

REVIEW ARTICLE**Tourette syndrome: a disorder of the social decision-making network****Roger L. Albin**^{1,2,3}

Tourette syndrome is a common neurodevelopmental disorder defined by characteristic involuntary movements, tics, with both motor and phonic components. Tourette syndrome is usually conceptualized as a basal ganglia disorder, with an emphasis on striatal dysfunction. While considerable evidence is consistent with these concepts, imaging data suggest diffuse functional and structural abnormalities in Tourette syndrome brain. Tourette syndrome exhibits features that are difficult to explain solely based on basal ganglia circuit dysfunctions. These features include the natural history of tic expression, with typical onset of tics around ages 5 to 7 years and exacerbation during the peri-pubertal years, marked sex disparity with higher male prevalence, and the characteristic distribution of tics. The latter are usually repetitive, somewhat stereotyped involuntary eye, facial and head movements, and phonations. A major functional role of eye, face, and head movements is social signalling. Prior work in social neuroscience identified a phylogenetically conserved network of sexually dimorphic subcortical nuclei, the Social Behaviour Network, mediating many social behaviours. Social behaviour network function is modulated developmentally by gonadal steroids and social behaviour network outputs are stereotyped sex and species specific behaviours. In 2011 O’Connell and Hofmann proposed that the social behaviour network interdigitates with the basal ganglia to form a greater network, the social decision-making network. The social decision-making network may have two functionally complementary limbs: the basal ganglia component responsible for evaluation of socially relevant stimuli and actions with the social behaviour network component responsible for the performance of social acts. Social decision-making network dysfunction can explain major features of the neurobiology of Tourette syndrome. Tourette syndrome may be a disorder of social communication resulting from developmental abnormalities at several levels of the social decision-making network. The social decision-making network dysfunction hypothesis suggests new avenues for research in Tourette syndrome and new potential therapeutic targets.

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Abbreviations: BNST = bed nucleus of the stria terminalis; MPOA = medial preoptic area; PAG = periaqueductal grey; SBN = social behaviour network; SDM = social decision-making network; VMH = ventromedial hypothalamus; VTA = ventral tegmental area

Introduction

Tourette syndrome is a common neurodevelopmental disorder defined by characteristic involuntary movements and

vocalizations, tics, accompanied frequently by specific comorbid behavioural syndromes (Robertson, 2000, 2012, 2014; Jankovic, 2001a; Ganos, 2016; Robertson *et al.*, 2017). The emergence of involuntary movements,

vocalizations and subsequent natural history of Tourette syndrome follows a predictable pattern in the first two to three decades of life, suggesting that Tourette syndrome results from altered brain development trajectories. Discussions of brain system abnormalities underlying Tourette syndrome are dominated by speculations that basal ganglia abnormalities underlie the pathophysiology of Tourette syndrome (Albin, 2006; Albin and Mink, 2006; Felling and Singer, 2011; Ganos *et al.*, 2013; Tremblay *et al.*, 2015; Worbe *et al.*, 2015b; Yael *et al.*, 2015; Ganos, 2016). This concept is based on the response of tics to treatment with dopamine antagonists, the occurrence of tics in diseases with unequivocal striatal pathology, evidence from structural and functional imaging studies implicating basal ganglia associated circuits (see below), and a persuasive conceptualization of tics as a form of habits gone awry. Habit formation and maintenance are strongly implicated as primary functions of basal ganglia circuits (Yin and Knowlton, 2006; Smith and Graybiel, 2016). Basal ganglia circuits may be particularly important in assembling individual stimulus-response associations into more complex behavioural sequences that are executed as units. Dysregulation of this ‘chunking’ function is a plausible substrate for complex tics and obsessive compulsive behaviours (Smith and Graybiel, 2016).

Recent application of imaging methods in Tourette syndrome research disclosed evidence of widespread morphologic and functional changes in the CNS of Tourette syndrome subjects (see below), suggesting alternate hypotheses about the systems involved in Tourette syndrome. Abnormalities of neocortical development and/or function are suggested by some of these studies, a plausible hypothesis underpinned by the concept that an important function of some neocortical regions is to provide inhibitory control (Ganos *et al.*, 2013; Worbe *et al.*, 2015b; Yael *et al.*, 2015).

These attractive and well supported ideas about the neurobiology of Tourette syndrome do not, however, account for some of the most conspicuous features of Tourette syndrome, specifically the marked sex disparity in Tourette syndrome prevalence, the natural history of the emergence and variation in tic severity, and the characteristic phenomenology of most tics. Recent developments in apparently unrelated areas of neuroscience related to sociality and emotion suggest additional brain systems that may be developmentally altered in Tourette syndrome. Here I explore the possibility that Tourette syndrome is characterized by abnormalities in a recently proposed brain system implicated in crucial aspects of social behaviour, the social decision-making network (SDM).

Tourette syndrome

Motor and phonic tics are repetitive, relatively stereotyped involuntary movements, usually brief in duration. Tics may be simple or complex. Simple tics are brief, meaningless movements, often involving a single muscle group.

Complex tics are slower, and may involve apparently coordinated movements or vocalizations. Some simple tics (‘dystonic tics’) are more sustained. The relatively stereotyped character of tics differentiates tics from the random movements of the chorea-athetosis-ballism spectrum and most forms of myoclonus. Tics are generally not as rapid as typical myoclonus. Motor tics have a characteristic anatomic distribution. While truncal and limb tics are seen in clinical practice, there is a rostrocaudal gradient of tic expression with the majority of motor tics involving eye, facial, neck, and shoulder movements. Eye blinking, eye rolling, grimacing, nares flaring, and other facial movements are common motor tics, as are shoulder shrugging and stereotyped head-neck movements. Typical phonic tics include repetitive snorting, sniffing, throat-clearing, and coughing. Complex tics resemble organized movements and vocalizations, of which the most famous, albeit rare, example is coprolalia. Many tics are accompanied by characteristic subjective experiences with Tourette syndrome patients reporting a sense of discomfort, often in the affected region, relieved by tic performance. Some Tourette syndrome patients report an element of compulsion with their tics. Tics can typically be suppressed temporarily with conscious effort. Tic expression is modulated commonly by attentional loading; Tourette syndrome patients concentrating intently on a task often experience a decline in tics during task performance.

Tics are a common phenomenon, generally with onset in childhood, and often transient. Adult-onset tics are rare. Some individuals may have just a single persistent tic and some individuals exhibit only motor tics. When both motor and phonic tics are present, onset is below the age of 18 years, and tics are sustained for a period of longer than 1 year, Tourette syndrome is the diagnosis. Recent estimates highlight the relatively high prevalence of Tourette syndrome in children with epidemiology studies converging on estimates of 0.5% to 1.0% of children exhibiting Tourette syndrome. Estimated prevalence of Tourette syndrome among adults is much lower, by approximately a factor of 10, reflecting the distinctive natural history of Tourette syndrome (see below). Tourette syndrome exhibits a marked sex bias; the ratio of male to female Tourette syndrome patients is ~3–4:1 (Knight *et al.*, 2012; Scharf *et al.*, 2015; Yang *et al.*, 2016).

