8 An associative analysis of Tourette syndrome

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The clinical problem

Tourette syndrome (TS) has been described as a developmentally regulated neurological disorder characterized by involuntary, repetitive, stereotyped movements (Albin & Mink, 2006; Chang, Tu, & Wang, 2004; Jankovic, 2001; Mink, 2003; Spencer et al., 1998). The Tourette Syndrome Classification Study Group (1993) has formulated a set of criteria for the diagnosis of TS. These include motor and vocal tics that cannot be explained by other medical conditions, lasting in excess of 1 year and with an onset during childhood (specifically before the age of 21). The cause of such tics is poorly understood but from the perspective of the sufferer they can have an apparent cause in the form of a prodrome. In other words, they are perceived as having been initiated by an urge or a sensation, and may increase during periods of stress. In particular, motor and phonetic tics are often preceded by premonitory sensations (such as burning sensation of the eye before a eyelink tic, or a sore throat sensation before grunting), which are alleviated by the performance of the tic (Jankovic, 2001).

The frequency of tics is variable over time. They may occur many times a day (usually in bouts), nearly every day or intermittently. Fortunately, they can also stop altogether. In form, tics may be simple motor (e.g., eyeblinks or nose twitches), simple vocal (e.g., grunts or throat clearing), complex motor (e.g., touching, hitting, or scratching), or complex vocal (the repeated uttering of obscenities or coporolalia, though this is not, as commonly believed, the most typical feature of TS). The type of tic generally displayed in any one individual can also change over time. This variability makes the diagnosis of TS difficult clinically because, for some individuals, the tics may go unnoticed, or be diagnosed as somatic tics. From a research perspective, this variability also raises issues: the same participant with diagnosed TS could arrive at the experiment with high levels of symptoms or relatively symptom-free. Thus, although clearly symptomatic of TS, the assumption has to be that tics are the (variable) manifestation of some underlying difference in the nervous system. Evidence on this point is
provided by the established techniques of neuropsychology and cognitive neuroscience: postmortem analyses of brain tissue; structural and functional imaging; and controlled behavioural experimentation.

The neural bases of TS

With regard to the likely neurological basis of TS, a number of studies, both structural and functional, have noted abnormalities in the dopamine (DA) system, basal ganglia and the striatum in particular. For example, Minzer et al. (Minzer, Lee, Hong, & Singer, 2004) reported postmortem changes in TS, including increased density of D2 receptors in prefrontal cortex, together with increased concentration of the DA metabolite (homovanillic acid, HVA) in the putamen. Similarly, another postmortem analysis of brain tissue from TS confirmed this evidence for increased DA D2 receptor density in five of six frontal lobe regions examined (Yoon, Gause, Leckman, & Singer, 2007). The same authors also reported another measure of DA abnormality: the DA transporter (that would normally promote DA reuptake) was elevated in TS (Yoon et al., 2007). However, these studies were each based on only three individuals diagnosed with TS and notably a total of three of the individuals included were over 60 years old and only one was under 20. Individuals who continue to suffer with TS in adulthood may not be typical (see below). Moreover, neuroleptic use over protracted periods could well explain these changes in DA function. Thus whilst indicative, postmortem studies of this kind are necessarily inconclusive.

Structural imaging studies in living patients point to more subtle differences in the brains of those with TS. For example, dysfunction in TS could also arise in relation to atypical laterality in key brain structures. Yazgan et al. (Yazgan, Peterson, Wexler, & Leckman, 1995) compared the performance of 11 TS participants on neuropsychological tests for lateralization of function (e.g., line bisection) with their level of basal ganglia asymmetry (as determined by volumetric assessment). The participants with TS demonstrated both basal ganglia asymmetry (left greater volume than right) and a reduction in normal functional lateralization on three of the four neuropsychological measures.

Functional neuroimaging studies have indicated that the normal role of the basal ganglia is to organize voluntary movements and inhibit other interfering movements (Mink, 2003; Wang et al., 2007). Thus, from a clinical perspective, disorder in the basal ganglia would be entirely consistent with motor symptoms of the kind shown in TS. The frontal lobe has also been implicated in the pathology of TS. With respect to the level of TS symptoms displayed, fMRI has shown a distinctive pattern of activation during tic suppression: significantly increased activity in the (right) frontal cortex; increased activity in the right caudate nucleus; along with reduced activity in the globus pallidus, the putamen, and the thalamus (Peterson et
al., 1998). However, it is unclear whether tic generation involves the same pattern of neural activation as seen during tic suppression.

