Effects of physical activity on the symptoms of Tourette syndrome: A systematic review

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\textbf{A B S T R A C T}

There is irrefutable evidence that routine physical activity or exercise can offer considerable health benefits to individuals living with various mental disorders. However, it is not clear what effect physical activity has on the symptoms of Tourette syndrome. Despite a paucity of evidence, physical activity or exercise has already been recommended by various health organizations for the management of tics. We provide a systematic review of the effects of physical activity or exercise on tic symptomology in individuals with Tourette syndrome. Major electronic databases were searched for all available publications before August 2017. Keywords and MeSH terms included “physical activity” or “exercise” or “exercise therapy” or “physical exertion” or “sports” and “tics” or “tic disorders” or “Tourette.” Eight studies were included, the majority of which were case reports. Despite a number of methodological limitations of the included studies, the review points to a trend that the effects of acute physical activity are intensity-dependent, where light intensity may alleviate and vigorous intensity may exacerbate tics. Chronic physical activity, however, appears to reduce the severity of tics even at higher intensity. Several physiological mechanisms may explain the differential effects of acute and chronic physical activity in Tourette syndrome. Future randomized controlled studies should better characterize the effects of different intensities and types of physical activity in Tourette syndrome.

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1. Introduction

Tic disorder is a neuropsychiatric condition characterized by short-lasting, sudden, habitual, non-rhythmic muscle contraction (motor tics) or vocalization (phonic tics) \cite{1}. Tourette syndrome (TS) is diagnosed when both motor and phonic tics are present for at least one year \cite{1}. The overall international prevalence of TS is approximately 1\% \cite{2}. The onset of tics is usually between 4 and 6 years of age, with peak severity occurring between ages 10 and 12 years \cite{1}. In the majority of children with TS, symptoms generally diminish or disappear as adults, but a small percentage (approximately a third) will have persistent symptoms that require clinical attention \cite{1,3}.

Several neural mechanisms have been proposed for TS. The observation that antipsychotics (i.e., agents that block dopamine \(\text{D}_2\) receptors) have been effective in treating tics has led to a hypothesis that heightened dopaminergic activity may be involved in TS \cite{3}. Studies using positron emission tomography further demonstrated elevated striatal dopamine release in individuals with TS \cite{4,5}. In addition, alpha\(_2\)-adrenergic agonists (e.g., clonidine) that inhibit the release of norepinephrine have also been effective anti-tic medications \cite{3}, suggesting heightened central noradrenergic activity in TS \cite{6}. Studies that examined cerebrospinal fluid biogenic amines further demonstrated elevated levels of norepinephrine in TS patients compared with healthy individuals \cite{7}. Moreover, stress-related neurobiological mechanisms seem to play a role, as evidenced by elevated cerebrospinal fluid levels of corticotropin-releasing factor in patients with TS \cite{8}. This further suggests that there may be secondary sympathetic activation as well as elevated beta-endorphin release \cite{9}. Alterations in other neurotransmitter, including cholinergic, gamma-aminobutyric acid (GABA)-ergic, and serotonergic, systems are also thought to play a role in the pathophysiology of TS \cite{10}.

Although pharmacological treatment can be effective for the symptoms of TS, use of medications, such as antipsychotics...
andalpha₂-adrenergic agonists, can be limited by their side effects [3]. In particular, antipsychotics are known for their cardiovascular, metabolic, and neuro-motor side effects [3]. There have also been rare cases of antipsychotic-associated worsening of pre-existing tics or induction of new tics in individuals with tic disorders [11,12]. Therefore, alternative or adjunct nonpharmacological treatment can be of substantial value in people living with TS. For instance, behavioral therapy that involves tic-awareness (i.e., observing the premonitory urge or other signs preceding the occurrence of a tic) and competing-response (i.e., engaging in a voluntary behavior that is physically incompatible with the tic to manage the premonitory urge) training has already demonstrated efficacy in TS [13]. A recent meta-analysis of 8 randomized controlled trials (N = 438) revealed a medium-to-large treatment effect for behavioral therapy in persons with TS [14].