Tourette syndrome is accompanied frequently by comorbid psychiatric disorders, which may lead to more distress and disability than tics. Attention deficit hyperactivity disorder is common in Tourette syndrome, as are anxiety disorders. Many Tourette syndrome patients exhibit obsessive compulsive behaviours, often arising to the level of obsessive compulsive disorder (Hirschtritt *et al.*, 2015). It is plausible to view simple tics and complex obsessions as opposite poles of a spectrum with compulsive behaviours occupying the middle of the spectrum. Differentiating complex tics from compulsions can be difficult (Worbe *et al.*, 2010a).

Tics usually first manifest around the ages of 5 to 7 years. Tics generally fluctuate significantly in severity,

distribution, and character. A common experience is for a child to exhibit one or more types of tics for weeks to months, with the specific tic type subsiding and replaced by another type of tic. Tic severity tends to peak between the ages of 10–14. Many Tourette syndrome patients subsequently experience declines in tic severity with some individuals experiencing tic remission as they enter adulthood. This relatively benign natural history accounts for lower prevalence of Tourette syndrome adults.

Tourette syndrome has a strongly heritable component. A high fraction of Tourette syndrome patients have a first degree relative with Tourette syndrome or tics. Efforts to define specific gene mutations associated with Tourette syndrome have been frustrating. Several large-scale association studies did not identify loci with strong connections to Tourette syndrome, indicating complex polygenic inheritance (Davis *et al.*, 2013; Scharf *et al.*, 2013; McGrath *et al.*, 2014; Paschou *et al.*, 2014; Yu *et al.*, 2015; Bertelsen *et al.*, 2016). Willsey *et al.* (2017) used whole exome sequencing and the strategy of studying ‘trios’ comprising an affected Tourette syndrome subject and unaffected parents to identify possible *de novo* coding variants associated with Tourette syndrome. Willsey *et al.* (2017) describe an excess of likely gene disrupting mutations associated with Tourette syndrome and identified four candidate genes. Rare pedigrees with apparent monogenic inheritance of Tourette syndrome were identified, most recently a family with a mutation in the gene encoding histidine decarboxylase (*HDC*) (Verkerk *et al.*, 2003; Ercan-Sencicek *et al.*, 2010; Lei *et al.*, 2012; Karagiannidis *et al.*, 2013; Dong *et al.*, 2016). Further study of these genes may yield clues about the pathophysiology of more common forms of Tourette syndrome.

Treatment options for Tourette syndrome are limited. Dopamine antagonist agents will reduce tics, though usually not completely at clinically tolerated doses. Use of dopamine antagonists carries the risk of significant side effects including sedation, impaired cognition, cardiac arrhythmias, weight gain, and tardive movement disorders (Pringsheim *et al.*, 2012). The monoamine depleting agent tetrabenazine, thought to have no risk of inducing tardive movement disorders, can be used. Side effects of reducing monoaminergic neurotransmission can limit clinical utility of this agent (Chen *et al.*, 2012). α_2 -Adrenergic agonists such as clonidine and guanfacine are used in clinical practice and exhibit modest efficacy but generally good tolerability (Pringsheim *et al.*, 2012). Behavioural interventions may play a larger role in treatment of Tourette syndrome. Solid trial data indicate that habit reversal therapy is useful for particularly bothersome tics (Piacentini *et al.*, 2010). An extension of habit reversal therapy, the Comprehensive Behavioural Intervention for Tics, incorporating additional behavioural interventions, is effective in Tourette syndrome (Whittington *et al.*, 2016). Appropriate behavioural interventions and psychiatric care, which may involve other classes of medications, are important for treating significant behavioural comorbidities. Some patients exhibit disabling

tics for which conventional medical and behavioural therapies are inadequate. These unfortunate individuals often exhibit disabling behavioural co-morbidities (Cheung *et al.*, 2007). For this population, deep brain stimulation (DBS) surgery may be a useful option (Schrock *et al.*, 2015). Many children with Tourette syndrome exhibit mild-to-moderate tics and manageable behavioural co-morbidities. Education and reassurance of family and school personnel is often sufficient. A supportive family and social environment is often the best treatment for Tourette syndrome, particularly in view of the often relatively benign natural history.

Basal ganglia changes and function in Tourette syndrome

Post-mortem, genetic and animal model studies

Efforts to understand the pathophysiology of Tourette syndrome are handicapped by the absence of gross pathologic changes in either the small number of autopsied brains or in routine imaging studies. The observation that dopamine antagonists ameliorate tics focused speculation about Tourette syndrome pathophysiology on the basal ganglia and specifically on the striatum. Additional lines of evidence support the concept that abnormalities of basal ganglia circuits are involved in Tourette syndrome pathophysiology. Tics are common in Huntington’s disease and other disorders with unequivocal striatal pathology (Jankovic, 2001*b*). In careful analyses of a small number of post-mortem Tourette syndrome brain specimens, Vaccarino’s group described changes of both pallidal and striatal neurons (Kalanithi *et al.*, 2005; Kataoka *et al.*, 2010; Lenington *et al.*, 2016). Tourette syndrome brains exhibited reduced numbers of neurons in the external segment of the globus pallidus with a corresponding increase in the number of internal segment pallidal neurons (Kalanithi *et al.*, 2005). In the same analysis, the number of striatal parvalbumin-immunoreactive interneurons was found to be reduced. In a subsequent analysis, both parvalbumin-immunoreactive and cholinergic striatal interneurons were reported as reduced in Tourette syndrome (Kataoka *et al.*, 2010). Vaccarino and colleagues made the interesting suggestion that these changes were due to a neuronal migration defect during brain development. Because of, presumably, a paucity of suitable post-mortem material, these observations are not yet replicated.

Recently developed PET methods allow *in vivo* quantification of cholinergic terminal density by measuring regional vesicular acetylcholine transporter expression with ^{18}F -fluoroethoxybenzovesamicol (^{18}F -FEOBV; Petrou *et al.*, 2014). Striatal ^{18}F -FEOBV binding is not different

between Tourette syndrome and control subjects, strongly suggesting normal striatal cholinergic neuron density in Tourette syndrome (Albin *et al.*, 2017). The prior post-mortem report of diminished striatal cholinergic interneurons may reflect post-mortem changes, agonal effects, and/or medication effects (Albin *et al.*, 2017).

