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#### Abstract

*The unstructured abstract of 200 words maximum should summarize the main points of the article. All information mentioned in the abstract must be addressed somewhere in the main article. The abstract should not contain references or display item citations.*

1. *Introduction* [suggested 500 words, is 544 words – 8 refs] **Mary Robertson**

#### **Thoughts for Mary**

- *Your word count when combining sections 1 and 2 is 1001 (1000 limit)- so OK*
- *please check refs are as you intended, especially those flagged below*
- *note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance” – I guess this means 2-3 from each of sections 1 & 2 (30 to 50 words is ideal -70 words maximum).*
- *Timeline can be one display item but any others? (DSM criteria in a box maybe a bit boring, but would fit) Agree - boring but would fit*

Gilles de la Tourette Syndrome (GTS), a reasonably common disorder, has had a long, tortuous and somewhat controversial history. First and well described in the 18th century<sup>1,2</sup>, the main features of GTS have, however, remained fairly constant. The core diagnostic features are multiple motor and one or more vocal (phonic) tics lasting for over a year. In addition, almost pathognomic, but not necessary, features described in the early documentations include coprolalia (involuntary, inappropriate swearing), and echo-phenomena (copying behaviours), as well as many co-morbidities and psychopathologies<sup>3</sup>.

GTS was originally described in France and the majority of early literature came from Europe. The World Health Organisation (ICD, now ICD 10; F95.2) criteria have remained reasonably constant over time and refer to GTS as a *syndrome*. The American DSM diagnostic criteria have been in place since 1952, when "tics" were first mentioned, but GTS was first included in DSM-III in 1980, giving "birth" to a tranche of publications, in particular from the USA: In the DSM system, currently in its 5<sup>th</sup> edition<sup>4</sup>, GTS is referred to as a *disorder* (307.23). Aspects of the DSM criteria have changed over the years, including age at onset, presence of impairment and "marked distress" and suppressibility. Other diagnostic systems exist, such as the Chinese Diagnostic Criteria (stipulating distress), but a majority of clinicians and in particular researchers opt for the DSM criteria as comparison of data is important<sup>5</sup>. The establishment of diagnostic criteria that resulted in research world-wide has led the scientific community to view GTS as a common disorder.

As with many syndromes, there have been numerous well-designed clinical and longitudinal studies that have clarified the clinical features, co-morbidities, and co-existent psychopathologies and resultant impairments associated with GTS, highlighted by the volume of Quality of Life (QoL) studies now being published. Many epidemiological studies have also been undertaken, but with inconsistent results. Further, many GTS-specific scales and standardised schedules such as diagnostic confidence, measurement of severity, QoL, and assessment of both co-morbidities and co-existent psychopathologies are currently available. Large international collaborative consortia are engaged in studies exploring aetiological factors in particular, and some international treatment studies are also underway. Perhaps as a result of earlier small patient numbers, the treatment trials have given good clues to management, but unsurprisingly systematic reviews and meta-analyses have been hampered, giving disappointing, if not unexpected, results. Intriguingly medications from the typical

antipsychotic family including haloperidol, which first had documented success in 1961<sup>6,7</sup> are still being used, although successive generations of "atypicals" are currently more in vogue, as are medications such as alpha-2-adrenergic agonists. Interestingly, haloperidol remains the only medication prescribed on licence in many parts of the world. In contrast to disorders such as ADHD, in which it is clear which treatments work and which do not require further study<sup>8</sup>, a variety of treatment studies in GTS are still being undertaken, including using other medications (trying to improve efficacy and reduce side effects), behavioural therapies, deep brain stimulation (for refractory cases), and other more "alternative" methods such as "orthotics" (teeth braces). The GTS community has to first agree on how common GTS is and then seek funding for research in the areas of major importance.

2. *Epidemiology* [suggested 500 words, is 444 words, 6 additional refs] Mary Robertson

GTS was for many years thought to be not only very rare, but a bizarre curiosity, with sporadic case reports peppering the literature. The belief that GTS was uncommon at the very least was held by many until Comings<sup>9</sup> controversially suggested that GTS occurred in between 0.66% and 1% of the general population, mostly in boys. Some controversy has reigned ever since, with a wide prevalence range being reported ( 0.25% - 5.7% )<sup>3</sup>. Studies have varied enormously in methodology, including reported "cases" actually being hospitalised for their GTS<sup>10</sup> (i.e., *not* a true prevalence study); and the "cases" *not* being interviewed/assessed directly (4/21 [19%] of available studies). In addition, other investigations were conducted by telephone, have included a variety of age ranges (4-17 years), varying assessment methods (1-3 stages) and different cohorts (birth cohort versus school pupils). Finally, different assessment schedules were used in different studies.

The investigations conducted in mainstream schools in Colombia, Denmark, Iran, Israel, Italy, Poland, Spain, Sweden, the USA and UK showed a somewhat higher prevalence compared with those from the Far East. The differing results from the Far East studies may be because the Chinese Diagnostic System requires both impairment and distress<sup>3</sup>, which were included but subsequently *excluded* from DSM.

It has been suggested that GTS does not occur in Sub-Saharan Black African populations potentially due to genetic factors<sup>11</sup>. The comparison with myotonic dystrophy, which does not occur in Sub-Saharan Black African people, has been made: Non-African populations have a subset of the haplotype diversity present in Africa, as well as a shared pattern of the allelic

association (CTG)18-35 alleles (normal range) which were observed in only North-Eastern African and non-African populations<sup>12</sup>.

Relatively recent reviews by experts have suggested world-wide GTS prevalence rates to be as low as 0.5% - 0.7 %<sup>13</sup> and as high as 0.85% - 1%<sup>3,11</sup>. A recent meta-analysis of childhood studies reported a prevalence rate of 0.77% - but when only boys were accounted for, the prevalence rose to 1.06%<sup>14</sup>. World-wide figures in general are somewhat higher than many studies from the USA: This may partially reflect the USA having relied on the idea that GTS is a "rare disorder", which may have biased results (e.g., CDC studies). The lower rates in an Israeli study could be because of the older ages (16-17 years) and because participants were military recruits, who it was suggested might have hidden their symptoms. Two studies from Denmark, based on national GTS registers, suggest that the incidence of GTS may be rising. It is suggested, however, that this may reflect an increase in awareness of GTS. Finally, GTS is more common in people with both autism spectrum disorder (ASD) and learning disabilities<sup>3</sup>.

### 3. *Mechanisms/pathophysiology*

3a. Neurotransmitter abnormalities (suggested 500 words, is 1106 words excluding figure (caption another 230 words), 21 additional refs) Harvey Singer

#### ***Thoughts for Harvey***

- *Will need to reduce text overall*
- *We need copyright permission for the Figure? Or "tweak"?*
- *note that the author guidelines ask that we "annotate 2–3 references from each main section describing why these papers are of particular importance". In this section please ask Harvey Singer to do 1 (30 to 50 words is ideal -70 words maximum).*
- *There was a reference in your list that I don't think was cited. Important to include?*  
*(Tian Y, Gunther JR, Liao IH, Liu D, Ander BP, Stamova BS, Lit L, Jickling GC, Xu H, Zhan X, Sharp FR. GABA- and acetylcholine-related gene expression in blood correlate with tic severity and microarray evidence for alternative splicing in Tourette syndrome: a pilot study. Brain Res. 2011; 1381:228-236.*
- *Some minor comments in text to review*

In GTS, there is broad consensus that the functional alteration resides within cortical-striato-thalamo-cortical (CSTC) circuits. Which one, or combination, of the multiple

neurotransmitters located within these pathways is the primary pathological factor remains to be determined. In general, neurochemical hypotheses are derived from data acquired from several areas including medication trials; quantification in CSF, blood, and urine; neurochemical assays on post-mortem brain tissues; PET/SPECT/MR spectroscopy studies; and genetic analyses. In this section, we will briefly review those neurotransmitters with important roles in conveying messages via CSTC circuits and are likely candidate abnormalities in GTS.

### Dopamine

Evidence supporting a dopaminergic abnormality in GTS is derived from therapeutic responses to dopamine antagonists, data from post-mortem studies, and a variety of nuclear imaging protocols<sup>15</sup>. Hypotheses regarding dopamine abnormalities have included presynaptic, intrasynaptic, and postsynaptic dysfunctions. Suggested presynaptic alterations include a developmental hypofunction of dopamine neurons, hyperinnervation, and an increased number of dopamine transporters. Postsynaptic studies have reported variably increases in the number of striatal and cortical dopamine receptors. Other investigations, based on an increased release of dopamine following amphetamine stimulation, have suggested a potentially unifying hypothesis involving the tonic release of dopamine<sup>16</sup>. Further supporting an involvement of dopaminergic systems is the significant interaction with both glutamatergic and GABAergic neurotransmitter systems<sup>17</sup>. Mouse models evaluating a dopamine abnormality have included DAT knockdown and D1CT-7 mice. Candidate gene association studies have reported variations in dopamine receptors, transporters and catabolising genes, however, sample sizes have been small and results variable<sup>18</sup>.

