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Review

The psychopathological spectrum of Gilles de la Tourette syndrome

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ABSTRACT

Gilles de la Tourette syndrome (GTS) holds a unique status as quintessentially neuropsychiatric condition at the interface between neurology (movement disorder) and psychiatry (behavioural condition). This is a reflection of the common observation that the vast majority of patients present with behavioural problems in association with the motor and vocal tics which define GTS. The present article focuses on the relationship between GTS and obsessive–compulsive disorder (OCD), attention-deficit and hyperactivity disorder (ADHD), affective disorders (both major depression and bipolar affective disorder), and personality disorders. Over the last decade, converging lines of research have pointed towards the concept of a 'GTS spectrum', encompassing motor phenomena and behavioural symptoms, with important implications for the clinical management of patients.

Contents

1. Journey of a neuropsychiatric disorder

The Gilles de la Tourette syndrome (GTS) has captured the interest of both the public and scientific communities for similar reasons. To the public, the idea of a condition that compels the sufferer to transgress social norms is both fascinating and anxiety-provoking (Robertson and Cavanna, 2008; Monaco et al., 2009). To the scientific community, GTS is a condition that presents with symptoms which seemingly mock the divisions between neurology, psychiatry and psychology (i.e. motor, behavioural and cognitive symptoms) (Rickards, 2010; Bloch et al., 2011; Jankovic and Kurlan, 2011; Cavanna and Termine, 2012; Robertson, 2012). GTS therefore compels us to think differently about notions of personal responsibility but also to look at brain function in a more holistic and radical way. Arguably, understanding of GTS as a truly neuropsychiatric condition has helped the neuroscience community to start to move away from dualism as a dominant clinical paradigm (Arambepola et al., 2012).

References to GTS-like clinical syndromes date back to the middle ages, mainly in association with demonic possession (Robertson and Cavanna, 2008). In the XIX Century, there are a number of descriptions of disorders that encompass tics and compulsions and which were familial. The historical description that best fits the modern conceptualisation of GTS is that of Armand Trousseau, who described a familial tic disorder which was not necessarily

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disabling, in 1873 (Rickards et al., 2010). Georges Gilles de la Tourette gained eponymous fame for the syndrome at the behest of his mentor, Jean-Martin Charcot, in 1885 after writing a monograph on nine cases (Gilles de la Tourette, 1885; Rickards and Cavanna, 2009). Gilles de la Tourette's description was of a rarer and more exotic condition including coprolalia (compulsive swearing), echolalia and palilalia. In the latter part of the XIX Century and most of the XX Century, GTS was seen through the lens of psychoanalytic theory and talk of tics as "masturbatory equivalents" was commonplace and unhelpful (Robertson and Cavanna, 2008).

A number of forces led to the re-conceptualisation of the idea of GTS as being a "biological" disorder (McNaught and Mink, 2011). In 1961, the first recorded use of a dopamine blocking drug to reduce tics in a man with severe GTS sparked interest in pharmacological treatment for tics (Rickards et al., 1997). Arthur and Elaine Shapiro collected and analysed the first large sample of people with GTS and started to apply (mainly epidemiological) falsifiable scientific method to the problem (Shapiro and Shapiro, 1968). Patient support groups, initiated in the United States, tended to advocate a "biological" model as a way of challenging what they viewed as a "parent blaming" culture of family therapy, exemplified by child therapists such as Bruno Bettelheim. Applying the scientific method has delivered definite, if modest results. Arguably, the best results have come through epidemiology and have resulted in the development of the 'GTS spectrum', which extends beyond tics to include specific behavioural problems (Robertson, 2000, 2011; Cavanna et al., 2009a). We can see that GTS is probably a heterogeneous, largely heritable neurodevelopmental disorder (Deng et al., 2012). We have a clear idea of the clinical history of the disorder, although prognostication is difficult (Hassan and Cavanna, 2012). We can see that the disorder presents with similar frequency and symptoms around the world and is not particularly subject to racial or cultural differences (Robertson, 2003, 2008; Robertson et al., 2009). Finally, and most importantly, we have found genuine co-morbidity with other developmental disorders, such as obsessive–compulsive disorder (OCD) and attention-deficit and hyperactivity disorder (ADHD) (Robertson, 2000; Cavanna et al., 2009a). We have therefore started to create valid sub-groups, which may pave the way towards the pathophysiology of the illness, which is currently elusive. It has been difficult to define a boundary between GTS and normality and this has been done on an pragmatic basis; the condition reaches medical attention if it leads to disability or impairment. The current fashion for definition is broad and so GTS is seen as relatively common (0.5–1% of school aged children), although complex tic-related symptoms such as coprolalia, are present only in a minority of patients and prognosis is good. Through clinical trials, there are now a number of moderately effective treatments for cases of persistent severity (Singer, 2010; Eddy et al., 2011a; Cavanna et al., 2012a; Rickards et al., 2012; Roessner et al., in press).