The paucity of specific genes associated with Tourette syndrome inhibited efforts to develop animal models that might provide insight into the pathophysiology of Tourette syndrome. Information from a small number of models is consistent with basal ganglia dysfunction in Tourette syndrome. Verkerk *et al.* (2003) described a pedigree with Tourette syndrome and complex chromosomal rearrangements leading to loss of contactin-associated protein 2 (*CNTNAP2*), a member of the neurexin superfamily of transmembrane proteins. *CNTNAP2* knockout mice manifest neuronal migration abnormalities, including reduced striatal parvalbumin containing interneurons (Peñagarikano *et al.*, 2011). This line exhibits increased repetitive behaviours, including increasing grooming, reduced by dopamine antagonist treatment. Ercan-Sencicek *et al.* (2010) reported a pedigree in which tic occurrence is associated with *HDC* mutations. Affected individuals exhibit other abnormal features, including abnormal oropharyngeal anatomy and some cardiovascular abnormalities. *HDC* is responsible for the synthesis of histamine, the neurotransmitter of widely ramifying tuberomammillary neurons. These projections innervate the striatum and modulate dopaminergic neurotransmission. *HDC* knockout mice exhibit exacerbation of stereotyped behaviours and increased striatal dopamine release after stimulant treatments (Castellan Baldan *et al.*, 2014). A potential problem with the paradigm of amphetamine induced stereotypies is that it may not mimic natural behavioural sequences such as grooming, weakening their relevance to Tourette syndrome (Berridge and Aldridge, 2000). Subsequent work with *HDC* knockout mice showed that this line exhibits excessive grooming under some stressful conditions, consistent with Tourette syndrome-related phenomena (Xu *et al.*, 2015a).

There were also efforts to model Tourette syndrome in mice by duplicating the changes in striatal interneuron populations described by Kataoka *et al.* (2010), including selective depletion of striatal cholinergic interneurons (Xu *et al.*, 2015b; Martos *et al.*, 2017), parvalbumin-immunoreactive neurons (Xu *et al.*, 2016), and combined depletion of striatal cholinergic and parvalbumin-immunoreactive neurons (Rapanelli *et al.*, 2017). The *in vivo* imaging evidence for preserved striatal cholinergic interneurons (Albin *et al.*, 2017) in Tourette syndrome subjects mentioned above undermines the relevance of models based on depletion of striatal cholinergic interneurons. These modelling experiments have implications for efforts to model Tourette syndrome in mice. These models have behavioural phenotypes and as they apparently result from striatal changes not found in Tourette syndrome, these behavioural assays may not be appropriate tools for evaluating putative Tourette syndrome models. In these experiments, striatal

cholinergic interneuron depletion was performed in adult mice. Selective depletion of dorsal striatal cholinergic interneurons during brain development produces a markedly different phenotype (Pappas *et al.*, 2015). Lesioning adult brain may not be appropriate for modelling a neurodevelopmental disorder such as Tourette syndrome.

Several non-human primate experiments support a key role for basal ganglia dysfunction in tic pathophysiology (François *et al.*, 2004; Grabli *et al.*, 2004; Worbe *et al.*, 2009, 2011, 2013; Bronfeld *et al.*, 2011, 2013a, b; McCairn *et al.*, 2009, 2013, 2016; Godar *et al.*, 2014; Israelashvili and Bar-Gad, 2015). Focal inhibition of striatal and external pallidal neurons by localized injections of the GABA-A receptor antagonist bicuculline produce involuntary movements and behavioural abnormalities consistent with tics and other phenomena characteristic of Tourette syndrome. Depending on the location of injection, these involuntary movements range from simple movements to complex behavioural sequences including stereotyped behaviours mimicking normal grooming behaviours. Involuntary movements following focal inhibition of neurons in the sensorimotor territories of the putamen are described as particularly faithful tic mimics. Vocal tics are reported to follow focal inhibition of nucleus accumbens neurons. The distinct involuntary movements and vocalizations following focal inhibition of different subregions of the striatum and pallidum reflect the anatomic and functional segregation of parallel specialized circuits that course through the basal ganglia (Alexander *et al.*, 1986), a function of the topographic organization of corticostriate projections (Kemp and Powell, 1970). One study using similar approaches in rats reported similar phenomena with intrastriatal bicuculline injections (Bronfeld *et al.*, 2013a, b).

Another potentially relevant rodent behavioural model implicating striatal dysfunction is grooming chains (Kalueff *et al.*, 2016). Rodents groom in multi-component, relatively stereotyped behavioural sequences. Individual components of grooming chains appear to be ‘hardwired’ into lower motor centres in brainstem and spinal cord. The dorsal striatum is crucial for appropriate sequencing and completion of grooming chains (Cromwell and Berridge, 1996). The subpopulation of striatal projection (direct pathway) neurons expressing dopamine D1 receptors appears to be particularly important for grooming chain performance with administration of D1 agonists inducing excessive, highly repetitive grooming chains termed super-stereotypy (Berridge and Aldridge, 2000; Taylor *et al.*, 2010). D1 receptor agonist induced super-stereotypy is reduced by concurrent administration of the D2 antagonist haloperidol (Taylor *et al.*, 2010). These findings suggest that dopamine D1 receptors would be logical targets for treatment of tics (Albin and Mink, 2006). Consistent with this prediction, preliminary trial data suggest that tics are reduced by D1 antagonists and functional imaging data suggest increased activity of D1 expressing (direct pathway) striatal projection neurons in Tourette syndrome (Baym *et al.*, 2008; Gilbert *et al.*, 2014).

Clinical experience with DBS for treatment of severe Tourette syndrome is consistent also with basal ganglia circuit dysfunction. Some series report improvement with DBS. The most frequent DBS targets in Tourette syndrome are midline thalamic nuclei strongly interconnected with the basal ganglia, and the internal segment of the globus pallidus.

Imaging results

More direct demonstration of basal ganglia circuit abnormalities comes from application of modern imaging methods, particularly MRI methods. An important point about imaging studies in Tourette syndrome is that this is a confusing literature with papers reporting conflicting findings. Discrepant findings likely occur because of the many difficulties inherent in studying Tourette syndrome subjects. Important confounds include the difficulties of comparing subjects at different phases of brain development, the possibility that detected changes represent plastic adaptations to primary pathologies in Tourette syndrome, and potential effects of medications. Tourette syndrome study populations are heterogeneous, with varying mixtures of potentially relevant comorbidities and differing medication regimens. Recent useful reviews of imaging studies in Tourette syndrome highlight these issues but also provide some clarity about what appear to be abnormalities in Tourette syndrome with a consensus favouring abnormalities of basal ganglia structure and connectivity (Plessen *et al.*, 2009; Felling and Singer, 2011; Neuner *et al.*, 2013; Church and Schlagger, 2014). One apparently robust result, described best in a relatively large prospective study by Peterson and colleagues (Peterson *et al.*, 2003; Bloch *et al.*, 2005), is decreased caudate nucleus volume. Recent, relatively large morphometry studies in Tourette syndrome and control children, however, did not identify changes in caudate or putamen volumes in Tourette syndrome subjects (Greene *et al.*, 2017; Forde *et al.*, 2017). Greene *et al.* (2017) identified only volume changes in the thalamus, hypothalamus, and midbrain.