### Glutamate

Suggestive evidence that the glutamatergic system has a role in GTS includes its essential role in pathways involved with CSTC circuits; and extensive interaction between the glutamate and dopamine neurotransmitter systems; and a beneficial therapeutic effect of glutamate-altering medications on obsessive-compulsive symptoms<sup>15,17</sup>. Reduced levels of glutamate were identified in post-mortem globus pallidus interna (GPi), globus pallidus externa (GPe), and substantia nigra pars reticulata (SNpr) regions<sup>19</sup>. In contrast, glutamate was increased within the striatum and premotor cortex when measured by 7T MR spectroscopy<sup>20</sup>. Animal models support a role for cortico-striatal glutamatergic afferents in the generation of tic-like movements<sup>21</sup>. Therapeutically, tic suppression did not differ from a

placebo control group following treatment with either a glutamate agonist (D-serine) or a glutamate antagonist (riluzole)<sup>22</sup>. A missense mutation in the glutamate transporter gene (SLC1A3) has been identified in a small number of GTS patients<sup>15,23</sup>.

### Gamma-Aminobutyric Acid (GABA)

An alteration of GABA is supported by post-mortem, PET and MR spectroscopy studies<sup>15</sup>. In the striatum, post-mortem studies have identified a reduction of GABAergic parvalbumin containing interneurons, however, 7T-MRS showed elevated concentrations of GABA within the striatum<sup>20</sup>. PET imaging of GABA<sub>A</sub> using [(11C)] flumazenil showed decreased binding bilaterally in the ventral striatum, globus pallidus, thalamus, amygdala and right insula<sup>24</sup>. In the cortex, a deficiency of inhibitory interneurons is suggested by a reduction of short-interval intracortical inhibition measured by transcranial magnetic stimulation and a reduction of GABA measured by 3T MRS in the primary sensorimotor cortex<sup>25</sup>. In contrast, 7T-MRS has shown elevated concentrations of GABA within the supplementary motor area<sup>26</sup>. In rodent and primate models, disruption of striatal and cortical GABAergic connectivity by local injections of GABA<sub>A</sub> antagonists has produced tic-like behaviors<sup>21,26,27</sup>. Other supporting evidence for GABA involvement includes the beneficial therapeutic effect of benzodiazepines and an association between GABA-related genes and tic severity<sup>28</sup>.

### Acetylcholine

Results of pharmacological studies using agents that affect nicotinic and muscarinic receptors (e.g., transdermal nicotine, mecamylamine, donepezil) have been variable. Post-mortem studies have shown a decrease in choline acetyltransferase containing striatal interneurons, supporting reports of an anatomical reduction of cholinergic interneurons<sup>15</sup>. 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 stereotypic behaviours<sup>29</sup>. Striatal cholinergic interneurons may co-opt dopamine terminals and drive GABA release<sup>30</sup>.

### Serotonin

Evidence supporting serotonergic involvement in GTS includes reduced serum and CSF levels of serotonin and tryptophan, and PET imaging showing diminished serotonin transporter binding capacity<sup>15</sup>. Reported findings, however, may be associated with the

presence of OCD. PET imaging of tryptophan (alpha-[<sup>11</sup>C] methyl-L-tryptophan) uptake demonstrated decreased uptake in the dorsolateral prefrontal cortical regions and increased uptake in the caudate and thalamus<sup>31</sup>. Polymorphic variants of tryptophan hydroxylase 2 and the serotonin transporter gene (SLC6A4) have been reported, but there are no differences in the serotonin receptor HTR2B gene<sup>15,32</sup>.

### Norepinephrine

Evidence for a NE mechanism in GTS is limited and partly based on the therapeutic effect of alpha-adrenergic agonists (clonidine and guanfacine)<sup>15</sup>. Clonidine, however, also decreases the release of glutamate and regulates spontaneous and glutamate-modulated firing activity in medial frontal cortical pyramidal neurons. Measurements of NE are normal in post-mortem cerebral cortex, basal ganglia and plasma; and levels of its metabolite, 3-methoxy-4-hydroxyphenylethylene glycol are normal in plasma and CSF, but variable in urine. Alpha-receptor densities have been variable in post-mortem cortex, and either normal or increased in BA10 and BA11. The later, if confirmed, could lead to a reduction in the basal release of dopamine, since activation of  $\alpha$ -2A receptors has been shown to inhibit dopamine release in the prefrontal cortex.

### Histamine

Histamine is a monoamine neurotransmitter synthesized from histidine via L-histidine decarboxylase (HDC). A heterozygous nonsense point mutation in exon 9 of the HDC gene has been identified in a single family with tics<sup>33</sup>. To date, however, this mutation has not been identified in other families<sup>15</sup>. Results in several animal models, including a HDC knockout mouse, support a role for deficient HDC in GTS<sup>34,35</sup>. A clinical trial with the H3 receptor antagonist (AZD5213) is currently in progress (Clinical Trials.gov ID: NCT01904773).

### Endogenous opioids

The endogenous basal ganglia opioid system interacts with dopamine and other neurotransmitters. Dynorphin A [1-17] immunoreactivity was decreased in a severely affected patient with GTS within striatal fibres projecting to the GPe. Dynorphin A [1-8], was increased in the CSF of people with GTS; the concentration of this opiate correlated with the severity of obsessive compulsive symptoms, but not with tic severity. The use of the opiate antagonist naloxone in the treatment of tics has produced conflicting results, whereas

several studies have suggested that cannabinoids (smoking marijuana or using oral delta-9-tetrahydrocannabinol) has a beneficial effect on tics. Limited SPECT studies analysing the cannabinoid CB1 receptor with [123I] AM281 have been published. GTS is not associated with mutations in the central cannabinoid receptor (CNR1) gene.

### Summary

Neurochemically, in GTS the strongest evidence continues to favour a major role for dopamine. However, as emphasised in this section, there is expanding evidence to support an important role for other neurotransmitters. See Figure XXXXX. Recognising the complexity of interactions between potential neurotransmitters, it remains likely that several interacting neurotransmitter systems are involved. Clearly, our current understanding of this disorder is incomplete and further study is required.

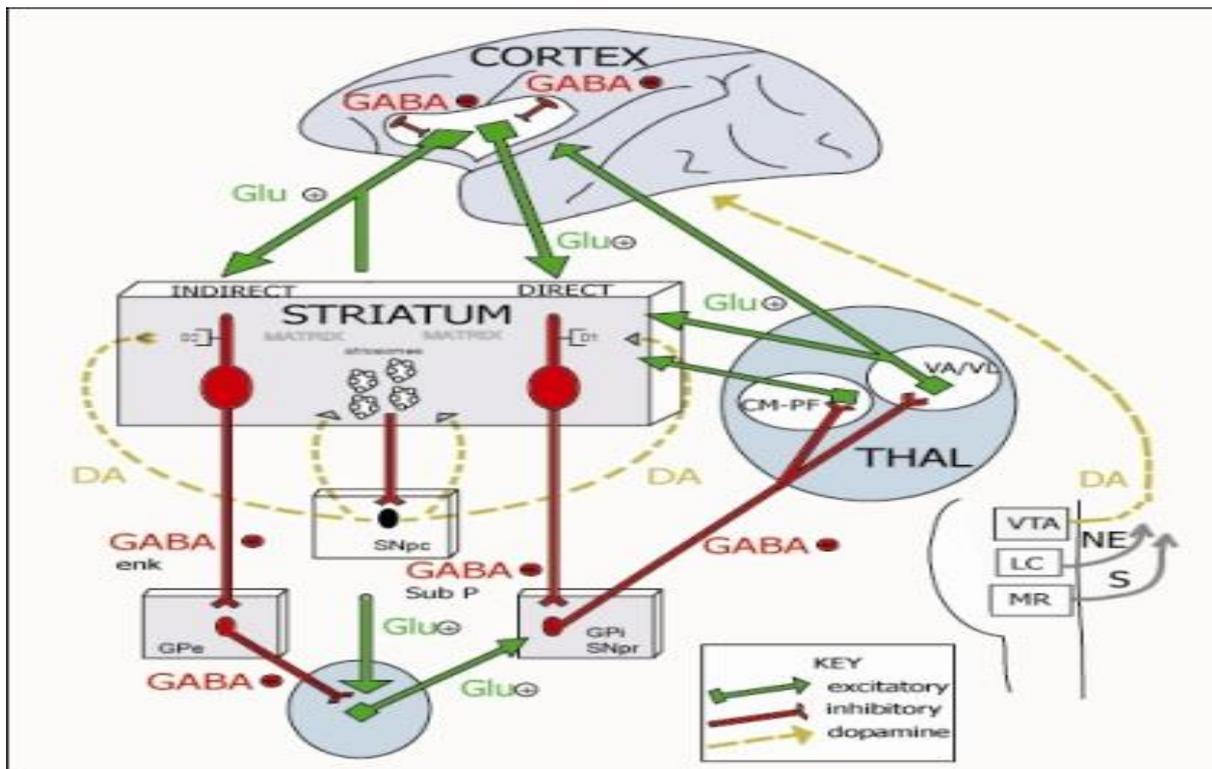


Figure XXXXXX. Neurotransmitters in CSTC circuits

### Figure caption

Dopamine: Substantia nigra pars compacta (SNpc) outputs synapse on i) presynaptic receptors located on glutamatergic fibre terminals (inhibitory); ii) striatal projection neurons

