ABSTRACT

Older adults with Down syndrome are at greatly increased risk for dementia, Alzheimer’s disease, and functional decline compared to the general populations. Physical activity and fitness is associated with a lower risk of these ailments and greater independence in regards to activities of daily living. This study examined the effects of exercise on aerobic walking capacity and leisure physical activity levels in adults with Down syndrome (mean age = 39 years). All participants completed 8 weeks of stationary cycling exercise on 3 days per week. Four participants underwent Assisted Cycling Therapy (ACT), which meant that they cycled with the assistance of an electric motor which augmented their cadence to 135% of their voluntary cadence. The remaining four participants completed Voluntary Cycling (VC) and cycled without the motor at their own self-selected cadence and a light to moderate intensity. A reduction in leisure physical activity levels from pre- to post-test was observed in the VC group while the ACT group maintained their physical activity levels. The ACT group displayed improved aerobic walking capacity after the intervention as measured with the 6 minute walk test while the walking capacity of the VC group did not change. These findings are discussed in regards to the activitystat hypothesis and...
underlying neural mechanisms that may explain changes in leisure physical activity levels of the VC group and the improved walking capacity in the ACT group.

**Keywords:** Cardio respiratory fitness; Activitystat hypothesis; Central fatigue; Brain-derived neurotrophic factor; Neuroplasticity

**Abbreviations:** 6MWT = Six Minute Walk Test; ACT = Assisted Cycling Therapy; BDNF = Brain-Derived Neurotrophic Factor; CDC = Centers for Disease Control; DS = Down syndrome; GDNF = Glial-Derived Neurotrophic Factor VC = Voluntary Cycling

**INTRODUCTION**

The Centers for Disease Control (CDC) reports that about six thousand children per year are born with Down syndrome (DS) in the United States. This means that 1 in every 700 babies born will have DS [1]. Although individuals born with DS had a life expectancy of about 10 years or less in the 1970s, these individuals are now expected to live to their mid-50s [2]. Persons with DS often present with hypotonia and hyper mobile ligaments and adults with DS are at a greatly increased risk for deterioration in their vision, coordination, depth-perception and balance as well as dementia and Alzheimer’s disease [3,4].

The average cardio respiratory fitness of persons with DS is also below the general population average [5-7]. The reduced cardio respiratory fitness levels in people with DS has been found to impair their performance of functional tasks of daily living including getting up from a chair, walking speed, and ascending and descending stairs [8]. Low aerobic fitness levels have also been associated with an elevated risk of cardiovascular disease and mortality, and low cognitive function [9-11]. The risk factors of cardiovascular disease appear to be elevated as early as the childhood and adolescent years in persons with DS [12] and persons with DS possess relatively low levels of cognitive function [13]. Thus, exercise interventions which can improve or maintain the cardiovascular fitness of persons with DS are of special importance. However, the evidence from previous exercise intervention studies is too sparse to be able to recommend a type, frequency, intensity, and duration of activity that would effectively improve cardiorespiratory fitness levels in individuals with DS [14].

The single most powerful modifier of fitness, besides genetics, is physical activity [10,15,16]. However, only moderate to vigorous leisure physical activity levels have been found to share a positive relationship with cardiorespiratory fitness [17]. Unfortunately, leisure physical activity levels are reduced in persons with DS compared with the general population and persons with DS may not engage in sufficient amounts of moderate to vigorous physical activity [18-20].

In the typical population, it has been shown that exercise improves physical health and function [21-23]. However, the voluntary aspect of exercise may impose limitations for persons with disabilities, including DS. Persons with DS may not be able to sustain exercise intensities and rates of movement that are necessary for improvements in fitness and motor function [24-
Individuals with DS have lower cardiorespiratory fitness levels, poor motor control, reduced movement speed, lower muscular strength, and reduced exercise tolerance and motivation compared to individuals without DS [27-31]. Previous physical activity interventions have shown very limited success in improving the fitness level of persons with DS [14,32].