However, little is known about physical activity (PA) or exercise. Although routine PA has demonstrated efficacy in a number of mental disorders [15], limited evidence exists for TS. To our knowledge, there is no randomized controlled trial examining the effects of PA or exercise in TS. Questionnaires and self-reports have revealed that PA was helpful in attenuating tics in up to 32% of youth and adults with TS [16,17]. In other studies, however, PA as an attenuating factor was endorsed only in 7–9% of cases [18]. Despite such a paucity of evidence, some health organizations have already been promoting PA for the management of tics [19–22]. Although there is irreputable evidence of health-related benefits associated with routine PA [23], more evidence seems to be required for TS. We conducted a systematic review of the literature to better characterize the effects of PA or exercise, either acute or chronic, on the symptoms of TS.

2. Methods

2.1. Data sources and searches

This systematic review was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24]. A comprehensive search of the literature was performed using the Medline, Embase, and PsycINFO databases to find all available publications until 12 August 2017. Reference lists from identified studies were also examined. Keywords and MeSH terms used were as follows: “physical activity” or “exercise” or “exercise therapy” or “physical exertion” or “sport” and “tics” or “tic disorder” or “Tourette.”

2.2. Eligibility criteria

To be included in our systematic review, studies had to meet the following criteria: i) participants were diagnosed with tic disorders or TS, ii) participants were exposed to certain types of PA or exercise, iii) the outcome measure included the change in severity or frequency of tics in response to PA or exercise, and iv) randomized controlled trials, observational studies, and case reports were included. Studies were not excluded on the basis of age, sex, or ethnicity of participants. Studies were excluded if the type of PA or exercise protocol was not specified.

2.3. Data extraction

Descriptive data were extracted according to: i) author, year, country, study design, sample size, sex, age, diagnosis, and medication, ii) type of PA or exercise or training protocol, and iii) change in severity or frequency of tics in response to PA or exercise. If the intensity of PA or exercise was not specified by the study, we referred to the 2011 Compendium of Physical Activities to obtain a metabolic equivalent (MET) value for a certain type of PA and then the 2011 American College of Sports Medicine Position Stand to identify the absolute intensity of the given MET value [25,26].

3. Results

Out of 343 studies screened, 8 studies were included in this review (Fig. 1). Of the 8 included studies, 5 studies reported the effects of acute PA [27–30,33], and 4 studies reported the effects of chronic PA on tic symptomatology [31–34]. The studies are summarized in Table 1 and in detail in the following section. Overall, there was a trend that the effects of acute PA are intensity-dependent, where light intensity may alleviate and vigorous intensity may exacerbate tics. Chronic PA, however, appears to improve tics even at higher intensity. The relationship between PA intensity and tic expression is presented in Table 2. Lastly, there is some evidence that tics remain reduced after exercise but tends to be short-term.

3.1. Effects of acute physical activity

3.1.1. Light intensity

In the study by Nixon et al. [30], 18 young participants with TS (13 male, 5 female; age range: 10–20 years) completed an acute bout of aerobic exercise (i.e., aerobic kickboxing) at an easy followed by a more cognitively demanding (hard) level. Six of the 18 participants were being treated with one or a combination of 2–3 medications, including clonidine, aripiprazole, risperidone, and sertraline. Although the exercise session was designed to be moderately vigorous, participants overall performed at 43–63% of their estimated maximum heart rate (HRmax), which is estimated to be of light intensity according to the 2011 American College of Sports Medicine Position Stand [26]. Compared with baseline, there was a significant reduction in tic frequency during the exercise session (p = 0.001) as well as during the post-exercise session (p = 0.039). The authors noted that the reduction was greater during the easy than the hard level (p = 0.022); however, because the hard level was always followed by the easy level, the differential impact of the two tasks was difficult to establish [30]. The authors attributed the overall reduction in tic frequency to the activation of executive control circuits, sensory/motor tricks (i.e., gestes antagonistes), and/or reduced anxiety associated with exercise [30].

Garcia-Ruiz and del Val [29] reported a case of a 76-year-old woman with chronic motor tics, who had been treated with tetrabenazine 12.5 mg tid. It was reported that a complete disappearance of her tics was noted when she engaged in sweeping floors. Sweeping may require intensities ranging from 2.3 METs (light intensity) to 3.8 METs (moderate intensity) for a 76-year-old woman [25,26]. According to the supplementary video provided by the authors, it can be estimated that the woman was sweeping at light intensity. Other chores, such as ironing (1.8 METs) [25], were also reported to partially attenuate her tics. The attenuating effect of sweeping on tic expression was attributed to its complex action that involves axial dorsal and cervical muscle groups, which may serve as a sensory/motor trick [29].