(SPN, also known as, medium sized spiny neurons) containing D1 receptors (direct pathway); enhancing glutamatergic cortical/thalamic stimulation; iii) SPN containing D2 receptors (indirect pathway); reducing glutamatergic cortical/thalamic stimulation; and iv) striatal interneurons. The ventral tegmental area (VTA) provides dopaminergic innervation to the cortex, primarily to the frontal lobe and ventral striatum.

Glutamate: The excitatory neurotransmitter of cortico-striatal projection neurons, as well as output neurons from the subthalamic nucleus (STN) and thalamo-striatal and thalamo-cortical projections. Frontal glutamatergic afferents modulate VTA and SNpc dopaminergic neurons.

GABA: GABAergic inhibitory SPNs form two efferent pathways from the striatum - the “direct” (striato-globus pallidus interna (GPi) and “indirect” (striato-globus pallidus externa (GPe) pathways. The direct pathway is ultimately movement activating, whereas the indirect pathway is more inhibitory. Cortical and several striatal interneurons utilise GABA.

Acetylcholine: Cholinergic large aspiny striatal interneurons influence both SPNs and local interneurons.

Noradrenaline: Noradrenergic (NA) fibres from the locus coeruleus project to the cerebral cortex.

Serotonin: Medial raphe (MR) serotonergic projections innervate the striatum, SNpc, VTA, nucleus accumbens and prefrontal cortex.

Histamine: G-protein coupled histamine 3 receptors (H3) are located post-synaptically on SPNs and modulate dopamine neurotransmission.

Opiate systems: GPe is rich in enkephalin; GPi is rich in dynorphin, and the ventral striatum contains a mixed distribution.

3b. Immune and environmental influences in GTS (suggested 500 words, is 536 words, 13 additional refs) Davide Martino

***Thoughts for Davide***

- *Need to cut 36 words*
- *note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section you would need only to do 1 (30 to 50 word is ideal but 70 words maximum).*
- *James Leckman cited an in press article of yours – could you confirm the full citation with co-authors etc. We currently have - (Martino, D. Severity scales and screening instruments for tics: A systematic review and recommendations for use. Movement Disorders (in press).*
- *Mary said, “please try & give a small figure/table/flow-chart/ diagram”. Would it be possible to combine Mary’s table with scales with that of Martino et al if there is a table of scales in the Movement Disorder (in press) paper)? Davide to please action with Mary*

Increasing evidence links the crosstalk between neural and immune/inflammatory mechanisms to the pathogenesis of GTS, with relevant analogies to other neurodevelopmental disorders like ASD and schizophrenia. Recapitulating a model elaborated for psychosis<sup>36</sup>, pre- and peri-natal factors (e.g., infections, maternal stress during pregnancy, gestational smoking)<sup>37</sup> could, on a background of genetic vulnerability, trigger the ‘priming’ of glial cells belonging to the monocytic/macrophagic lineage, e.g., microglia, which are highly involved in synaptic formation and elimination. Later ‘hits’ (psychosocial stressors, infections) could, at a central level, activate the microglia, thus influencing synaptic plasticity close to symptom onset, and enhance peripheral immune/inflammatory responses<sup>38,39</sup>. Initial evidence suggests that these later ‘hits’ might contribute to the ‘waxing and waning’ course of tics in an interactive manner. For example, the predictive effect of psychosocial stressors upon tic and obsessive compulsive severity becomes three times stronger when an infection (e.g., a group A streptococcal pharyngitis) co-occurs with raised psychosocial stress levels<sup>40</sup>. Exploring the effect of ‘early’ and ‘late’ environmental influences in the context of face-valid animal models of tic generation, such as the ‘striatal disinhibition’ model<sup>41</sup>, would add to our understanding of their complex aetiology.

The genetic basis of the dysregulation of immune-mediated mechanisms in GTS is poorly understood. In particular, the relative contribution of meiotic genetic variants, somatic mutations and epigenetic influences remains unknown. A study on a Danish healthcare population registry has shown that a maternal history of autoimmune disorders is associated with a 29% higher risk of GTS in the male offspring<sup>42</sup>. However, this finding does not clarify

whether this association depends on inherited genetic factors, whether it involves transplacental transfer, or is merely epiphenomenal. Likewise, the interesting association between tics in the context of ADHD and common allergies is still unexplained<sup>43</sup>.

Direct evidence of altered function of CNS immune cells in GTS is limited, but intriguing. The post-mortem analysis of the striatal transcriptome of 9 patients with GTS and 9 closely matched control individuals showed a widespread up-regulation of inflammatory response transcripts related to the activity of cells of the macrophage/monocyte lineage, e.g., microglia<sup>44</sup>. Some of these transcripts reflect the expression of ‘hub’ genes that are crucial in the regulation of both innate and adaptive immune mechanisms. In addition, there is preliminary in vivo evidence of activated microglia in the caudate of children with GTS, obtained using a common PET ligand for this cell type (PK11195)<sup>45</sup>. These early findings support the hypothesis that immune-competent neural cells play an important role 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 also indicates an up-regulated expression of transcripts which control pathogen recognition and cell-mediated innate and adaptive response, from early childhood to adolescence<sup>46</sup>. Interestingly, some of these transcripts involve cholinergic and noradrenergic signalling (relevant to pathogen recognition) as well as GABAergic machinery (relevant for its immunosuppressant properties both at a central and a peripheral level)<sup>47,48</sup>. In addition, clinical studies reported several immunological changes in the periphery (e.g., dysgammaglobulinemia, decreased number of T regulatory cells, increased antibody response to pathogens) which point to chronically hyperactive innate and adaptive mechanisms<sup>39</sup>.

3c. The genetic basis of GTS (suggested 1000 words, is 1000 words, 32 additional refs)

Peristera Paschou & Jeremiah Scharf

### ***Thoughts for Peristera & Jeremiah***

- *Some type of “display item” (box, figure, table) might be useful*
- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section you would only need to do 1 (30 to 50 word is ideal but 70 words maximum).*

- Some minor comments in text to review

Multiple twin and family studies have repeatedly demonstrated that GTS is one of the most heritable non-Mendelian neuropsychiatric disorders, with a recent population-based heritability estimate ( $h^2$ ) of 0.77 (95% CI, 0.70-0.85) and a 15-fold increased risk of GTS/Chronic Tic disorder to full siblings compared to that of the general population<sup>49-51</sup>. Despite this high heritability and nearly three decades of research on many large, multigenerational GTS families, no definitive GTS gene of major effect has been identified<sup>52,53</sup>. Instead, GTS appears to be highly polygenic, with a large proportion of disease heritability attributable to common risk variants distributed widely across the genome<sup>54</sup>. Inter-individual variation in polygenic burden, combined with rare, inherited or *de novo* mutations in a subset of patients, as well as environmental (i.e., non-genetic) factors may account for the substantial heterogeneity of the phenotype and its complex aetiology. This genetic architecture parallels that of other developmental neuropsychiatric disorders such as schizophrenia and ADHD<sup>55,56</sup>. While no individual genes have yet met statistical criteria as definitive GTS risk factors, several have been implicated and may provide intriguing clues to the neurobiology of the disorder.

### SLITRK1

The implication of a member of the SLIT and TRK family of proteins (SLITRK1) in GTS aetiology has spurred intense debate. Studying a patient with GTS with a *de novo* chromosome 13 inversion, Abelson and colleagues mapped one of the breakpoints approximately 350 kb from *SLITRK1* and subsequently identified two rare, functional *SLITRK1* mutations in three additional people with GTS: a single truncating, frameshift mutation (varCDfs) and two independent occurrences of a missense variant (var321) in the 3' untranslated region (3' UTR) that was demonstrated *in vitro* to alter a binding site for microRNA hsa-miR-189 and to impair neurite outgrowth<sup>57</sup>. Subsequent sequencing and association studies have produced mixed results<sup>58-61</sup> supporting the notion that, if *SLITRK1* is involved in GTS aetiology, it may, however, only account for a small fraction of cases.

