# Tic frequency and behavioural measures of cognitive control are improved in individuals with Tourette syndrome by aerobic exercise training.

Georgina M. Jackson[1], Elena Nixon[1†] and Stephen R. Jackson[2]

Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, UK[1]

School of Psychology, University of Nottingham, UK[2]

[†] Correspondence to:

Dr Elena Nixon

Division of Psychiatry and Applied Psychology

School of Medicine

The University of Nottingham

Nottingham, NG7 2TU, UK

Email: elena.nixon@nottingham.ac.uk

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***Abstract***

Previous observations of improvements in cognition in typically developing children following moderate to vigorous exercise (e.g. Budde, Voelcker-Rehage, Pietrabyk-Kendziorra, Ribeiro, and Tidow, 2008; Hillman et al., 2009) have led to increased interest in the potential benefits of exercise for children with neurodevelopmental disorders, involving difficulties in self-regulation (e.g. Halperin and Healy, 2011; Archer and Kostrzewa, 2012). Using a within-sample design, the current study looked at the beneficial effects of non-aerobic movement training (Tai Chi), compared to aerobic movement training (Kick Boxing), on behavioural measures of cognitive control and clinical measures of tic severity in a group of young people with Tourette Syndrome (TS). We demonstrate that Kick Boxing, but not Tai Chi, led to a significant enhancement in cognitive control task performance. Furthermore, while tic frequency (tics per minute) was reduced during both types of exercise, this reduction was significantly greater, and sustained for longer, following Kick Boxing. Importantly, the magnitude of the increase in cognitive control following Kick Boxing predicted the degree of reduction in tic frequency. These findings suggest that aerobic exercise may be a useful intervention for improving self-regulation of tics in young people with TS, probably through enhancements in associated cognitive control circuits.

***Introduction***

A number of common neurodevelopmental conditions, such as Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD) and Tourette Syndrome (TS), have been associated with impairments in the self-regulation of behaviour. In TS, impaired self-regulation is manifested through the presence of unwanted, repetitive vocalisations and movements, referred to respectively as vocal and motor tics, which typically begin around 6-7 years of age (Leckman, 2002). Premonitory urges, i.e. sensations preceding tics, are also commonly experienced in TS (Robertson, 2008). Tic severity varies between individuals in terms of frequency (ranging from multiple times an hour most hours of the day to tic free times an hour of the day); complexity (ranging from a single utterance or muscle movement to a complex sequence of vocalisations and movements) and intensity (from a barely noticeable utterance and movement to very obvious or forceful ones). The disorder typically follows a developmental time course in which tics seem to become increasingly more controlled during adolescence (Leckman, 2002) and fully or partially remit in adulthood (Groth, 2018; Hassan and Cavanna, 2012; Yaniv et al., 2018). Notably, however, many individuals who reported that they are in remission still have observable tics (Pappert, Goetz, Louis, Blasucci, and Leurgans, 2003). The cause of the decrease in tics over time is not known but it has been suggested that control of tics may be gained through the development of compensatory self-regulatory mechanisms, which are notably implemented by neural circuits linking frontal and primary and secondary motor regions (Plessen et al., 2004; Serrien, Orth, Evans, Lees, and Brown, 2005; Jackson et al., 2011).

Current tic severity is related to cognitive control ability, with less severe tics being associated with better performance on tasks requiring a high degree of control (Jackson , Mueller, Hambleton, and Hollis, 2007; Jackson et al., 2011; Jung, Jackson, Nam, Hollis, and Jackson, 2015; Yaniv et al., 2018). There are mixed findings as to whether there are differences in cognitive control performance in TS relative to controls. A recent meta-analysis of 61 studies using inhibitory control tasks showed small to medium effect size deficits in TS; importantly, it was also reported that tic severity was negatively associated with cognitive control ability (Morand-Beaulieu et al., 2017). Overall, the pattern of findings in TS children suggests that they may shift to a more controlled mode of responding to regulate their tics and potentially this adaptation to their executive control may be trainable (e.g. Eichele et al., 2010; 2016; 2017; Jackson et al. 2007; Jackson et al., 2011; Jung et al., 2015; Yaniv et al., 2018).

