Skype[163] and through nurses[164] has also been shown to be effective. The mechanisms by which CBIT is effective are unclear, but improved motoric inhibition and habituation to the aversive premonitory urge are suggested to be involved[165,166].

Finally, exposure and response prevention (ERP)[167], a technique that encourages the patient to fully experience urges to tic while actively suppressing tics during therapeutic sessions, seems promising in pilot tests. Unlike CBIT, ERP focuses on all tics at the same time, whereas CBIT addresses tics sequentially. It is possible that ERP and CBIT share a similar mechanism of action.

Psychopharmacological treatments

In situations where behavioural therapies are ineffective, not available, not age-appropriate or not the patient's or the family's preference, then pharmacological treatments should be considered (BOX 3). Indeed, the European, Canadian and American guidelines suggest that tic-specific psychopharmacotherapy should be considered when tics are causing pain or injury, social and emotional problems, and/or functional interference (for example, impairing academic achievement)[11,154,168]. If tics are not severe or disabling, the use of a medication may not be warranted. Although these guidelines are in place, the choice of psychopharmacological treatment of tics is still often based on personal experience. Additional impediments to the development of a consensus psychopharmacological treatment algorithm are the waxing and waning course of GTS and the presence of comorbid and coexistent disorders that can influence tic severity. The required doses, response time and efficacy are highly variable, which makes decisions on when and how to treat tics difficult and not well standardized. For those who do not respond to a particular agent, a switch to another agent or group of agents as well as combining two agents will generally lead to the desired benefits. Refractory disease only occurs in a minority of patients[169]. With respect to managing the key comorbidities, prescribing practices that are used when GTS is not present generally apply.

The aim of psychopharmacological treatment of GTS is to ameliorate tics and to improve psychosocial functioning as soon as possible with as few adverse effects as possible. On average, anti-tic medication can reduce tics by 25–70% depending on the dose within 2–4 weeks. Over-medication, driven by the belief that higher dosages will necessarily be more effective, can cause considerable adverse reactions, particularly sedation, apathy, extrapyramidal effects, weight gain and metabolic abnormalities.

Historically, pharmacological management of tics involved dopamine receptor blockers (also called neuroleptics) and α_2-adrenergic agonists, although they can result in adverse effects that can limit tolerability[12,170–173]. Haloperidol and pimozide were among the earliest neuroleptics that were shown to lead to improvements of motor and behavioural symptoms in GTS[8,9], but are not often used in many countries owing to problematic adverse effects. Indeed, little difference in efficacy among the different dopamine receptor blockers exists. However, the adverse-effect profile is very different[10], and the tolerability profile and the treatment requirements of the comorbid conditions would also merit consideration[170,171]. Substituted benzamides, particularly sulpiride and tiapride, have been recommended as first-line treatment for GTS in Europe because of their favourable benefit-to-risk ratio[10,172]. However, these agents are not available in the United States, Canada and other parts of the world. In the United States, Canada and the United Kingdom, atypical neuroleptics, such as risperidone and aripiprazole, have become the preferred choice over the older neuroleptics described above because of their improved tolerability.

In the United States, Canada and Australia, α_2-adrenergic agonists (clonidine and guanfacine) are considered first-line pharmacotherapy, particularly in children, primarily because of their preferable adverse-effect profiles compared with the typical antipsychotics. In a recent meta-analysis, superiority for both α_2-adrenergic agonists to placebo was confirmed,