A Novel Exercise Modality – Assisted Cycling Therapy

Assisted exercise may be a safe and effective approach to augment voluntary movement rates and time spent exercising. This paradigm first emerged in studies with animals which were exercised on a motorized treadmill at a rate greater than their voluntary running pace [33,34]. The rodents experienced neuroplasticity in the brain which includes neuroprotection, neurogenesis and increased neuronal density and these changes were partially explained by the up regulation of Glial-Derived Neurotrophic Factor (GDNF) and Brain-Derived Neurotrophic Factor (BDNF) [34].

It may not be feasible, however, to exercise humans on a treadmill at greater than voluntary rates and to force them to keep going for longer than they want to. This would likely lead to very low exercise compliance and, for ethical reasons, participants cannot be forced to exercise, unlike rodents, when they do not want to. Instead, bicycles have been used for assisted exercise studies in human beings. The first study in this line of research was completed with patients with Parkinson’s disease [35,36]. A tandem bicycle was used with a trainer on the front seat and a patient on the back seat (Figure 1) [36]. The trainer ensured that the cycling cadence was maintained at approximately 86 rpm by increasing or decreasing his or her power contribution when the patient’s power output was low or high, respectively. This assisted cadence was approximately 30% faster than the voluntary cadence of patients who exercised without a trainer. Eight weeks of assisted cycling with the trainer resulted in greater improvements in upper extremity motor function and clinical function than eight weeks of Voluntary Cycling (VC) [9]. Since this initial study, other studies have used stationary, recumbent bicycles with an electric motor instead of a trainer to augment the cadence of the participants. Ridgel and colleagues [9] found that a single bout of assisted cycling on a stationary bicycle can acutely reduce tremor and improve bradykinesia in people with Parkinson’s disease. In fact, the first trial with patients with Parkinson’s disease revealed that cortical and subcortical activation patterns after assisted cycling were similar to the activations patterns when patients were on antiparkinsonian medication [34]. This most likely indicates that assisted cycling results in the upregulation of dopamine which would mimic the effect of dopaminergic pharmacotherapy. Additionally, the patients in the VC group had approximately the same heart rate during exercise bouts as the participants in the assisted cycling group. This indicates that improvements in motor function, bradykinesia, and tremor following assisted cycling were not due to the cardiovascular stimulus of the exercise. Otherwise, the VC group should have experienced similar improvements. In fact, the voluntary cyclers should have experienced slightly greater improvements because their average heart rates and power output were slightly higher than those of the assisted cyclers. Instead, increased and more consistent
afferent corticospinal stimulation induced by assisted cycling has been hypothesized to be part of the causal link between assisted cycling and improved motor function.

Figure 1: Tandem bicycle set-up for initial intervention trial in persons with Parkinson’s disease. The front fork was secured and the trainer rode in the front and the patient in the back. (Ridgel et al., 2009).

The mechanical stimulation of somatosensory receptors through movement of the limbs has been shown to stimulate cortical activation and is thought to upregulate GDNF, BDNF and other growth factors [34]. Assisted cycling, compared to VC, appears to result in more consistent and frequent afferent sensory input to cortical and other brain structures [24,34,36-38]. The rate of movement is of particular importance as greater movement rates have been shown to result in greater cortical activation [39]. Assisted cycling may result in greater afferent stimulation due to greater flexion and extension moments of force in the lower extremity musculature which in turn activates velocity dependent muscle spindle fibers [37,40]. Activated muscle spindle fibers in turn send proprioceptive information to cortical areas and as a result stimulate corticospinal excitability [37].