**Frontal compensation in TS**

This neuropsychological evidence raises the possibility that there is functional compensation in the frontal lobes of TS sufferers. Since the disorder is neurodevelopmental and the frontal cortex is known to show late developmental changes (e.g. Sowell, Thompson, Holmes, Jernigan, & Toga, 1999), it is quite plausible that such compensation could be triggered by the need to suppress tics. One mechanism for functional compensation could be increased interactions between key cortical areas, developed to allow the inhibition of inappropriate motor responses. Serrien and colleagues have found support for this conjecture in the form of EEG evidence: coherent firing across a cortical network including dorsolateral prefrontal, premotor, sensorimotor, superior parietal, and supplementary motor cortical areas was seen whilst TS participants suppressed tics or voluntary movement during a Go–NoGo task (Serrien, Orth, Evans, Lees, & Brown, 2005).

Such findings suggest the hypothesis that, over time, the long term use of frontal pathways to suppress tics could result in generally increased cognitive control. Indeed, experimentally, G. M. Jackson and colleagues have shown that, despite their general difficulties with inhibition, TS participants show paradoxically enhanced volitional control in suppressing established stimulus–response (S–R) associations. Specifically, this deficit was in suppressing automatic visual saccades to salient peripheral cues upon switching from a prosaccade test, where participants were allowed to attend to the peripheral cue, to an antisaccade test, where participants were required to look away from the peripheral cue. This task relies on executive processes to show the required flexibility when the response requirement is changed. “Switching” procedures are ideal for this purpose in that they require participants to inhibit the prepotent response that has first been performed in the task, and to produce an alternate response. In normal participants, this generates a switch cost – measured as an increased number of errors, particularly when the required switch is unpredictable. However, the switch cost is not seen to the same extent in TS participants, irrespective of the predictability with which the switch is required (Mueller, Jackson, Dhall, Datsopoulos, & Hollis, 2006; Mueller, Swainson, & Jackson, 2007). These findings suggest that TS participants who remain susceptible to unwanted tics can nonetheless show enhanced cortical inhibition. Such enhanced cortical inhibition would be expected to have wide-ranging effects including improved performance on certain kinds of cognitive tests in TS and in particular on tasks that are believed to depend on frontal function. However, the persistence of unwanted tics in TS patients despite compensatory mechanisms in frontal cortex is consistent with the known basal ganglia
abnormalities in TS and points to the relative autonomy of S–R learning from executive control.

**TS as dysfunctional S–R habit learning?**

Habitual responses are ready-assembled routines that link sensory cues in the environment with motor action and are carried out in the absence of conscious thought or without awareness of the goal of the action. They allow us to perform seemingly complex behaviours such as driving effortlessly and automatically. The ability of stimuli in the environment to elicit these complex sequences of actions maps onto the theoretical suggestion that habit learning depends on the development of S–R associations. Habits are enormously adaptive as they free up cognitive resources and allow attention to be directed to the attainment of other goals. However, the notion of “bad” habits has long formed part of folk psychology and it is clear that as complex repertoires of actions come to be triggered by the mere presence of stimuli in the environment, behaviour can become inappropriate and maladaptive. Action slips (the performance of actions that are unattended or inappropriate in response to a stimulus in the environment) is a frustrating but arguably innocuous example of this phenomenon.

Similarly, TS is defined by the production of seemingly purposeless, involuntary, and repetitive behaviours that usually resemble aspects of normal behaviour. Tics, like habits, are coordinated ensembles of action that can be triggered by both internal and external stimuli. As discussed above, tics are often preceded by premonitory urges or internal sensations that build up and produce stress that is relieved by the expression of the tic. Seen in this context, tics can be viewed as a form of operant conditioning with premonitory urges acting as discriminative stimuli that lead to tic production and the resultant reduction in stress serving as negative reinforcement of the tic response according to classical S–R reinforcement learning theory. This phenomenological similarity between tics and habits has led to the suggestion that the repetitive behaviours seen in TS could represent a form of aberrant and dysfunctional S–R habit learning (e.g., Leckman & Riddle, 2000; Graybiel, 2008).