With regards to the 'GTS spectrum', finding final common biological pathways for this range of disorders is the pressing task for researchers. This would also allow for fusion of biological and psychological models (Langen et al., 2011a,b). An example of this is the possible role that psychosocial stress can play in the exacerbation of tics. The striatum is the part of the brain most commonly implicated in the pathophysiology of GTS, according to converging lines of evidence (Draganski et al., 2010; Bronfeld and Bar-Gad, in press). Of particular interest are the results of post-mortem studies conducted in the last decade (Kalanithi et al., 2005; Kataoka et al., 2010), which revealed interneuron migration deficiencies in GTS. Until the last 30 years, the striatum was principally thought of as a moderator of movement. More recently, following the work of Alexander, DeLong and others (Alexander et al., 1986; DeLong et al., 1984), the striatum has been shown to subserve a variety of frontal functions, namely have cognitive, behavioural and motor functions. Later anatomical work by Haber et al. (1990, 2006) has led to a questioning of the idea of separate cognitive, behavioural and motor domains. These functions appear not to be "parallel" as Alexander suggested, but widely interconnected. It may be that the striatum acts as a supervisor for all thoughts and actions along the compulsive–impulsive spectrum (Frank et al., 2011; Wright et al., 2012). This concept allows us to see more clearly how a single disorder can present with motor, psychiatric and cognitive features and challenges the traditional professional demarcations of the last century.

2. On the complex nature of tics

Prior to Gilles de la Tourette's description of multiple tic disorders, there had been phenomenological descriptions by Itard, Trousseau and Hughlings-Jackson (Robertson and Cavanna, 2008). Perhaps the closest of these descriptions to the modern idea of GTS comes from Trousseau (Rickards et al., 2010). He described tics as common, non-painful, familial and most common around the face. He noted that the type and location of tics could change over time. He wrote about the occurrence of vocalisations alongside movements and described their stereotyped nature thus: "*I recall that I have often related the fact that I recognised one of my former colleagues. . .after a gap of twenty years. . .when he was walking behind me from the kind of "bark" that i had heard him make in the earlier years when we were studying together*". On the other hand, Gilles de la Tourette himself described 9 cases in 1885, not all of whom he had met personally. His focus was on the more exotic symptoms of the syndrome, including coprolalia and echolalia, which will be described further in this article (Gilles de la Tourette, 1885).

Descriptions of movements and behaviours over the years tend to involve division into voluntary and involuntary. Voluntariness implies a decision to move and the ability to prevent movement immediately. Tics, the cardinal features of GTS, transcend the boundaries between voluntary and involuntary movements in a way that defies concise definition (Lang, 1991; Tourette Syndrome Classification Study Group, 1993). They are movements, vocalisations or behaviours that are preceded by a strong desire or drive, often referred to as a premonitory sensation (Bliss et al., 1980; Leckman et al., 1993). Premonitory sensations have been described by some as physical phenomena (itchy, tense or tight feelings with a specific anatomic location) and by others as a mental phenomenon (a mental feeling of tension and of "having to" act). This has been likened to the feeling of wanting to cough or scratch an itch. In general, this collection of tense sensations will increase until the act is performed and then be relieved (usually quickly) before returning shortly afterwards. Suppression is possible but is often followed by "rebound" (a temporary worsening of symptoms). This group of symptoms is fairly specific to tic disorders, although it is not always described in the early stages of the illness. Premonitory sensations are common in a range of normal human behaviours (hunger, coughing, sneezing, sexual drives). These behaviours also share a further quality with tics: their tendency to occur in clusters or "bouts". The presence of sensory symptoms, the occurrence in bouts and the stereotyped nature of the behaviours are therefore the cardinal features of tics (Leckman, 2003). Tics are fragments of motor or behavioural programming which occur out of social, grammatical or affective context. Tics can be simple (such as blinking, sniffing, throat clearing) (Martino et al., 2012) or more complex (squatting, turning, spinning, swearing, laughing, staring, copying) (Cavanna et al., 2008a, 2010), occasionally resulting in rather bizarre self-injurious behaviours (Cavanna et al., 2006a, 2009b; Weil et al., 2008). The level of voluntariness of a tic can vary between and within individuals. Sometimes people with tics will voluntarily release their suppression in order to allow the tic to happen