### HDC

The recent discovery of a deleterious L-histidine decarboxylase (*HDC*) gene mutation in a GTS family with an affected father and eight affected children has raised the intriguing hypothesis of the involvement of neuronal histaminergic pathways in GTS

pathophysiology<sup>33</sup>. *HDC* is the rate limiting enzyme in histamine biosynthesis and catalyses the oxidative decarboxylation of histidine to histamine. Following up on a linkage signal on chromosome 15, Ercan-Sencicek and colleagues sequenced all genes within the linked interval and identified a single coding mutation, a premature termination codon (p. W317\*, c.951G>A) that was not found in 1,500 European ancestry controls. Subsequently, a genome-wide analysis of *de novo* GTS copy number variants (CNV) found enrichment in histaminergic pathway genes<sup>62</sup>, and a targeted study of 520 GTS nuclear families found a significant association to *HDC* tagging variants<sup>63</sup>, though the largest GTS genome-wide association study to date did not confirm this association<sup>64</sup>.

#### Genome-wide association and copy number variant studies for GTS

One GTS genome-wide association study (GWAS) has been published including 1285 cases and 4964 ancestry-matched controls. No marker achieved genome-wide significance, though the strongest signal ( $p=1.85 \times 10^{-6}$ ) was located within an intron of *COL27A1*, the type XXVII collagen alpha chain gene<sup>64</sup>. A subsequent study of 42 of the top GWAS loci in 609 independent cases and 610 ancestry-matched controls revealed the most significant GTS association to date with a SNP lying closest to *NTN4*, an axon guidance molecule expressed in the developing striatum<sup>65</sup>.

Genome-wide investigations of copy number variation (CNV) in relation to GTS aetiopathogenesis have revealed multiple *de novo* or recurrent rare exon-affecting CNVs in various genes. The largest reported GTS CNV study to date (2,285 GTS cases and 3,791 controls) identified two genome-wide significant loci (*NRXN1*, OR=20.2,  $p=7.6 \times 10^{-5}$  and *CNTN6*, OR=6.0,  $p=1.7 \times 10^{-4}$ )<sup>66</sup>. Rare *NRXN1* deletions were also implicated in GTS pathogenesis in two previous studies of 111 and 210 GTS cases each<sup>67,68</sup>. In addition, recurrent exon-affecting microdeletions of the arylacetamide deacetylase (AADAC) were also observed in one of these early studies<sup>67</sup> and recently identified in a larger meta-analysis, including a total of 1181 patients with GTS and 118,730 controls from six European countries ( $p=4.4 \times 10^{-4}$ )<sup>69</sup>.

#### Shared genetic basis with other neuropsychiatric and neurological disorders

The high rates of co-occurring psychiatric disorders in patients with GTS patients lend support to the hypothesis of shared/overlapping neural circuitry and genetic susceptibility<sup>70-72</sup>. Two studies analysed genome-wide genotyping data to examine the unique and shared

components of GTS and OCD heritability attributable to common (polygenic) variation<sup>54,73</sup>. Davis and colleagues demonstrated a significant proportion of shared heritability between the two disorders ( $r=0.41$ ,  $se=0.15$ )<sup>54</sup>, though the majority of genome-wide OCD and GTS heritability was distributed differently across chromosomes and allele frequencies. Yu and colleagues used polygenic risk scores to identify distinct differences between polygenic risk burden of OCD with and without co-occurring GTS/Chronic Tic Disorder<sup>73</sup>. Also noteworthy is the significant overlap of rare GTS CNVs in loci previously shown to harbour recurrent deletions/duplications in other developmental neuropsychiatric disorders, including autism, ASD, schizophrenia, and epilepsy including 1q21, *NRXN1*, and 16p13.11 deletions, as well as 22q11 duplications<sup>67,74</sup>. The first reported epigenome-wide association study for GTS, although limited in size, also found significant enrichment among the top hits in genes related to neuropsychiatric and neurological disorders<sup>75</sup>. Another study independently identified an overall enrichment of CNVs spanning ASD genes<sup>62</sup>. Lastly, singleton CNVs and chromosomal rearrangements have implicated cell adhesion molecules, such as neurexins and neuroligins, in GTS and other neurodevelopmental phenotypes.

A recent large-scale cross-disorder study using GWAS summary statistics from 23 different neurologic and psychiatric disorders demonstrated that a significant proportion of GTS polygenic heritability is shared with OCD, ADHD and migraine<sup>76</sup>. While OCD and ADHD have long been known to share heritability with GTS<sup>70</sup>, the shared genetic relationship between migraine and GTS is novel. GTS and migraine have been observed to co-occur more frequently than control rates<sup>77</sup>, and abnormal serotonin levels have been proposed in both disorders<sup>78</sup>. Interestingly, a cross-disorder meta-analysis of top loci from published GTS and ADHD GWAS studies<sup>79</sup> reported the top signal ( $rs1866863$ ,  $p=3.2 \times 10^{-7}$ ) at *TBC1D7* (the third subunit of the GTSC1/2 complex), which has been previously also implicated by GWAS in the aetiology of migraine.<sup>80</sup>

#### 4. *Diagnosis, screening and prevention*

4a. Symptoms and clinical course (suggested 1000 words, is 1127 words (excluding figure and caption), 16 additional refs) James Leckman

***Thoughts for Jim***

- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section 1 or two would suffice (30 to 50 words is ideal- 70 words maximum).*
- *Please confirm if we need copyright for the figure OR can you “Tweak” it better?*
- *Some minor comments in text to review*
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## Symptoms

Tics are sudden, repetitive movements, gestures, or utterances that often mimic some aspect of normal behaviour<sup>3,81</sup>. Usually of brief duration, individual tics rarely last more than a second. Many tics tend to occur in bouts with brief inter-tic intervals of less than one second. Individual tics can occur singly or together in orchestrated sequence. They vary in their intensity and forcefulness. Motor tics, which can be viewed as disinhibited fragments of normal movement, vary from simple, abrupt movements such as eye blinking, nose twitching, head or arm jerks, or shoulder shrugs to more complex movements that appear to have a purpose, such as facial or hand gestures or sustained looks. These two phenotypic extremes of motor tics are classified as simple and complex motor tics, respectively. One form of complex motor tics are referred to as dystonic tics: These tics involve the need to the individual to maintain a specific abnormal distorted posture for a period of time<sup>82</sup>. Another is echopraxia, which entail the need to mimic a movement made by someone else in the immediate environment<sup>3,81,83</sup>. Similarly, phonic tics can be classified into simple and complex categories. Simple vocal tics are sudden, meaningless sounds such as throat clearing, coughing, sniffing, spitting, or grunting. Complex phonic tics are more protracted, meaningful utterances, which vary from prolonged throat clearing to syllables, words or phrases and to even more complex behaviours such as repeating one’s own words (palalalia) or those of others (echolalia) and, in rare cases, the utterance of obscenities (coprolalia)<sup>3,81,83</sup>.

The severity of tics in GTS waxes and wanes throughout the course of the disorder. The tics of GTS and other tic disorders are highly variable from minute-to-minute, hour-to-hour, day-to-day, week-to-week, month-to-month and even year-to-year<sup>84</sup>. Tic episodes occur in bouts, which in turn also tend to cluster<sup>85</sup>. Tic symptoms, however, can be exacerbated by stress, fatigue, extremes of temperature and external stimuli (i.e., in sensory and in echolalic tics)<sup>81</sup>. When individuals engage in behaviours that require focused attention and motor control, like playing the piano, reciting a poem, or participating in sport, their tics often completely disappear.

By late childhood a majority of individuals with tics are acutely aware of premonitory urges, i.e., 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<sup>86,87</sup>. These premonitory urges are usually only experienced by young people older than ten years and indeed the widely used PUTS (Premonitory Urge for Tics Scale<sup>87</sup>) score increases after the age of ten years<sup>88</sup>. These premonitory urges are similar to the sensation preceding 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. Of note, enhancing an individual's awareness of their premonitory urges followed by a competing response is at the core of behavioural treatments that have proven to be the most effective<sup>89</sup>.

Direct observational methods are the most objective measure of tic severity. However, the frequency of tics varies dramatically according to setting and activity. In addition, many individuals with GTS can suppress their symptoms for brief periods of time, thus clinical rating scales are the preferred method used by most clinicians experienced in evaluating tic disorders for assessing initial tic severity and for measuring change in tic severity. The Yale Global Tic Severity Scale (YGTSS) is the most widely used assessment tool that records an individual's current repertoire of tics and estimates their severity based on the number, frequency, intensity, complexity, and interference associated with their motor and vocal tics viewed in separate aggregates<sup>90,91</sup>. Among the currently available screening instruments, the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES) has been recommended as the most promising instrument for future epidemiological studies<sup>91,92</sup>.