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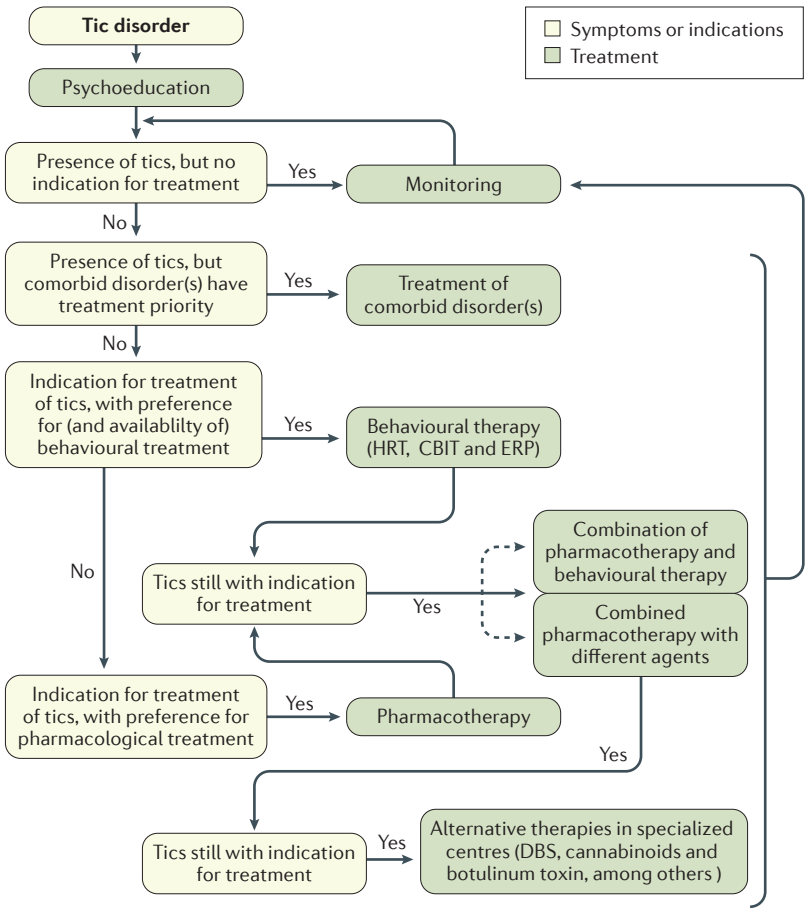

Figure 5 | **Decision tree for the management of Gilles de la Tourette syndrome.** If Gilles de la Tourette syndrome (GTS) is suspected, diagnosis needs to be confirmed by considering other tic disorders and carrying out the indicated investigations. If symptoms are not distressing and/or causing dysfunction, supportive therapy (for example, psychoeducation) is recommended. If symptoms are distressing, pharmacological or non-pharmacological interventions should be given. However, if comorbid conditions are present and more impairing than GTS, they should have treatment priority. When treatment is successful, monitoring remains essential. Solid arrows indicate the next level of evaluation or treatment; dashed arrows indicate alternation between two treatments. CBIT, comprehensive behavioural intervention for tics; DBS, deep brain stimulation; ERP, exposure and response prevention; HRT, habit reversal therapy. Adapted with permission from REF. 11, Springer.

but this benefit was significant only for children or adolescents with GTS and comorbid ADHD, and minimal in those with GTS without ADHD[173].

A meta-analysis examined the adverse effects associated with several of the widely used neuroleptics[174]. Although olanzapine, risperidone and, to a lesser extent, aripiprazole were all associated with weight gain, this was greatest for olanzapine and the least for aripiprazole. Other adverse effects vary depending on the study, but risperidone and aripiprazole have been found to be associated with increased prolactin levels and olanzapine with increased glucose, total cholesterol and prolactin levels. Clinician surveys have found that the most common neuroleptic medications used to treat tics are risperidone and aripiprazole[11,175]. Although aripiprazole has one of the best benefit-to-risk ratios[10], it is not available in many countries.

Finally, it is noteworthy that interest remains in alternative agents, particularly in cases that are refractory to classical agents[12]. Local injections of botulinum toxin can be an effective treatment for focal, cervical spine and phonic tics, which does not have systemic adverse effects[176]. There is some promising evidence regarding cannabinoids and Chinese herbal medicines[177,178]. In addition, numerous other agents have been tried for the treatment of tics, although none of these agents have support from adequately powered controlled trials[168,179]. Several new agents are currently either in early development or in the midst of ongoing clinical trials[180] (BOX 3).