involuntarily. At other times, people will deliberately perform the tic in order to get rid of the premonitory sensation.

The current definition of GTS is not a scientifically defined category, as this does not exist currently. The definition reflects history, custom, personal interests and the needs of health systems. DSM-IV-TR states that for the diagnosis of GTS, both motor and vocal tics should be present for at least a year without an interval of greater than 3 months. The onset should be in childhood and not due to dependence, intoxication or withdrawal of drugs, or to a separate, specific medical condition (American Psychiatric Association, 2000).

GTS has its onset between the ages of six and eight; tics typically start simple and become more complex moving towards the teenage years (Leckman, 2003). The first tic is usually motor, such as a blink or head nod, with vocalisations characteristically occurring at a later stage. The more complex symptoms, such as coprolalia (or compulsive, non-contextual swearing) usually start in late childhood or early teenage years. Coprolalia is relatively rare in GTS as it is currently defined. Tic symptoms tend to be at their most severe between the ages of ten and twelve years (Leckman et al., 1998). They run a typical "waxing and waning" course with individual symptoms lasting months or years before being replaced by other symptoms. Sometimes a tic can be replaced by a compulsion and vice versa. Symptoms tend to stabilise and remit into late teenage years and early adulthood (Leckman, 2003). The repertoire of tics tends to become narrowed at this time. A long-term follow-up study using video recording showed that, although tics frequently improve over time, they rarely remit entirely (Pappert et al., 2003).

Coprophenomena (coprolalia and copropraxia) are present in around a third of patients coming to specialist clinics with a diagnosis of GTS (Robertson, 2000), although the prevalence of these symptoms varies across centres and can be considerably lower in the community (Cavanna et al., 2009a,b,c). Unlike "normal" swearing, coprolalia occurs non-contextually (grammatically, socially and affectively). The person with coprolalia is insightful into this and this can lead to attempts to cover up or change the behaviour, as well as considerable social embarrassment. The use of swear words represents a fragment of language programming rather than a random vocalisation. This has been clearly shown by the existence of sign language coprolalia in a pre-linguistically deaf individual. Paliphenomena (palilalia and palipraxia) represent a form of perseveration where by the person gets "stuck" on the most recent action in a series. This form of behaviour can be seen in about a third of clinic patients, but is also seen in people with autistic spectrum disorders and, sometimes, after brain injury. Echophenomena (echolalia and echopraxia) represent a form of copying where the person feels impelled to copy what another person has done or said immediately following them. Again, this behaviour is seen in around a third of people with GTS in clinic and can be seen in people with autistic spectrum disorders, brain injuries and dementia. Some of these complex tics have recently been documented in patients' handwriting (Cavanna et al., 2011a; Mitchell and Cavanna, in press), and represent transitional symptoms between motor and behavioural manifestations.

3. The relationship between tics, compulsions and obsessions

At first inspection, tics do not appear to have much connection to compulsions and obsessions. The former are motor phenomena and the latter mental and behavioural phenomena. However, the common co-existence of these symptoms has led to a closer inspection (Worbe et al., 2010; Cath et al., 2011). On a basic level, tics, compulsions and obsessions are all things that people feel compelled to go through. They can be resisted at the expense of internal tension. Performance of the thought, movement or behaviour leads to relief which, in itself, might reinforce the symptom through operant conditioning. Researchers have attempted to distinguish tics from obsessions and compulsions on the grounds that obsessive–compulsive phenomena are usually accompanied by autonomic anxiety and by complex thinking processes (e.g. "*if I don't wash my hands I might contaminate my children*") which might be lengthy. Tics, on the other hand, are usually preceded by short-lived sensory symptoms, not by the thought "*I have to tic*", and are not associated with autonomic arousal. Although this distinction works well to distinguish some tics from some compulsions, significant exceptions have been reported (e.g. Robertson and Cavanna, 2007a) and many behaviours appear to fall along the "tic-compulsion" spectrum (Prado et al., 2008).