Recent studies in typically developing children have demonstrated improvements in cognition and executive control following moderate to vigorous exercise (Budde et al., 2008; Hillman et al., 2009), raising the potential of aerobic exercise for regulating the symptoms of hyperkinetic disorders through executive control training (e.g. Halperin and Healy, 2011; Archer & Kostrzewa, 2012). To date a few studies have shown post-exercise improvements in clinical symptomatology as well as cognition in children with neurodevelopmental disorders involving hyperkinetic symptomatology. A recent review of physical exercise interventions in ADHD suggested that physical activity, and in particular moderate to vigorous aerobic exercise, has beneficial effects in young people and adults with regard to several symptoms such as inattention and impulsivity, as well as functions, including cognitive and behavioural performance measured through attentional and response-time tasks (Den Heijer et al., 2017).

A limited number of studies looking at the effects of physical activity in TS symptomatology have been recently reviewed (Kim et al, 2018; Reilly, Grant, Bennett, Murphy, and Heyman, 2019) pointing to beneficial effects of exercise on tic frequency or severity. Only a few of these studies involved more than one participant and utilised experimental designs (e.g. Nixon, Glazebrook, Hollis, and Jackson, 2014; Packer-Hopke & Motta, 2014; Simms, 2005). Of these, the Nixon et al. (2014) study was the first to present an experimental demonstration of the effects of acute aerobic exercise on tic expression in a large group of young people with uncomplicated, i.e. comorbidity-free TS (n=18). Using video-based tic frequency estimates, we presented in this study preliminary evidence that a single bout of Kick Boxing resulted in a two-third reduction in tics during exercise, which was sustained below baseline levels for up to 30 minutes. However, the mechanisms that underlie the observed improvements in tic symptomatology associated with aerobic exercise are not known. Alterations in tic expression during exercise could be due to a number of factors contributing to the observed reductions in tic frequency or severity.

In light of the reviewed evidence demonstrating the beneficial effects of moderate to vigorous physical activity on executive functions (e.g. Diamond, 2015; Best, 2010) and the previously shown neural enhancements in TS associated with executive control training (e.g. Jackson et al., 2011), the present study aims to explore the potential link between exercise-induced improvements in cognitive control and tic reduction in TS. Specifically, we intend to investigate whether the decrease in tic frequency reported by the authors previously (Nixon et al., 2014) may have resulted from an exercise-induced improvement in cognitive control linked to high-intensity Kick Boxing training as compared to a control exercise type involving low-intensity body movement, i.e. Tai Chi training. Both Kick Boxing and Tai Chi training delivered in this study involved participants executing a series of movements instructed by a virtual coach (Exergame). As the presentation of the movements and mode of instruction is identical and equally demanding of attention in both types of exercise, Tai Chi training provides a sound control to Kick Boxing training. In the current study, we compared the beneficial effects of both aerobic movement training (Kick Boxing) and non-aerobic movement training (Tai-Chi) on behavioural measures of cognitive control that have been previously linked with tic frequency, and clinical measures of TS symptoms, in a group of young people with TS.

## Method

### Participants

In this section, we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. A total of 18 young participants with uncomplicated, i.e. comorbidity-free TS (13 Male/5 Female), aged 10 to 20 years were recruited to the study. All participants had a clinical diagnosis of TS. Twelve of the 18 participants displayed complex tic patterns in addition to simple motor and/or phonic tics. Of the 18 participants, 6 were on medication; 4 were on clonidine (participants 8, 11, 17 and 18), 3 on aripiprazole (participants 1, 6 and 18) and 1 on risperidone and sertraline (participant 6). Data from one participant (participant 6) was omitted from the analyses as they did not complete the behavioural task. The mean age of the remaining 17 participants was 14.4 years (SD=2.49; range=10.7-20.1). Participants were recruited through the UK charity Tourettes Action (TA). Exclusion criteria included: a clinical diagnosis of a comorbid psychiatric or mental disorder (e.g. ADHD or OCD), serious physical illness or handicaps, major neurological disease, and presence of severe learning disabilities. All participants were screened for suitability for performing the physical activity tasks. The inclusion criterion was a minimum of one discernible tic per minute (e.g. Himle, Woods, Piacentini, and Walkup, 2006). Sample size and recruitment criteria were established prior to determining the data analysis, manipulations and measurements in the study. The study was approved by the University of Nottingham Medical School Ethics Committee, in accordance with the ethical standards specified in the 1964 Declaration of Helsinki. Parents/carers and participants provided written consent and assent. Parents/carers received £10 to cover travel expenses while participants received an inconvenience allowance of £10 in shopping vouchers.