DBS

Although DBS (that is, the modulation of pathological neuronal activity in specific brain networks using high-frequency electrical current delivered by implanted tiny electrodes connected to a neuropacemaker) might be an option for some patients with GTS[181], the paucity of evidence-based publications, the heterogeneity of results and the lack of consensus on the optimal brain target all point to the fact that DBS for GTS is not yet established. Some of the issues surrounding studies on DBS in GTS are related to the small number of patients who would require surgery, the young age of most patients, the waxing and waning disease course, the variability in GTS phenotypes and comorbidities, and the improvement of symptoms with age for many individuals. Furthermore, which of the hitherto nine brain targets[182,183] within the CTCS circuitries is the best target for DBS remains unclear. Well-designed trials that collect data on the outcome (tics or comorbidities) to define patient selection criteria are needed. Noteworthy, the rate of infection seems high in patients with GTS[184,185], which might be owing to tic-related behaviours (for example, scratching or picking at the surgical wound) and comorbidities, or indeed distinct immunological profiles: this remains unclear[185] and further research is needed. The relatively recent initiative of the Tourette Association of America to launch an international GTS DBS registry and database to share data, determine best practices, improve outcomes and to provide information to regulatory agencies, is a step in the right direction[186].

Quality of life

Since the pioneering study by Elstner *et al.*[187], patients with GTS have consistently been shown to have a lower QOL than the general population. Several GTS-specific tools have been developed that will facilitate the incorporation of QOL into research studies and clinical practice[188,189].

Consistent with the idea that GTS is more than having motor and phonic tics, subsequent studies have highlighted the compounding effect of numerous factors associated with GTS in reducing QOL[190] (FIG. 6). In addition to tic severity and the presence of coprophenomena, these factors include associated comorbidities and coexisting psychopathologies (BOX 2). Patients with pure GTS have a higher QOL than patients who have GTS and comorbidities[191]. Meta-analyses have suggested that, although OCD is a common factor affecting QOL

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throughout a patient's lifetime, other factors may vary across the lifespan, with tic severity and ADHD being particularly associated with lower QOL in children, whereas in adults, anxiety and depression become increasingly relevant[190,192]. Another study[193] found strong associations between parent-reported comorbidity and decreased QOL, increased emotional symptomatology, impaired emotional and school functioning as well as impaired social functioning and peer relationships in children and adolescents with GTS. Patients may develop coping strategies over time to manage difficulties that are prominent in childhood, which may also moderate with age, only to then be confronted with new challenges in adulthood.

Numerous QOL domains are affected in people with GTS, including psychological, obsessional, social, physical, school-based or work-based and cognitive[194] (FIG. 6). As a consequence of these, psychological distress, frustration and depression are commonly experienced by patients with GTS[195,196]. Depressed mood and low QOL may be outcomes of the heavy psychosocial burden that can be experienced by patients with GTS over time[197]. OCD, OCB, obsessionality and perfectionism also contribute to this psychosocial burden, which in turn makes the process of adapting to life with tics difficult. Difficulties with social skills and poor peer relationships are common in GTS[130,144,198,199], as are the additional difficulties of dealing with stigma and bullying. Severe tics can result in physical pain and injuries[200] as well as in difficulties with activities of daily living[201]. Tics with comorbid ADHD often result in school-based problems due to reduced concentration associated with ADHD that is further compounded by difficulties in task completion due to the time and mental energy spent on performing the tics or trying to suppress the tics, which underscore the importance of the teachers' knowledge, understanding and flexibility[202].

Reciprocal effects on QOL of parents and family members of patients with GTS are likely, although these are presently less well understood[203]. Caregiver burden was shown to be significantly higher in parents of patients with GTS than in parents of age-matched young people with asthma[204]. The correlates of increased caregiver burden and greater parental psychopathology included a GTS diagnosis and behavioural difficulties in the index children[204].

Box 3 | **Treatment options for Gilles de la Tourette syndrome***

Behavioural therapy‡

- Comprehensive behavioural intervention for tics (CBIT)
- Exposure and response prevention (ERP)