Liu et al. [33] reported a case of a 12-year-old boy with TS. The child complained of pain in his lower extremities, for which he went through a 3-month physical therapy program. It was reported that the child frequently engaged in the prescribed stretching exercises to inhibit his tics. Mild stretching generally requires 2.3 METs, which is equivalent to light intensity [25,26].
potential mechanism by which stretching promotes tic attenuation was not discussed in the study.

3.1.2. Moderate-to-vigorous intensity
Lombroso et al. [28] reported a case of a 17-year-old male with TS, who had been treated with clonidine 0.05 mg qid and fluoxetine 40 mg/day. In addition, the participant had obsessive-compulsive disorder and a history of heightened sensitivity to heat. Motor tic frequency (i.e., the number of tics per 2 minutes), body core (esophageal) temperature, and sweat rate were measured prior to, during, and after treadmill walking at 3.5 mph. There was a parallel increase in tic frequency, body core temperature, and sweat rate. Tics exacerbated to the extent that exercise was terminated prematurely after approximately 24 minutes. Walking at 3.5 mph generally requires 4.0 METs, which is equivalent to moderate intensity [25,26]. The participant also reported that his tics often exacerbated when engaging in vigorous-intensity PA. Under identical conditions, the participant’s father, who had a diagnosis of TS but no history of heightened sensitivity to heat, did not exhibit any change in tic frequency during treadmill walking at 3.5 mph. The exacerbation of tics in the child was attributed to increased thermal stress associated with exercise [28].

Jacome [27] reported a case of a middle-aged man with mild TS. Whether the man was on medication was unknown. It was reported that his usual stereotyped, shouting utterances were exacerbated when he jogged medium distances despite feelings of well-being from exercise. Jogging generally requires 7.0 METs, which is equivalent to vigorous intensity [25,26]. The exacerbation of tics associated with jogging was attributed to an exercise-induced release of endorphins (to be further discussed below) [27].

3.2. Effects of chronic physical activity
Wang et al. [32] reported a case of an 11-year-old boy with TS. Whether the child was on medication was unknown. He engaged in a 6-month table-tennis training program that consisted of two 3-hour sessions per weekday. The intensity of training was not specified; however, it can be estimated that the overall intensity was moderate because table tennis generally requires 4.0 METs (i.e., moderate intensity) [25,26]. The intensive design of the training program could have made it vigorous for the child, although the child never complained of being exhausted. The child’s Yale Global Tic Severity Scale (YGTSS) score changed from a moderate to minimal level (36–5). The improvement in the severity of the child’s tics was attributed to improved regulation of the cortico-striato-thalamo-cortical circuitry associated with repetitive practice of PA [32].

In the aforementioned case report by Liu et al. [33], the 12-year-old boy with TS, who complained of pain in his lower extremities, went through a 3-month physical therapy program that consisted of one 2-hour session per week of combined exercise modalities, including aerobic, resistance, and flexibility exercises. The intensity of training was not specified; however, it can be estimated that the intensity could have reached a vigorous level because each session consisted of running for 20 minutes in addition to other exercises for up to 2 hours. After the physical therapy program, the
Although (not age therapy modalities (age range: 5–17 yr); 2) Age: middle age; Diagnoses: TS (both)

Table 1
Summary of studies examining tic response to acute or chronic physical activity.