**Materials**

***Clinical assessment:***

- The Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989) is used to rate the type, frequency, duration, intensity and complexity of motor and vocal tics; and provides an overall impairment score and a global (motor+vocal+overall impairment) tic severity score.
- The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997) is a 10-item obsession-compulsion screening scale, each item being rated from 0 (no symptoms) to 40 (extreme symptoms); it includes questions on the amount of time the patient spends on obsessions and compulsions, the amount of distress they experience, and the extent to which they can exert control over such thoughts.
- The CONNERS- 3rd Edition- Parent (CONNERS; Multi-Health Systems, Inc., 2008) assesses the likelihood of whether a child has ADHD or ADHD-related problems.
- The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) contains 25 items that are grouped around the following psychological attributes: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and pro-social behaviour.
- An estimate of general cognitive ability was also obtained using the Wechsler Abbreviated Scale of Intelligence (WASI-II; The Psychological Corporation, 1999), two-subset form: vocabulary testing and matrix reasoning, yielding a full-scale IQ score.
- A Physical Activity Readiness Questionnaire (PARQ) was used as a mandatory screen to check that participation in exercise would not pose any problems to the young person's physical health.

***Saccadic task apparatus***

The cognitive control saccadic task was delivered via an Ober saccadometer (Ober Consulting, Poznan) which allows for the recording of eye movements. The saccadometer projects simple visual stimuli (coloured dots) onto a surface and records horizontal eye movements using infra-red oculography. It comes with a number of pre-programmed saccadic paradigms that include the randomly mixed pro-saccade and anti-saccade trial sequences used in the current study and in previous studies by the authors (e.g. Jung et al., 2015).

On each trial two dots were projected centrally onto a screen with one green dot presented immediately above a second, red dot. These two stimuli appeared briefly before disappearing to be replaced by only one of the two central dots (Green or Red) -- the instructional cue -- that was accompanied by a red peripheral target dot that could appear 10° to the left or right of the central cue. Depending on the colour of the instructional cue, participants were required to look either towards (pro-saccade) or away (anti-saccade) from the target dot positioned either to the left or the right of the centre dot. Pro-saccades are fast and accurate while anti-saccades are slower and prone to errors. This is because pro-direction movements are relatively automatic and can be triggered by the location of an object while anti-direction movements require greater cognitive control to prevent the pre-potent pro-direction action being executed, and this slows responses. Similarly, switch trials require more cognitive control than repeat trials as a change of task from a pro-saccade to an anti-saccade or vice versa is required (Monsell, 2003). Participants performed two blocks of 40 trials before and after each exercise. Trials were classified as either repeat or switch (see Figure 1) depending on whether they were preceded by the same task type (i.e. repeat trial: pro-saccade trial preceded by pro-saccade or anti-saccade trial preceded by anti-saccade trial) or the other task type (i.e. switch trial: pro-saccade preceded by anti-saccade or anti-saccade task preceded by a pro- saccade trial). The order of the presentation of the 40 trials within each of the two blocks was pseudo-randomised, containing 10 trials for each of the four possible trial case combinations (i.e. left anti-saccade; right anti-saccade; left pro-saccade; right pro-saccade). Experimental stimuli and presentation code were pre-programmed on and presented through the saccadometer device, and are not able to be exported beyond the hardware. An excel template of the saccadic task parameters is provided in Supplementary data (see Appendix A).

