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Chapter 7

Assisted Cycle Therapy (ACT): Implications for Improvements in Motor Control

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Abstract

Assisted Cycle Therapy (ACT) is an innovative exercise in which the participant pedals on a bicycle at 35% greater than their preferred cycling rate with the assistance of a mechanical motor. Previous research in Parkinson's Disease patients found improvements in bimanual dexterity (e.g., grasping forces, interlimb coordination) and clinical measures of movement (e.g., UPDRS) after ACT but not after voluntary exercise or no exercise. Recent research with adolescents with Down syndrome found improvements in manual dexterity as measured by the Purdue Pegboard after an acute 30 minute bout of ACT but not after similar Voluntary or No exercise sessions. Improvements in the upper extremity functioning when the lower extremities were exercised suggests that changes are occurring at the cortical level to create improvements in global motor control. Possible central mechanisms include neurogenesis caused by upregulation of neurotrophic factors (e.g., BDNF) or increased sensory input to the motor cortex due to the high pedaling rate. Neurologic disorders that inhibit movement rate are suggested to benefit from ACT. The implications for improving motor, cognitive, clinical and health outcomes in several neurologic disorders will be discussed.

Keywords: Exercise, neurological disorders, executive function

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Assisted Cycle Therapy (ACT): Implications for Improvements in Motor Control

Voluntary exercise (VE) has long been researched as having a positive influence on mental and physical health (Penedo & Dahn, 2005). There is an emerging body of literature in healthy older adults and individuals with Alzheimer's disease indicating that exercise results in structural and functional changes in the brain (Colcombe et al., 2004; Kramer et al., 2002; Kramer et al., 2003; Kramer, Erickson, & Colcombe, 2006). These alterations in brain structure and function suggest that central nervous system function can be altered via VE in individuals with relatively normal patterns of activation within the motor cortex. However, an important limitation of Voluntary Exercise is its applicability to atypical populations, especially those who for physiological, cognitive, or behavioral reasons move too slowly to gain the aforementioned benefits.

Evolution of Forced Exercise

Forced exercise (FE) is an approach mainly used with animals in which they are exercised on a motorized treadmill at a rate greater than their voluntary exercise rate (Cotman & Berchtold, 2002; Tajiri et al., 2009; Zigmond et al., 2009). Failure to keep pace with the motorized treadmill results in a noxious stimulus (e.g., electric current). FE has been demonstrated in rodents to increase Nerve Growth Factor (NGF) (Counts & Mufson, 2005) which plays a role in promoting myelin repair (Allen & Dawbarn, 2006). Low levels of NGF are also associated with cardiovascular disease (Manni, Nikolova, Vyagova, Chaldakov, & Aloe, 2005). Thus, the clinical importance of increasing NGF is clear for improving motor control in persons with multiple sclerosis, dementia, autism, Alzhiemers, obesity, cardiovascular disease, diabetes, etc. Furthermore, research in animals shows that high intensity exercise promotes behavioral recovery in the atypical brain by modulating genes and proteins important to basal ganglia function which is crucial to voluntary motor control, cognitive, and emotional functions (Fisher et al., 2004).

The innovation of our research is to strategically and ethically apply forced exercise (FE) to humans. The first application, to our knowledge, of FE in humans was conducted in 2009 in the Alberts lab at the Cleveland Clinic (Ridgel et al., 2009). They used a tandem bicycle in which a healthy trainer maintained a pedaling rate of 80-90 RPMs, which was approximately 30% faster than the Parkinson's Disease (PD) patients' voluntary pedaling rate. Because the pedals of each rider are mechanically linked via a timing chain, the trainer and the patient were both pedaling at 80-90 RPMs. We will refer to this as Assisted Cycling (AC). Another group of PD participants pedaled at their voluntary rate. Both groups exercised for 40 minutes three times per week for eight weeks at the same relative aerobic output; the only difference in terms of the exercise performance was pedaling rate. The results of this study showed that AC improved motor function in PD patients. Specifically, following AC, clinical measures of motor control (e.g., rigidity, bradykinesia, etc.) improved, as seen by a 35% improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) on the motor subscale; however no improvements in motor control were found following VE. Furthermore, the control and coordination of upper limb movements, specifically grasping forces during a bimanual

