Dispatch

Neurodevelopmental Disorders: Sensing Tourette's Tics Away

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Though still shrouded in mystery, Gilles de la Tourette's syndrome is widely regarded as an archetypal neurodevelopmental disorder of central, motor control. New evidence that its cardinal manifestation — prominent tics — may be ameliorated by a peripheral, sensory intervention compels us to revise not only our conception of the syndrome, but of the motor system itself.

Were biology's objective to puzzle neurologists, it could hardly have come up with a better phenomenon than the tic [1]. Pathological by definition, tics are both common and transient enough in the young to fall within the spectrum of normality. Highly stereotyped in form, the constituent movements of a tic may nonetheless be far more complex than any simple reflex. Involuntary by self-report, a tic is not only voluntarily suppressible to some degree, but characteristically prompted by an explicit and specific urge. And though purposeless, tics may be richly symbolic, sometimes exhibiting sensitivity to the external environment, if not — as notoriously in Tourette's, the neurodevelopmental syndrome where it is most floridly manifest — to established social norms. If there is anything we are tempted to conclude from so bewildering a set of contrasts it is that, though highly complex, the underlying disorder must be fundamentally a motor one. But a bold study reported in this issue of *Current*

Biology by Maiquez *et al.* [2], which has revealed a new and surprisingly simple therapeutic effect, suggests this is a temptation we ought to resist.

The conventional perspective on Tourette's is corroborated by observing abnormalities, associated with corresponding patterns of dysregulated cortical excitability, within the cortico-striato-thalamo-cortical network that links the basal ganglia via the thalamus to an array of predominantly frontal cortical areas [3]. But deep brain stimulation of putative subcortical targets is too invasive to be widely deployed [4], the response to transcranial cortical stimulation is modest [5], and the usual dopaminergic drugs mostly disappoint [6], as they so often do, leaving cognitive behavioural therapy as the mainstay of what is all too often only modestly effective treatment.

Reasoning from the observation that cortical excitability can be modulated sensorially, Maiquez *et al.* [2] explored a radically different therapeutic approach. Instead of seeking to perturb function through direct action on the central neural substrate, they used the brain's natural afferent interface with the outside world. As strikingly captured in videos of patients with pronounced manual and vocal tics, they found that 10 Hz surface electrical stimulation of the median nerve of a patient's dominant arm has a profound impact on symptoms — both objectively and subjectively — at intensities most patients found tolerable, and without evidence of fatigue over the periods of a few minutes surveyed in the study. Though perceptible, the stimulation was not arresting enough to impair performance on an attentionally demanding task in healthy participants, removing distraction as a trivial explanation. Synchronous stimulation induced entrainment of cortical rhythms to frequencies associated with movement suppression, whereas asynchronous stimulation did not, suggesting that the nature of the stimulation, rather than the bare fact of it, may be material to its impact on behaviour.

In short, the key to suppressing tics may be a sensory rather than a motor intervention, safely delivered peripherally rather than centrally, with the aid of simple technology available for over a century.

Before we offer our surprise as reason to demand replication on a grander scale — numerical and temporal — we should consider *why* we are surprised in the first place, and what might be wrong, conceptually wrong, with our prior beliefs about the horizon of explanatory possibility. After all, we may be missing many other astonishingly simple interventions simply because we mistakenly exclude them *a priori*. Reflection on three aspects of voluntary action in general, and its specific derangement in Tourette's, shows how important — yet often neglected — conceptual considerations can be here.