The modern literature indicates that GTS and OCD are intrinsically related, although the percentage of patients with GTS who present with co-morbid OCD varies from 11% to 80% (Robertson, 2000; Cavanna et al., 2009a). Family studies have consistently showed that the frequency of OCD in the absence of tics among first degree relatives was significantly elevated in families of both GTS + OCD and GTS–OCD probands, and that these rates were increased compared to the general population and control samples (e.g. Pauls et al., 1986). Moreover, it has been observed that obsessive–compulsive symptoms in people with tics have their own character (Frankel et al., 1986; George et al., 1993). Compulsions tend to be more related to counting, symmetry and "just right" thoughts or actions. Typical examples of this include having to cross a door threshold in a certain manner, counting all the floor tiles in a room or having to perform a tic in a particular way (which can lead to repetitive tics). Intrusive aggressive or inappropriate sexual thoughts and images are relatively common in people with GTS, whilst the obsessive–compulsive symptoms in pure OCD tend to be more related to fears about contamination or harm coming to another person (e.g. Frankel et al., 1986; George et al., 1993; Cavanna et al., 2006b; Worbe et al., 2010). Frankel et al. (1986) reported that patients with GTS had significantly higher obsessional scores on a specially designed inventory when compared to controls. The obsessional items endorsed by GTS patients changed with increasing age, with younger patients endorsing more items to do with impulse control, and older subjects endorsing items about checking, arranging and fear of contamination. Cluster analysis of the inventory responses revealed a group of seven questions that were preferentially endorsed by GTS patients (blurting obscenities, counting compulsions, impulsions to hurt oneself) and eleven questions elicited high scores from OCD patients (ordering, arranging, routines, rituals, touching one's body, obsessions about people hurting each other). George et al. (1993) showed that patients with GTS and co-morbid OCD have significantly more violent, sexual and symmetrical obsessions and more touching, blinking, counting, and self-damaging compulsions, compared to patients with OCD only, who have more obsessions concerning dirt or germs and more compulsions about cleaning. The phenomenological differences between the repetitive behaviours encountered in GTS and OCD have been consistently reported in further studies (e.g. Worbe et al., 2010). The current view is that GTS and OCD can share some neurobiological underpinnings, and that specific obsessive–compulsive symptoms are likely to be intrinsic to GTS (Robertson, 2000; Lombroso and Scahill, 2008; Cavanna et al., 2009a).

The association between GTS and OCD can have treatment implications. While antidopaminergic agents (neuroleptics and atypical antipsychotics) are the most effective medications for tic symptoms (Pringsheim et al., 2012; Roessner et al., 2011; Waldon et al., in press), antidepressants (especially the Selective Serotonin Reuptake Inhibitors or SSRIs) are useful for affective disturbances

and, at higher dosages, for OCD (Miguel et al., 2003). Clomipramine (a tricyclic antidepressant) may also be useful in OCD, but has been associated with more side effects than SSRIs and is not safe in overdose. A small dose of antidopaminergic medication can prove useful as add-on therapy for treatment-refractory OCD in the context of GTS. With regards to non-pharmacological interventions, cognitive behavioural therapy is the first-line treatment for OCD and (in the form of habit reversal therapy) GTS (Verdellen et al., 2011; Steeves et al., 2012). It should however be noted that there are considerable differences in the specific behavioural strategies used to target tics or obsessive–compulsive symptoms. Deep brain stimulation has shown positive results in selected cases of severe, treatment-refractory GTS with and without co-morbid OCD (Hariz and Robertson, 2010; Cavanna et al., 2011b; Muller-Vahl et al., 2011; Piedad et al., 2012). Although existing data are preliminary and partly conflicting, there is some evidence that thalamic DBS in GTS might improve obsessive–compulsive symptoms alongside tics (e.g. Porta et al., 2009).