Recent structural and functional imaging studies identify changes in basal ganglia structure, connectivity, and function in Tourette syndrome. Worbe and colleagues (2012, 2015a) used MRI tractography and functional connectivity methods to identify abnormalities in connections within the basal ganglia and associated cortices. This group suggests that these abnormalities represent immature and atypical development of these circuits. In a particularly interesting study, this group demonstrated an increased propensity for subjects with Tourette syndrome to develop habits and correlated this tendency with abnormal connectivity of the putamen and supplementary motor cortex (Delorme *et al.*, 2016). Other work supports abnormalities of basal ganglia circuit connections in Tourette syndrome and a recent study of brain control networks in Tourette syndrome also suggests immature development of these circuits (Church *et al.*, 2009; Makki *et al.*, 2009). A number of

functional imaging studies of tic generation and suppression are consistent with basal ganglia circuit abnormalities in Tourette syndrome (Peterson *et al.*, 1998; Wang *et al.*, 2011; Neuner *et al.*, 2014).

Studies in both Tourette syndrome children and adults describe thinner cortices in several regions, though some studies report increased regional cortical thickness, with suggestions that these are compensatory changes (Sowell *et al.*, 2008; Draganski *et al.*, 2010; Fahim *et al.*, 2010; Muellner *et al.*, 2015). Worbe *et al.* (2010b) suggest that differing patterns of cortical thinning correlate with Tourette syndrome subtypes. These structural studies are complemented by data suggesting abnormalities of cortical function in Tourette syndrome (Bohlhalter *et al.*, 2006; Tinaz *et al.*, 2014; Martín-Rodríguez *et al.*, 2015).

Other work describes structural and functional changes in yet more regions, including the thalamus, amygdala, midbrain, and cerebellum (Garraux *et al.*, 2006; Peterson *et al.*, 2007; Ludolph *et al.*, 2008; Makki *et al.*, 2008; Miller *et al.*, 2010; Neuner *et al.*, 2010a; Tobe *et al.*, 2010; Werner *et al.*, 2011). A recent molecular imaging study of GABA-A receptor binding sites suggests widespread changes in GABA-A receptor expression in Tourette syndrome, including the ventral striatum, globus pallidus, thalamus, amygdala, cerebellum, some cortices, substantia nigra, and periaqueductal grey (PAG) (Lerner *et al.*, 2012). The cumulative results of imaging studies suggest widespread developmental abnormalities in Tourette syndrome. This inference suggests that alterations in previously unexamined regions may be important in Tourette syndrome pathophysiology.

What basal ganglia dysfunction does not explain

There is convergent evidence for basal ganglia circuit abnormalities in Tourette syndrome, but there is no obvious way to connect basal ganglia circuit abnormalities with several salient features of Tourette syndrome. What accounts for the natural history of Tourette syndrome with the emergence of tics around ages 5 to 7 years and the subsequent peri-pubertal exacerbation? Why the marked sex disparity in prevalence? What accounts for the specific character of tics—specifically the expression of tics as eye movements, facial movements, head and neck movements, and involuntary phonations? A satisfactory account of the neurobiology of Tourette syndrome should account for the following cardinal features: (i) the characteristic distribution of tics with preferential expression of involuntary eye, facial, head, and shoulder movements; (ii) the presence and character of involuntary phonations; (iii) the stereotyped character of tics; (iv) the natural history of tic expression with tic emergence around ages 5 to 7 years and peri-pubertal exacerbation; (v) the sex disparity with male

predominance of tic expression; and (vi) an important role for basal ganglia circuitry.

A successful account would also explain some other features of Tourette syndrome including: (i) the moderation of tic expression by task performance; and (ii) the high frequency of anxiety disorders in Tourette syndrome.

Unexplained cardinal features as clues to neurobiology of Tourette syndrome

While explaining these features of Tourette syndrome is challenging, they also provide clues suggesting an expanded view of Tourette syndrome neurobiology. A useful starting point is to consider one of the primary functions of eye, facial, and head movements—conspecific social signalling. A major, perhaps the major, function of these movements is non-verbal communication between conspecifics, particularly of emotional states. As demonstrated by psychologist Paul Ekman (2015), this aspect of non-verbal communication is both important and universal among humans. The use and interpretation of facial expressions, including eye position, is remarkably uniform across all cultures. This is likely also true of movements involving head position and shoulder movements, which contribute to aspects of emotional body language (de Gelder, 2015). Darwin (2009) famously argued that many of these aspects of non-verbal communication are not only universal among humans, but also phylogenetically conserved across a broad range of species. The concept that tics are distorted social signals explains why Tourette syndrome and related tic syndromes are perceived as disorders (Davis *et al.*, 2004). Motor tics introduce confusion into an important and largely subliminal channel for social communication. The same is obviously true for involuntary phonations. A corollary of the concept that Tourette syndrome involves dysfunctional inter-conspecific social communication is that Tourette syndrome subjects should manifest abnormal social perceptions and socially inappropriate behaviours in addition to the disordered social signalling of tics. Emerging evidence indicates that this is the case, with research documenting altered social cognition, social disinhibition, and a phenomenon called non-obscene socially inappropriate symptoms (NOSIS) in subjects with Tourette syndrome (Kurlan *et al.*, 1996; Channon *et al.*, 2003, 2004, 2012; Eddy and Cavanna, 2013*a, b*; Hirschtritt *et al.*, 2016). In their useful review of altered social cognition in Tourette syndrome, Eddy and Cavanna (2013*b*) offer the interesting interpretation that differences in performance on social cognitive tasks between Tourette syndrome and controls reflect inappropriate responses to social information.

Another clue follows from the period of tic onset and the peri-pubertal exacerbation of tics. These features suggest

involvement of systems influenced by gonadal steroids, particularly androgens, as suggested some years ago by Cohen and colleagues (Peterson *et al.*, 1992, 1994; Alexander and Peterson, 2004; Bortolato *et al.*, 2013; Martino *et al.*, 2013). An important role of androgens in the expression of tics is consistent with average tic onset around the ages of 5–7. This is approximately the period of the onset of adrenarche, when the development of the adrenal zona reticularis results in increasing production of the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulphate (Auchus, 2011; Conley *et al.*, 2012). Peri-pubertal exacerbation of tics has obvious correlations with rising gonadal steroid levels, including androgens. Dynamic changes in brain systems regulating social behaviours during sexual maturation is hardly surprising. Adolescence is a period of social experimentation necessary for the establishment of social independence, a necessary prelude to mating (Crone and Dahl, 2012; Sisk, 2016).

A final clue is the male predominance observed in Tourette syndrome. The marked difference in tic prevalence between sexes suggests developmental abnormalities of sexually dimorphic brain systems.