After the initial trial in persons with Parkinson’s disease, the assisted cycling paradigm has been and is still being tested in persons with DS. In these studies, assisted cycling is termed Assisted Cycling Therapy (ACT). An initial pilot study with adolescents and young adults with DS revealed that a single 30 minute (min) bout of ACT lead to greater improvements in cognitive planning ability, reaction time, and fine manual dexterity than a single 30 min bout of VC [25]. The acute effects of ACT and VC were also compared in adolescents with autism spectrum disorder. Inhibition, cognitive control, and set-shifting improved only after ACT. These two studies indicated that arousal and cortical activation allowed for acute improvements in
cognitive function and global motor function. These pilot studies were followed by an eight week intervention where adolescents with DS were randomized to eight weeks of ACT, VC, or no cycling [24,39]. Improvements in cognitive planning ability, inhibitory control, reaction time, and manual dexterity were greatest after ACT. Improvements in set-shifting ability were greatest after VC and verbal fluency was improved after both ACT and VC. These results are heavily in favor of assisted cycling and they indicate that ACT is more effective than VC in stimulating neuroplasticity in the prefrontal and motor cortex. The prefrontal cortex seems to benefit as it is the main control center for executive functions such as planning, inhibition, reaction time, and set-shifting [41-48]. The motor cortex is the control center for global motor function [49,50] and also appears to benefit more from ACT.

We have recently applied the ACT intervention to adults with DS aged 30 or older. ACT holds promise as an effective intervention for adults with DS as they age because they are at a greatly increased risk for Alzheimer’s disease [4,51-54]. Improvements in cognitive and motor function and continued physical activity participation could help delay the onset of Alzheimer’s disease or slow its progression [55-57]. Here we report the effects of eight weeks of ACT and VC on leisure physical activity levels and aerobic exercise capacity in adults with DS aged 30 or older. We hypothesized that both interventions would result in an increased exercise capacity but our hypothesis regarding leisure physical activity levels was non-directional. This is the first study to investigate the effects of ACT on aerobic exercise capacity and physical activity levels in persons with DS.

**METHODS**

**Participants**

Eight adults with DS (3 male, 5 female) were recruited from the local community. Participant characteristics are listed in Table 1. On average, participants were 39.2 ± 6.4 (mean ± SD) years old, displayed a mental age of 6.0 ± 2.0 years, and had a BMI of 30.1 ± 9.6 kg/m². Participants did not present with other developmental disabilities, psychological, or psychiatric disorders. Participants had no contraindications to moderate or vigorous physical activity and no physical impairments that would have precluded lower extremity cycling exercise. The participants were introduced to the lab and equipment and read (or were read to) and signed assent forms. For all participants, parents or guardians signed a consent form before data collection began. All protocols were approved by the Human Subjects Institutional Review Board of our University and the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.
Table 1: Participant characteristics and pre- and post-test scores

| Condition | Participant | Gender | CA (years) | MA (years) | BMI (kg/m²) | Godin<sub>pre</sub> | Godin<sub>post</sub> | 6MWT<sub>pre</sub> (m) | 6MWT<sub>post</sub> (m) |
|-----------|-------------|--------|------------|------------|-------------|----------------|----------------|----------------|----------------|---|
| ACT       | 1           | f      | 51.1       | 3.4        | 22.3        | 6.0            | 22.0           | 182.9           | 221.2           |
| ACT       | 2           | m      | 32.6       | 8.8        | 32.5        | 53.0           | 53.0           | 375.0           | 420.7           |
| ACT       | 3           | f      | 38.5       | 5.5        | 43.6        | 10.0           | 14.0           | 228.7           | 274.4           |
| ACT       | 4           | f      | 31.6       | 8.7        | 16.6        | 20.0           | 12.0           | 265.2           | 329.3           |
| Mean<sub>ACTION</sub>± SD<sub>ACTION</sub> | |     | 38.4 ± 7.8 | 6.6 ± 2.2 | 28.8 ±10.3 | 22.3 ±18.5 | 25.3 ±16.5 | 263.0 ± 71.0* | 311.4 ± 73.8* |
| VC        | 5           | f      | 35.3       | 6.8        | 45.4        | 23.5           | 13.0           | 292.7           | 285.7           |
| VC        | 6           | m      | 40.2       | 6.8        | 32.0        | 33.0           | 3.0            | 365.9           | 372.9           |
| VC        | 7           | m      | 47.1       | 4.3        | 23.6        | 18.0           | 10.5           | 201.2           | 208.4           |
| VC        | 8           | m      | 37.4       | 3.8        | 24.4        | 51.5           | 31.5           | 274.4           | 266.5           |
| Mean<sub>VOC</sub>± SD<sub>VOC</sub> | |     | 40.0 ± 4.5 | 5.4 ± 1.4 | 31.4 ± 8.7 | 31.5 ± 12.7* | 14.5 ± 10.5* | 283.5 ± 58.6   | 283.4 ± 59.0   |
| Mean<sub>Comb</sub>± SD<sub>Comb</sub> | |     | 39.2 ± 6.4 | 6.0 ± 2.0 | 30.1 ± 9.6 | 26.9 ± 16.5 | 19.9 ± 14.8 | 273.2 ± 65.9   | 297.4 ± 68.2   |