Psychopharmacological treatments§

- Neuroleptics (also known as antipsychotics):
  - Typical neuroleptics: haloperidol and pimozide
  - Atypical neuroleptics: aripiprazole, risperidone, ziprasidone, olanzapine and quetiapine
  - Substituted benzamides: sulpiride and tiapride
  - Other typical neuroleptics less frequently used: fluphenazine, trifluoperazine, penfluridol and thioproperazine
- Other dopamine antagonists (dopamine depletors): tetrabenazine, piquindone and inosine
- Dopamine agonists: pergolide, amantadine, selegiline and pramipexole
- α_2-Adrenergic agonists (in cases of coexisting attention-deficit/hyperactivity disorder): clonidine and guanfacine
- Botulinum toxin injections (in cases of stable, single tics or isolated group of muscles, for example, blepharospasm and vocal cords)
- Antiepileptics: topiramate, carbamazepine, clonazepam and levetiracetam
- Others:
  - Cannabinoids
  - Agent with γ-aminobutyric acid (GABA) type B receptor and phenylmethylamine actions: baclofen (children only)
  - Agents acting on endogenous opioid system: naloxone and naltrexone
  - Calcium channel blockers: verapamil, nifedipine and flunarizine
  - Androgen receptor antagonist: flutamide
  - Benzamide: metoclopramide (children only), usually used as antiemetic and is not antipsychotic in normal doses
  - Selective serotonin 5-HT_3 antagonist: ondansetron
  - β-Blocker: propranolol
  - Alternative therapies: omega-3 fatty acids and Chinese traditional medicine, such as Ningdong granule and the 5-Ling Granule

Deep brain stimulation‖

Reserved for individuals with severe, treatment-resistant 'malignant' Gilles de la Tourette syndrome (GTS).

- Thalamus
- Globus pallidus
- Nucleus accumbens (some evidence)

Emerging therapies¶

- Dopamine D1 receptor antagonist: ecopipam
- Vesicular monoamine transporter type 2 (VMAT2) inhibitors: deutetrabenazine or valbenazine
- Histamine H_3 receptor antagonist: AZD5213
- New deep brain stimulation targets: subthalamic nucleus and globus pallidus interna versus globus pallidus externa

*The references cited with regard to each treatment domain include the recommendations from the currently available European, Canadian and American guidelines, as well as recent scientific reviews and advances concerning the treatment of GTS. ‡See REFS 12,154,155,157,160,220. §See REFS 11,12,154,157,168,172,177,178,220. ‖See REFS 12,154,157,160,220. ¶See REFS 12,154,157,178,220.

Outlook

Epidemiology and clinical course

From a clinical and epidemiological perspective, there is wide variation in GTS prevalence rates in the literature ranging from 0.25% to 5.7%[1], which is attributed to varying sample size, methodology, changing diagnostic criteria over the years and the use of different assessment methods and measures in different studies. However, consensus is emerging, aided by two meta-analyses and one meta-regression of GTS prevalence rates, suggesting the rate to be between 0.6% and 0.8% (95% CI: 0.3–1%)[18,19]. Future research using uniform methodology to inform longitudinal course and predictors of long-term outcome, including focus on individual variability in tic symptoms, are important considerations along with risk and resilience factors for successful long-term outcomes.

Genetics and epigenetics

The field of GTS genetics is poised for an upsurge in the discovery of definitive GTS susceptibility genes. Current sample sizes are approaching those for which

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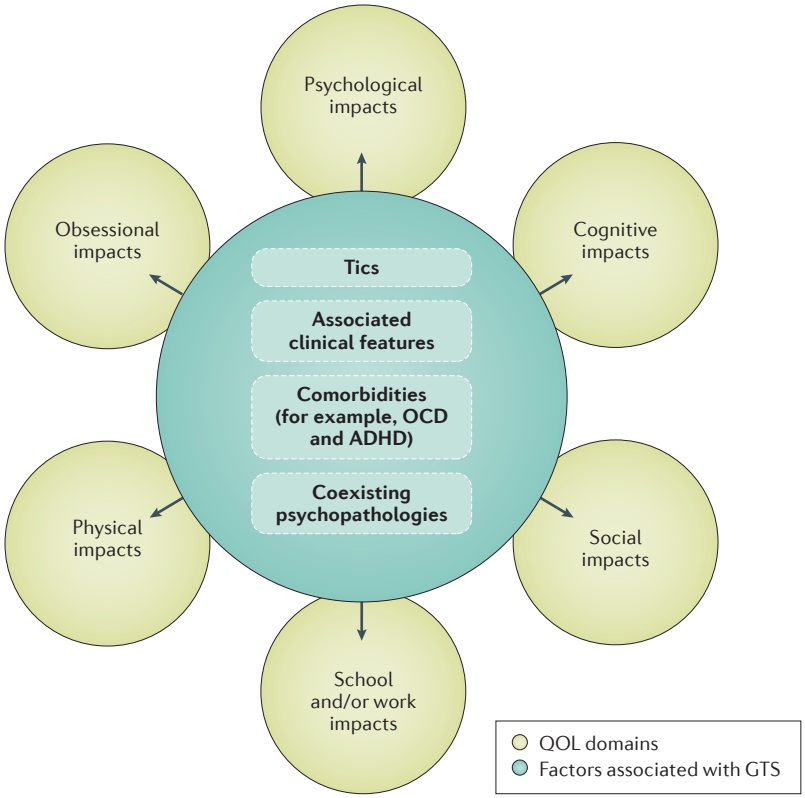

