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Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome

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Abstract

Background—Between 250,000 and 400,000 individuals in the United States are diagnosed with Down syndrome (DS). Nearly all adults with DS will develop Alzheimer's disease pathology starting in their thirties. Recent studies suggest that increased physical activity (PA) may be important for maintaining components of cognition, including memory.

Objective—The purpose of this study was to evaluate changes in cognitive function after completion of a 12-week exercise intervention in adults with DS.

Methods—Participants were randomized to attend 30-minute group exercise sessions 1 or 2 times a week for 12 weeks. The exercise sessions were delivered via video conferencing on a tablet computer to groups of 5–8 participants. Sessions consisted of aerobic based exercises such as walking and jogging to music, dancing, as well as strength based exercises such as vertical jumps, bicep curls, and squats. Cognitive function was measured at baseline and end of study using the Cantab Dementia Battery for iPads, which assessed the cognitive domains of memory, attention, and reaction time.

Results—Twenty-seven participants (27.9 ± 7.1 years of age, 40.7% female) enrolled and completed the 12-week intervention. Participants randomized to 1 session/week averaged 26.6 ± 3.0 mins/week of PA from the group exercise session. Participants randomized to 2 sessions/week averaged 57.7 ± 15.3 mins/week of PA from the group exercise sessions. Participants improved their performance on the two memory variables (p=0.048 and p=0.069).

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Conclusion—Increased exercise may have positive changes on memory and other cognitive functions.

Keywords

Down syndrome; exercise; cognitive function; memory; physical activity

INTRODUCTION

Nearly all adults with Down Syndrome (DS) will develop Alzheimer's disease (AD) pathology starting in their thirties. Based on a current lifespan of 55 to 60 years, approximately 70% will develop AD, a number that will grow with increased life expectancy (1). It is difficult to identify early signs of AD related dementia in adults with DS. However, deficits in cognitive control and features of frontotemporal dementia are thought to be early indicators of dementia in this group (2–6). Previous research has identified that increased physical activity (PA), may limit declines, or improve cognitive control in individuals with early dementia, thus improving quality of life (6).

Recent studies suggest that increased PA may be important for maintaining components of cognition, including attention, memory, and executive control, in patients with AD (7–16). For example, Ruscheweyh et al (17) conducted a six-month intervention where 62 healthy older adults were randomized to a moderate intensity PA intervention (nordic walking), low-intensity PA intervention (gymnastics) or a control group. The two exercise intervention groups met for 50 minutes 3/week across the 6-month study. Results found that memory scores improved in both the low and moderate intensity intervention groups, but not the control group.

Similarly, research has also shown that PA may improve cognitive function in adults with DS (18–21), who are at risk for AD. For example, Chen et al.(19) conducted a study in 20 adults with DS in which 10 adults walked one time on a treadmill for 20 minutes at moderate intensity, and the other 10 watched a video. There was significant improvement in inhibition ($p=0.03$) in the adults with DS who completed the single bout of moderate activity compared to those who watched the video. Similarly, Pastula and colleagues (19) completed an 8-week moderate intensity exercise-training program in 14 young adults with DS. Participants completed ~30 minute moderate-intensity circuit-training workouts 3 times a week. The intervention resulted in a significant improvement in aerobic fitness ($p<0.002$) and perceptual and mental speed ($p<0.002$). Together, these findings suggest that participation in moderate intensity exercise may produce improvements in cognition in individuals with DS. However, additional research is needed.

A recently completed trial examining the feasibility of group exercise session delivered remotely to young adults with DS, across 12-weeks afforded us the opportunity to conduct a secondary analysis to evaluate changes in cognitive function in adults with DS who attended 30- minute group exercise session either one or two times per week. Therefore, the purpose of this study was to evaluate the influence of a 12-week moderate PA program on changes in cognitive function in adults with DS without dementia.

METHODS

Overview of study design

Adults with DS participated in a 12-week, at home, group exercise program delivered by video conferencing (Zoom Inc., San Jose, CA) on an iPad mini tablet computer (Apple Inc., Cupertino, CA). This study took place in the (Blinded for Review) metropolitan area from December 2015–July 2016. Participants were randomized to receive the group activity sessions for 30 minutes, either once or twice per week to determine the optimal dosage of weekly sessions needed to see changes in cognitive function. To examine changes in cognitive function, a battery of cognitive tests was assessed pre-and post-intervention. A detailed method, attendance to group sessions, and PA obtained in the sessions has previously been reported (citation blinded For Review). This study was approved by the Human Subjects Committee at the (Blinded For Review).