**Tics and S–R habit learning – same neural substrates?**

There is good, albeit indirect, evidence to suggest that the same brain systems responsible for the development of S–R habits may also underpin the production and maintenance of tics. As reviewed above, evidence from various sources including imaging and postmortem studies has implicated abnormalities in cortico–striato–thalamo–cortical (CSTC) loops and dopaminergic systems in the neurobiology of TS (e.g., Singer & Minzer, 2003) (see Figure 8.1). S–R habit learning has similarly been shown to depend on neural plasticity within the basal ganglia and prefrontal cortex (Jog, Kubota,
Connolly, Hillegaart & Graybiel, 1999; Killcross & Coutureau, 2003; Yin & Knowlton, 2006). This evidence comes in part from studies that have dissociated implicit S–R learning within the dorsal striatum from explicit forms of learning mediated by hippocampal and medial temporal cortical systems as well as from stimulus–stimulus (S–S) learning in limbic structures such as the amygdala (Packard & Knowlton, 2002). Furthermore, our understanding of the neuroanatomical and neuropharmacological basis of S–R habit learning has been greatly advanced in recent years through the application of modern behavioural assays of instrumental performance that allow the underlying associative structure of behaviour to be probed.

Behavioural studies in rodents have shown that instrumental performance can be controlled by two dissociable associative processes; as indexed by the sensitivity of instrumental response to outcome devaluation (changing the value of the instrumental outcome so that it is no longer motivationally significant or desirable for the animal). Early on in acquisition, instrumental responding is goal-directed and selectively sensitive to changes in outcome value (i.e., outcome devaluation leads to a decline in instrumental performance) but as training proceeds animals’ instrumental performance becomes habitual, stimulus-bound, and no longer guided by the current value of the reinforcer (Adams & Dickinson, 1981; Adams, 1982). Lesion studies combined with outcome devaluation procedures have highlighted a critical role for the infralimbic region of the prefrontal cortex and dorsolateral striatum (the rat analogue of the putamen) in the performance of habitual lever press responding in rats (Killcross & Coutureau, 2003; Yin, Knowlton, & Balleine, 2004). Conversely, plasticity within the prelimbic prefrontal cortex and dorsomedial striatum (the rat analogue of the caudate nucleus) appears to underpin the performance of goal-directed instrumental action (Killcross & Coutureau, 2003; Yin, Knowlton, & Balleine, 2005). These findings reveal the importance of interactions between prefrontal and striatal systems in the control of habitual behaviour. It is likely that the same brain regions are involved in the expression of tics (Leckman & Riddle, 2000). Indeed, findings from an fMRI study — showing that tic suppression requires activation of the caudate nucleus and deactivation of the putamen — parallel evidence that these structures are critical to the expression of goal-directed and habitual responding in rodents (Peterson et al., 1998).

Consistent with putative dopaminergic abnormalities in TS, there is good evidence for dopaminergic modulation of the development of S–R habits. For example, lesions to the nigrostriatal DA pathway, the major dopaminergic input into the striatum, have been shown to disrupt habit formation (Faure, Haberland, Conde, & El Massiouli, 2005). Similarly, repeated exposure to the indirect catecholamine agonist amphetamine appears to accelerate habit formation such that amphetamine-sensitized animals display habit-based goal-insensitive instrumental performance even after limited amounts of training (Nelson & Killcross, 2006). Significantly,
amphetamine exposure leads to the preferential activation of the striosomal compartment (see Figure 8.1) of the striatum (Graybiel, Moratalla, & Robertson, 1990) and this activation has been directly related to the occurrence of psychostimulant-induced stereotypies (Canales & Graybiel, 2000). Such stereotypies include a range of repetitive tic-like head and paw movements that resemble the motoric tics that occur in TS. It has been proposed that the changes in neuronal activity within the striosomal and matrix system associated with the production of behavioural stereotypies may also underpin the development of S–R habits (Canales, 2005; Nelson & Killcross, 2006). Moreover, these data have led to the suggestion that imbalances in the functional activity of striosome and matrix neurons may be related to the repetitive aimless behaviours seen in TS (Leckman & Riddle, 2000; Saka & Graybiel, 2003).

**S–R learning in TS and therapeutic implications**

The conceptualization of TS in terms of dysfunctional S–R habit learning is not only supported by the possibility of common neurobiological mechanisms but also by evidence that S–R learning is deficient in patients with TS. Studies have shown that both children and adult sufferers of TS are impaired in the acquisition of probabilistic classification tasks (Kéri, Szlôbodnyik, Benedek, Janka, & Gádoros, 2002; Marsh et al., 2004).