### Clinical Course

Tics usually have their onset in the first decade of life. Boys are at increased risk to develop tics with a male-to-female ratio of 3 or 4 to 1<sup>3,13</sup>. Most investigators report a median onset of simple motor tics between five and seven years of age<sup>3,81</sup>. The first symptoms usually occur in the head and neck area and may progress to include muscles of the trunk and extremities. Motor tics generally precede the development of vocal 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, if not longer. That said, an individual's tic repertoire typically evolves over time with new tics emerging. Most patients experience peak tic severity from 9

to 12 years of age following which there is a gradual decline in tic severity<sup>93,94</sup> (See Figure XXXXX). A complete remission of both motor and phonic symptoms can occur, but estimates vary considerably<sup>13,81,93</sup> with some studies reporting rates of remission as high as 30 to 50%<sup>93,94</sup>. In such cases, the legacy of GTS in adult life is most closely associated with what it “meant” to have severe tics as a child. For example, the individual who was misunderstood and punished at home and at school for their tics or who was teased mercilessly by peers and stigmatised by their communities will fare worse than a child whose immediate interpersonal environment was more understanding and supportive<sup>95</sup>. Intriguingly, in a study in which patients were videoed when they were young and then at over twenty years of age at follow-up<sup>96</sup>, adult patients said they were “tics free”, but on video it was demonstrated that 90% of the adults still had tics: However the tics no longer caused distress and the need for medication was much less<sup>96</sup>.

Figure XXXXX: Course of Tic Severity in GTS

Figure caption

Plot of average tic severity in a cohort of 36 children aged 1 to 18 years<sup>94</sup>. Adapted with permission. ARRTS (Annual Rating of Relative Tic Severity) is a parent-rating on a six-point ordinal scale (Absent [0], least severe, mild, moderate, severe and most severe [6]). Similar data are also available from an independent cohort<sup>93</sup>.

Tics typically have their onset between ages 4 to 6 years, reach their worst ever between 10 and 12 years, and then decline in severity throughout adolescence. Tics can persist into adulthood and the most severe and debilitating cases occur in adulthood.

In contrast, adulthood is also the period when the most severe and debilitating forms of tic disorder are encountered. In this small minority of adult patients, severe tics can persist or re-emerge with frightening intensity. At their worst, tics can be self-injurious and disabling, placing in serious jeopardy an individual's health and well-being. Indeed, treatment refractory, severe tics can lead to permanent disability and injury (e.g., severe head snapping tics leading to permanent injury to the cervical spinal cord or persistent eye-poking tics leading to blindness). Adults with persistent severe tics often feel socially excluded and have resultant symptoms of a post-traumatic stress disorder. These patients have also been the focus of experimental neuromodulatory interventions, including deep brain stimulation<sup>97,98</sup>.

4b. Comorbidity and co-existent psychopathology (suggested 1000 words, is 1253 words, 37 additional refs) Mary Robertson

***Thoughts for Mary***

- *May need to be shortened. Reducing QoL section would save space and doesn't detract from "core business" of comorbidity and co-existent psychopathology in this section. Please check refs are as intended*
- *Note that the author guidelines ask that we "annotate 2–3 references from each main section describing why these papers are of particular importance". This means 1 or perhaps 2 from this section (30 to 50 words is ideal and 70 words maximum).*
- *Some minor comments in text*
- *Would your assessment measures Table fit here perhaps?*

In medicine and psychiatry, it is the ideal to give a patient only one diagnosis<sup>99</sup>. However, in many instances an individual patient has more than one diagnosable disorder. This is particularly true in individuals with GTS (), where only around 10% have "pure GTS" (i.e., tics only) whilst the remaining approximately 90% also have other disorders, with this pattern arising both in community and clinical settings<sup>3</sup>. How should the relationship between these other disorders and GTS be described?

The term comorbidity, first used by Feinstein<sup>100</sup> regarding patients with rheumatic fever, defined as a "*proven pathogenic mechanism*"<sup>101,102</sup> and exemplified in the description of psoriasis and inflammatory bowel disease<sup>103</sup>, is now widely used in psychiatry<sup>104</sup>. There are, however, varying definitions in use<sup>105,106</sup>, including within the GTS literature. Although we have used *comorbid* and *co-existent* separately for some time<sup>5,107</sup>, the latter has otherwise rarely been used in the GTS literature, except when the tics are clearly secondary to insults such as head trauma, encephalitis, toxins, or have arisen post infection<sup>108</sup>.

In GTS the best documented and most common psychopathologies include ADHD (in around 60% of GTS clinic patients), then OCD [(40-60% of patients); ego-dystonic, symptoms for more than an hour a day] and Obsessive Compulsive Behaviours (OCB) [(60-90% of patients]; ego-syntonic, symptoms for less than an hour a day], and ASD (6-11%)<sup>3</sup>. A variety of other co-existent psychopathologies occur in GTS, including depression (13-76%), non-OCD anxiety, separation anxiety, substance abuse and personality disorders. Other behavioural or emotional problems such as aggression, difficulties with anger control, sleep disturbances, self-injurious behaviours (SIB), and non-obscene socially inappropriate behaviours occur at higher rates than expected in people with tic disorders, usually when ADHD or OCD are already present. In addition, learning problems (in about 30-40%) may co-exist in GTS<sup>3,109</sup>.

We have chosen to use the term "*comorbid*" in GTS where the disorder in question is not only more common in GTS than in the general population, but there are also clinical similarities (although also differences)<sup>110</sup> and a definite or purported genetic link exists between GTS and the disorder. We suggest the comorbid disorders meeting these criteria are include: i) OCD/OCB<sup>49, 54, 73, 110</sup>; ii) ASD<sup>111</sup>, and CNVs<sup>62</sup>; and iii) ADHD<sup>111</sup> See the section above on Shared genetic basis with other neuropsychiatric and neurological disorders for additional information..

An exciting study showed that the lifetime prevalence of any psychiatric disorder being associated with GTS was 85.7%, and 57.8% of individuals with GTS had two or more additional psychiatric disorders<sup>70</sup>. Moreover, the mean (SD) number of associated disorders was 2.1 (1.6), but when OCD and ADHD were excluded, this reduced to 0.9 (1.3), given 72.1% of the GTS group also met criteria for ADHD or OCD. Other disorders including mood, anxiety and disruptive behavioural disorders, were each thought to occur in about 30%

of individuals. The authors therefore suggested that genetic correlations between GTS and mood, anxiety and disruptive behavioural disorders may be accounted for by ADHD; whilst mood disorders may be accounted for by a genetic relationship with both ADHD and OCD. They also showed that GTS and substance abuse were *not* genetically related. These results are in keeping with others who have shown no genetic relationships between GTS and depressive and anxiety disorders<sup>113</sup>, and conduct disorders<sup>114</sup>. Eapen & Robertson<sup>5</sup> reported in a sample of 222 patients, that those with “pure GTS” (13.5%) had no coprolalia and intriguingly, that pure GTS was associated with no family history of OCD suggesting that additional genes or environmental factors may be at play when GTS is associated with comorbidities.

Both OCB/OCD<sup>115</sup> and ADHD<sup>116</sup> have been widely studied and documented in individuals with GTS. It has also been suggested in at least one study that OCB was associated with the presence of ADHD and also with SIB<sup>117-119</sup>.

We would therefore argue that, at present, GTS is understood to be genetically related in some GTS patients to OCD/OCB, ADHD and ASD, but not to depression, anxiety, disruptive behaviours, conduct disorder and substance abuse. We further suggest that OCD/B, ADHD and ASD are therefore *comorbid*, whilst the latter disorders are *co-existent* with GTS. However, it must be remembered that recent studies have demonstrated that the genetics of GTS and associated disorders are far from simple<sup>54,73</sup>.

When discussing phenotype, we first acknowledge that there are many “tic phenotypes”(eg dystonic tics) and associated neurological conditions, especially migraine<sup>3</sup>. Further, with respect to phenotyping studies, of importance is that in all eight investigations to date – despite using differing methods including using cluster analysis, latent class analysis, hierarchical cluster analysis and principal component factor analysis - have reported several classes (phenotypes), based on tics (7/8), behaviours and comorbidities as per based on tics. The resulting phenotypes have included variously OCD/B, ADHD, depression, phobias and panic attacks<sup>120</sup>. The only one phenotype that has been replicated however is “Pure GTS”. Interestingly, coprolalia does not seem to be class specific, other than not arising in Pure GTS<sup>5</sup>. Clearly, with regard to psychopathology, more research is required.

