THE BRIDGE

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Tourette Syndrome Issue

Can physical exercise improve tics and associated mental health difficulties in Tourette syndrome?: The jury is out

By Tara Murphy & Colin Reilly

Sensory-action binding: a new facet of Gilles de la Tourette Syndrome?

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Research highlights from our journals JCPP and CAMH
Welcome to the February 2019 edition of The Bridge. The focus of this edition is Tourette Syndrome, a condition, which has much stigma attached, stereotyped views by society about what it means and a lack of national clinical guidance.

We are gradually gaining better understanding of how common it is, the nature of the symptomatology as well as the effectiveness of treatments. Tourette Syndrome is seen clinically by both paediatric and child and adolescent mental health settings. This reflects possible differing clinical perspectives that this is either a motor or a behaviour/habit/impulse disorder. There is ongoing debate regarding what kinds of services should take responsibility for diagnosing and treating it. Clinically it also appears to be worsened by stress and anxiety and having Tourette Syndrome can affect an individual’s mood and self-esteem. The waxing and waning of symptoms certainly does not help in establishing whether a treatment is working or not and clinical views also differ on what medications are helpful, what works best or how to treat effectively in a non-pharmacological way.

In this edition of The Bridge, we have summaries of research published by ACAMH within our portfolio of journals by the original authors, as well as by one of our in-house science writers.

Hopefully some of your questions about its nature as well as what is shown to work and how well for managing the symptoms will be answered. You may be surprised by what you read...

Mark Lovell
ACAMH Lead for CPD and Training
In 2016, Chris Hollis and colleagues compiled a Practitioner Review for the Journal of Child Psychology and Psychiatry evaluating the most effective and well-supported interventions for children and young people affected by Tourette syndrome and chronic tic disorder. Here, they discuss the key findings from their systematic review, and highlight that children and young people affected by tics require improved access to evidence-based behavioural interventions.

Tourette syndrome (TS) and chronic tic disorder (CTD) are characterised by the presence of combined or singular motor and phonic tics. These tics generally begin in childhood around the age of 6-7 years, peak in severity between ages 8 and 12 years, and wane during early adulthood. Although TS was first described in 1885, systematic evidence-based clinical guidance for the treatment of tics in affected children and young people is still lacking. “TS and CTD affects 1-2% of children and young people and cause significant psychosocial impairment”, explains Hollis. “For practitioners, however, there remains uncertainty regarding the relative benefits and risks of medication and behavioural interventions for affected patients”.

To address this issue, Hollis et al., conducted a comprehensive systematic review covering pharmacological, behavioural and other physical and alternative interventions (e.g. botulinum toxin, deep brain stimulation) for tics in children and young people. They searched 21 databases from their inception to October 2014 to identify placebo-controlled trials of pharmacological, behavioural, physical and alternative interventions for tics in children and young people with TS or CTD. Their search resulted in 41 trials performed in children (or mixed studies) that met their eligibility criteria. These trials included 32 pharmacological, five behavioural, two physical and one dietary intervention. The GRADE approach was used to assess the level of certainty in the effect estimates (quality of evidence) for each outcome.

The researchers broke down the data by intervention type and level of certainty (namely moderate, low or very low certainty) in the estimates of the effect. For pharmacological interventions, $\alpha$ adrenergic receptor agonists — namely clonidine and guanfacine — showed a medium-sized benefit on tics when data were pooled. Despite their widespread use for treating tics, antipsychotic drugs (including aripiprazole, haloperidol, pimozide, risperidone and ziprasidone) showed low-to-very-low certainty.

“Overall, we found that $\alpha$ adrenergic receptor agonists were equally effective as antipsychotics but had a more favourable adverse effect profile”, explains Hollis. “However, among practitioners, $\alpha$ adrenergic receptor agonists are typically viewed as less effective in treating tics than antipsychotic; this view is challenged by our results”. Consequently, the researchers recommend that $\alpha$ adrenergic receptor agonists should be considered as the first-line pharmacological treatment for moderate to severe tics in children and young people,
and that antipsychotics should be reserved for when noradrenergic agents are ineffective or poorly tolerated.