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*Figure 8.1* Simplified schematic representation of cortico–striato–thalamo–cortical loops implicated in tic expression and the development of S–R (stimulus–response) habits.
Probabilistic classification tasks involve learning the relationship between combinations of cues and outcomes. Task acquisition relies not on explicit declarative memory, but rather on a general sense of the rules acquired over numerous trials, and may therefore depend on the gradual learning of S–R associations. TS patients’ performance on such tasks does not improve over time and they show higher latencies and fewer correct responses compared to controls. Significantly, in both the aforementioned studies, symptom severity was negatively correlated with task performance indicating that participants with more severe tic symptoms were proportionally more impaired in S–R learning (Keri et al., 2002; Marsh et al., 2004). Furthermore, Marsh and colleagues (2005) found no evidence of deficits in the same cohort of TS patients on two perceptual-motor skill tasks (the pursuit rotor task and the mirror tracing task), suggesting that deficits seen on the probabilistic classification task cannot be explained in terms of impaired motor learning. The finding of intact motor learning in TS patients mirrors evidence that TS patients are unimpaired on Go–NoGo tasks that rely on the inhibition of pre-potent motor responses (Serrien et al., 2005; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008). These preserved abilities may be due to compensatory mechanisms within frontal cortex (see above) and the authors suggest that deficits in their probabilistic classification task may relate to specific abnormalities within CSTC circuits that subserve S–R habit learning (Marsh et al., 2005). However, although not identified as important, S–S associations are also likely to play a role in performance on the probabilistic learning task described by these authors. The role of S–S associations in TS is returned to below.

Of course, the ultimate goal of translational research is to ameliorate the clinical condition. Pharmacological interventions have proven effective in treating the symptoms of TS but are often associated with unwanted side effects (especially neuroleptics) and hence the need for psychological therapies is ever present (Leckman & Riddle, 2000; Singer, 2005). In this respect, the conceptualization of TS in terms of dysfunctional S–R learning has proven most promising as habit reversal therapy is becoming increasingly popular as a behavioural alternative to pharmacological treatment. Habit reversal therapy involves changing the contingency between the urges and sensations that precede tics and interfering with the production of the tic through the introduction of competing incompatible responses (Azrin & Peterson, 1988). Significantly, habit reversal therapy has been shown to substantially reduce tic severity compared to supportive psychotherapy and the beneficial effects of this behavioural intervention appear to be long lasting (Deckersbach, Rauch, Buhlman, & Wilhelm, 2006; Wihelm et al., 2003).

Disinhibited behaviour and TS

The changes in spontaneous behaviour diagnostic of TS also point to a problem with inhibitory mechanisms that would normally prevent these
kinds of outbursts. Therefore, a number of researchers have hypothesized that TS is the result of dysfunction in behavioural and/or cognitive inhibition (Gilbert et al., 2004; Ozonoff, Strayer, McMahon, & Filloux, 1998; Sheppard, Bradshaw, Purcell, & Pantelis, 1999). In addition to the standard Go–NoGo test variants, where subjects are instructed to respond to certain cues and withhold responding to other cues, “purer” tests of cognitive inhibition have also been developed. For example, in a negative priming task which measured the ability to inhibit the processing of irrelevant distractor stimuli presented on a visual display, it has been reported that TS participants with the most severe symptoms and presenting with comorbid ADHD or OCD showed deficits (Ozonoff et al., 1998).

Gilbert et al. (2004) investigated the relationship between motor cortex inhibition and tic severity in TS (and related disorders). This was done using transcranial magnetic stimulation (TMS) to produce motor-evoked potentials, measured using electrodes on the muscles, to manipulate the threshold for a stimulus-driven response: specifically cortical inhibition was measured through short interval intracortical inhibition (SICI). Gilbert et al. found that the level of symptom severity in TS (and ADHD, see also the section below on related disorders) was inversely related to cortical inhibition as indexed by SICI. This suggests that hyperactive or impulsive behaviours as seen in TS appear in consequence of diminished motor cortex inhibition (see also Sheppard et al., 1999 for review of other pathways involved).