Participants

Participants were men and women, 18–35 years of age with a diagnosis of Down syndrome, as verified by their primary care physician. Participants over the age of 35 were excluded as they may have already begun to develop dementia. Additional inclusion criteria included: 1) Functional ability sufficient to understand directions, ability to communicate through spoken language, 2) Reside in a supported living condition either at home or with no more than 1–4 residents and have a caregiver. 3) Wireless Internet access in the home. 4) Ability to participate in PA verified by physician consent. Participant exclusion criteria included: 1) Currently pregnant, planning on becoming pregnant during the study. 2) Participation in a regular exercise program, defined as greater than 500 kcal/wk. of planned activity as estimated by questionnaire (22).

Recruitment procedures

Participants were recruited through local community programs serving adults DS and with print and web advertisements in the target area. Home visits were scheduled with potential participants and their legal guardian (if applicable) to obtain written consent or legal guardian consent and participant assent. Participants were randomized by computer into either the once a week group or twice a week group with equal allocation between groups.

Intervention

Thirty-minute sessions were delivered via video conferencing either one or two times per week over 12 weeks to groups of 5–8 participants, each in their own home. Group video conferencing was chosen as this approach requires no travel commitment from care providers or parents, and offers the potential for peer support and socialization. Additional details regarding the rational for this approach have been previously published (23).

A health educator, who was a specialist in adapted physical education and experienced in working with adults with DS, led the exercise sessions. The 1 session/week and 2 sessions/ week groups were conducted separately but led by the same health educator. Sessions consisted of a 5-minute warm-up, 20 minutes of moderate to vigorous intensity PA (i.e., 3–6

METs), and a 5-minute cool-down period. Exercise intensity increased progressively across the first 6 weeks of the intervention and then remained steady weeks 7–12.

Outcomes

The intensity and duration of all group exercise sessions were assessed with a Fitbit monitor worn on the non-dominate wrist during all group exercise sessions.

Cognitive function was assessed using the Cantab Dementia Battery for iPad at baseline and 12-weeks. This battery assesses all cognitive domains including: processing speed, psychomotor speed, sustained attention, visual episodic memory, working memory, and cognitive control. In addition to numerous AD specific trials (24, 25), this battery has also been used in several DS trials (26, 27). The specific cognitive tests administered were the attention switching task, paired associates learning, and reaction time.

Attention Switching Task (AST) is a measure of attention and cognitive flexibility. For this task, the test displayed an arrow which could appear on either side of the screen and point in either direction. Each trial displayed a cue at the top of the screen that indicated to the participant whether they had to select the right or left button according to the “side on which the arrow appeared” or the “direction in which the arrow was pointing”. Some trials displayed congruent stimuli (e.g. arrow on the right side pointing to the right) whereas other trials display incongruent stimuli “switching”, which requires a higher cognitive demand (e.g. arrow on the right side of the screen pointing to the left). Two AST measurements were collected. AST 1 measured the median latency of response (from stimulus appearance to button press) in assessed block(s) in which the rule is switching. Higher scores indicate worse performance. AST 2 measured the median latency of response (from stimulus appearance to button press) on congruent trials. Higher scores indicate worse performance.

Paired Associates Learning (PAL) assesses visual memory and new learning. For this task boxes were displayed on the screen and were “opened” in a randomized order. One or more of them contained a pattern. The patterns were then displayed in the middle of the screen, one at a time and the participant had to select the box in which the pattern was originally located. If the participant made an error, the boxes were opened in sequence again to remind the participant of the locations of the patterns. Two PAL measurements were collected. PAL 1 assessed is the number of times the subject chose the incorrect box for a stimulus on assessment problems. Higher scores indicate worse performance. PAL 2 measured the number of correct box choices that were made on the first attempt during assessment problems. Higher scores indicate better performance.

Reaction time (RTI) provides assessments of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity. For this assessment the participant selected and held a button at the bottom of the screen. Circles were presented above. In each case, a yellow dot appeared in one of the circles, and the participant was asked to react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared. Two reaction time tests were measured. RTI 1 measured the median duration between the onset of the stimulus and the release of the button. Higher scores indicate worse performance. RTI 2 measured the mean

time taken to touch the stimulus after the button has been released. Higher scores indicate worse performance.