4. Attention-deficit and hyperactivity in Gilles de la Tourette syndrome

ADHD and GTS present with a high rate of co-morbidity: as many as 60–80% of young patients with GTS can fulfil current diagnostic criteria for co-morbid ADHD (Robertson, 2000; Cavanna et al., 2009a), and the clinical spectrum of these two neurodevelopmental disorders tends to overlap. However, the precise nature of the relationship between GTS and ADHD is complex and still debated. Whether the combination of GTS plus ADHD reflects a separate entity and not merely two-coexisting disorders, as suggested for example by Gillberg et al. (2004), is still controversial. Attentional difficulties and problems with hyperactivity and impulse control frequently precede the emergence of the actual tics (Jankovic, 2001; Leckman, 2002; Cavanna et al., 2009a; Simpson et al., 2011). In general, it is important that a thorough assessment is conducted in order to disentangle the partially overlapping symptomatology of GTS and ADHD. Some young patients with GTS may appear to have poor concentration simply because they are constantly trying to suppress their frequent tics. Importantly, it has been pointed out that the symptoms of ADHD may significantly contribute to the behavioural disturbances, poor school performance and impaired executive functioning testing in children with GTS (Eddy et al., 2009; Robertson and Cavanna, 2009).

Over the last few years, several studies have examined the behaviour of children with GTS only, in comparison with other groups such as GTS + ADHD, ADHD only and unaffected controls (e.g. Carter et al., 2000; Sukhodolsky et al., 2003). Overall, the results of these studies indicated that patients with GTS only did not differ from unaffected controls on many ratings, including aggression, delinquency and/or conduct difficulties. By contrast, children with GTS + ADHD reported indices of disruptive behaviour which were significantly higher than unaffected controls and similar to those with ADHD only. Again, the possibility that these challenging behaviours could be related to GTS-specific anger symptoms rather than co-morbid ADHD, has not been completely ruled out (Rizzo et al., 2007; Cavanna et al., 2008b).

In summary, ADHD symptoms are common in people with GTS and it appears that they may occur in even mild GTS cases who are identified in epidemiological studies. Moreover, patients with GTS only appear to be different to those with co-morbid ADHD, and this clearly has major management and prognostic implications. Robertson (2006a) reviewed the relationships between GTS and ADHD particularly as far as treatment is concerned, and suggested that when a patient has a dual diagnosis of GTS and ADHD, the clinician should carefully assess which symptoms are the most problematic, and attempt to treat the target symptoms. In children, it is important that the assessment incorporates feedback from teachers, parents or other relatives, whenever possible (Termine et al., 2011; Cavanna et al., in press-a). Medications such as alpha-2 agonists clonidine and guanfacine, which have proven efficacious for both tics and ADHD symptoms, could be particularly useful as first-line agents (Robertson, 2006a; Eddy et al., 2011a). However, the management of ADHD symptoms in the context of GTS is particularly challenging and requires caution, since in some patients central nervous system stimulants (which are mainstream treatment for children with ADHD) can precipitate tics. Evidence from pharmacological studies conducted over the last decade supports the use of stimulants to prioritise the treatment of debilitating ADHD symptoms in patients with GTS (Erenberg, 2005; Robertson, 2006a; Bloch et al., 2009).

5. Affective disorders and personality in Gilles de la Tourette syndrome

Depression has long been found in association with GTS (e.g. Montgomery et al., 1982). There is now good evidence from both controlled and uncontrolled studies reviewed by Robertson (2006b) to support the view that affective disorders are common in patients with GTS, with a lifetime risk of 10%, and a prevalence of 1.8–8.9%. In patients with GTS seen at specialist clinics, depressive symptomatology was found to occur in between 13% and 76% of cases (Robertson, 2006b). Depression in people with GTS has also been shown to result in hospitalisation and even suicide in a few people. The presence of depression in patients with GTS has been associated with a number of factors, including tic severity and duration, complex tics (echophenomena, coprophenomena, self-injurious behaviours), premonitory sensations, sleep disturbances, OCD, aggression, childhood conduct disorder, and possibly ADHD (Robertson, 2006b). GTS *per se* can be a distressing condition, particularly if tics are moderate to severe. Thus, depression in the context of GTS could be explained, at least in part, by the fact that patients have a chronic, socially disabling and stigmatising disease. In fact, it is a common experience for children with GTS to be bullied, teased and given pejorative nicknames, possibly leading to reactive depression. Both OCD and ADHD have been shown to have a high rate of co-morbidity with depression, suggesting that the presence of such co-morbidities might be responsible for depressive symptoms in a substantial group of patients with GTS (Robertson, 2000, 2006b). A further possible cause for the development of affective disturbances in patients with GTS could be the presence of associated learning disabilities in clinical subgroups. Finally, depression may also be a side effect of chronic therapy with antidopaminergic agents for tic management, as well as other medications commonly used in GTS. Depression has been commonly reported with, for example, haloperidol, pimozide, sulpiride, tiapride, and risperidone, as well as tetrabenazine and clonidine (Robertson, 2000; Eddy et al., 2011a). In summary, the aetiology of depression in GTS is highly likely multifactorial, as in primary depressive illness, and less likely to be caused by a single etiological factor. The precise phenomenology and natural history of depression in the context of GTS deserve more research, as well as their contribution to the GTS phenotype(s). A better characterisation of the phenomenology of depressive symptoms in GTS may help address factors of particular relevance to the aetiology of depression in the individual patient, thus improving its recognition, treatment and outcome.