While we will discuss Quality of Life (QoL) later in detail, note that several *recent* studies have demonstrated that the comorbidities and psychopathologies encountered with

GTS have a disproportionate negative impact on QoL (121, 122) with GTS having poorer QoL than healthy controls and people with epilepsy: in addition ADHD and OCD/B had widespread, if differential, effects on QoL scores, and were in combination the best predictors of QoL. In another controlled study, individuals with GTS had poorer psychosocial outcomes than healthy controls and this was associated not only with tic severity but also specifically ADHD and OCD<sup>127</sup>. Other factors encountered in patients with GTS but for which the ADHD is largely responsible, include maladaptive behaviours and decreased cognitive functioning in young people<sup>124</sup>, greater substance abuse, more aggression and more encounters with the justice system<sup>128</sup>. In summary, there is a consensus that comorbidities in general have a profound negative effect on the QoL, social functioning and peer relationships of patients with GTS while people with GTS and ADHD have significantly more maladaptive behaviours across the lifespan.

One of the major co-existent psychopathologies that occurs in GTS is depression with 13-76% of all patients with GTS affected<sup>129</sup>, and in controlled studies involving over 700 patients with GTS, those with GTS are more depressed than controls<sup>129</sup>. Clinical correlates of depression include echo- and coprophenomena, premonitory sensations; sleep disturbances, self-injurious behaviours; childhood Conduct Disorder; OCD/B and ADHD. Depression also leads to lower QoL, and potentially to hospitalisation and suicide. It was suggested that the aetiology of the depression in the context of GTS was multifactorial<sup>129</sup> but not genetic<sup>113</sup> and may be related to the OCD<sup>70</sup>.

Caregiver burden, rarely studied, was shown to be significantly higher in parents of young people with GTS when compared to parents of matched young people with asthma. The two groups were significantly different with parents of young individuals with GTS being the most disadvantaged. The correlates of increased caregiver burden and greater parental psychopathology included a GTS diagnosis and behavioural difficulties<sup>130</sup>.

Finally, suicidality (thoughts/ideation or behaviours including deliberate self-harm), is an important but relatively neglected aspect of GTS research with studies showing a higher prevalence in GTS (9.7%) when compared to healthy controls (3%)<sup>131</sup>. Since the first documentation of completed suicide in GTS by Robertson and colleagues<sup>132</sup>, few studies have examined this in detail with findings suggesting that factors associated with suicidality

include tic-related factors such as severity, coprolalia, SIB etc. and the presence of co-morbidities and co-existent psychopathologies.

## 5. Management

5a. Psychopharmacologic treatments (suggested 800 words, is 895 words, 14 additional refs) Veit Roessner

### **Thoughts for Veit**

- *Need to cut some words*
- *Some minor comments in text, including question about references to include for main points and about potentially including some type of display item (figure, table, flowchart etc.).*
- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section, you would need to do 1 only (30 to 50 words is ideal and 70 maximum).*

As a consequence of the high individual variability, idiosyncratic response to medications and complexities in symptom presentation and resulting impairment, decisions when and how to treat tics differ significantly across patients with GTS, particularly in children and adolescents. There are no psychopharmacologic or other "cures" in GTS, nor clear evidence that not starting treatment has a negative impact on the prognosis of the core tic symptoms.

For most individuals with GTS whose tics are mild-to-moderate and do not impair social functioning, the provision of psychoeducation and exploration of associated coping strategies is typically sufficient. If additional treatment is indicated, this should be based on the most prominent and disabling symptoms, which often are not tics (see the European Society for the Study of Tourette syndrome (ESSTS) guidelines for a GTS management decision-tree<sup>136</sup>). In addition to tic severity, the ESSTS guidelines suggest tic-specific psychopharmacotherapy should be considered where tics are causing i) pain or injury; ii) social and emotional problems (e.g., reactive depressive symptoms); and/or iii) functional interference (e.g., impairing academic achievement)<sup>136</sup>, in the context where behavioural therapies are either not available or not the patient's preference.

With respect to managing the key comorbidities, prescribing practices used when GTS is not present generally apply. It is now widely held that stimulants can be used to manage comorbid ADHD without much deleterious impact on tic severity in the majority of patients<sup>137</sup>. Non-stimulant ADHD treatment options such as atomoxetine, guanfacine and clonidine are also available<sup>8</sup>. Comorbid OCD can be managed with cognitive behavioural therapy and/or medication such as SSRIs or clomipramine, as per published guidelines<sup>138</sup>, similarly for depression where lower SSRI doses are typically required<sup>139</sup>.

The choice of psychopharmacologic treatment of tics is still often based on personal experience and there are widespread methodological limitations in the extant evidence base. An additional impediment to the development of a consensus psychopharmacological treatment algorithm for tics is the waxing and waning course of GTS. Moreover, tic severity can be influenced by comorbid disorders, which, apart from some exceptions, are not targeted by anti-tic medications.

The aim of psychopharmacologic 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, medication can reduce tics dose-dependently by 25-70% and normally within two-to-four weeks. “Over-medication”, driven by the belief that higher dosages will necessarily be more effective, can cause significant adverse reactions (see  $\alpha$ -2-agonists below), particularly sedation, apathy and extrapyramidal effects, in addition to weight gain and metabolic abnormalities.

Since the first case reports of haloperidol use in GTS in 1961<sup>6,7</sup> and subsequent open-label studies in the 1970s and 1980s, mainly using haloperidol and pimozide, there is both increasing evidence from clinical trials and broad clinical consensus that dopamine receptor blockers lead to a good response for motor and behavioural symptoms in the majority of patients. For those who do not respond to a particular agent, a switch to another dopamine receptor blocker or group of agents as well as combining two agents will generally lead to the desired benefits. There is only a minority of patients who evidence refractoriness to psychopharmacological treatment for tics, however the exact percentage is difficult to quantify, partly because the first definition has only recently been published<sup>140</sup>.

In general, there is no difference in efficacy among the different dopamine receptor blockers (haloperidol, pimozide, sulpiride, tiapride, risperidone, ziprasidone), however the adverse effect profile is very different with respect to weight, prolactin and other factors<sup>141</sup>, and the tolerability profile and the treatment requirements of the comorbid conditions have to be considered<sup>142,143</sup>. In this context, it is not surprising that the substituted benzamides, particularly sulpiride and tiapride, have been recommended as first line treatment of GTS mainly in Europe because of their favourable benefit to risk ratio<sup>141,144</sup> but unfortunately, both have too little evidence from randomised control trials, potentially because of low interest from an economic perspective, despite there being excellent efficacy in routine clinical care. With respect to differences in prescribing patterns internationally, in the United States and Canada,  $\alpha$ -2-agonists (clonidine and guanfacine) are considered first-line therapy, primarily because of their preferable side-effect profile compared with typical antipsychotics. In a recent meta-analysis, superiority to placebo for both  $\alpha$ -2-agonists was confirmed, however, this benefit was significant only for children/adolescents with GTS and comorbid ADHD, and minimal in patients with GTS without ADHD<sup>145</sup>. Thus, while dopamine blocking agents such as haloperidol is still the mainstay of tic-treatment internationally based on availability, due to the numerous adverse reactions of typical antipsychotics, second generation antipsychotics such as Risperidone is being used widely where available and more recently the better tolerated agents such as aripiprazole are being favoured, where cost and availability permits, as they appear to have the best benefit to risk ratio<sup>141</sup>.

Finally, it is noteworthy that interest remains in alternative agents, particularly in cases refractory to classical agents<sup>146</sup>. These patients often suffer from more severe and very complex symptomatology. There is some promising evidence regarding cannabinoids<sup>147</sup>. In addition, numerous other agents have been tried for the treatment of tics (e.g., tetrabenazine, baclofen, pramipexol, ecopipam, topiramate, naloxone, naltrexone, calcium channel blockers, flutamide, lecithin, metoclopramide, ondansetron, physostigmine, propranolol) with varying benefits and a number of new agents are currently either in development or in clinical trial phase<sup>148</sup>. Complementary and alternative medicine approaches such as  $\Omega$ -3 fatty acids and Chinese Traditional Medicine (Ningdong granule) have recently attracted growing interest<sup>149</sup>.