Aggregation of these clues suggests that we should be looking for a phylogenetically conserved brain system critical to social behaviour, influenced strongly by gonadal steroids, and exhibiting structural and/or functional sex dimorphism.

The social behaviour and the social decision-making networks

Newman (1999) synthesized a large array of behavioural, neurochemical, and anatomic data to propose the existence of a pan-mammalian social behaviour network (SBN; Fig. 1). The SBN consists of a densely interconnected group of subcortical nuclei regulating male and female mating behaviours, aggression, and parental behaviours. A defining feature of all SBN nuclei is expression of high levels of gonadal steroid receptors. SBN components include the medial amygdala-bed nucleus of the stria terminalis (MA-BNST; functionally conjoint structures part of the extended amygdala), the hypothalamic medial preoptic area (MPOA), the anterior hypothalamus, the ventromedial hypothalamus (VMH), the lateral septum, and the mid-brain periaqueductal grey-central grey (PAG). Recent comparative studies describe this system as conserved across all vertebrate phyla (Goodson, 2005; O'Connell and Hofmann, 2011, 2012; Goodson and Kingsbury, 2013). SBN nuclei express relatively high levels of receptors for the nonapeptides oxytocin and arginine vasopressin, recognized as key modulators of social behaviour and social cognition (Donaldson and Young, 2008; Soares *et al.*, 2010; Gabor *et al.*, 2012). The paraventricular hypothalamus (PVH) is a major source of these nonapeptides and

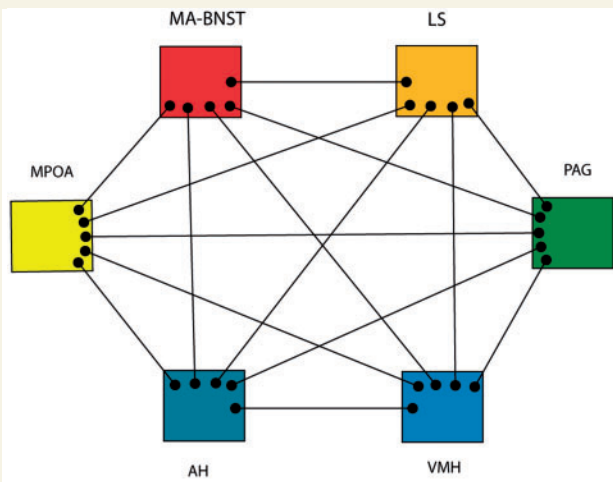


Figure 1 The Social Behaviour Network (SBN). Adapted from Newman (1999). This network mediates a large number of relatively stereotyped social behaviours, is modulated by gonadal steroids, and has sex dimorphic components. The PAG is the main efferent node, driving lower circuits responsible for specific behaviours. AH = anterior hypothalamus; MA = medial amygdala; LS = lateral septum.

densely interconnected with the SBN nuclei identified by Newman (1999). Goodson and Kingsbury (2013) recently suggested classifying the PVH as one of the core nuclei of the SBN. Some of these nuclei also exhibit structural sex dimorphism (for reviews see Simerly, 2002; Dulac and Kimchi, 2007). A key point is that the SBN does not mediate exactly the same behaviours across all species and phyla. Rather, it is a crucial system for the expression and modulation of sex-specific and species-specific social behaviours. The SBN, for example, is critical to the expression of the wide variety of male and female parental behaviours seen in diverse vertebrate groups (Dulac *et al.*, 2014).

Studies of a crucial female rodent sexual behaviour, lordosis, provides a nice example of SBN functions. Lordosis, a relatively complex but stereotyped motor behaviour, is the receptive posture adopted by female rats to facilitate successful sexual intercourse. Appropriate lordosis depends on gonadal steroid effects within the brain with the VMH as the crucial node for oestrogen effects (Harlan *et al.*, 1984). The expression of lordosis depends on projections from the VMH to the PAG with the PAG controlling lower brainstem nuclei responsible for this stereotyped motor behaviour. Stolzenberg and Numan (2011) suggested an analogous pathway for maternal, female sexual, and male sexual behaviours with the MPOA and VMH as key SBN nodes for gonadal steroid action. MPOA/VMH projections to the PAG drive activation of lower circuits that generate these stereotyped behaviours. In a good example of functional sex dimorphism, the same circuit supports markedly different behaviours in male and female rats. In Newman's model (1999), different patterns of activity in the

interconnected SBN nuclei generate differing outputs to the PAG with PAG neurons ultimately driving different downstream effectors. In Tourette syndrome, aberrant PAG activity would result in generation of inappropriate activation of brainstem circuits needed for social signalling via stereotyped eye, face, head movements, and vocalizations (see below).

Recent studies using modern neurobiologic tools such as genetic manipulation and optogenetic stimulation of specific neuron populations within these nuclei confirm that SBN nuclei control a wide array of complex social and relatively stereotyped behaviours involving grooming, aggression, defensive behaviours, social submission, mating behaviours, feeding behaviours, predation behaviours, vocalizations, and parental care behaviours (Sternson, 2013; Lee *et al.*, 2014; Dietrich *et al.*, 2015; Wang *et al.*, 2015; Anderson, 2016; Sakurai *et al.*, 2016; Han *et al.*, 2017). Control of these kinds of social behaviours is complex and depends partly on interactions of different neuronal populations within individual SBN nuclei. Hong *et al.* (2014), for example, describe optogenetic stimulation of a subpopulation of medial amygdala GABAergic neurons as eliciting aggressive behaviour, mating behaviours, and social grooming. Stimulation of closely adjacent medial amygdala glutamatergic neurons, in contrast, produced self-grooming in a non-social context. The functional behaviour of SBN nuclei is strongly influenced by gonadal steroids. Xu *et al.* (2012) demonstrated marked sexual dimorphisms in gonadal steroid regulation of gene expression within mouse SBN nuclei. Genetic manipulation of these gonadal steroid hormone regulated genes markedly altered sex specific social behaviours. Similarly, androgens have sex-specific effects on social behaviours via modulation of different populations of medial amygdala neurons (Unger *et al.*, 2015).