<table>
<thead>
<tr>
<th>Publication, country, study design</th>
<th>Objective</th>
<th>Participants: sample size, sex, age, diagnosis</th>
<th>Medication</th>
<th>Physical activity: type/protocol</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Physical Activity</strong></td>
<td></td>
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<tr>
<td>Jacome, 1987; USA; Case study [27]</td>
<td>To present a case of tic exacerbation following jogging in a man with TS.</td>
<td>N = 1 (male); Age: middle age; Diagnosis: TS</td>
<td>Unknown</td>
<td>Jogging medium distances</td>
<td>Exacerbation of phonic tics when jogging.</td>
</tr>
<tr>
<td>Lombroso et al., 1991; USA; Case study [28]</td>
<td>To examine the effect of thermal stress on tic expression in a family with TS.</td>
<td>N = 2 (100% male); 1) Age: 17 yr; 2) Age: middle age; Diagnosis: TS (both)</td>
<td>1) Clonidine 0.05 mg qid and fluoxetine 40 mg/d; 2) Unknown</td>
<td>Walking at 3.5 mph on a treadmill (≥24min)</td>
<td>Tic exacerbation in the child during walking but no change in the father.</td>
</tr>
<tr>
<td>Garcia-Ruiz et al., 2012; Spain; Case study [29]</td>
<td>To present a case of tic attenuation following sweeping in a woman with chronic motor tic disorder.</td>
<td>N = 1 (female); Age: 76 yr; Diagnosis: chronic motor tic disorder</td>
<td>Tetrabenazine 12.5 mg tid</td>
<td>Sweeping floors</td>
<td>Complete disappearance of tics noted during sweeping.</td>
</tr>
<tr>
<td>Nixon et al., 2014; UK; Observational study [30]</td>
<td>To examine the effect of an acute bout of aerobic exercise on tic expression in young people with TS.</td>
<td>N = 18 (72% male); Age: 10–20 yr; Diagnosis: TS</td>
<td>33% on medication (clonidine, aripiprazole, risperidone, sertraline)</td>
<td>Aerobic kickboxing (at 43–63% of HRmax) at easy and hard levels</td>
<td>Both difficulty levels decreased tic frequency compared to baseline (p = 0.001).</td>
</tr>
</tbody>
</table>

**Chronic Physical Activity**

| Simms, 2005; USA; Observational study [31] | To examine the effect of 8-week aerobic training on tic expression in children with TS. | N = 4 (treatment), N = 3 (control); 80% male; Age: 8–14 yr; Diagnosis: TS (80%); chronic motor tic disorder (14%) | Medicated but not specified (no change throughout the study) | Three 46-min sessions per week of aerobic (with some resistance) exercise for 8 weeks | 10–22% reduction from severe (64.5) to less severe (55.3) in YGTSS scores. No change in tic frequency. |
| Wang et al., 2011; China; Case study [32] | To examine the effect of 6-month table-tennis training on tic expression in a child with TS. | N = 1 (male); Age: 11 yr; Diagnosis: TS | Unknown | Two 3-hr sessions per week of table-tennis training for 6 months | 86% reduction from moderate (36) to minimal (5) in YGTSS scores. |
| Liu et al., 2011; China; Case study [33] | To examine the effect of 3-month physical therapy on musculoskeletal fitness in a child with TS. | N = 1 (male); Age: 12 yr; Diagnosis: TS | Untreated during the study period | One 2-hr session per week of combined aerobic (running for 20 min), resistance, and flexibility exercises for 3 months | 24% reduction from moderate (37) to mild (28) in YGTSS scores. |
| Packer-Hopke et al., 2014; USA; Observational study [34] | To examine the effect of 6-week aerobic training on tic expression in children with TS. | N = 5 (100% male); Age: 9–13 yr; Diagnosis: TS | 80% on medication but not specified | Two 30-min sessions per week of aerobic exercise (kickboxing aerobics, dance aerobics, or Tae Bo) at 60–80% of HRmax for 6 weeks | 21–61% reduction from severe (53.1) to mild (29.8) in YGTSS scores. 32–91% reduction in tic frequency. |

\( \text{HRmax} \): percentage of maximum heart rate; qid: four times a day; tid: three times a day; TS: Tourette syndrome; YGTSS: Yale Global Tic Severity Scale.

In the preliminary study by Simms [31], 7 participants with TS (age range: 8–14 years) were assigned to an 8-week aerobic exercise program (n = 4) or to a control group (n = 3). No changes in medications (not specified) were reported. The exercise program consisted of three 46-minute sessions per week of exercise modalities that included mostly aerobic and some resistance training at 60–80% of HRmax (moderate-to-vigorous intensity). Although the exercise program did not have a significant effect on tic frequency, there were noticeable decrements of approximately 10–22% in tic severity. The author suggested that exercise training may improve tics by increasing serotonin levels and cerebral blood flow, regulating the dopaminergic system, and reducing stress [31].