Statistical Analysis

Sample demographics and all outcome measures were summarized by descriptive statistics —means, standard deviations, and 95% confidence limits for continuous variables and frequencies and percentages for categorical variables. General linear mixed models (intention-to-treat), was used to assess for the impact of number of exercise sessions/week (1 session versus 2 sessions), time (treated as a categorical variable; baseline, 12-weeks), and the group-by-time interaction effects on cognitive function outcomes. Autoregressive and unstructured covariance structures were tested and unstructured covariance was used as the −2 restricted log likelihood was smaller. Analyses were adjusted for baseline measures: age, education level, race/ethnicity, BMI, number of support staff, and number of individuals living at home. The estimated marginal mean change in each cognitive function task score for 1 or 2-session/per week groups was calculated using general linear mixed models. Cohen's d effect sizes were calculated using the unstandardized mean change scores (12 weeks - baseline) and the pooled standard deviations (28). Effect sizes are interpreted as d = 0.20 (small), d = 0.50 (medium), and d = 0.80 (large) (28). Statistical significance was determined at 0.05 alpha level and all analyses were performed using SAS Software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Participants

Twenty-seven participants enrolled in the study, and all participants completed both the baseline and 12-week outcomes assessments. The sample included 40.7% females, and 10.1% minorities with a mean age of 27.9 years. Baseline characteristics for the total sample, and for participants who completed 1 session per week and 2 sessions per week are presented in Table 1.

Physical Activity

Participants randomized to 1 session/week averaged 26.6 ± 3.0 minutes/week of PA from the group exercise sessions. Participants randomized to 2 sessions/week averaged 57.7 ± 15.3 minutes/week of PA from the group exercise sessions.

Attention Switching

Results of the linear mixed model analyses for the attention switching tasks showed no significant group, time, or group-by-time interaction effects. Small effect sizes for the number of exercise sessions/week on attention switching tasks were demonstrated (Attention Switching Task 1 = 0.25; Attention Switching Task 2 = 0.07; Table 2).

Paired Associates Learning

Results for the paired associates learning tasks are presented in Table 2. Main effects for time were found for Paired Associates Learning 1 (p=0.048). Regardless of group

assignment, both groups had decreased scores over 12 weeks. Main effects for time approached significance for Paired Associates Learning 2 (p=0.069). At 12 weeks, the difference between the 1 session/week group and 2 session/week group approached statistical significance (Paired Associates Learning 1 = 0.054; Paired Associates Learning 2 = 0.052). This suggests that the 2 sessions/week group had greater improvements in paired associate learning compared to the 1 session/week group. Effect sizes were large for the Paired Associates Learning 1 (d=0.76) and for the Paired Associates Learning 2 (d=0.82).

Reaction Time

Results of the linear mixed model analyses for the reaction time tasks showed no significant group, time, or group-by-time interaction effects. Medium effect sizes for the for number of exercise sessions/week on attention switching tasks were demonstrated (Reaction Time Task 1 = 0.32; Reaction Time Task 2 = 0.43; Table 2).

DISCUSSION

Research suggests that PA may limit declines or improve cognitive function in individuals with DS, a population at high risk for AD(6). Our results found that individuals who attended 2 sessions per week improved their performance on both of the Paired Associates Learning tasks, which assess memory, after 12-week of a PA intervention. To our knowledge no previous studies have examined the relationship between PA and memory in individuals with DS. However, previous research in older adults without DS have found similar improvements in memory after a PA intervention (17, 29). For example Ruscheweyh et al (17) found that memory scores improved in older adults who were prescribed 150 minutes per week of either low or moderate intensity PA. Together these results suggest that PA may be beneficial to improve or prevent loss of memory in individuals with DS. While the exploration of the mechanism by which PA may impact memory in individuals with DS is necessary, previous research suggests that positive memory changes are associated with increases in local gray matter volume in the prefrontal and cingulate cortex, and brain-derived neurotrophic factor (BDFN) levels as a result of increased PA (17).

While there were no significant changes across time or between groups in attention or reaction time, participants randomized to the 2 sessions/week group saw improvements in attention switching task 1 and in both of the reaction time variables. The 1 session/week group, only saw an improvement in one attention variable, with scores declining in both reaction time variables. Similarly, Pastula and colleagues (19) observed significant improvement in decision speed and mental processing speed, which are similar to reaction time and attention, respectively. Chen at (21), found that adults with DS who completed moderate-intensity PA demonstrated improvements in reaction time, while those who did vigorous intensity had impaired scores. Together these results indicate that increased PA may lead to improvements in attention and reaction time, but additional research on the dosage and intensity is warranted.

Our results suggest that increased PA may have positive changes on cognitive function. However, this study is limited by a small sample (n= 27) of mostly white (89%) adults with DS, who were incentivized to participate in a short-term (12 week) trial. Additionally, this

study was not powered to detect changes in cognitive function task scores. Therefore, these results should be interpreted cautiously. Next, we did not include a non-exercise control group to which we could have compared the cognitive changes of those who did group PA to those who did not. An additional limitation is that minutes of PA were only obtained from group exercise sessions, and thus, the relationship between weekly minutes of PA (including activities of daily living) and cognitive function was not examined. Finally, this study required participants to have Internet in their home, which may limit the generalizability of these results.