Given considerable empirical data indicating that basal ganglia circuit abnormalities are associated with Tourette syndrome, and a plausible theoretical rationale for suspecting involvement of the SBN in Tourette syndrome, a satisfactory conception of Tourette syndrome neurobiology requires incorporation of both systems into models of Tourette syndrome pathophysiology. In a detailed comparative analysis, O'Connell and Hofmann (2011) proposed the existence of a phylogenetically conserved larger network for adaptive social behaviours; the SDM (Fig. 2). As defined by O'Connell and Hofmann (2011), the SDM consists of much of the basal ganglia circuitry and their connections, with an emphasis on the mesolimbic component of the basal ganglia and including the basolateral amygdala and hippocampal formation, plus the nuclei of the SBN. Key nodes for interactions between the basal ganglia component of the SDM and the SBN component are the lateral septum and the MA-BNST (Fig. 2). In addition to these proposed interaction nodes, there are also significant direct projections from SBN nuclei to midbrain dopaminergic neurons, notably the ventral tegmental area (VTA; Watabe-Uchida *et al.*, 2012; Beier *et al.*, 2015). SBN interactions with the VTA and the ventral striatum

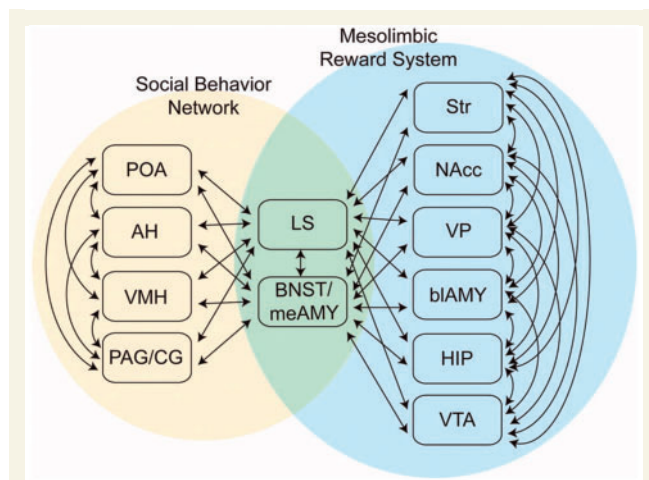


Figure 2 The Social Decision-making Network (SDM).

Reprinted with permission from O'Connell and Hofmann (2011). This network combines crucial basal ganglia circuits with the SBN to form a greater network mediating evaluation of social signals, selection of appropriate social behaviours, and the initiation of relevant social behaviours. This cartoon omits direct projections from SBN hypothalamic nuclei to the VTA. AH = anterior hypothalamus; biAMY = basolateral amygdala; HIP = hippocampal formation; LS = lateral septum; meAMY = medial amygdala; NAcc = nucleus accumbens; PAG/CG = periaqueductal grey/central grey; POA = medial preoptic area; Str = striatum; VP = ventral pallidum.

(including nucleus accumbens) may be particularly important given the key role of the VTA and ventral striatum in the regulation of motivated behaviours, including identification of salient environmental stimuli and appropriate action selection (Robinson and Berridge, 1993; Salamone and Correa, 2012). Further research is required to determine if O'Connell and Hofmann's ambitious concept is valid for all vertebrate taxa, but one recent re-evaluation of the SDM concept concluded that it is well supported in mammals (Goodson and Kingsbury, 2013). Results of recent functional studies of social behaviours in non-human primates and monogamous voles are consistent with the SDM concept (Amadei *et al.*, 2017; Sliwa and Freiwald, 2017). There is also interesting convergence between the SDM concept and models put forward in recent discussions of the 'emotional brain' (LeDoux, 2012; Etkin *et al.*, 2015). LeDoux (2012) reconceptualized emotion in terms of functions and circuits crucial to survival. This conceptualization of emotion certainly overlaps with the SDM concept and the implicated circuits overlap considerably with much of the circuitry proposed as parts of the SDM.

Two limbs of the social decision-making network

In their discussion of MPOA/VMH control of maternal and male sexual behaviours, Stolzenberg and Numan (2011)

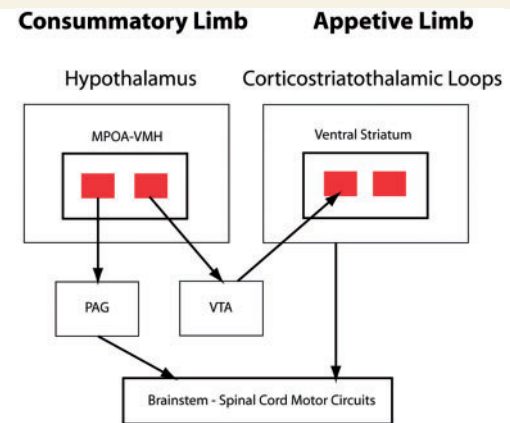


Figure 3 Two limb model of the SDM for maternal, and male and female sexual behaviours. Projections from VMH and MPOA to PAG are responsible for consummatory behaviours. Projections from the MPOA to the VTA, with subsequent dopaminergic signalling in the ventral striatum, are responsible for appetitive behaviours, including evaluation of the motivational significance of stimuli. Adapted from Stolzenberg and Numan (2011).

proposed an interesting model suggesting that the basal ganglia circuit and SBN components of the SDM have complementary functions (Fig. 3). For many behaviours, psychologists distinguish an appetitive phase involving actions bringing animals into contact with a goal stimulus and a consummatory phase in which animals actually interact with the desired object. For some rat reproductive behaviours, Stolzenberg and Numan (2011) suggest that the consummatory phase is mediated by output from the MPOA/VMH to the PAG, with the latter controlling lower circuits producing the actual motor acts. The appetitive phase results from MPOA interactions with dopaminergic systems, particularly the VTA. In this model, MPOA outputs to the VTA modulate dopaminergic inputs from the VTA to the ventral striatum, a key basal ganglia circuit node regulating motivational states. McHenry *et al.* (2017) recently described a sophisticated partial validation of this model. MPOA neurons of female mice are critical for appropriate responses to male reproductive social cues such as male urine odours. This response is modulated powerfully by circulating oestradiol levels. McHenry *et al.* (2017) demonstrated that optogenetic stimulation of oestrogen receptor expressing MPOA neurons projecting to the VTA evoked ventral striatal dopamine release and enhanced female attraction to males in a gonadal steroid dependent manner. Generalizing the Stolzenberg and Numan (2011) model to all SDM functions, the basal ganglia component of the SDM may be responsible for the evaluation and valuation of relevant stimuli and actions with the SBN component responsible for driving social actions. Normal social function would require appropriate integration of the functions of both SDM limbs.

The generalized Stolzenberg and Numan (2011) SDM model is sensible in view of the widely accepted role of

midbrain dopaminergic neurons and the basal ganglia as critical components of brain reward and valuation systems. Baez-Mendoza and Schultz (2013, 2016) and Baez-Mendoza *et al.* (2016) emphasize the critical role of the striatal complex and associated circuits in a wide variety of social behaviours including evaluating social rewards, trust of other social agents, assessing inequities, evaluating actions of conspecifics, pair-bond formation, and maternal behaviours.