**Insert Figure 1 about here**

**Exercise task**

The exercise task was delivered through an X-Box 360 Kinect platform, using the Kick Boxing and Tai Chi exercise-based routines included in the 'Your Shape' DVD, and projected through a 23-inch Full HD 1080p Samsung widescreen LCD monitor. This mode was well-suited for use with video-based recordings for the purposes of tic monitoring; it ensured that participants' face and upper body would face the camera most of the time as participants had to follow the instructions of the virtual coach on the screen and remain in the target space in order to engage in the appropriate execution of the desired movements. A SONY DCR-DVD150E digital video-camera recorder was placed at a 2-metre distance from the point where the participant stood (whilst performing the exercise) or sat (during the pre- and post-exercise interviews). Participants were also fitted with a transmitter chest belt of a polar FT7 Heart Rate Monitor (Electro, Finland).

**Procedure**

All participants completed Kick Boxing and Tai Chi (in counterbalanced order) on two separate days (Session 1, Session 2) with a gap of approximately two weeks between each session. Both sessions followed a fixed order and the timing of each component (i.e. tic ratings, HR ratings and cognitive control data) was kept consistent within each participant between the two exercise types. Both sessions were video-recorded and the first session began with participants engaging in a clinical assessment pre-exercise interview that included administration of the YGTSS, CYBOCS, SDQ and WASI (with the YGTSS being repeated on the second session). Upon completion of this interview, participants were fitted with the HR monitor and proceeded with the non-clinical pre-exercise interview that included the administration of the PARQ and questions about hobbies and other leisure activities. This was followed by exercise training (Kick Boxing/Tai Chi). Each exercise lasted approximately 10 minutes. The saccadic task was performed immediately prior to and following exercise. Finally, a non-clinical post-exercise interview was carried out. Tic frequency was assessed during the non-clinical pre-exercise and post-exercise interviews to avoid the issue of tic-related conversation elevating tic frequencies (O'Connor, Brisebois, and Brault, 2003; Woods, Watson, Wolfe, Twohig, and Friman, 2001).

**Tic coding**

Tic classification and counting was performed using a professional video-editing tool (Ultimate Corel VideoStudio Pro x4). A continuous 5-minute time segment was sampled from the pre-exercise and post-exercise interviews, and the exercise training. Motor and vocal tics were counted and averaged per minute for each 5-minute segment by an experienced rater, in accordance with previous protocols (e.g. Himle et al., 2006).

## Statistical Analysis

To ensure equivalence in tic severity at baseline, a paired t-test was carried out to assess any differences in YGTSS between the Kick Boxing and Tai Chi. To control for any pre-exercise differences in heart rate and tic rate, percentage change measures were calculated for each exercise type. Exercise-induced percentage change in heart and tic rate were analysed using simple effects paired t-tests. The cognitive control data, i.e. mean reaction times (RTs) and accuracy percentage (%) for each condition, were entered into a 2 x 2 x 2 repeated measures ANOVA which included the factors: exercise type (Kick Boxing vs. Tai Chi), time period (pre vs. post exercise) and trial type (switch vs. repeat trial). Interactions were explored by computing the simple effects using paired t-tests. Hedges's g (g) was used to estimate effect sizes where necessary.

To explore the relationship between exercise and clinical symptoms, correlations were performed between ***switch cost RT*** (i.e. response time difference between task switch and task repeat trials pre- and post- exercise) and clinical severity (i.e. YGTSS and motor subscale scores); and ***switch RT*** (i.e. response time difference for switch trials pre- and post- exercise) and clinical severity (i.e. YGTSS and motor subscale scores).

Due to the sensitive nature of the study data and to ensure confidentiality as per University of Nottingham ethical guidelines, raw data supporting the reported results have been stored on limited-access folders and password-protected University of Nottingham servers. Anonymised electronic processed data will be provided to interested researchers upon request, and without conditions, by emailing the corresponding author. The primary raw data (non-anonymised) consists of patient videos and due to ethical restrictions cannot be made available to any individual outside the authors' research team. Digital study materials include either the X-Box (Kick Boxing and Tai Chi) programmes that are in the public domain and thus available to purchase, or standardised neuropsychological tests that are available from respective copyright holders in the cited references.