Personality disorders represent an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture. The seminal study by Shapiro et al. (1978) was the first one to report personality disorders in 36 patients with GTS. Three quarters of the patients (27/36) were

diagnosed as having a personality disorder (passive-aggressive: $n = 6$; schizoid: $n = 4$; inadequate: $n = 3$; other: $n = 14$). Robertson et al. (1997) used standardised interviews and measures to compare 39 adult patients with GTS of moderate severity, with 34 age and sex matched normal controls. Personality disorders were diagnosed using the Structured Clinical Interview for DSM-III-R Personality Disorders II (SCID-II), plus a self-report instrument for personality disorders (SCTPD). According to the SCID-II, 25/39 (64%) of patients with GTS had at least one personality disorders, compared with only 2/34 (6%) of control subjects. The types of personality disorders included borderline ($n = 11$), depressive ($n = 9$), obsessive–compulsive ($n = 9$), paranoid ($n = 9$), passive aggressive ($n = 9$), avoidant ($n = 8$), antisocial ($n = 4$), narcissistic ($n = 4$), hysterical ($n = 3$), schizoid ($n = 3$), schizotypal ($n = 2$), self defeating ($n = 2$). More recently, a study by Cavanna et al. (2007) quantified the prevalence of schizotypal personality traits in GTS and explored the relationship between schizotypy, tic-related symptoms and co-morbid psychopathology. A total of 102 patients with GTS were evaluated using the Schizotypal Personality Questionnaire along with standardised neurological and psychiatric rating scales. Fifteen percent of the patients were diagnosed with schizotypal personality disorder according to DSM-IV criteria. The strongest predictors of schizotypy were obsessionality and anxiety ratings; moreover, the presence of multiple psychiatric co-morbidities correlated positively with schizotypy scores. Schizotypal personality traits appear to be relatively common in patients with GTS, possibly reflecting the presence of co-morbid psychopathology, such as obsessive–compulsive symptoms (see also Cavanna et al., 2009c). It is important to note that, at present, little is known about the direction of the possible causal relationship between the presence of tics and specific personality disorders or traits. Overall, based on these findings it seems likely that personality disorders in GTS are under-investigated and under-diagnosed: this clearly is an important area of future research to achieve a fuller understanding of the psychopathological spectrum of GTS.

6. More than one Gilles de la Tourette syndrome?

As we have shown in the present article, our concept of GTS has evolved since Georges Gilles de la Tourette's first description in 1885, following a constant increase in scientific interest and publications about this condition (Mariam and Cavanna, 2012). Our current view is that GTS is a neurodevelopmental disorder consisting of multiple tics, and often associated with complex tic-related symptoms and behavioural problems. GTS is increasingly recognised as a relatively common lifelong neuropsychiatric disorder, diagnosed in early childhood. Co-morbid neuropsychiatric disorders occur in approximately 90% of patients, with ADHD and OCD being the most common ones, followed by affective and personality disorders (Robertson, 2000; Cavanna et al., 2009a). Of note, whilst we chose to focus on these behavioural problems as frequent co-morbidities in GTS, autistic spectrum disorders (Clarke et al., in press) and impulse control disorders (Frank et al., 2011; Wright et al., 2012) are also commonly diagnosed in GTS populations, especially among patients seen in paediatric clinics, The concept of the 'behavioural spectrum' of GTS has recently been confirmed by the remarkably similar findings from large studies conducted both across specialist clinics (Freeman et al., 2000; Cavanna et al., 2011c) and in the community (Khalifa and Von Knorring, 2005), although a more recent population study based on maternal screening questionnaires downsized the prevalence of behavioural co-morbidities (Scharf et al., 2012). The World Health Organization (1992) and the American Psychiatric Association (2000) criteria currently in use imply that GTS is a unitary condition. However, over the last decade