For the behavioural interventions, Hollis and colleagues found that after pooling the results of two trials, habit reversal therapy (HRT) and comprehensive behavioural intervention for tics (CBIT) had a medium-sized effect in improving tics compared to waitlist/supportive psychotherapy. The data pertaining to all other behavioural interventions (including anger control training, parent training and relaxation training) were inconclusive. “HRT/CBIT for tics demonstrated similar effectiveness to medication, but a more favourable adverse effect profile”, describes Hollis. “Thus, our data suggest that behavioural intervention should be offered as a first-line intervention for young people with mild to moderate tics, either alone or in combination with pharmacological treatment”.

The study did raise questions as to the relative value of behavioural interventions when delivered alone or in combination with pharmacological interventions. “There is currently no evidence regarding the relative benefits of HRT/CBIT alone compared to benefits of combining medication and behavioural intervention”, says Hollis. “Randomised controlled trials assessing the relative benefits of HRT/CBIT alone compared to combining medication and HRT/CBIT are needed.”

Finally, the researchers found no evidence for benefit of physical, dietary or alternative interventions on tics — including deep brain stimulation, repetitive transcranial magnetic stimulation, botulinum toxin, IV immunoglobulins, omega 3 fatty acids and acupuncture. More research is required to determine whether any of these approaches are sufficiently safe to be considered as treatments for tics in children and young people with TS.

The researchers identified numerous areas in need of further research in order to advance the field. Overall, the cost-effectiveness of different treatment interventions for tics now needs to be assessed. Furthermore, the moderating effects of age, tic severity, premonitory urges and common co-morbidities (such as attention deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety and depression) on the treatment of tics needs to be addressed, as well as the moderating effects of tics on treatment outcomes for common co-morbidities.

Most importantly, the researchers noted the difficulties surrounding access and financial constraints that may hinder delivery of behavioural treatments. Strikingly, they reported that <20% children and young people are offered and access evidence-based behavioural interventions. The review highlighted that remote online digital delivery could play an important role in increasing access to behavioural interventions for tics. “A key question is whether behavioural interventions are as effective when delivered remotely compared to face-to-face”, proposes Hollis. “Future research should focus on the development and evaluation of digital technologies that can increase access to behavioural interventions”.

To begin addressing this question, Hollis and colleagues are conducting the ORBIT (Online Remote Behavioural Intervention for Tics) interventional clinical trial (NCT03483493) funded by the National Institute of Health Research (NIHR) Health Technology Assessment programme and sponsored by the Nottingham Healthcare NHS Trust. The primary objective of this 4-year trial is to evaluate the clinical effectiveness of ORBIT — a therapist-guided, parent-assisted, internet-based behavioural therapy intervention for tics in young people — compared with usual care plus online education. They hope to find out whether young people and their families find online therapist-supported treatment acceptable and determine how the treatment may be best delivered by the NHS. This clinical trial is currently underway and will run until September 2021.
In summary, Hollis et al. uncovered two key areas in this field that now require urgent attention. First, they found that understanding the clinical value of most interventions for tics were limited by the paucity of available evidence, the small number of trials performed and the small sample sizes for any given intervention. Many interventions had no, or very low quality evidence, rendering it difficult to draw firm conclusions regarding efficacy. Second, they noted that too few affected children and young people are able to access an evidence-based behavioural intervention for tics. Consequently, efforts must now be made to develop and evaluate digital technologies that could significantly increase access to evidence-based behavioural interventions.

In the future, they hope that a personalised medicine approach, with better prediction as to who responds best to which therapy, will be developed and that more trials of combinations of interventions will be conducted. Finally, they hope that NICE Clinical Guidance for TS and tic disorders will be available.

Referring to:

Further Reading
2 https://clinicaltrials.gov/ct2/show/NCT03483493

Glossary:
Habit reversal therapy (HRT): a behavioural treatment used to reduce repetitive behaviours that serve no adaptive purpose. Habit reversal focuses on bringing repetitive behaviours into conscious awareness and replacing them with less bothersome behaviours.