In summary, our results suggest some evidence that obtaining higher amounts of PA from group exercise sessions, may improve cognitive function, especially memory, in adults with DS. While adequately powered trials to further evaluate the relationship between PA and cognitive function over longer time frames (e.g. ≥ 6 months) are warranted, those working with adults with DS should promote increases in PA. Future research should concentrate on examining the long-term changes in cognitive function between those receiving a PA intervention compared to a non-exercise control group, as well as examining the dosage and intensity of weekly PA needed to see changes in cognitive function.

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Table 1

Baseline characteristic of young adults with Down syndrome participating in a 12-week group PA program

	Total Sample		1 Session/Week		2 Sessions/Week	
	N	**Mean+SD/%**	**N**	**Mean+SD/%**	**N**	**Mean+SD/%**
Age (years)	27	27.9 ± 7.3	14	29.9 ± 7.5	13	25.8 ± 6.7
Weight (kg)	27	77.1 ± 18	14	80.1 ± 20.1	13	73.9 ± 15.6
Height (cm)	27	59.9 ± 3.6	14	59.4 ± 3.2	13	60.5 ± 4.1
Waist Circumference (cm)	27	91.7 ± 12.1	14	93.7 ± 13.6	13	89.6 ± 10.2
BMI (kg/m^2)	27	33.5 ± 8.5	14	35.4 ± 9.7	13	31.4 ± 6.8
Number of Support Staff	27	3.1 ± 1.9	14	3.1 ± 1.8	13	3.0 ± 2.0
Education level (%)						
9th-12th	4	14.8	3	21.4	1	7.7
HS/GED	19	70.4	10	71.4	9	69.2
Some College	4	14.8	1	7.1	3	23.1
Ethnicity (%)						
Not Hispanic/Latino	25	92.6	13	92.9	12	92.3
Hispanic/Latino	2	7.4	1	7.1	1	7.7
Race (%)						
American Indian	1	3.7	1	7.1	0	0.0
Black	1	3.7	1	7.1	0	0.0
White	24	88.9	12	85.7	12	92.3
Mixed Race	1	3.7	0	0.0	1	7.7
Sex (%)						
Male	16	59.3	8	57.1	8	61.5
Female	11	40.7	6	42.9	5	38.5

Note: BMI = body mass index

Table 2

Changes in cognitive function from baseline to 12 weeks in young adults with DS participating in a physical activity intervention

	Baseline		12 Weeks		Mean Change			Group effect	Time effect	Group*Time effect	
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**95% CI**		**p-value**	**p-value**	**p-value**	**Effect size (cohen's d)**
Attention Switching Task 1								0.122	0.414	0.517	0.25
1 session/week (n=14)	843.7	186.1	838.4	223.7	−5.3	−93.5	82.9				
2 sessions/week (n=13)	979.1	250.3	933.2	215.6	−45.9	−137.5	45.6				
Attention Switching Task 2								0.134	0.622	0.868	0.07
1 session/week (n=14)	841.0	211.3	849.8	205.9	8.8	−66.9	84.5				
2 sessions/week (n=13)	930.9	222.0	948.6	270.1	17.7	−60.9	96.3				
Paired Associates Learning 1								0.772	0.048	0.054	0.76
1 session/week (n=14)	46.8	19.2	46.6	19.4	−0.1	−6.5	6.2				
2 sessions/week (n=13)	53.3	13.3	43.3	19.1	−9.5	−16.6	−2.4				
Paired Associates Learning 2								0.816	0.069	0.052	0.82
1 session/week (n=14)	4.4	4.5	4.4	4.0	−0.1	−1.4	1.2				
2 sessions/week (n=13)	3.2	2.6	5.0	3.5	1.9	0.4	3.4				
Reaction Time 1								0.309	0.863	0.514	0.32
1 session/week (n=14)	549.5	195.4	579.7	378.3	30.2	−71.4	131.9				
2 sessions/week (n=13)	479.6	77.9	479.5	109.2	−17.6	−126.8	91.5				
Reaction Time 2								0.387	0.857	0.802	0.43
1 session/week (n=14)	372.9	140.4	374.6	112.3	1.7	−63.2	66.5				
2 sessions/week (n=13)	370.5	91.0	412.8	255.5	−10.1	−235.2	90.9				

Note. Adjusted for age, education level, race/ethnicity, BMI, number of support staff, number living at home.