Figure 6 | **Stylized depiction of quality-of-life domains affected in Gilles de la Tourette syndrome.** The quality of life (QOL) of patients with Gilles de la Tourette syndrome (GTS) is affected in several domains, which are influenced by tics and other conditions associated with GTS. ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive–compulsive disorder.

other polygenic disorders, such as schizophrenia, began to identify individual genes with certainty[205,206]. A genome-wide association study 'inflection point' is suggested, which corresponds to the sample size at which a study is adequately powered to identify any one of possibly hundreds of small effect, polygenic risk variants (~10,000 cases for schizophrenia)[205]. Parallel accelerations in disease gene discovery for CNVs and *de novo* gene-disrupting coding mutations have also been observed, suggesting that large-scale, rare variant discovery efforts will be equally successful[207]. As such, the success of GTS genetics will require continued expansion of international genetic collaborations and concerted efforts to identify innovative approaches to large-scale sample collection. On the collaborative front, US and European GTS genetics consortia have already harmonized phenotypic assessments and established pre-publication data sharing and joint meta-analyses[30,43]. For sample collection, multiple strategies are being pursued, including leveraging of data-rich electronic health records linked to biobanks[208], identifying cases among population registry studies with available DNA[209] and the development of validated, internet-based assessments combined with local biospecimen collection to bring sample collection to the patients, rather than focusing on collections that are limited to academic medical centres with GTS specialty clinics[210]. In fact, the US National Institute of Mental Health (NIMH) Strategic Plan identified GTS as a priority disorder for expansion of DNA samples that are available for study (Strategy 1.2, Priority A.4)[211].

Once GTS susceptibility variants are identified, the often-discussed challenge of transitioning from genes to biology will benefit greatly from technological advances in systems biology and international efforts to generate large-scale, publicly available gene expression and epigenomic data sets from multiple mouse and human brain regions across different neurodevelopmental time points[212,213]. These spatiotemporal maps of gene activity and gene regulation will be instrumental in pinpointing the specific brain region (or regions) and critical periods where susceptibility genes influence GTS pathophysiology at the molecular level[214,215]. In parallel, collaborations in the field of neuroimaging genetics (the largest example of which is the ENIGMA Consortium; http://enigma.ini.usc.edu) will facilitate integration of GTS genetics with systems neuroscience to uncover underlying GTS biology at the neural circuit level[216].

A third strategy already in progress is to leverage data from related neuropsychiatric disorders to identify gene variants in common across these disorders[31,55]. The Psychiatric Genomics Consortium (PGC; https://www.med.unc.edu/pgc) has led the field in this work[32,33] and both GTS and OCD consortia have joined the latest PGC cross-disorder analyses. Similarly, the emergence of robust, alternative symptom-based GTS phenotypes that cut across traditional diagnostic boundaries may benefit GTS genetics, neuroimaging and treatment studies by addressing phenotypic heterogeneity and comorbidity[146]. For example, two recent studies in 3,500 patients with GTS and their relatives demonstrated that the subgroup of individuals with socially inappropriate tics (including coprophenomena) and those with a combination of GTS, OCD and ADHD had the most heritable form of the disorder[145,146]. In addition, individuals with GTS and family members who endorsed symmetry, ordering or arranging and counting obsessions had higher mean GTS polygenic risk scores (but not higher OCD polygenic risk scores) than those without these symptoms, despite the fact that this set of symptoms is traditionally considered to be OCD-related[145].