The existence of excitatory projections from SBN hypothalamic nuclei to midbrain dopaminergic neurons is the basis for an alternative model of SBN and basal ganglia integration. The Stolzenberg and Numan SDM model emphasizes functional division with ventral striatum involved in evaluation of and the SBN responsible for execution of social behaviours. In this model the PAG plays a particularly important role as the initiator of socially relevant, stereotyped motor acts via its action on relevant brainstem and spinal circuits, a plausible explanation for nature of and pattern of expression of tics. The primate basal ganglia microstimulation studies discussed above, however, suggest that tics can be initiated from focal basal ganglia disinhibition (François *et al.*, 2004; Grabli *et al.*, 2004; Worbe *et al.*, 2009, 2011, 2013; Bronfeld *et al.*, 2011, 2013a, b; McCairn *et al.*, 2013, 2016; Godar *et al.*, 2014; Israelashvili and Bargad, 2015). Caligiore *et al.* (2017) developed a computational model of one of these tic models (McCairn *et al.*, 2013). In this model, increasing dopaminergic input is a key feature of tic initiation. The primate nigrostriatal projection is somewhat topographically organized (Haber *et al.*, 2000). SBN hypothalamic nuclei might project specifically to dopaminergic midbrain neurons innervating striatal subregions particularly important for control of eye, facial, vocal, and head-neck movements. SBN hypothalamic neuron activity might produce increased dopaminergic inputs to striatal subregions initiating tics. This model also provides an explanation for the character and pattern of tic expression. A hybrid model is also plausible. In normal social functioning, SBN hypothalamic nuclei might coordinate the activity of relevant striatal subregions and the PAG. In Tourette syndrome, this coordination might be disrupted.

A persuasive hypothesis suggests that evolution of unusually large brains among primates, particularly hominins, is driven by needs for complex computations intrinsic to elaborate social lives (Dunbar and Shultz, 2007). Comparative studies indicate that both the SBN and the basal ganglia are phylogenetically ancient features of the CNS. Their close functional integration is likely to be particularly important for highly social humans.

The role of the amygdala

If efficient functional integration of the basal ganglia and SBN components of the SDM is important in social behaviour, then interaction nodes should be associated with social functions. As described above, this appears to be

the case for SBN to VTA connections. In the SDM model, the amygdala is a major interaction node with the MA-BNST as an interface between the basal ganglia and the SBN (Fig. 3). The amygdala is a complex structure consisting of several nuclei and receiving a wide variety of cortical and subcortical inputs (for concise overview see Benarroch, 2015). Amygdala nuclei are strongly interconnected, the MA-BNST, for example, receives input from the basolateral nucleus, and these interconnections represent important channels for basal ganglia–SBN interactions.

Amygdala function is strongly implicated in different aspects of social behaviours. Starting with the pioneering lesion work of Kluver and Bucy in the 1930s, a large body of data indicates a significant role for amygdala function in social behaviours (Fusar-Poli *et al.*, 2009; Adolphs, 2010; Bickart *et al.*, 2012, 2014; Chang *et al.*, 2015; Rutishauser *et al.*, 2015). Probably the best known aspect of amygdala function in social behaviour is the role of the amygdala in perception of the significance of facial expressions, but components of the amygdala likely play a role in social actions. Based in part on functional connectivity MRI studies and review of a wide range of other work, Bickart *et al.* (2012, 2014) proposed that the amygdala is a hub for a variety of related social functions. Bickart *et al.* (2012, 2014) propose that different amygdala nuclei are central nodes in at least three major social function networks; one for social perception (evaluating social signals), one for social affiliative behaviours (prosocial acts), and one for social aversion behaviours (social avoidance). The affiliative network is centred on the medial amygdala. The dense interconnections of amygdala nuclei allow these networks to interact.

There are considerable data that amygdala function and structure changes during puberty, very likely under the influence of gonadal steroids (Scherf *et al.*, 2013; Herting *et al.*, 2014; Mills *et al.*, 2014; Herting and Sowell, 2017). Some functional and structural changes may evolve over relatively prolonged intervals. Chung *et al.* (2002) suggested that sexual differentiation of the human BNST extends into adulthood. As mentioned above, morphometric imaging work suggests abnormal volume of the amygdala in Tourette syndrome and Lerner *et al.* (2012) documented abnormal amygdala GABA-A receptor expression in Tourette syndrome. These results are consistent with abnormal amygdala function in Tourette syndrome. In the context of social perception, Neuner *et al.* (2010b) described abnormal amygdala activity in subjects with Tourette syndrome viewing emotional facial expressions.

Amygdala abnormalities might contribute to other features of Tourette syndrome. Emerging data suggest that amygdala abnormalities, particularly within the central nucleus of the amygdala and the BNST, are important substrates of anxiety (Kim *et al.*, 2013; Tovote *et al.*, 2015; Marcinkiewicz *et al.*, 2016; Shackman and Fox, 2016). The suggestion that SDM dysfunction, specifically dysfunction of functional social circuits centred on the amygdala, has another potential correlate in Tourette syndrome. Bickart

et al. (2014) point out that their social affiliative network, centred on the medial amygdala, overlaps significantly with the brain default mode network, and that their social aversion network, centred on the dorsal amygdala, overlaps with the brain salience network. The participation of different brain regions in the default mode and salience networks, and their functions, are altered by attention and task engagement. It is plausible, then, that attentional loading and task engagement could alter the function of amygdala nuclei that participate in the social function networks centred on the amygdala. This might explain the modulation of tic expression by task engagement.

The periaqueductal grey, vocalizations, and facial expressions

A basic feature of the SDM concept is that the PAG is the key node for the activation of lower circuits that result in the expression of relatively stereotyped social behaviours. This aspect of the SDM concept is consistent with data indicating that the PAG controls or influences a variety of motor behaviours, including many crucial for survival (Zhang *et al.*, 1994; Koutsikou *et al.*, 2015; Deng *et al.*, 2016; Tovote *et al.*, 2016). These behaviours can be relatively complex, involving freezing, flight, running, and predation. Older literature on the PAG also indicates that it controls a variety of socially significant motor behaviours relevant to tic characteristics. Stimulation of the PAG in decerebrate cats, for example, produces natural sounding vocalizations (Zhang *et al.*, 1994). The PAG controls a wide variety of lower circuits that regulate speech, coughing, sneezing, and respiratory movements, as well as facial movements (Holstege, 2002, 2014; Holstege and Subramanian, 2016). The PAG is a key node in Holstege's emotional motor system, a set of pathways that coordinate motor acts and regulation of autonomic functions in the expression of emotional behaviours. Holstege's work particularly emphasizes the role of the emotional motor system and PAG in speech production, which involves control and coordination of brainstem nuclei regulating facial movements, tongue movements, pharyngeal function, laryngeal function, and diaphragm movements. SDM dysfunction leading to abnormal or uncoordinated PAG regulation of these downstream components of Holstege's emotional motor system is a plausible explanation for the presence and character of vocal tics.

There is less detailed literature on PAG function and control of facial movements; however, Holstege emphasizes the importance of PAG inputs to premotor brainstem nuclei that innervate the facial nucleus. In addition, the primate facial nucleus itself receives substantial direct projections from the BNST and other amygdala subregions (Müri, 2016). The implication of these studies is that the PAG is an efferent node of SDM for control of facial expression.