S–S learning in TS and therapeutic implications

S–S associations provide a mechanism through which environmental events can act as symptom triggers and moreover provide some explanation of the variability in frequency of symptoms and time course. This kind of analysis has furthered our understanding of a number of disorders (Ferguson & Cassaday, 1999; Lishman, 1987; Siegel, 1977; Stewart, de Wit, & Eikelboom, 1984; Watson, 1924). In TS, a variety of associative triggers for tics have been documented, for example a person’s cough or gesture (Jankovic, 2001; Leckman, 2003; Leckman, Walker, & Cohen, 1993; The Tourette Syndrome Classification Study Group, 1993; Prado et al., 2008). Likewise premonitory urges in the form of somatic sensations, for example “burning” of the eye before a eyelink tic, sore throat preceding grunting, and the everyday life events and emotional variables that affect pre-tic urges and sensations (Leckman et al., 1993; Conelea & Woods, 2008), provide a source of stimuli that could become associated with tic-generated stimuli through S–S associations. Moreover, controlled experimental studies have demonstrated that repeatedly reinforcing tic suppression in the presence of a particular antecedent discriminative stimulus results (as would be expected by operant learning theory) in that stimulus acquiring some control over tic expression (Woods, Walther, Bauer, Kemp, & Conelea, 2009). Thus, a chain
of antecedents – providing both classically conditioned and (ultimately) discriminative stimuli – may be important in the triggering of a particular tic response, which can thus depend on other aspects of the environment beyond the immediately preceding stimulus. Such an associative chain reaction would be fully consistent with the triggering of the compulsive ideas which often accompany the urge to tic. Only recently have such environmental stimuli been targeted in behavioural treatments for TS: through extinction of the excitatory association (Verdellen et al., 2008); and in their capacity as discriminative stimuli in relation to tic reinforcement (Woods et al., 2009).

A role for Pavlovian inhibition in TS?

The variety of inhibitory deficits that have been reported in TS subsume a range of inhibitory mechanisms, some of which as we have seen are already under intensive investigation. For example, motor impulsivity is measured as reaction time in a variety of discrimination learning procedures that show excellent translational validity with human task variants (Robbins, 2002; Eagle & Robbins, 2003).

The common feature of these tasks is that they measure the participants’ ability to inhibit a prepotent response in the presence of an environmental cue that means it will not be reinforced. Formally, in Pavlovian procedures the equivalent “conditioned inhibition” is demonstrated when the meaning of one signal (conditioned stimulus, CS) is qualified by another (conditioned inhibitor, CI). Whilst the CS presented alone reliably predicts the outcome (unconditioned stimulus, US), when presented in conjunction with the CI the otherwise expected US will not occur. In other words, animals learn a discrimination that is shown within-subjects and this discrimination can be improved or impaired in the animal model.

Conditioned inhibition thus provides a mechanism through which the chain of antecedents to a tic, or any other unwanted behavioural or cognitive response, for which S–S associations provide an underlying mechanism, could be broken. In human studies, Cassaday and colleagues have demonstrated that individual variation in conditioned inhibition can be predicted from personality characteristics, themselves predictive of predisposition to disorder (Migo et al., 2006). The likely relevance of impaired conditioned inhibition in producing the cognitive deficits of schizophrenia was confirmed by the inverse relationship between the level of inhibitory learning displayed and schizotypy. In addition, there was a positive relationship between increased conditioned inhibition and a measure of reward sensitivity, potentially relevant to our understanding of a wide range of disorders including TS. Moreover, TS often occurs together with cognitive symptoms of attention deficit and obsessional behaviours. These deficits indicate the potential for wider changes, also in the inhibition of S–S associations – that result in unwanted thoughts – as well as actions.
Notably, the Pavlovian phenomenon of latent inhibition, widely investigated in connection with schizophrenic attention deficit (Moran, this volume), has been reported to be normal in TS (Swerdlow, Magulac, Filion, & Zinner, 1996). However, so-called latent inhibition refers to the reduction in associative learning produced by stimulus preexposure which establishes an otherwise effective CS as “irrelevant”. This preexposure has been shown to be an effective bar to inhibitory as well as excitatory learning. Thus although so-called latent inhibition procedures retard later learning they do not render the pre-exposed stimulus truly inhibitory: In other words, latent inhibition is a dissociable effect (Baker & Mackintosh, 1977).

Testing inhibition of S–S learning

We have recently adapted the task used by Migo et al. (2006) to make it more suitable for younger participants, including those with TS and ADHD. The stimuli to be conditioned are presented in the course of a “Mission to Mars”: participants play the role of a starship commander travelling towards Mars with a fleet of spaceships, some of which explode en route. Participants are required to count the number of surviving spaceships and are asked to guess what might predict their survival.

In fact CSs are provided by planets displayed on screen. Additional smaller planets act as distractors [Figure 8.2(a)]. Because the goal is the success of the mission, presentation of an intact spaceship provides the US. The normal predictive relationship between the planet CSs and spaceship US does not hold when their presentation is preceded by a CI in the form of a discrete white border on an otherwise the blank screen. On these trials the absence of the spaceship US is depicted by an exploded spaceship [Figure 8.2(b)].