**Note**: Abbreviations: **ACT** = Assisted Cycling Therapy, **VC** = Voluntary Cycling, **CA** = Chronological Age, **MA** = Mental Age, **BMI** = Body Mass Index, **6MWT** = 6 Minute Walk Test, **SD** = Standard Deviation

**Baseline and Outcome Measures**

Vision was assessed with a modified Kindergarten Snellen Eye Chart and hearing was assessed with an audiometer (Maico Ma 25, Maico Hearing Instruments, Minneapolis, MN). All participants had functional vision and hearing for the purpose of testing. Mental age was assessed using the Peabody Picture Vocabulary test (4<sup>th</sup> Ed.; PPVT-IV [58]) during the first visit. Height and weight were measured to the nearest mm and 0.1 kg, respectively.

The parent or guardian of each participant completed the Godin’s Leisure Time Physical Activity Questionnaire [59] to determine the amount and type of physical activity their child completed in the week prior to coming into the lab. The Godin questionnaire was filled out during pre- and again during post-testing. On the questionnaire, the respondent lists the weekly frequencies of light, moderate, and strenuous physical activity bouts which were at least 15 min of duration not including the intervention (ACT or VC) exercise sessions. These frequencies are then multiplied by three, five, and nine, respectively. Finally, the scores for light, moderate, and strenuous physical activity are added together into a composite physical activity score (Godin score). The weighting factors (3, 5, or 9) correspond with Metabolic Equivalents (METs) for each activity category, whereas one MET, or a weighting factor of one, would be equivalent to a person’s average energy expenditure per min at rest. For example, in this questionnaire, light physical activities are deemed equal to an energy expenditure per minute that is three times greater than the energy expenditure at rest. The U.S. Surgeon General physical activity recommendations call for an equivalent of at least 14 Godin points for health benefits [59,60]. The Godin questionnaire has been shown to have good test-retest reliability and it correlated well with other self-report measures of physical activity and with daily energy expenditure [61].
The participants completed a Six Minute Walk Test (6MWT) during pre- and post-testing to assess their exercise capacity. This test is often used as a measure of cardio respiratory fitness for persons with disabilities [62-64] and it has been used to predict VO\textsubscript{2} max in persons without DS [65,66]. It has been shown to have acceptable test-retest reliability for adolescents and young adults with DS [67]. The 6MWT was completed indoors around two cones which were spaced 30 ft. apart. The participants were instructed to walk as fast as possible, without running, in order to complete as many laps as possible. A researcher walked the first 2-3 laps with the participant, if necessary, to familiarize the participant with the task. Participants were encouraged and provided with positive feedback throughout the test. The number of completed laps was recorded and any additional distance the participant walked if they did not complete the last lap they started.