This inference is consistent with a suggestion made by Devinsky (1983) that the PAG and associated midbrain tegmentum are crucial for tic expression. Devinsky (1983) pointed to tic-like phenomena associated with encephalitis lethargica, a disorder characterized by PAG pathology. As mentioned above, some prior MRI morphometry data describe midbrain abnormalities in Tourette syndrome (Garraux *et al.*, 2006) and Lerner *et al.* (2012) identified the PAG as an area of aberrant GABA-A receptor expression in Tourette syndrome.

Conclusions and potential implications

Conceiving of Tourette syndrome as a disorder of SDM function resulting in abnormal social communication appears to explain several previously cryptic cardinal features of Tourette syndrome. The SDM dysfunction hypothesis accounts for the characteristic distribution of tics, the presence and character of vocal tics, their stereotyped quality, the natural history of tic expression, the male sex predominance, and the role of the basal ganglia. This hypothesis may also explain other features of Tourette syndrome such as the modulation of tic expression by task engagement and the high frequency of anxiety disorders in Tourette syndrome. Recent imaging data (Lerner *et al.*, 2012; Greene *et al.*, 2017) are consistent with the SDM hypothesis.

The SDM dysfunction hypothesis suggests new directions for Tourette syndrome research. In general, exploring all components of the SDM in Tourette syndrome subjects may prove rewarding. Altered developmental trajectories of SDM components is a plausible general explanation for Tourette syndrome. There could, for example, be discordant development of the two limbs (basal ganglia and SBN) of the SDM. Systematic, prospective, longitudinal neuroimaging and neuroendocrinologic studies of Tourette syndrome and control children would be a logical approach to evaluating this hypothesis. While many of the SBN nuclei hypothesized to be involved may be too small for conventional morphometric analysis, Greene *et al.* (2017) identified increased volume of the hypothalamus as one of the few abnormalities in their morphometric study of Tourette syndrome children. More recently developed functional connectivity and network methods might be a way of addressing this hypothesis. For example, is there altered connectivity between the PAG and other SDM structures in Tourette syndrome? Do Tourette syndrome subjects exhibit differences from control subjects in the amygdala centred social networks described by Bickart *et al.* (2014)? Do these networks develop normally in Tourette syndrome subjects? As described above, social neurobiology is a fertile research field where the combination of modern tools and well established behavioural paradigms is allowing precise dissection of SDM pathways involving a variety of stereotyped social behaviours. As more detailed

understanding of SDM function emerges, insights from this work might be extended to human experiments. More detailed knowledge of SDM circuitry might allow application of molecular imaging methods to identify potentially abnormal pathways in the same way that Lerner *et al.* (2012) used GABA-A receptor ligand molecular imaging to identify abnormalities in the PAG and other structures. At a minimum, this knowledge might be applied to putative animal models of Tourette syndrome as a way of improving model validation and outcome measures for preclinical intervention studies.

The SDM dysfunction hypothesis may also have implications for other aspects of Tourette syndrome research. Tourette syndrome genetics research has been frustrating. Despite an apparent high heritability, association studies are largely barren. The SDM is a rather large network, encompassing many nuclei and connected to many other regions, such as cortical regions found in morphometric studies to be abnormal in Tourette syndrome. This raises the possibility that abnormal development of many, many structures could result in a Tourette syndrome phenotype. Tourette syndrome would be less a syndrome than a meta-syndrome. As a large number of genes affect the developmental trajectories of the many structures composing the SDM, it is plausible that small effects involving many genes would be responsible for Tourette syndrome. It would also be plausible that there would be considerable heterogeneity of such genes among Tourette syndrome subjects, though many would be predicted to be involved in brain development. These inferences from the SDM model are consistent with the recent work of Willsey *et al.* (2017). With statistical modelling, this group estimated that >400 genes are involved in Tourette syndrome. The available information about all four candidate genes identified in their study suggest involvement in brain development (Willsey *et al.*, 2017). Candidate genes discovered in these kinds of association studies might be further evaluated in rodents to determine if they influence the development of SDM nuclei and circuits. Those that do could be prioritized for further investigation.

The SDM hypothesis might also be useful in guiding the search for Tourette syndrome subtypes. Hirschtritt *et al.* (2016) suggest the existence of a subgroup characterized by social disinhibition. Different subgroups of Tourette syndrome might be characterized by abnormalities in different limbs of the SDM. Correlation of social behaviour measures with structural, connective, and functional MRI measures of SDM components might assist the identification of biologically valid Tourette syndrome subgroups.

Dopaminergic signalling is a significant focus of Tourette syndrome research. There is little evidence of abnormalities of striatal dopaminergic innervation in Tourette syndrome (Albin *et al.*, 2009). Functional studies of striatal dopamine release in Tourette syndrome subjects yielded conflicting results though one study suggested increased amphetamine-evoked dopamine release in the ventral striatum, possibly consistent with increased ventral striatal dopaminergic signalling driven by SBN activation of VTA neurons

(Wong *et al.*, 2008; Denys *et al.*, 2013). Definition of the precise projection targets of SBN neurons projecting to the midbrain dopaminergic neuron complex would be interesting. Do they project primarily to the VTA, as suggested in the two limb SDM model discussed above, or do they project also to substantia nigra dopaminergic neurons that preferentially innervate striatal subregions involved in head, face, and eye movements, and vocalizations? Studies in non-human primates addressing this question might cast light on the specific mechanisms generating tics.

The SDM dysfunction hypothesis, however, suggests alternative important sites of dopaminergic signalling in Tourette syndrome. Dopaminergic signalling within the MPOA, which receives dopaminergic innervation from the incerto-hypothalamic projection, regulates maternal behaviour in rats (Numan and Stolzenberg, 2009). The amygdala itself receives a significant dopaminergic innervation from midbrain dopaminergic neurons. Recent functional imaging studies suggest that dopaminergic signalling within the amygdala modulates the affiliative social network centred on the medial amygdala (Atzil *et al.*, 2017). Recent data also indicate the existence of a significant projection from the VTA to the lateral septum, another interaction node between the basal ganglia and SBN components of the SBN (Khan *et al.*, 2017).

In terms of potential therapies, it is plausible that the burgeoning and increasingly detailed understanding of the circuitry underlying social behaviours will suggest new pharmacologic approaches to Tourette syndrome. In the short term, the SDM hypothesis suggests new targets for DBS in Tourette syndrome. The amygdala, as a key interaction node for the two major components of the SDM and as a major actor in social behaviours, is a plausible target for DBS in Tourette syndrome. The PAG, as the main output structure of the SDM and key regulator of social motor behaviours, may be a good target for treatment of particularly troublesome tics. Both the amygdala and PAG (Satpute *et al.*, 2013) have complex architecture and it is plausible that improving DBS technologies, or more speculatively, clinical use of optogenetic methods, could target amygdala and PAG subdivisions to produce useful clinical effects.

In conclusion, the SDM dysfunction hypothesis provides a cogent and potentially fruitful framework for future Tourette syndrome research.

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