Pathophysiology

At this point, we have limited understanding of the pathophysiology, with unresolved questions on what constitute GTS phenotypes and the modulators of phenotypic variability. Although genetic factors further modified by sex and numerous non-genetic factors or second hits (such as prematurity; perinatal trauma, injury or hypoxia; oxidative stress; infections, inflammations or autoimmunity; and neural and psychosocial stressors) have all been implicated in the pathogenesis of GTS, these are not unique to GTS and are shared by several neurodevelopmental disorders, including autism, ADHD and OCD. Cross-disorder analysis examining genetic determinants to endophenotypic and clinical

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phenotypic characteristics in these neurodevelopmental disorders, for example, using neuroimaging, is expected to ultimately clarify the overlaps and delineations in the pathogenesis of GTS.

Although the precise pathophysiological basis of GTS remains unresolved, converging evidence suggests the involvement of the CSTC circuitry, which mediates the integration of movement, sensation, emotion and attention, and the dopamine system, which regulates the motor circuitry. Although the dopamine model has gained much attention through clinical treatment studies, recent research, including preclinical studies and post-mortem findings, has highlighted the role of careful calibration of the excitatory–inhibitory balance[135] through glutamate and GABA in conjunction with other neurotransmitter systems, as described earlier[78]. Furthermore, animal studies could assist in informing the effect of specific genetic and epigenetic influences on molecular pathways, cellular process or circuitry formation along with opportunities for new treatment development. Thus, a deeper understanding of the neurochemical systems in GTS will ultimately translate to empirically supported pharmacological interventions (several such agents are currently under trial)[180], whereas neurophysiological studies will unravel the mechanism of action in brain stimulation techniques, such as transcranial magnetic stimulation[217] and transcranial direct current stimulation (ANZCTR clinical trial ID: ACTRN12615000592549 and ClinicalTrials.gov identifier: NCT02216474).

Animal models of tic generation and the affect of modulating factors, such as stress and infections, will help to elucidate the complex interplay between genetic, environmental (including prenatal and perinatal factors) and neuroimmunological risk factors, which affect the phenotype and outcome; however, considerable debate continues over the validity of most existing animal models of tics, given the inability to assess animals for premonitory sensations and tic suppression, which are crucial for distinguishing tics from other repetitive movements, such as myoclonus, stereotypies and psychogenic tics. Furthermore, gene-by-environment and epigenetic studies will provide valuable clues to the GTS pathophysiology.

DBS

The first DBS surgery for GTS was in 1999, and although this procedure is still considered to be an experimental treatment, since then, >150 individuals worldwide have undergone this treatment[218] and an international registry has recently been developed in an effort to track cases using consistent metrics and outcome measures[186]. Early case studies reported on several brain targets that were used in these surgeries[182,183,186]; more recently, three brain regions have emerged as the most commonly used: the thalamus, the posteroventrolateral sensorimotor part of the globus pallidus interna and the anteromedial 'limbic' part of the globus pallidus interna[186,218]. Of these, the evidence is strongest for the thalamus and the globus pallidus, although within those brain areas, there is still discussion about the precise targets (for example, anteromedial versus posteroventrolateral globus pallidus). One recent meta-analysis of existing cases suggests that, when all targets are considered, approximately 80% of individuals undergoing DBS show at least 25% reduction in symptoms and over half show >50% reduction in symptoms on stimulation compared with no stimulation[218]. Mean improvement for motor tic severity is approximately 45%, with a 50% improvement in vocal tic severity, and an effect size of 0.96 overall for DBS compared with controls[218]. However, more modest improvements were also seen in obsessive–compulsive symptoms and depressive symptoms in one meta-analysis[218].

These data indicate that DBS can be effective, at least in treatment-refractory cases. However, the number of patients who have undergone this treatment is still small, and some issues remain. For example, although a few children <18 years of age have undergone this surgery, the waxing and waning disease course and the improvement of symptoms with age for many individuals suggest that further work is needed to determine the best candidates for DBS (including symptom type and whether the treatment should be limited to adults only, among others), given the inherent surgical risks. DBS may be suggested for some patients, and well-designed prospective controlled trials that collect data on the outcome (tics or comorbidities) to define patient selection criteria are still needed, as are more thorough investigations of potential complications of DBS in individuals with GTS[219].

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