## Results

### Participants' clinical characteristics

As shown in Table 1, the mean (M) global YGTSS scores for Kick Boxing (M= 45.88, SD= 17.20; range= 19-78) and Tai Chi (M= 45.88, SD= 16.80; range= 19-78) were equivalent, indicating no difference in tic severity between the two sessions. Participants' mean scores on the other clinical measures were: CYBOCS, M= 6.35 (SD= 7.27); CONNERS, M= 67.35 (SD= 16.19); SDQ, M= 13.71 (SD= 7.10); and WASI, M= 98.71 (SD= 11.90) (see Table 1). Individual participant YGTSS (global, motor, phonic) scores for Kick Boxing and Tai Chi can be found in Table 2.

**Insert Tables 1 and 2 about here**

**Tic ratings**

There was a marginal difference in tic frequency in the non-clinical pre-exercise interviews between the two exercise types, with mean tic frequency being greater before Kick Boxing (KB) than Tai Chi (TC) [KB: M= 20.06 vs. TC: M= 23.81; t(16) = -1.958, p= 0.068; g= -0.22993]. Therefore, exercise-induced percentage change in tics was calculated.

Inspection of Figure 2 (B) indicates that, compared with pre-exercise levels, tics decreased substantially during both exercise types [KB: t(16)= -7.53, p< 0.0001; TC: t(16)= -2.14, p< 0.05]. Importantly, tic frequency decreased significantly more during Kick Boxing than during Tai Chi [KB: M= -59.76% vs. TC: M= -33.07%; t(16)= -3.288, p= 0.005; g= 0.32] and this difference between exercise types remained marginally significant after exercise had ended [KB: M= -21.74% vs. TC: M= -0.78%; t(16)= -2.007, p= 0.062; g= 0.32]. Importantly, whereas tic frequency following Kick Boxing continued to be reduced relative to baseline levels [t(16)= -3.99, p= 0.0011; g= -0.92], tic frequency returned to baseline levels following Tai Chi [t(16)= -0.1, p= 0.95; g= -0.02].

**Insert Figure 2 about here**

**Heart Rate (HR)**

Heart rate (HR) was significantly increased before Kick Boxing compared with Tai Chi (TC) [KB: M= 79.29 vs. TC: M= 74.59; t(16)= 2.679, p= 0.016; g= 0.61] which confirmed the need to measure exercise induced change in heart rate.

There was no significant difference in the mean percentage change in HR (relative to baseline, i.e. pre-exercise) during the two exercise types [KB: M= 33.82% vs.TC: M= 28.92%; t(16)= 0.988, p= 0.34; g= 0.32]. However post-exercise HR remained significantly elevated following Kick Boxing compared to Tai Chi [KB: M= 4.15% vs. TC: M= -1.11%; t(16)= 3.207, p= 0.005; g= 1.09] where HR returned to pre- exercise levels. Relevant data are presented in Figure 2 (A).

**Cognitive control task**

A repeated measures ANOVA conducted on the response time data revealed that there was no main effect of exercise type [F(1,16)= 0.09, p= 0.76], but there was a significant main effect of time period [F(1,16)= 11.71, p= 0.003] and a significant exercise type x time period interaction [F(1,16)= 10.19, p= 0.005]. Exploration of this interaction showed that improvement on the cognitive control task was found only after Kick Boxing [pre- KB: M=444.25ms vs. post-KB: M=378.49ms); t(16)= 4.328, p= 0.001; g=0.76], but not after Tai Chi [pre-TC: M= 415.51ms vs. post-TC: M=415.46ms; t(16)< 0.1, p= 0.996; g=0.001]. As expected, response times were significantly slower for task switch trials relative to task repeat trials [F(1,16)= 32.77, p= 0.00001]. However, this was the case for both exercise types [exercise type x trial type interaction: F(1,16)= 0.043, p= 0.83] and both time periods [time period x trial type interaction: F(1,16)= 3.32, p< 0.1]. Finally, there was a marginal 3-way interaction effect [exercise type x time period x trial type interaction: F(1,16)= 4.28, p= 0.06]. Relevant means are presented in Figure 3. An inspection of Figure 3 suggests that this may be driven by the greater decrease in RTs for switch trials relative to repeat trials in Kickboxing post exercise.