In the preliminary study by Packer-Hopke and Motta [34], 5 male participants with TS and obsessive-compulsive disorder (age range: 9–13 years) engaged in a 6-week aerobic exercise program. Four of the 5 participants were on anti-tic medications (not specified). The exercise program consisted of two 30-minute sessions per week of aerobic exercise (i.e., aerobic kickboxing, dance aerobics, or Tae Bo) at moderate-to-vigorous intensity (i.e., 60–80% of HRmax). After the exercise program, there were reductions in YGTSS scores that ranged from 21 to 61% (i.e., from a severe to mild level) and in Tourette’s Disorder Scale-Parent Rated (TODS-PR) scores that ranged from 9 to 35%. Also, reductions in the number of tics per 5 minutes ranged from 32 to 91%. The improvement in tic expression was attributed to reduced anxiety associated with exercise [34].

3.3. Lasting effects of physical activity

Three of the 8 included studies further examined whether exercise-associated alleviation of tics was sustained after the intervention [30,31,34]. Nixon et al. [30] noted that tic frequency remained reduced for approximately 30 minutes following the bout of exercise. In the study by Simms [31], a 6-month follow-up survey revealed that the 8-week aerobic exercise program was associated with a sustained, but short-term, reduction in tic frequency in 75% of the participants. Packer-Hopke and Motta [34] assessed their participants for additional 4 weeks after the 6-week aerobic exercise program. Although all participants’ YGTSS scores at follow-up were lower than their average baseline scores, tic severity and frequency returned to the baseline level for 2 participants (40%) based on the TODS-PR and for 3 participants (60%) based on the number of tics per 5 minutes.
4. Discussion

There is still a paucity of research on the current topic owing to the absence of randomized controlled trials. Nevertheless, several points can be drawn from this review: 1) PA at light intensity may acutely alleviate tics, 2) PA at vigorous intensity may acutely exacerbate tics, 3) chronic PA participation may improve tics even at higher intensity, and 4) tics can return to their baseline severity or frequency after discontinuation of chronic PA.

4.1. Acute physical activity

Different types of light-intensity PA (e.g., stretching exercises) or PA at light intensity (e.g., sweeping and aerobic exercise at 43–63% of HR$_{\text{max}}$) were reported to have positive effects on tics [29,30,33]. Suggested mechanisms include sensory/motor tricks and reduced anxiety and stress. PA that requires the use of certain muscle groups and body movements may act as a trick (i.e., gestes antagonistes) that simply replaces tics [35,36]. Acute bouts of exercise may offer additional benefits by positively influencing moods, which is relevant to TS as anxiety and stress are key factors that exacerbate tics [17]. Nixon et al. [30] found that reductions in tic frequency corresponded with improvements in perceived anxiety and mood after an acute bout of aerobic exercise at light intensity. This is consistent with other studies demonstrating reduced levels of anxiety and increased levels of positive affect following acute bouts of exercise at light intensity [37,38]. Vigorous-intensity PA, such as jogging, can also offer positive affect; however, according to the case report by Jacombe [27], feelings of well-being from vigorous exercise may be outweighed by other exercise-related factors that may exacerbate tics (discussed below).

Higher-intensity PA seems to have a different effect on tics. Understanding the pharmacology of anti-tic medications and exercise physiology may help explain the potential association of vigorous-intensity PA with tic exacerbation. Agents that agonize the presynaptic alpha$_2$-adrenergic receptor, such as clonidine, are often prescribed for the treatment of TS [3]. These agents inhibit norepinephrine release from the presynaptic terminal, suggesting that there may be heightened central noradrenergic activity in TS [6–8]. Given the evidence that norepinephrine release is proportional to the intensity of PA [39–42], vigorous-intensity PA may acutely exacerbate tics by stimulating central noradrenergic activity. Also, mu-opioid receptor antagonists, such as naloxone and naltrexone, have been shown to reduce tics [43–46], suggesting that endogenous endorphins may also play a role in the pathophysiology of TS [8,9]. Studies show that these peptides are released in a significant amount only after vigorous-intensity PA [39,42,47], which may provide another explanation for tic exacerbation in response to vigorous-intensity PA [27]. Similarly, exercise (particularly at vigorous intensity) can significantly increase serotonin levels [48]. Although this may be of benefit to individuals with TS as serotonin levels tend to be reduced in this population [31,49], vigorous-intensity exercise can cause fatigue, for which an increased serotonin-to-dopamine ratio is believed to be a central mediating factor [50]. Fatigue is another factor highly associated with tic exacerbation [17]. Vigorous-intensity PA can also cause thermal stress that may exacerbate tics [28].