During the testing sessions, participants are required to rate the likelihood of spaceship survival on a scale of 1 to 9 [Figure 8.2(b)]. When conditioned inhibition is shown, participants respond with a number less than 5 (the midpoint of uncertainty on the response scale). Critically, this procedure uses the summation test in that transfer of inhibition to a novel planet (novel stimulus, SN) and one not explicitly paired during training (transfer stimulus, CST), provides the key measure of conditioned inhibition. Figure 8.3 shows conditioned inhibition in normal participants as measured on the critical summation tests (Migo et al., 2006).

We have established that this “Mission to Mars” task is suitable for younger participants: they learn the discrimination in the modified variant readily and in fewer trials (Kantini, Cassaday, Hollis, & Jackson, 2011). This procedure was used to test the hypothesis that enhanced cortical inhibition in TS should enhance the discrimination between predicted and inhibited trials by selectively depressing spaceship expectancy on inhibited trials; thus to determine whether the enhanced cortical control demonstrated in tasks of executive function (Mueller et al., 2006, 2007) can
similarly improve performance in a Pavlovian procedure. We have yet to demonstrate significantly improved conditioned inhibition in TS. In the study conducted to date, TS participants showed overall normal inhibition of S–S associations in this task, and there was no correlation between inhibitory learning scores and symptom severity ratings measured using the Yale Global Tic Severity Scale. However, there was a clear reduction in the expression of conditioned inhibition in TS participants under medication with the noradrenergic alpha-2 agonist clonidine (Kantini et al., 2011). This finding has implications for the likely effectiveness of behavioural treatments in alleviating symptoms in cases of TS who are concurrently medicated. Through impaired conditioned inhibition, medication could impair potential cognitive control mechanisms for the suppression of tics (via an action on the associative chain that generates triggers). Thus impaired inhibition of S–S associations would leave TS sufferers potentially less able to inhibit the unwanted thoughts and premonitory associations that can lead to tics.

Figure 8.2(a) The set of conditioned stimuli (CSs) and distractor stimuli used. (b) The top set of screens show the presentation of a planet CS (screen 2), followed by a spaceship US (unconditioned stimulus; screen 4). In the test phase participants are required to rate their confidence of spaceship survival (screen 3). The bottom set of screens show an inhibited transfer test trial. When the white border has been presented (screen 1) the CS (screen 2) does not predict spaceship survival, as represented by the exploded spaceship (screen 4). As above, participants are required to rate their confidence of spaceship survival (screen 3). Procedures are based on Migo et al. (2006), see text for further details.
Brain systems involved in Pavlovian conditioning

The majority of Pavlovian conditioning studies are concerned with excitatory (S–S) learning. Basic associative learning ability and Pavlovian inhibitory learning are inevitably confounded in the sense that prior learning is essential to the successful demonstration of conditioned inhibition. In other words it is necessary to learn that a US is expected before one can learn that a stimulus signals its absence. Thus the substrates identified for excitatory learning will be necessary, if not sufficient, for inhibitory learning also.

Although all Pavlovian conditioning follows general laws of associative learning, there are known to be differences in the specific neural circuitries involved depending on the type of conditioning in use. For example, eyeblink conditioning is known to be impaired by cerebellar lesions in humans as well as other animals (Daum et al., 1993) whilst an equally compelling body of evidence underscores the importance of the amygdala for normal fear conditioning (see Fanselow & Poulos, 2005; Kim & Jung, 2006, for review). Related to this issue, the nature of the conditioned
responses that allow us to quantify the strength of associative learning varies from one task to the next. These conditioned response measures range from motor responses (in the case of eyeblink conditioning) to conditioned emotional responses that can show as response suppression (in fear conditioning). Thus differences in the nature of the learned response could (at least in part) account for differences in the underlying neural substrates.

The modulation of classical conditioning can depend on particular additional structures. For example, the hippocampus is required where associative learning must bridge a time gap between CS offset and UCS delivery, in both fear conditioning (McEchron, Tseng, & Disterhoft, 2000) and eyeblink trace procedures (Beylin et al., 2001). However, the role of hippocampus has yet to be demonstrated in appetitive trace procedures (Thibaudeau, Potvin, Allen, Doré, & Goulet, 2007). Therefore, the role of hippocampus in bridging across temporal intervals, as distinct from a role in fear and eyeblink conditioning that may be accentuated under conditions that increase task difficulty, remains to be determined. Inhibition similarly presents as a process that should modulate normal excitatory learning, both in terms of expression (in summation tests) and acquisition (in retardation tests) (Rescorla, 1969).