Comprehensive behavioural intervention for tics (CBIT): a behavioural therapy that teaches an affected individual to become aware of their behaviour and help them change this behaviour in a careful and systematic way. This comprehensive approach uses psychoeducation and self-awareness to understand the premonitory urge behind tics and know when a tic occurs. Habit reversal techniques are used to block the tic, or train a competing alternative response, when the urge is recognized and relaxation techniques are taught to reduce stress levels when tics occur.

Learning Outcomes:
1. Tourette syndrome and chronic tic disorder affect 1-2% of children and young people and cause notable psychosocial impairment. However, there is a lack of evidence-based clinical guidance for practitioners.
2. Behavioural intervention for tics (HRT/CBIT) demonstrates similar effectiveness to medication, and a more favourable adverse effect profile, which suggests that it should be offered as a first-line intervention for young people with tics.
3. When medication is considered appropriate, the balance of clinical benefits to harm may favour alpha 2 agonists (i.e. clonidine and guanfacine).
4. Access to evidence-based behavioural interventions is often limited: only ~20% of young people who would benefit from this intervention can currently access it. New forms of delivery, such as digital online interventions are needed.

Policy Impact:
1. There is currently no NICE Clinical Guidance for Tourette syndrome and tic disorders. Therefore, there is no formal mechanism (supported by NICE) to disseminate and implement treatment recommendations in practice.
2. Children and young people should have better access to digital/online therapy. However, this would require the development of a national digital IAPT (Improving Access to Psychological Therapies) programme for children and young people – equivalent to what exists for adults.
Gilles de la Tourette Syndrome (GTS) is a multi-faceted neuropsychiatric developmental disorder with onset in childhood or adolescence. It is characterised by multiple motor and vocal tics that can cause considerable problems including social stigmatisation, low self-esteem and secondary comorbidity, particularly depression. Because these tics are perceived as a motor problem, GTS is typically considered a movement disorder. However, this view is beginning to change. In fact, there are many aspects of GTS, which do not fit to the concept of a straightforward movement disorder (Beste & Münchau, 2018) these aspects include that (i) tics are associated with premonitory sensations, (ii) tics can be controlled and (iii) tics may be related to motor learning and habit formation.
It seems that the symptoms of GTS do not or only incompletely fit to the characteristics of “classical” movement disorders. When taking a broader perspective, it seems more likely that tics represent an excess of purposeful actions and some kind of over-learned behaviour in the sense that the coupling between “perception” and “action” is altered in GTS. It has been suggested that GTS is associated with stronger connections between perception and actions and that the underlying deficit in GTS is the inability to weaken strong connections between perceptions and actions. In a recent study by Petruo et al. (2018), this novel perspective on GTS was examined for the first time; i.e. it was tested whether there are indeed stronger connections/bindings between perception and action in these patients.

To test this, the authors examined a group of children with GTS and healthy control children in a task where it is important to occasionally suppress responses. In other words, situation-appropriate behaviour was examined, which is a task relevant in daily life and sometimes difficult to accomplish by patients. In their experiment, the authors took advantage of the fact that especially multi-modal stimuli (i.e. stimuli that combine auditory and visual aspects) are very useful to guide actions. Critically, the authors also included conditions (situations) where the actions needed to be inhibited, but where the perceptual input was altered (i.e. the auditory aspect was lacking). This is critical for GTS patients, because these patients likely establish strong expectations that a particular action is preceded by the same input. If this expectation is violated, this will cause problems to guide actions. The authors showed that this is indeed the case in GTS patients. Moreover, they also showed what neural mechanisms underlie these processes. Their analyses revealed that altered action selection processes are indeed associated with the observed behavioural deficits. Attentional selection processes do not seem to be important for the observed problems in GTS. Taken together, the results provide first direct evidence for a new conceptual framework for GTS; i.e. that GTS might be conceived as a disorder of purposeful actions and alterations of the connection between perception and action. Notably, this finding has strong implications for the treatment of GTS.