### Design and Intervention

Upon completion of pre-testing, participants were randomized to eight weeks of VC or eight weeks of ACT. Cycling sessions took place on non-consecutive days of the week. Three cycling sessions per week for a total of 24 cycling sessions across 8 weeks were completed. Two participants missed one cycling session each which lead to an overall compliance rate of 99.0 %. The resistance was kept on the lowest setting (≈ 0.5 kp) for all participants during all sessions in the VC condition. VC sessions consisted of a 5 min warm-up followed by a 30 min cycling session. The warm-up data was discarded and not used for further analysis because heart rates and cadences tended to be lower and fluctuate more during the first 5 min. Participants in the VC condition were instructed to pedal at their own, preferred cadence against minimal resistance. Participants were encouraged to keep cycling if they stopped and every participant continued to cycle within 1-5 seconds of encouragement. Voluntary stops by participants were very rare.

On the first day of the eight week intervention, all participants regardless of the intervention type were instructed to pedal as fast as they could for 60 seconds against minimal resistance, following the warm up. We will refer to this as the 1-min cadence test. The average cadence during this 1-min test was recorded. The 1-min cadence test was repeated during the last cycling session at the end of the eight weeks.

The ACT sessions began with a 5 min voluntary warm-up against minimal resistance. Following the warm-up or 1-min cadence test, the electric motor in the bicycle was turned on and set to a cadence which was 35% faster than the cadence during the 1-min test. The motor maintained this cadence for the 30 min cycling session. The cadence was only lowered if participants expressed discomfort due to the cadence. This was the case for one participant during the first cycling session. The cadence was lowered by 10 rpm and then increased slightly from session to session. The participant reached and maintained the target cadence from session 6 on. One participant in the ACT condition, for unknown reasons, refused to continue cycling after 19 min of ACT on one occasion only. The participant did not want to disclose their reason for stopping.

To assess the maximal voluntary cadence, each participant also completed a 10 second sprint
against minimal resistance during the last 5 min of each cycling session. Participants were instructed to pedal as fast as they could until their cadence did not increase anymore and the researcher instructed them to slow down. Participants were encouraged during the sprint. Pre- and post-testing occurred at least 48 hours before the first cycling session and 48 hours after the last cycling session, respectively.

The Bicycle

A Theracycle (Exercycle, Franklin, MA) which was built for research purposes, was used for this study (Figure 2). This is a specialized stationary recumbent bicycle that contains an electric motor which can transmit power to the crank arms. The motor can be programmed to turn the crank arms at a desired cadence regardless of the power contribution by the participant. Thus, control mechanisms in the bike monitored the power contribution by the participant and the motor continuously adjusted its power contribution to maintain the set cadence.

Figure 2: Theracycle (Exercycle, Franklin, MA) research model. 1) Time and cadence control panel with time and cadence display, 2) SRM (Schoberer-Rad Messtechnik, Jülich, Germany) Powercontrol V, 3) magnetic resistance belt, 4) electric motor, 5) pedal arm fulcrum (the SRM Powermeter is incorporated in the crank arm located on the other side), 6) lever to adjust seat horizontally, 7) resistance dial, 8) magnetic safety tether.
As mentioned above, the motor was programmed to maintain a cadence that was 35% faster than the 1-min cadence of the participants in the ACT group. The bicycle was equipped with platform pedals with a strap and cage device to assist in holding participants’ feet stable while cycling at a fast rate. Some of the bicycle’s safety features and other features are indicated in Figure 2. The participants were fitted with a Polar heart rate monitor (Polar Electro, Kempele, Finland). The SRM Powercontrol V (Schoberer-Rad Messtechnik, Jülich, Germany) which was mounted on the bicycle displayed the participants’ heart rate (bpm) and cadence (rpm).

**Data Analysis**

The VC and ACT groups were analyzed independently to test for changes in the outcome measures (i.e. Godin score and 6MWT distance) from pre- to post-test. Two-tailed paired sample t-tests were conducted despite low sample sizes due to normal distribution of the data and sufficient intervention effects for statistical significance. The t-tests were repeated for each dependent measure. The average intervention cadence, heart rate, and sprint cadence were compared between groups using independent sample t-tests. The average 1-min cadence was compared between pre- and post-tests within each group using paired sample t-tests. The average 1-min cadence of the VC group at each time point was also compared to the average 1-min cadence of the ACT group at each corresponding time point using independent samples t-test (comparisons: VC,ACT

|RESULTS |

Table 1 summarizes the baseline measures and outcome measures at each time point for each participant. There were no statistical differences between the two groups in regards to chronological age, mental age, or BMI.