**Insert Figure 3 about here**

This pattern of results was replicated in the accuracy data, i.e. percentage (%) of errors. Specifically, the ANOVA revealed that there was no main effect of exercise type [F(1,16)= 0.29, p= 0.6] but a main effect of time period [F(1,16)= 7.09, p= 0.01]. Importantly, the exercise type x time period interaction was statistically significant [F(1,16)= 4.36, p= 0.05]. Relevant data are presented in Figure 4. Once again, improvements in cognitive control were seen following Kick Boxing [pre-KB: M= 27.70% vs. post-KB: M= 20.04%; t(16) = 3.465, p= 0.003; g=0.83], but not Tai Chi [pre-TC: M=25.16% vs. post-TC: M= 24.67%; t(16)= 0.203, p= 0.842; g=0.05]. As expected, accuracy was reduced for switch trials relative to repeat trials [F(1,16)= 38.65, p= 0.0001] for both types of exercise [task x trial type interaction: F(1,16)= 1.32, p= 0.27] and both time periods [session x trial type interaction: F(1,16)< 0.1, p= 0.38]. Finally, there was no significant 3-way interaction (exercise x time period x trial type interaction [F(1,16)= 0.47, p= 0.50].

**Insert Figure 4 about here**

**Cognitive control and clinical symptoms**

We examined whether changes in behavioural measures of cognitive control were associated with tic severity. Specifically, we examined whether the change in mean RT on switch trials (post-exercise – pre-exercise ***'switch RT'***) and the change in switch RT costs (Switch – Repeat RT ***'switch cost RT'***) were associated with tic severity (YGTSS) scores.

The magnitude of the improvement in cognitive control, as measured by the change in mean ***switch RT*** post vs. pre exercise, that was observed following Kick Boxing, was significantly associated with both global tic severity (YGTSS global score: r= 0.68, p= 0.0025) and motor tic severity (YGTSS motor tic subscale score: r= 0.53, p= 0.028). Relevant data are presented in Figure 5. Inspection of this figure illustrates that a greater improvement in cognitive control (i.e. a reduction in switch trial mean RT) was associated with having less severe tics. By contrast, the mean switch RT observed pre- and post- Tai Chi was associated with neither global tic severity (YGTSS global score: r= -0.37, p= 0.14) nor motor tic severity (YGTSS motor tic subscale score: r= -0.4, p= 0.11).

**Insert Figure 5 about here**

The improvement in cognitive control, as measured by the change in ***switch cost RT*** that was observed following Kick Boxing, was not significantly associated with either global tic severity (YGTSS global score: r= 0.31, p> 0.1) or motor tic severity (YGTSS motor tic subscale: r= 0.25, p> 0.1). Any improvement in cognitive control, as measured by the change in ***switch cost RT*** that was observed following Tai Chi, was not associated with either global tic severity (YGTSS global score: r= -0.26, p> 0.1) or motor tic severity (YGTSS motor tic subscale score: r= -0.34, p> 0.1).

## Discussion

In the current study we investigated whether a single session of aerobic exercise, i.e. Kick Boxing, led to an improvement in behavioural measures of cognitive control over motor outputs and/or a significant reduction in tic frequency in a group of young people with TS. Furthermore, to rule out alternative explanations, we directly compared the effects of a session of Kick Boxing against a closely matched session of Tai Chi. Importantly, while both types of exercise involved participants attending to a computer screen and executing a series of instructed movements delivered by a virtual coach, the Kick Boxing -- but not the Tai Chi— involved highly aerobic movement sequences. The results of the study indicated evident differences between Kick Boxing and Tai Chi on behavioural measures of cognitive control and tic frequency. The main results of the study are summarised below:

**Tic rate**: Kick Boxing and Tai Chi both resulted in a significant decrease in tic rate during exercise relative to baseline (pre-exercise). However, the decrease in tic rate was significantly greater for Kick Boxing compared to Tai Chi and also persisted after exercise had ended. Specifically, tic frequency continued to be reduced relative to baseline levels following Kick Boxing but returned to baseline levels after Tai Chi.