Aside pharmacological treatments, also behavioural therapy (e.g. habit reversal training) is an important treatment approach that has been shown to ameliorate tics in GTS. The aim of this behavioural intervention is to replace tics with other movements that do not appear to be misplaced in context. The new concept that GTS might be a disorder of purposeful actions corroborates the usefulness of this approach and provides the missing theoretical background to this form of treatment. Importantly, the new framework and ways to test this framework in GTS will provide new diagnostic procedures. In addition, research in this domain will provide novel tools to examine different cognitive facets of GTS. Consequently, these new tools may prove useful in the diagnostic process of GTS and may also serve as new outcome parameters and endpoints for clinical studies in GTS. Currently, a study is underway that examines the effects of a habit reversal training using the above-mentioned experiment. This is important because this study will test whether a major treatment approach is able to modify problems that are central for a new theoretical framework for GTS.

Referring to:
Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterised by a persistent motor or vocal tic present for >1 year. Although traditionally considered a movement disorder, some have suggested that GTS may be considered a condition of purposeful actions mediated by the relationship between sensory processes and motor responses, i.e. altered sensory-action integration (“binding”). Now, researchers in Germany have investigated this concept in the context of inhibitory control. Here, 35 adolescents with GTS and 39 healthy controls completed a visual-auditory Go/NoGo-task: the participants had to press a key when the word “Press” was presented on a computer screen (Go trial) or refrain from key pressing when the word “Stop” was presented (NoGo trial). Some NoGo trials also incorporated a compatible (spoken word “Stop”) or conflicting (spoken word “Go”) auditory stimulus. During the task, the participants were monitored by EEG and event-related potentials (ERPs) were recorded and analysed. At the behavioural level, patients with GTS showed a worse performance than controls, and larger performance differences when inhibitory control had to be exerted in tasks employing uni-modal (visual only) rather than bi-modal (visual and auditory) stimuli. The researchers suggest that this behaviour is indicative of increased binding between bimodal stimuli and responses. At the neurophysiological level, this perturbed behavioural response seemed to be due to altered stimulus-response translation processes (or sensory-action binding) in the right inferior parietal cortex (BA40). The researchers propose that response-inhibition processes are affected in patients with GTS by the nature of the sensory stimuli that are needed to trigger behavioural control, supporting the theory of altered sensory-action binding in GTS.

Referring to:

Further reading:

Glossary:
Inhibitory control: the voluntary capacity to inhibit or regulate strong attentional or behavioural responses. Inhibitory control requires the ability to focus on relevant stimuli in the presence of irrelevant stimuli, and to override strong but inappropriate behavioural tendencies.
Event-related potentials (ERPs): the measured electrophysiological response to a stimulus; the ERP waveform is measured by electro-encephalography and consists of a series of positive and negative voltage deflections.
Can physical exercise improve tics and associated mental health difficulties in Tourette syndrome? The jury is out

By Tara Murphy & Colin Reilly

Dr Tara Murphy is a Consultant Paediatric Neuropsychologist and Clinical Psychologist. She worked at Great Ormond Street Hospital between 2003 and 2017 in neuropsychology and intervention services. In 2012, Tara co-led the National specialist Tourette syndrome clinic and developed services and completed research. She has written two books (Chowdhury and Murphy, 2017; Murphy and Millar, 2019) and many papers on Tourette syndrome. Tara is currently living in Kampala, Uganda volunteering at Butabika National Referral Hospital as part of the Butabika east London Link. She is treating and teaching other professionals how to treat children with tics and many other disorders.

Colin Reilly has worked as an educational psychologist in the UK and Ireland. He currently works as an educational psychologist at Young Epilepsy and as an honorary research associate at UCL Great Ormond Street Institute of Child Health. His clinical work to date has primarily been with children with neurodevelopmental disabilities and neurological conditions (e.g. epilepsy). His research focuses on psychosocial aspects of these conditions.

Physical exercise is increasingly being recommended as part of management for children and young people with mental health problems. There is a growing evidence base that shows physical exercise is associated with improvements in functioning for conditions such as attention deficit hyperactivity disorder (ADHD), although studies are small, they are significant.