Table 1
Summary of clinical studies on symptom factors/clusters in Gilles de la Tourette syndrome.

Study	Country	Patients	Variables	Method(s)	Factors/clusters
Alsobrook and Pauls (2002)	USA	85	26 (clusters of tic symptoms)	HCA + PCFA	Aggression Tics Compulsions Tapping + absence of grunting
Eapen et al. (2004)	UK	91	11 (behavioural symptoms only)	PCFA	Obsessionality Anxiety/depression
Storch et al. (2004)	USA	76	15 (tic symptoms + behavioural symptoms)	PCFA	Aggression ADHD OCD Tics
Mathews et al. (2007)	USA	254	38 (tic symptoms + specific complex tics)	HCA	Simple tics Complex tics + OCS
Robertson and Cavanna (2007a,b)	UK	69 from 1 large pedigree	18 (clusters of tic symptoms + behavioural symptoms)	HCA + PCFA	Tics ADHD + aggression Anxiety/depression/obsessionality + SIB
Grados et al. (2008)	International	952 subjects from 222 families	3 (diagnosis of GTS + OCD + ADHD)	LCA	GTS + OCS GTS + OCD GTS + OCD + ADHD Minimally affected class CMT + OCD
Robertson et al. (2008)	UK	410	20 (clusters of tic symptoms + specific complex tics)	HCA + PCFA	NOSIB + CVT CMT Simple tics Compulsions Self touching
Cavanna et al. (2011a,b,c)	UK	639	12 (complex tics + behavioural symptoms)	PCFA	Complex motor tics + echo/paliphenomena ADHD symptoms + aggressive behaviours Complex vocal tics + coprophenomena

Abbreviations: GTS, Gilles de la Tourette syndrome; PCFA, principal-component factor analysis; HCA, hierarchical cluster analysis; LCA, latent class analysis; ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; SIB, self-injurious behaviours; NOSIB, non-obscene socially inappropriate behaviours; CVT, complex vocal tics; CMT, complex motor tics; OCS, obsessive compulsive symptoms.

clinical studies using hierarchical cluster analysis (Mathews et al., 2007; Robertson et al., 2008), principal component factor analysis (Alsobrook and Pauls, 2002; Eapen et al., 2004; Storch et al., 2004; Robertson and Cavanna, 2007b; Robertson et al., 2008), and latent class analysis (Grados et al., 2008) have suggested that there may be more than one GTS phenotype (Table 1). This multifaceted clinical picture raises the issue of whether GTS should still be considered as a unitary nosological entity and poses major challenges to treatment strategies aimed at improving patients' health-related quality of life (Cavanna et al., 2008c, 2012b, in press-b; Eddy et al., 2011b,c, in press).

With its behavioural spectrum, GTS is a paradigmatic condition bridging neurology and psychiatry. Since the first suggestions that psychiatric diseases are in fact brain diseases (Griesinger, 1845), dualism has somewhat fallen out of favour, even in 'pure' psychiatry. In modern textbooks, it is rather challenging to find a central neurologic condition (especially movement disorders, but also epilepsy, multiple sclerosis, etc.) devoid of psychiatric complications. Intriguingly, GTS also challenges our notions of normality. Most of the disability caused by GTS is primarily social, although it can be considerable. Perhaps the problem lies in other people's concepts of normality and the drive to exclude those who appear to transgress social norms (even if the transgression is not by choice). The next steps for research into GTS would ideally include well-characterised cohort studies and identification of biomarkers for specific sub-types of the disorder (Singer, 2005; Albin and Mink, 2006; Felling and Singer, 2011). This could lead to more specific treatments for the majority of patients with co-morbid behavioural problems.

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