**Heart rate**: Kick Boxing and Tai Chi both increased heart rate relative to baseline (pre-exercise) levels, however only Kick Boxing produced elevated heart rate after the exercise had ended.

**Behavioural measures of cognitive control**: Cognitive control improved substantially following Kick Boxing but not following Tai Chi. This was the case for both RT and accuracy measures of cognitive performance. Importantly, improvements in cognitive control persisted after Kick Boxing had ended but this was not the case for Tai Chi.

**Relationship between cognitive control measures and clinical severity in TS:** The improvement in cognitive control following Kick Boxing was significantly associated with tic severity scores. Greater improvement in the most demanding trial type, i.e. switch trials, was associated with less severe tic symptomatology. By contrast, there was no relationship between cognitive control following Tai Chi and tic severity scores.

**Behavioural effects of aerobic exercise on cognitive control and tic severity in TS**

TS is a developmental neurological disorder that has been linked to dysfunction within cortical-striatal-thalamic-cortical brain circuits (Albin & Mink, 2006); specifically, the impaired operation of GABA (inhibitory) signalling within the striatum (Albin & Mink, 2006; Kalanithi et al., 2005) and cortical motor areas (Gilbert et al., 2004; Orth, Munchau, and Rothwell, 2008; Orth & Rothwell, 2009; Lerner et al., 2012), as well as hyper-excitability of limbic and motor regions of the brain that contribute to the occurrence of tics (Heise et al., 2010; Vaccarino, Kataoka, and Lennington,, 2013). Nonetheless, TS often follows a developmental time course that is characterised in many individuals by a *reduction* in the frequency and intensity of tics during adolescence (Leckman, 2002; Lerner et al., 2012).

It has been proposed that individuals with TS may gain control over their tics through the development of compensatory behavioural regulation mechanisms that lead to enhanced control over motor outputs (e.g. Mueller et al., 2006; Jackson et al., 2007; Plessen, Bansal, and Peterson, 2009; Jackson et al., 2011; Jung et al., 2015; Yaniv et al., 2018). Evidence for this is provided by behavioural studies of cognitive control over motor outputs which have shown that some individuals with TS may exhibit paradoxically *enhanced* volitional control over their motor behaviour (Mueller et al., 2006; Jackson et al., 2007; Jackson et al., 2011; Jung et al., 2015) and that *increased* cognitive control over motor outputs is associated with *decreased* tic severity scores (Jackson et al., 2007; Jackson et al., 2011; Yaniv et al., 2018). In the current study we found that cognitive control over motor outputs improved substantially in a group of individuals with TS following a session of Kick Boxing, but not following a similar session of Tai Chi, while this improvement was associated with decreases in tic severity scores. These findings are consistent with the growing body of evidence that links aerobic exercise with alterations in brain structure and function as well as improvements in cognition (Hillman et al, 2008). While aerobic exercise appears to benefit a wide range of cognitive processes, it is important to note that exercise disproportionally benefits cognitive control functions and the frontal brain areas that support them (Hillman, Erickson, and Kramer, 2008). It has been argued previously that decreases in tic severity may follow compensatory alterations in frontal lobe function and structure that give rise to increased cognitive control over motor outputs (Plessen et al., 2004; Serrien et al., 2005; Jackson et al., 2011).