Moreover, group differences in Godin score and 6MWT distance were not significant at pre-test. The physical activity level of the ACT group, as indicated by the Godin score, did not change across the intervention (Figure 3). The Godin score of the VC group was significantly reduced after the intervention (post-test) as compared to before the intervention (pre-test; Figure 3). The ACT group showed a significant improvement in 6MWT distance from pre- to post-test (Figure 4). The 6MWT distance of the VC group did not change (Figure 4).
Figure 3: Godin score by intervention and time point. Abbreviations: ACT = Assisted Cycling Therapy, VC = Voluntary Cycling.

*Significant mean difference between pre- and post-test mean (p< 0.05)

Figure 4: 6MWT distance by intervention and time point. Abbreviations: 6MWT = Six Minute Walk Test, ACT = Assisted Cycling Therapy, VC = Voluntary Cycling.

*Significant mean difference between pre- and post-test (p< 0.05)

As expected, the mean intervention cadence of the VC group was significantly slower than the intervention cadence of the ACT group (see Table 2 & Figure 5). During the cycling sessions, the heart rates in the ACT group were slightly lower than the heart rates in the VC group (Table 2 & Figure 5).
Table 2: Heart and cadence measures by group (mean ± standard error)

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACT</th>
<th>VC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>87.1 ± 3.0</td>
<td>90.7 ± 3.3**</td>
</tr>
<tr>
<td>Cad_{interv.}</td>
<td>69.5 ± 2.7</td>
<td>39.2 ± 2.5**</td>
</tr>
<tr>
<td>Cad_{1-min}</td>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td></td>
<td>44.0 ± 8.0</td>
<td>61.8 ± 5.2</td>
</tr>
<tr>
<td>Cad_{max}</td>
<td>79.1 ± 6.3</td>
<td>112.3 ± 7.0</td>
</tr>
</tbody>
</table>

Note. Abbreviations: ACT = Assisted Cycling Therapy, VC = voluntary cycling, HR = average Heart Rate during the intervention, Cad_{interv.} = average intervention cadence that was maintained during cycling sessions, Cad_{1-min} = average cadence during the 1-min cadence test before (pre) and after (post) the intervention, Cad_{max} = highest cadence achieved during sprint test (the cadences of the first three cycling sessions (pre) and the cadence of the last three cycling sessions (post) were averaged).

The maximal cadences of each day were averaged across the intervention (24 days) and the average maximal cadence of the ACT group was compared to the average maximal cadence of the VC group using an independent samples t-test. However, the pre- and post-test cadence shown in this table represents the average maximal cadence across the first four and four last intervention days, respectively.

*significant group difference (p < 0.05)

Figure 5: Average intervention cadence and heart rate by group and day. Abbreviations: Cad = Cadence, HR = Heart Rate, ACT = Assisted Cycling Therapy, VC = Voluntary Cycling.

*Significant mean differences between pre- and post-test mean (p< 0.01)

The 1-min cadence improved non-significantly in the ACT group and deteriorated slightly in the VC group (Table 2 & Figure 6). The 1-min cadence did not differ between groups during pre-testing but the ACT group produced a significantly faster 1-min cadence than the VC group during post-testing (Table 2 & Figure 6).
Figure 6: Individual and average cadence during first (pre) and last (post) cycling session of the 1-min test. Abbreviations: rpm = Revolutions per Minute, ACT = Assisted Cycling Therapy, VC = Voluntary Cycling.