What is Tourette syndrome?
Tourette syndrome is characterised by persistent, involuntary motor movements and sounds which occur throughout childhood. For some children, the tics are bothersome and for others they do not bother them. Importantly, most children with Tourette syndrome will have a co-occurring mental health problem such as ADHD or obsessive compulsive disorder (OCD) (Groth, 2018). The co-existing conditions are as likely to have an impact on the child’s life alongside the tics themselves (Eapen, Snedden, Crncec, Pick and Sachdec, 2016) but tics can be painful, embarassing and are often misunderstood by families and teachers.

What do we hear in clinic?
Parents report that physical exercise is beneficial in reducing tics and improving symptoms of co-occurring disorders. However, there is a lack of formal guidance on the role of physical exercise in the management of children with Tourette syndrome.
This review was carried out to evaluate the evidence base for physical exercise as a management intervention on tics and associated mental health disorder in children and young people with Tourette syndrome.

How was the review carried out?
A range of online databases were searched including those focussing on medicine, psychology and physical exercise/sport. Studies investigating interventions aimed at reducing tics and mental health difficulties and survey based studies exploring the relationship between physical exercise and tic severity in children (0-18 years) were included in the review.

Results of the search and subsequent analysis
Seven studies which met inclusion criteria were identified. Five focused on physical exercise interventions and two were survey-based studies investigating the relationship between tic severity and physical activity. Two of the intervention studies were case studies whilst in the other three studies sample size ranged from 5 to 13 participants.

What were the physical activities
The physical exercise interventions included a one off 2.5-hour intervention whereas others involved regular exercise sessions on a weekly, bi-weekly or tri-weekly basis for 6 weeks to 3 months. The interventions included a kickboxing exercise routine, a 30-min aerobic exercise session and a group aerobic exercise class. In one of the studies which involved a number of sessions, support was provided via teleconference while in another a certified physical trainer facilitated the sessions.

What did we find in relation to tics?
There was some evidence that physical exercise reduces tic severity in the short term. In the two survey studies more participants reported a decrease in tic frequency than reported an increase, but in both studies, the majority reported no difference in tic expression as a result of participation in physical activity.

Our findings were not clear on what happens after the exercise has happened. In one study which included a four-week follow-up, tic frequency which had reduced initially, returned to pre-intervention levels suggesting that improvements may not be maintained. This needs careful investigation.

What did we find in relation to co-existing mental health problems?
Mental health difficulties were considered in three of the five studies. In one study, a reduction in OCD and anxiety symptoms on standardised measures was noted. In another study, parents reported a positive influence on their child’s self-esteem as a result of participation in the exercise intervention which was based on a qualitative report and not a standardised measure.

Not all studies investigating additional conditions included a follow up measure of mental health function. Of note is that none of the studies to date have considered symptoms of ADHD despite ADHD being one of the most common comorbidities and evidence that exercise can impact positively on ADHD symptoms.

Limitations of the studies
None of the intervention studies involved randomisation so we don’t know is a particular preference of the subjects meant that they received a particular type of exercise. Sample sizes of participants were small which means that it is difficult to know how many people the results can be relevant for and if the results are truly meaningful. Importantly, as the interventions were so varied in terms of content and duration, it’s difficult to know how much, when and what type works for children with Tourette syndrome, who are very different from each other anyway.

Discussion and Implications for practice
There are some reports of reductions in tic severity and frequency associated with physical exercise in children with Tourette syndrome. However, there is not enough evidence to state with any certainty or confidence whether engaging in physical activity has an impact on tic severity. Similarly, there is also not enough evidence regarding the effect of physical exercise on symptoms of co-existing mental health conditions in children and young people with Tourette syndrome.
It is possible that any improvements in tics are short lived, as both studies which had a follow-up evaluation indicated that reported improvements were not sustained. This finding is similar to results of studies using relaxation training in tic management (Bergin, Waranch, Brown, Carson and Singer, 1998).