First, it is tempting to presume a correspondence between our natural classification of behaviour and the functional segregation of the underlying neural substrate. That perception and action are dissociable behaviourally does not imply they must be dissociable neurally along the same lines. It is, of course, obvious that action must always be linked to perception: it is definitionally a response to the environment — external or internal — even if not necessarily a contemporaneous one, and where learnt can only emerge via reinforcement from sensorially-conveyed outcomes [7]. But it is not obvious to many that the more complex a voluntary action is, the *more* dependent it is on the sensorium, for complexity scales on *both* the afferent and efferent limbs of the circuit. Moreover, a movement performed in the dark is not *less* reliant on afferent input but potentially more so, for the interpretation of proprioceptive signals is now no longer helpfully corroborated by the visual. The false dichotomy between complex 'internally-guided' and comparatively simple sensorially-guided action [8] is easily betrayed by the wide diversity of inputs to the dorsomedial frontal areas supposedly devoted to the former more than the latter, and the ease with which sensory phenomena may be elicited by electrical stimulation of the medial wall (Figure 1) [9,10]. But

we do not need empirical evidence for something that is conceptually given: without afferent signals, actions lose the teleology that so deeply marks their voluntariness, and so *any* disorder of voluntary motor function could conceivably be explicable — and remediable — through sensory mechanisms alone.

Second, a motor deficit need not be accompanied by a perceptual deficit for its cause to lie on the afferent side. Perception tests only the afferents it requires, and may be entirely unaffected by a defect confined to parallel afferent pathways whose destination lies within the motor domain. Nothing compels action and perception to rely on the same afferent neural inputs: far from surprising, the classical distinction between vision for action and vision for perception, made nearly three decades ago [11], is precisely what the radical difference in the underlying functions would predict. The absence of an accompanying perceptual deficit does not exclude an afferent cause for a motor deficit, it merely excludes circuitry — both afferent and efferent — on which reportable perception depends. That a patient with Tourette's, or any other complex motor disorder, reports no perceptual deficits is no reason to neglect the possibility of a decisive afferent contribution to the field of causation.

Third, perhaps the most distinctive feature of tics — the presence of an antecedent urge they temporarily satisfy [12] — inescapably implies not just an afferent component but an explicitly perceptual one. This is not because urges have, in part, a sensory phenomenal quality, but because their satisfaction implies overt feedback of a successfully executed movement. Since one cannot fail to attend to an urge — it arrests attention — one cannot fail to notice whether or not its resolution is conditional on what it specifically compels. It would be absurd for someone to say, "I feel urges, but I have no idea whether yielding to them has any effect", because it is precisely by the overt connection with a specific movement that an urge is defined. Consider the contrast with chorea, where pathological, involuntary, semi-purposeful movements of not dissimilar morphology are performed with neither an

antecedent urge nor contemporaneous attention. It is constitutive of the phenomenology of tics that they may in theory be extinguished by a perceived afferent signal of their execution, real or spurious.

Somatosensory cortex is prominent in the neuroanatomical terrain found to be altered in Tourette's [13], and urges are not the only phenomena with a sensory dimension here. Perhaps these empirical observations have been neglected because conceptual unclarities have needlessly obstructed the line of enquiry now attractively pursued by Maiquez *et al.* [2]. Far from epiphenomenal, conceptual aspects are often crucial to the vital last link in the translational chain: the connection with the real world that is so strained by neuroscience's habit of 'operationalising' biological reality within highly artificial experimental paradigms. Conversely, excessive attention is often paid to empirical aspects that are either irrelevant to therapeutic application or presuppose answers we cannot obtain. For example, though it might be natural to demand a mechanistic explanation of a phenomenon before it is put to therapeutic use, neither explanation nor a single mechanism need be possible. If the normal organisation of the brain itself is learnt through feedback adaptation of stochastically initialised neural states under the influence of wide arrays of unknown and unmodellable external influences, resulting in heterogenies of equally good individual solutions, then the patterns of optimal corrective perturbation may well be heterogeneous too. We must become accustomed to working with mechanistically-agnostic, self-learning, dynamically-adaptive methods of individualised therapeutic intervention: the freedom to operate in relative safety through the periphery of the nervous system revealed here allows us to pursue this approach far more aggressively than before. And it may turn out to be the only approach plausibly faithful to the underlying realities of the brain.

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Figure 1. Glyph-based probabilistic representation of the spatial distribution of sensory responses evoked by direct electrical stimulation of the medial wall.

Data and methods reported in Trevisi *et al*. [10].

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