*Significant mean differences between ACT and VC during post-testing (p< 0.05)

Lastly, the sprint cadence improved in the ACT group across the eight weeks but not in the VC group (Table 2 & Figure 7). On average, the ACT group produced a significantly faster maximal cadence than the VC group (Figure 7).

Figure 7: Average daily sprint cadence by group across the intervention. Abbreviations: ACT = Assisted Cycling Therapy, VC = voluntary cycling.

*Significant mean differences between ACT and VC (p< 0.001)
DISCUSSION

This was the first study to examine the effect of exercise, specifically ACT, on aerobic exercise capacity and leisure physical activity levels in older adults with DS. The results only partially support our first hypothesis of improved 6MWT distance following ACT and VC. The mean distance walked only improved in the ACT group while the mean distance of the VC group did not change. We did not predict the direction of change in leisure physical activity levels as an increase, maintenance, or decrease could have been argued for.

For instance, the activity stat hypothesis postulates that an increase in physical activity in one domain is counterbalanced by a decrease in physical activity in another domain to keep total physical activity levels relatively constant [68-70]. Therefore, an increase in physical activity due to the ACT or VC interventions may have been compensated by less activity during the rest of the day or on other days of the week. Hence, a Godin leisure physical activity score that did not change from pre- to post-testing would indicate that compensation for the physical activity obtained through the intervention did not occur, because the Godin score only included leisure physical activity outside of the intervention. On the other hand, a reduced Godin score would show that physical activity levels outside of the intervention decreased indicating compensation for the increase in activity due to the intervention. The opposite of the activity stat hypothesis is activity synergy [70]. Goodman and colleagues [70] found that small increases in moderate to vigorous physical activity of children through structured play or sports lead to small increases in moderate to vigorous physical activity in other settings. However, the current results do not support the activity synergy hypothesis because Godin scores did not increase.

Instead, the ACT group maintained leisure physical activity levels, but the VC group reduced their activity levels. Hence, compensation for the increase in physical activity obtained through VC seems to have occurred in the VC group, in accordance with the activity stat hypothesis, whereas the ACT group did not compensate. It has been argued that each individual has an activity set point which is centrally controlled by the brain [68]. If there is a central executive, in theory referred to as the sensor, integrator, and effector, which regulates physical activity around a set point, then many questions, remain unanswered in light of the present findings. For instance, why did compensation only occur in the VC group? Do humans only compensate for certain types of activities? Does the origin of the movement production (i.e. internal and voluntary or external and assisted) differentially affect the activity stat? In the case of VC, the cycling movement is produced through efferent signals from the central nervous system, but in the case of ACT, movement is mainly passive with more frequent and consistent afference. Perhaps, the efferent nature of movement production is a necessary quality for physical activity in order for the central executive to recognize it as such. This leads to the question if fatigue of the central nervous system, termed central fatigue, plays a role in the reduction of physical activity [71,72]?
Certain neurological disorders such as multiple sclerosis, post pollomyelltis, stroke, and chronic fatigue syndrome are often associated with central fatigue [73]. Central fatigue manifests as an increase in perceived exertion and the inability to sustain physical and/or mental efforts [73]. Persons with DS are often diagnosed with symptoms of central fatigue such as depressed mood, psychomotor slowing, slow reaction times, reduced muscular strength, low exercise tolerance, and general fatigue [31,74-76]. More specifically, central fatigue after exercise has been demonstrated. A reduction in motor evoked potentials following exercise indicates fatigue in the motor cortex and efferent motor neurons [73]. The resulting increase in effort to produce movement could explain increased inactivity following exercise and provide a biological basis for the activitystat hypothesis in regards to voluntary exercise. The increase in the 1-min maximal cadence and maximal sprint cadence of the ACT group across the eight week intervention (Figure 6 & 7) indicates that the ACT intervention did not induce central fatigue because maximal short duration movement rates depend on efferent drive from the central nervous system rather than aerobic fitness. A shift from slow twitch (myosin heavy chain I) to fast twitch muscle fibers (myosin heavy chain II) is unlikely to explain the increased voluntary movement output in the ACT group as the 1-min and sprint test were done against minimal resistance and because the ACT intervention was aerobic and of low intensity.