4.2. Chronic physical activity

Although the effects of acute PA on tics may be intensity-dependent, studies that examined the effects of chronic PA (ranging from 6 weeks to 6 months) demonstrated improvements in tic symptomology even at moderate-to-vigorous intensity [31–34]. This may be explained by several physiological adaptations associated with physical training. In TS, the evidence that alpha$_2$-adrenergic receptor agonists can treat tics suggests that autonomic imbalance (i.e., heightened central noradrenergic activity) may be associated with the illness [36–8]. Thus, the observed improvements in tic expression may be explained by sympathoinhibition and enhanced vagal outflow associated with physical training [51].

Also, dysregulation of the dopaminergic system may be another pathophysiological mechanism of TS. Studies using positron emission tomography suggest that amphetamine-induced striatal dopamine release is increased in individuals with TS [4,5]. There is evidence that physical training lowers basal extracellular dopamine levels as well as amphetamine-induced dopamine release in the rat striatum [52,53]. Moreover, a meta-analysis that included 2914 sedentary patients with a chronic illness has demonstrated that exercise training improves anxiety [54], which is a key factor that exacerbates tics [17].

Chronic or routine PA can be of benefit not only to the symptoms of TS, but also to the side effects associated with anti-tic medications. According to the 2011 European clinical guidelines for Tourette syndrome, antipsychotics, such as risperidone, and alpha$_2$-adrenergic receptor agonists, such as clonidine, are highly recommended by experts for the treatment of tics in children and
adolescents [3]. However, these medications are frequently associated with cardiovascular adverse effects, in particular orthostatic hypotension [3]. Exercise can counteract this side effect by increasing plasma volume (e.g., through aerobic training) and increasing muscle tone and thereby reducing venous pooling (e.g., through leg resistance training) [55,56]. Also, antipsychotics that are frequently used to treat tics, such as risperidone and haloperidol, bind strongly to dopamine D2 receptors, increasing the risk of extrapyramidal symptoms. An animal study has shown that physical training can alleviate haloperidol-induced extrapyramidal-like symptoms in rats [57]. Lastly, exercise can effectively manage cardiometabolic side effects (e.g., weight gain and dyslipidemia), which occur commonly with the use of second-generation antipsychotics, such as clozapine, olanzapine, and risperidone [58,59].

4.3. Limitations

There are limitations that require consideration. First, there is no randomized controlled trial to date examining the effects of PA on the symptoms of TS. Second, the majority of the included studies (i.e., 5 of the 8 studies) are case reports. The remaining 3 studies had small sample sizes and only one of them included a control group. Third, other than 3 studies, the relative intensity of PA was not provided via objective measures. However, this limitation could be addressed by approximating MET values using the 2013 Compendium of Physical Activities [25].

4.4. Conclusion

This review points to a trend that the effects of acute PA are intensity-dependent in TS, where light-intensity PA may alleviate and vigorous-intensity PA may exacerbate tics. However, chronic PA appears to be beneficial even at higher intensity. It should be noted, however, that there is still a paucity of evidence on this topic due to the absence of randomized controlled trials. Nevertheless, with current evidence, it is recommendable that individuals with TS should first engage in PA at light intensity and gradually increase it. When tics become severe during vigorous-intensity PA, one should attempt to decrease the intensity and gradually increase it back. As tics can return to their baseline levels after discontinuation of PA, one should engage in PA on a routine basis. Doing so may not only reduce tics, but will also offer a myriad of other mental and physical health benefits [15,23]. Future randomized controlled trials should investigate the effects of different intensities and types of PA on tic symptomatology. Studies should also better characterize other components of exercise prescription, such as exercise frequency and duration, in individuals with TS.

References