**What does work then?**

The evidence-base for behavioural treatments for tics such as habit reversal training and exposure with response prevention is robust and has forty years of supportive research (Verdellen, Van De Griendt, Hartmann, & Murphy, 2011). Although, not a cure, it is typically associated with a reasonable reduction in tics for most children who receive it. In the past ten years, there have been exciting developments in the provision of behavioural therapy for tics such as group interventions, online treatment and remote delivered therapist assisted self-help interventions such as the National Institute for Health Research sponsored study ORBIT (Online Remote Behavioural Intervention for Tics: https://www.institutemh.org.uk/research/projects-and-studies/current-studies/orbit/199-what-is-orbit).

**Take-Home Message**

The take-home message is that, conclusions about the benefits of physical exercise on TS symptoms or comorbidities cannot be drawn at this stage. There is a need for better data including studies which use randomised controlled designs and a consideration of the impact of exercise on a broader range of areas of the child’s life including mental health, cognition and quality of life. For now it is important that children and young people with troublesome tic disorders have access to therapies with an established evidence base for both tics and comorbid mental health difficulties (Whittington et al, 2016).

**Key points**

- Tourette is a fairly common neurodevelopmental disorder which often co-occurs with additional conditions, such as attention deficit hyperactivity disorder and obsessive compulsive disorder.
- Physical exercise is recommended as aspect management for children with mental health problems and informally families report that it seems to help manage tics.
- Few studies, which are of limited quality, have been carried out evaluating the efficacy of exercise on tic management in children to date. No conclusions can be drawn from what we know currently.
- Behavioural treatments such as habit reversal training and exposure with response prevention and pharmacotherapy have been demonstrated to have significant benefits for children with chronic tic disorder.
Barriers to improving access to therapy treatment for tics in the UK

By Dr. Tara Murphy & Seonaid Anderson

The European clinical guidelines for Tourette Syndrome suggest that behavioural therapies (BT) are ‘first line treatments for tics for both children and adults’. However, according to Dr. Tara Murphy and Dr. Seonaid Anderson and colleagues, a barrier to delivering this in the UK is a lack of access to specialised psychologists and therapists. To relieve this problem there has been successful work on BT delivered by telemedicine, group interventions and there are current projects using remote access and online treatments. Tourettes Action (TA) is a national charity in the UK that offers subsidised training in BT with the hope of increasing the access of patients to BT. The researchers examined the number of people attending the BT training and whether this translates into additions to the TA list of available therapists. TA has a list of therapists across the UK who have been trained and have expert knowledge and experience in delivering BT for tics both privately and via the NHS which is made available to patients on request.

195 clinicians were trained in the UK by TA from 2013-2017 in Glasgow, Liverpool and London. Many of the trainees said they would be happy to have their details added to the TA list after training however, this only translated to a quarter of them joining. On examination, some of the reasons for therapists not joining the TA list included having no patients with tics at that time, although they perhaps might in the future. Issues relating to NHS services, such as having no capacity to see additional patients and being unable to take on more referrals. A lack of positivity from employers or service managers often related to service commissioning or lack of awareness of TS. Some trainees were willing to consider private work (in conjunction with their NHS work) which would allow them to join the TA therapist list. Importantly, once trained the lack of access to supervision expertise & subsequent lack of confidence seems to be an issue. TA aims to provide support in their clinical consultation sessions provide support to therapists who lack this peer-support opportunity in their current work situations.

To conclude Dr. Murphy and Dr. Anderson would surmise that it is very difficult to measure the impact TA training has had and whether it has increased the numbers of clinicians/therapists offering BT in the UK. What there does seem evidence of, is that there is extreme patchiness in the UK in terms of commissioning arrangements for Tourette Syndrome. Without NICE guidelines or clear clinical pathways (such as those for other neurological conditions such as epilepsy), the situation may well remain unclear with patients having to find therapists themselves and fight to get funding for behavioural therapy to manage their tics.

About the authors:

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Seonaid Anderson
Seonaid is a Chartered Psychologist and a member of ACAMH and BPS. I have experience of clinical research with children and young people. I am currently research manager for Tourettes Action where I manage the research awards programme. A large part of my job involves being an ambassador for Tourettes Action and to raise public awareness of Tourettes Syndrome and the role of research in improving the lives of people with Tourettes Syndrome and their families via Patient and Public Involvement (PPI) initiatives and providing professional support to clinicians.