Reduced muscular strength in persons with DS, is likely to be caused by lower lean tissue volume and maybe neurological limitations [12,77] including the factors that contribute to lower muscle tone (hypotonia) [78]. Hypotonia may be caused by reduced alpha-gamma co-activation, and therefore hypotonia has been linked to abnormalities in the frontal and motor cortex, basal ganglia, and cerebellum [79-81]. Fatigue, caused by exercise, may be associated with hypotonia [82,83] and hypotonia is commonly associated with low physical activity tolerance and levels [84]. Thus, if exercise causes an exacerbation in hypotonia then it might also lead to a reduction in physical activity. Exercise has also been proposed to induce central fatigue through the upregulation of serotonin in the central nervous system which in turn causes lethargy and loss of motivation [72]. Thus, it may be possible that central fatigue and an upregulation of serotonin through VC may have led to decreased physical activity levels outside of the intervention.

The differences in the maintenance of physical activity levels between the VC and ACT groups may also be partially due to differential changes in self-efficacy due to perceived levels of exertion or enjoyment. Future studies will explore the relationship between ratings of perceived exertion, enjoyment, self-efficacy, and leisure physical activity because enjoyment and self-efficacy can also influence activity behavior [85,86].

The increase in 6MWT distance in the ACT group is consistent with the findings of the 8-week cycling intervention study with patients with Parkinson’s disease by Ridgel et al. [36]which demonstrated that assisted cycling but not VC, produced global improvements in motor function. The findings of Ridgel’s [36] study, as well as our study, are consistent with animal model studies suggesting that exercise rate is an important factor contributing to the positive effects of exercise
on motor function [33]. Maybe the limitation in 6MWT distance for persons with DS is mostly neurological as only ACT improved.

It may be that less fatigue and stress due to exercise in those in the ACT group compared to those in the VC group allowed for better neurological adaptations. The upregulation of BDNF and other growth factors has been implicated as the mechanism for neural plasticity in cortical regions of the brain following exercise [34,35]. Stress, e.g. vigorous intensity exercise, has been shown to upregulate cortisol levels which in turn counteract neural plasticity [87-90]. Previous results also indicate that the increased movement rate during ACT is more effective in stimulating neuroplasticity than voluntary movement rates [24,35]. Hence, increased neuronal density and plasticity in motor areas of the cortex may have allowed for greater efferent stimulation of locomotor muscles and thus allowed the participants in the ACT group to walk further in 6 min. This increased stimulation of effectors as the mechanism explaining the increased 6MWT is also supported by the improvement in 1-min and sprint cadence across the eight week ACT intervention (Figure 6, Figure 7).

Agiovlasitis et al. [91] found that, after controlling for walking speed, gait patterns common to individuals with DS are more energetically costly and are associated with a higher net metabolic rate compared to their typically developing counterparts. Individuals with DS walk with greater center of mass mediolateral motion, more variable center of mass anterio-posterior velocity, greater step width variability, and greater step length variability. These characteristics collectively suggest a less precise control of body motion and difficulty maintaining stability during walking for this population. The results of the current study are particularly important because interventions that improve the distance able to be walked and the walking speed of individuals with DS can lead to improvements in their mobility and overall health [91].

**CONCLUSION**

The 6MWT is typically used as an assessment of cardiovascular fitness [62-66]. The improvement in the ACT group suggests that their aerobic fitness and exercise capacity was improved while leisure physical activity levels were maintained. These findings have important implications for older adults with DS because they are at greatly increased risk for dementia and Alzheimer’s disease [4] as both physical fitness and physical activity are associated with lower risks of dementia and Alzheimer’s disease [55-57]. Therefore, an assisted form of exercise, such as ACT, which augments voluntary movement rates, could help persons with DS preserve their ability to perform activities of daily living and retain more of their functional independence.

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