5b. Behavioural treatments (suggested 600 words, is 524 words, 13 additional refs)

Doug Woods

**Thoughts for Doug**

- *MMR wrote – Doug, I feel a table/figure would be nice - we could get copyright from JAMA or JAMA Psychiatry - given that we have time - a new table from you showing effect sizes for CBIT/HRT would also be good - the only thing is that my sense is that readers for our NRDP paper - wish a good up to date state of the art summary - they are unlikely to read all GTS papers in detail - & may not know all tables etc. As long as ours is informative & up to date maybe this is your call*
- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section, you would need to do 1 only (30 to 50 words is ideal, 70 maximum).*

Behavioural treatments are based on the idea that tics are influenced by contextual forces. By restructuring contextual factors and teaching patients tic-inhibition skills, symptoms can be effectively managed. Habit reversal therapy (HRT)<sup>150</sup> was the first behavioural treatment with a significant evidence base. HRT involves three primary components; awareness training, competing response training, and social support. In HRT, tics are treated one at a time; at a rate of one per week. In awareness training, the patient learns to notice tics as they occur or when the premonitory urge to tic appears. In competing response training, the patient learns to do an action that prevents the target tic from occurring. The patient uses this “competing response” contingent on the urge to do the target tic or on the tic itself. Competing responses are to be held for one minute or until the urge goes away; whichever is longer. With social support, an identified "support person" praises proper use of the competing response and prompts proper use when the patient forgets to do so.

Building on traditional HRT procedures, treatment researchers have started to include function-based treatment elements. In using function-based procedures, therapists assess contextual factors that reliably increase tics and reactions to tics that may inadvertently reinforce tics. The clinician then suggests therapeutic strategies that may reduce tics, to the patient and/or his or her parents. The strategies suggested are directly linked to the results of the assessment.

In addition to HRT and function-based interventions, relaxation training, psychoeducation about GTS, and a reward procedure to enhance treatment compliance have been added to treatment. Implemented in 8, structured 60-90 minute sessions over 10 weeks, this comprehensive behavioural intervention for tics (CBIT)<sup>151</sup> was tested through two large

randomised controlled trials<sup>89,152</sup>. Both studies compared CBIT to a psychoeducation and supportive therapy control condition. Children with GTS who received CBIT showed significant improvements in tics and tic-related impairment at the end of acute-phase treatment relative to those receiving supportive therapy. 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<sup>89</sup>. Wilhelm and colleagues studied adults with GTS and found that those receiving CBIT demonstrated significant reductions in tics and tic-related impairment at the end of acute-phase treatment relative to supportive therapy. Gains were maintained for post-treatment responders at the 6-month follow-up<sup>152</sup>. In both studies, adverse events were tracked, and none were associated with CBIT. Based largely on these two large studies, CBIT has been recommended as a first-line treatment for those with GTS in multiple practice guidelines<sup>153-155</sup>.

Researchers have attempted to effectively disseminate CBIT. CBIT delivered via teleconferencing devices have been shown to be as effective as face-to-face delivery<sup>156</sup>, and CBIT has also been shown to be effectively delivered via Skype<sup>157</sup>, and in abbreviated format as delivered by nurse practitioners<sup>158</sup>.

The mechanisms by which CBIT is effective are unclear, but suggested processes include improved motoric inhibition and habituation to the aversive premonitory urge. Nevertheless, few studies exist that have adequately tested these hypotheses<sup>159,160</sup>.

CBIT is the most well-studied behavioural treatment, but exposure and response prevention<sup>161</sup> and cognitive physiological therapy<sup>162</sup> appear promising in pilot tests.

5c. Surgery (Deep Brain Stimulation) (suggested 350 words, is 403 words, 6 additional refs) Marwan Hariz

### ***Thoughts for Marwan***

- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section, you would need to do 1 only (30 to 50 words is ideal and 70 words maximum).*

A survey of PubMed (June 18, 2016) on Deep Brain Stimulation (DBS) and GTS yielded 232 publications, far more than the number of published patients who have undergone DBS. Vandewalle, who pioneered DBS for GTS in 1999, recently noted that “DBS has emerged as an established effective and safe treatment option for a small subset of patients with severe GTS...”<sup>163</sup>. She also highlighted, however, the paucity of evidence-based publications (5 reports on a total of 32 patients worldwide), the heterogeneity of results, and the lack of consensus on “best” brain target, all of which point to the fact that DBS for GTS remains anything but “established”. Deeb and colleagues documented recently the International GTS DBS registry, totalling 157 patients to date: of these 58.5% had DBS in the thalamus and 39% in the GPi<sup>164</sup>.

Some of the issues surrounding DBS in GTS are related to the small number of patients who would actually “require” surgery (as reflected in the great difficulty to recruit “suitable” patients for DBS trials) and to the syndrome itself, such as the young age of most patients, the waxing and waning course, the variability in GTS phenotypes and comorbidities.

Numerous issues contribute to the difficulty in deciding which of the hitherto nine trialled brain targets<sup>165,166</sup> within the basal ganglia thalamo-cortical circuitries of GTS disorders (which involve motor networks for tics and limbic-associative ones for comorbidities), is the “best” target for DBS, and little is known concerning the predictive selection criteria for efficacy of DBS for both tics and/or psychiatric comorbidities and co-existent behaviours and psychopathologies. Additionally, it is documented that the rate of infection of DBS hardware seems increased in patients with GTS patients<sup>167,168</sup>. Whether this is due to tic-related behaviours and comorbidity (e.g., picking at wound), or distinct immunological profiles remains unclear<sup>168</sup>.

The recent initiative of the Tourette Association of America to launch an international GTS DBS registry and database to share data, uncover best practices, improve outcomes, and to provide information to regulatory agencies, is a step in the right direction<sup>164</sup>. Despite 17 years of surgery for GTS, there is still no consensus about the best brain target for DBS, and this procedure remains investigational, and is still far from “established”, although it may be legitimate to offer DBS to patients where other options have been exhausted, especially in patients in whom the severity of refractory motor tics threatens their life or risks inducing irreversible neurological deficit<sup>167</sup>.

6. *Quality of Life* [suggested 500 words, is 499 words – 17 additional refs] Valsamma Eapen and Rudi Črnčec

***Thoughts for Valsa and Rudi***

- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance” (70 words would be a long annotation).*
- *Need to reconcile this with any comments on QoL MMR makes in 4b. Comorbidity and co-existent psychopathology: MMR I have reduced mine - BUT more to go - but yours has increased to 586 as I moved some of my QoL text to your section*

Elstner and colleagues<sup>169</sup> first observed in 2001 that patients with GTS had lower Quality of Life (QoL) than the general population and patients with epilepsy. Consistent with the idea that GTS is *more* than having motor and vocal tics, subsequent studies have highlighted the compounding effect of a number of factors in reducing QoL<sup>170</sup>. In addition to tic severity and the presence of coprophenomena, these factors include associated clinical features such as self-injurious behaviours, non-obscene socially inappropriate behaviours, and social difficulties; co-morbidity with OCD/OCB and ADHD; and co-existing psychopathologies including depression, and drug and alcohol use. As expected, it has recently been reported that patients with "Pure GTS" have higher QoL than GTS-Plus-Co-morbidities groups<sup>123, 124</sup>. In multiple regression analysis, the number of comorbid/co-existent diagnoses and the presence of coprophenomena emerged as significant predictors of poorer QoL<sup>123</sup>. Meta-analysis has suggested that factors affecting QoL may vary across the lifespan, with tic severity, ADHD, and OCD particularly associated with lower QoL in children, whereas in adults anxiety and depression become increasingly relevant<sup>170,171</sup>. . Another study<sup>125</sup> reporting on young individuals with GTS found self-reported strong associations between comorbidity and decreased global QoL, increased emotional symptomatology, impaired emotional and school functioning as well as impaired social functioning and peer relationships. The primary care-givers of the youth with GTS separately reported that the youngsters experienced lower QoL, increased emotional, behavioural and social difficulties, and elevated rates of insecure peer attachment relative to controls<sup>126</sup>.

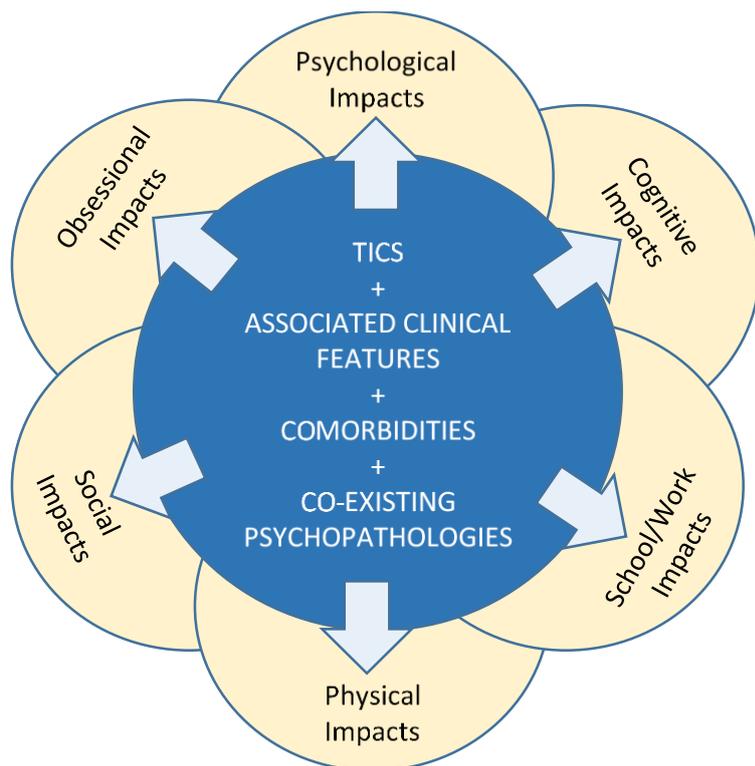
Patients may develop coping strategies over time to manage difficulties that are prominent in childhood, which may also moderate with age, only to then be confronted with

new challenges into adulthood. There are also likely to be reciprocal QoL effects upon parents and family members, although these are presently less well understood<sup>172</sup>.