However, the additional brain circuitry necessary for normal Pavlovian inhibition has yet to be firmly established. As seems to be the case in trace conditioning, this may vary depending on the conditioning procedure in use. Similarly, it has yet to be determined in what ways Pavlovian S–S associations – and the inhibition thereof – are dysfunctional in TS. However, encouragingly, what we do know about the substrates of inhibitory learning is fully consistent with the possibility that its dysfunction could contribute to the symptoms of TS. Specifically, in electrophysiological studies, DA neurons have been found to show opposite patterns of activity in inhibitory and excitatory conditioning: depression in firing when a CI was presented, whereas CSs that predicted reward increased firing in DA cells (Tobler, Dickinson, & Schultz, 2003). However, this dissociation in terms of the electrophysiological neuronal response was seen in functionally diverse brain regions.

Again consistent with an important role for the brain DA system, treatment with the indirect catecholamine agonist amphetamine enhanced the acquisition of conditioned inhibition (Harmer & Phillips, 1999). However, this was a study of the effects of chronic pre-treatment to produce sensitization: The acute, regionally localized, effects of more selective agonists might well be different. Moreover, amphetamine is also a noradrenalin (NA) agonist and a role for NA in conditioned inhibition is indicated by the effect of clonidine identified in our studies of TS participants (Kantini et al., 2011). The role of cortex in modulating the acquisition and expression of Pavlovian inhibitory learning has yet to be fully determined. Although much work has yet to be done, already the known role of catecholaminergic
systems in both conditioned inhibition and TS supports the view that the deficits in this form of inhibition may be a contributing factor. Whether such deficits can arise in relation to TS per se or rather only in consequence of medication is yet to be established.

Related disorders

A syndrome such as TS refers to a set of symptoms perceived to “run together” in patients needing diagnosis. However, there can be overlap with related disorders, which should also be considered given that diagnostic boundaries are somewhat arbitrary and may be interpreted differently in different cultures. In the case of TS, there is a high level of comorbidity with ADHD (Comings & Comings, 1987; Gilbert et al., 2004; Ozonoff et al., 1998; Robertson, 2006; Sheppard et al., 1999; Spencer et al., 1998). In a study by Comings and Comings (1997), the authors found that TS patients were significantly different from controls with respect to DSM III symptoms of inattention, impulsivity, and hyperactivity. Moreover, they found that ADHD was diagnosed in 48.8 percent of the TS patients compared with 4.2 percent in the controls. Similarly, there is evidence for comorbidity between TS and OCD (Rankins, Bradshaw, & Georgiou-Karistianis, 2005; Swerdlow, 2001; Thibault et al., 2008) and there is evidence that participants who are comorbid for OCD perform worse on tests of inhibition than those with a diagnosis restricted to TS (Ozonoff et al., 1998; Gilbert et al., 2004). This means that studies which do not explicitly screen for comorbid illness could be argued to overestimate the level of impairment due to TS.

Superficially, TS, ADHD, and OCD present as quite different conditions. However, behavioural disinhibition is a feature of all these disorders (Ozonoff et al., 1998; Sheppard et al., 1999; Thibault et al., 2008), and both rely on the normal functioning of the DA system (Gilbert et al., 2004). Surprisingly then, relatively few studies have directly compared participants with TS and ADHD. Where this has been done, this has generally been in the context of studying comorbid groups rather than comparing separate groups.

As discussed earlier, Gilbert et al. (2004) investigated the relationship between motor cortex inhibition and tic severity using TMS. They found that the inverse association between tic severity and cortical inhibition was strongest in TS participants who were comorbid for ADHD. Indeed Gilbert et al. suggested that half of the variability in their index of cortical inhibition (SICI) was attributable to ADHD in participants with TS. Thus, hyperactivity and impulsive behaviours as well as the frequency of tics appear to be strongly linked with diminished motor cortex inhibition.

Similarly, returning to another study mentioned earlier in this chapter, whilst – as a whole – a large group of TS participants did not differ from controls, when this group was separated to distinguish those with “pure” TS
and those comorbid for ADHD and/or OCD, the comorbid group were found to show an inhibition deficit as measured by negative priming (Ozonoff et al., 1998). Similarly, Thibault et al. (2008) investigated TS in OCD comorbid groups using specific event-related potentials and the “oddball” task. The oddball task requires participants to respond to unpredictable targets presented amongst a series of more predictable standard stimuli and shows a known association with the P300 component of the event-related potential. This association was reduced in patients with TS. However, this result only held in those comorbid for OCD (and the relationship between oddball performance and P300 was also reduced in OCD participants). Thus again where comorbidity is present, experimental outcomes can be attributable to the comorbid disorder rather than to TS.