An important question is why a similar session of Tai Chi did not produce increases in cognitive control or why any changes in cognitive control following Tai Chi were not associated with changes in tic severity. The presentation of the movements and mode of instruction was identical in both types of exercise and equally demanding of attention. However, in contrast to Kick Boxing, Tai Chi is not a highly aerobic form of exercise. This suggests that the improvements in behavioural measures of cognitive control and decreases in tic frequency that outlast the immediate period of exercise may result from alterations in brain function that are particularly associated with aerobic exercise. In this context, it is relevant to note that aerobic exercise interventions have frequently shown alterations in brain activity as measured by functional Magnetic Resonance Imaging (fMRI) relative to a low-aerobic exercise, e.g. a stretching or toning exercise (e.g. Hillman et al, 2008).

It has been suggested that enhanced control over motor outputs in TS, and the suppression of tics, might arise as a result of localised increases in 'tonic' inhibition (Draper et al., 2014; Jackson, Draper, Dyke, Pépés, and Jackson, 2015). Specifically, adaptation to chronic hyper-excitability may lead to the suppression of motor excitability through an alteration in the inhibitory tone of cortical motor areas (Jackson et al., 2015). This is consistent with fMRI studies that report decreased activation within primary and secondary motor areas during volitional movements in individuals with TS (Jackson et al., 2011) and with transcranial magnetic stimulation (TMS) studies which report that motor gain function is significantly reduced in individuals with TS (Orth et al., 2008**;** Draper et al., 2014; Draper et al., 2015). It is also consistent with a recent magnetic resonance spectroscopy (MRS) study of GABA concentration differences in TS which demonstrated that GABA concentrations within the supplementary motor area (SMA) – an area previously linked to the cortical genesis of tics in TS (Draper et al., 2014) - were significantly *elevated* in individuals with TS, relative to a group of carefully matched controls, and that MRS-GABA in the SMA was inversely related to fMRI blood-oxygen-level-dependent (BOLD) activation (Draper et al., 2014). By contrast, GABA concentrations in a non-motor control site (occipital cortex) did not differ from those of the matched control group (Draper et al., 2014). Most importantly, this study also found that MRS-GABA levels within the SMA were predicted by clinical measures of motor tic severity and by the microstructure of white-matter pathways projecting through the corpus callosum and connecting the SMA regions in each hemisphere (Draper et al., 2014). In this context it is therefore of relevance to note that a recent MRS study has demonstrated that a single session of high intensity aerobic exercise led to a 20% increase in MRS-GABA within the sensorimotor cortex (Coxon et al., 2017). Brain networks involving the sensorimotor cortex have been implicated in both the cortical generation of tics and also the experience of the premonitory urge to tic (see Conceiçã, Dias, Farinha, and Maia, 2017: for a review of these networks). It would be of interest to determine in future studies if high intensity aerobic exercise leads to a sustained reduction in premonitory urges.

## Study Limitations

Although the sample of the current study was relatively small, the within-subject design provided more power to detect changes across the two time periods separated by the exercise type. Results on ADHD and OCD measures indicated elevated symptoms in some individuals which may reach clinical threshold; however, these measures are not used as diagnostic tools and none of the participants in this study had received a formal diagnosis of comorbid TS at the time of participation. Future studies should use controlled designs with bigger samples to further examine the potential impact of comorbidity on exercise-induced improvement in cognitive control.

## Conclusions

The findings reported in this study indicate that aerobic exercise may provide a useful intervention for improving self-regulation of tics in young people with Tourette syndrome. The results of this study provide a preliminary evidence basis for clinical recommendations on adopting an active lifestyle. Potentially, exercise may be incorporated in clinical practice in conjunction with current therapeutic approaches.

The suggestion that the exercise-induced reductions in tic severity may occur through enhancement of cognitive control warrants investigation of brain mechanisms underlying exercise-induced cognitive control and tic symptomatology

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**Authors' Declaration of Conflict of Interest**

All authors (GMJ, EN and SRJ) declare no conflict of interest.

**Author Contributions**

GMJ was the Primary Investigator of the Lottery Grant award and oversaw all aspects of research design and activities. SRJ was involved in the design set-up and the analysis of the results. EN carried out the assessments and tasks described in the present study and was also involved in the design set-up and analysis of the results. All authors contributed to the write-up of this paper.

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