A number of quality of life domains are impacted, including psychological, obsessional, social, physical, school/work-based, and cognitive<sup>173</sup>. As a consequence to these, psychological distress, frustration, and depression are commonly experienced by patients with GTS<sup>121,174</sup>, and there is mounting evidence that depression exerts a powerful negative effect upon QoL<sup>175,176</sup>. Depressed mood and low QoL may be outcomes of the heavy psychosocial burden that can be experienced over time<sup>177</sup>. OCD/OCB also contributes to this psychosocial burden, and there is evidence that obsessionalism and perfectionism may make the process of adapting to a life with tics more difficult. Social skills difficulties and poor peer relationships are common in GTS<sup>178-181</sup>, as are the additional difficulties of dealing with stigma and bullying. Severe tics can result in physical pain and injuries<sup>182</sup> as well as in difficulties with activities of daily living, including exercise<sup>183</sup>. School-based problems including academic problems, especially in the context of ADHD, have been noted in a number of studies - which underscore the importance of teacher knowledge, understanding and flexibility. Reduced concentration and inability to complete important tasks encompass cognitive aspects of QoL. Finally, while age-dependent improvement of comorbid ADHD seems likely to have a significant impact on cognitive functioning<sup>128</sup>, results from the Tourette Syndrome Impact Survey study highlighted a significant correlation between tic severity and cognitive domain scores<sup>182</sup>.

Thus, there are multiple pathways to negative impacts on QoL in patients with GTS, with these often co-occurring in an additive manner (see Figure **XXXXXX**). As a subjective marker of well-being, QoL has emerged during the past 15 years as an important component in understanding the experience of patients with GTS, and as a key assessment and treatment target in its own right. Several GTS-specific tools have been developed that will facilitate the incorporation of QoL into research studies and clinical practice<sup>184,185</sup>.

Figure XXXXX. Stylised depiction of Quality of Life domains affected in GTS



## 7. Outlook

7a. Genetics (suggested 500 words, is 502 words, 21 additional refs) Jeremiah and Carol

### ***Thoughts for Jeremiah and Carol***

- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section one or two would suffice (30 to 50 words is ideal, 70 words maximum).*

The field of GTS genetics is poised for an upsurge in discovery of definitive GTS susceptibility genes in the next five years. The most recent GWAS, CNV and sequencing studies have each indicated the presence of a significant number of GTS genetic risk variants in aggregate, and current sample sizes are approaching those at which other polygenic disorders, such as schizophrenia and height, began to identify individual genes with certainty<sup>186,187</sup>. Based on the trajectory of gene discovery in those disorders, there is strong evidence for the presence of a GWAS “inflection point”, corresponding to the sample size (~10,000 cases for schizophrenia) at which a study is adequately powered to identify any one of possibly hundreds of small-effect, polygenic risk variants<sup>186</sup>. While GWAS below this

sample size have minimal power to identify definitive disease loci, once the "inflection point" is reached, new gene discovery takes on a linear relationship with sample size, resulting in ~1-4 new genes for every 1000 additional cases. Parallel accelerations in disease gene discovery for CNVs and de novo, gene-disrupting coding mutations also have been observed, suggesting that large-scale, rare variant discovery efforts will be equally successful<sup>188,189</sup>. 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 harmonised phenotypic assessments and established pre-publication data sharing and joint meta-analyses<sup>53,65</sup>. For sample collection, multiple strategies are being pursued, including leveraging of data-rich electronic health records linked to biobanks<sup>190</sup>, identifying cases among population registry studies with available DNA<sup>191</sup> and development of validated, internet-based assessments combined with local biospecimen collection to bring sample collection to subjects, rather than focusing on collections limited to academic medical centres with GTS specialty clinics<sup>192,193</sup>. In fact, the NIMH Strategic Plan identified GTS as a priority disorder for expansion of DNA (Strategy 1.2, Priority A.4<sup>194</sup>).

Once GTS susceptibility variants are identified, the often-discussed challenge of transitioning from genes to biology will benefit greatly from technologic advances in systems biology and international efforts to generate large-scale, publically available gene expression and epigenomic datasets from multiple mouse and human brain regions across different neurodevelopmental time points<sup>195-197</sup>. These spatiotemporal maps of gene activity and gene regulation will be instrumental in pinpointing the specific brain region(s) and critical periods where susceptibility genes influence GTS pathophysiology at the molecular level<sup>198,199</sup>. In parallel, collaborations in the field of neuro-imaging genetics (the largest example of which is the ENIGMA Consortium) will facilitate integration of GTS genetics with systems neuroscience to uncover underlying GTS biology at the neural circuit level<sup>200,201</sup>.

A third strategy already in progress is to leverage data from related neuropsychiatric disorders to identify gene variants in common across these disorders<sup>202,203</sup>. The Psychiatric Genomics Consortium (PGC) has led the field in this work<sup>204,205</sup> 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, neuro-imaging and treatment studies by addressing phenotypic heterogeneity and comorbidity<sup>206</sup>.

7b. General (suggested 500 words, is 500 words, 3 additional refs) Valsamma Eapen

***Thoughts for Valsa***

- *Note that the author guidelines ask that we “annotate 2–3 references from each main section describing why these papers are of particular importance”. In this section one or two would suffice (70 words would be a long annotation).*

As described above, unprecedented opportunities currently exist in unravelling the etiopathogenesis of GTS through concerted international efforts but at this point we have limited understanding of the pathophysiology with unresolved questions on what constitute GTS phenotypes, and the modulators of phenotypic variability. While genetic factors further modified by gender and a number of non-genetic factors, or ‘second hits’ (e.g. prematurity, perinatal trauma/injury/hypoxia, oxidative stress, infections/inflammations/autoimmunity, neural and psychosocial stressors) have all been implicated in the pathogenesis<sup>36-38</sup>, these are not unique to GTS and are shared by a number of neurodevelopmental disorders (NDs). In this regard, a common association exists between GTS and other NDs including autism through neurodevelopmental genes such as the neurexin superfamily genes (e.g. neurexins and neuroligins) and the neurexin trans-synaptic connexus (NTSC) which regulates behaviour control<sup>207</sup>. Consequently dysregulation of the relevant genes can render varying pathogenic consequences for brain, mind, and behavior<sup>208</sup> resulting in a wide range of phenotypic presentations characteristic of GTS, Autism, ADHD, OCD etc. Cross disorder analysis examining genetic determinants to endophenotypic (e.g. neuroimaging) and clinical phenotypic characteristics in these NDs is expected to ultimately clarify the overlaps and delineations in the pathogenesis.

Although the precise pathophysiological basis of GTS remains unresolved, there is converging evidence to suggest involvement of the CSTC circuitry that mediates the integration of movement, sensation, emotion and attention, and the dopamine system that regulates the motor circuitry<sup>16</sup>. While the dopamine model has gained much attention through clinical treatment studies, recent research including preclinical studies and post-mortem findings have highlighted the role of careful calibration of the excitatory–inhibitory balance through glutamate and GABA in conjunction with other neurotransmitter systems as described earlier. Further, animal studies could assist in

informing the impact of specific genetic and epigenetic influences on molecular pathways and cellular development/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 (a number of such agents are currently under trial)<sup>148</sup> while neurophysiological studies will unravel the mechanism of action in brain stimulation techniques such as transcranial magnetic stimulation (rTMS)<sup>209</sup> and transcranial Direct Current Stimulation (tDCS) (Clinical Trial: ACTRN12615000592549).

Animal models of tic generation and the impact of modulating factors such as stress and infections will help elucidate the complex interplay between genetic, environmental (e.g. pre- and peri-natal) and neuroimmunological risk factors, which affect the phenotype and outcome. Further, gene-by-environment and epigenetic studies will provide valuable clues to the GTS pathophysiology.

From a clinical and epidemiological perspective, it is important to reconcile the wide variations in prevalence rates ranging from 0.25% - 5.7%<sup>3</sup> consequent to the varying methodology, changing diagnostic criteria over the years and the use of different assessment schedules in different studies which has made both comparison and pooling of data difficult. 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.

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