Inevitably, comorbidity is typically confounded with reported symptom severity in TS. Ozonoff et al. (1998) found that when the combined TS group was divided by TS symptom severity according to standardized diagnostic measures, the group with highest symptom severity did in fact show reduced inhibition (as measured by the negative priming scores), both relative to TS participants with lower symptom severity and the matched controls. However, in cases such as the study by Ozonoff and colleagues where TS participants without comorbidity performed as well as controls this would seem to suggest that TS symptom severity is not key to the deficits at issue. However, dealing with comorbid illness is not straightforward as distinctions between related disorders are driven by diagnostic fashion and increasingly “translational” studies that seek to bridge human and animal studies are focused at the level of symptoms rather than syndromes.

Conclusions and implications

The fact that TS sufferers show problems with motor inhibition and S–R habits in a variety of experimental tasks is entirely consistent with their symptoms in that by definition they continue to tic and show other unwanted behaviours. The enhanced cortical control shown in switching tasks is paradoxical and consistent with functional compensation. Such compensation could plausibly be driven by sufferers’ persistent attempts to suppress their tics. In terms of neural mediation of compensatory strategies, the frontal cortex is a likely substrate: task switching is an executive task likely to rely on frontal function; the development of the frontal cortex continues well into late adolescence. In some cases, TS behaviours would continue to persist because of the underlying dysfunction of the basal ganglia, in other cases cortical control might develop to the point where behavioural suppression is possible, in other words the basal ganglia dysfunction might be outweighed by the inhibition from frontal cortex. This model is consistent both with the fluctuating pattern of symptoms in TS and recovery in late adolescence in a high proportion of the cases who are motivated and able to
control their symptoms. There is a general impression clinically, that those with TS who are not also comorbid for ADHD are more successful at bringing their symptoms under control. This could be because comorbidity is confounded with severity or it could be that comorbid ADHD disrupts the ability to learn to suppress the unwanted TS behaviours.

A further consideration arises in that the response to show learning in tasks measuring S–S associations is generally less effortful than the response requirement to show S–R associations. Similarly, the conditioned responses that show learning of S–S associations are typically reflexive in any particular learning situation. In contrast, responses in instrumental tasks are voluntary, and to begin with somewhat arbitrary in form, though they can become highly automatic when S–R associations take over and habits are formed. Thus, whilst the level of learned responding in S–S and S–R tasks is generally taken to reflect the strength of the underlying association, other variables moderate the expression of learning through responding: (1) the level of motor requirement; (2) the level of automaticity with which the response is performed. These variables are both highly likely determinants of the role of motor versus cognitive inhibition required to suppress actions and thoughts. Such associative effects should be seen as modulating the expression of particular tics as associations are learned. Successful behavioural treatments to eliminate individual tics do not target the underlying neurological dysfunction responsible for the generation of tics. Thus (different kinds of) tics can and do reappear in cases of TS, in the same way an underlying anxiety disorder can result in different profiles of symptoms at different times.

We conclude that successful behavioural treatments will increasingly shift focus from the S–R association to target the S–S associations. In any chain of antecedent stimuli, the closest effective stimulus to the response will be cognitive, a perception or associated thought. Thus S–S associations provide the underlying mechanism whereby tics are triggered in particular contexts. Moreover, we have identified a potentially important role for conditioned inhibition that is susceptible to pharmacological manipulation.

Precisely because of the range and heterogeneity of disorders characterized by deficient inhibitory processes, as well as the confounded effects seen when these disorders co-occur in the same individual, and effects of medication that cannot always be clearly distinguished, human studies on their own will be insufficient to identify the neuropharmacological substrates of conditioned inhibition. Conditioned inhibition has long been established in animal research (Cole, Barnet, & Miller, 1997; Nicholson & Freeman, 2002; Rescorla & Holland, 1977), but the neural substrates have been little investigated to date. Thus further translational modelling will be necessary to pinpoint the key biological substrates of this important selective learning process and so identify its precise role in disorder. To date there is evidence for the likely role of DA and NA, but little if any direct evidence on where in the brain such effects are mediated.
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References


8. Analysis of Tourette syndrome