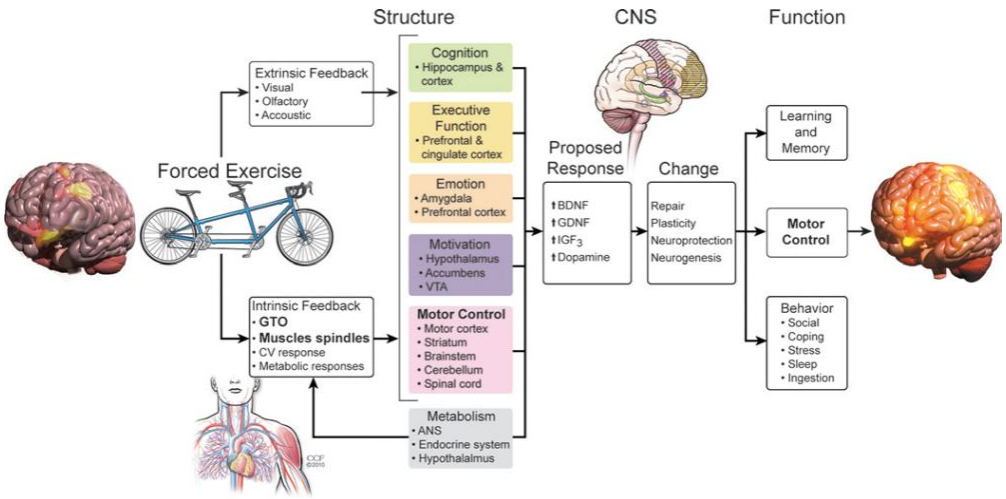
dexterity task, improved following AC but not VE in PD patients. The fact that a lower extremity exercise improved upper extremity movement function indicates improvements in global motor function and suggests that improvements are happening at the cortical level.

Further research developed a stationary bicycle with a mechanical motor in which the Assisted Cycling exercise could be delivered more efficiently. The results of an eight week intervention with the stationary cycle that delivered the AC also found improvements in motor function (i.e., reduced tremor and bradykinesia) in PD patients (Ridgel, Peacock, Fickes, & Kim, 2012). Currently, a 100 patient randomized control trial is being conducted with the motorized cycle that can deliver AC three times per week for eight weeks and will use fMRI scans to measure cortical and subcortical changes that occur with improvements in motor function (Alberts, NIH-NINDS).

Possible Mechanism for Effectiveness of Assisted Cycling (AC)

Although the precise mechanism underlying improved motor and non-motor functioning following AC is unknown. An emerging hypothesis gaining support is that the increased afferent information produced by the high pedaling rate of assisted exercise paradigms produces molecular level changes at the cortical level, including up-regulation of the neurotrophic factors, including Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), Insulin-like Growth Factor (IGF3), Dopamine, etc. in the prefrontal and motor cortices (Cotman & Engesser-Cesar, 2002; Tajiri et al., 2009; Alberts et al., 2011). These proteins are responsible for neural plasticity, neural repair and neurogenesis, which may account for improvements in motor, cognitive and behavioral function. Since the primary role of the motor cortex is related to motor function, use-dependent forms of neuroplasticity may explain this regional specificity following an AC intervention (Petzinger et al., 2010). Recently, non-motor as well as cortical and sub-cortical changes have been shown using AC in PD patients (Alberts et al., 2011). Recent examination of the central mechanisms using fMRI procedures have shown that PD patients who performed AC produced similar changes in brain activation patterns as PD patients on medication (Beall et al., 2013). Alberts and colleagues (2011) have proposed a model of the effect of ACon the central nervous system structure and function. This may serve as a model of the treatment of other neurological conditions.

The evolution of Forced Exercise (FE), along with the development of specialized equipment has also lead to a progression of terminology with respect to this exercise paradigm. In animals it seemed appropriate to refer to this high intensity exercise as Forced Exercise (FE). For ethical reasons, in humans the term Assisted Exercise (AE) is preferred. Ridgel et al. (2012) have used the term Active-Assisted Exercise to reflect the findings that the participant must actively exert power by pushing on the pedals to receive the motor benefits of the exercise. Our lab conducts a significant amount of research on special populations and has developed the term Assisted Cycle Therapy (ACT) for this exercise paradigm, which we will use in the remainder of this chapter.



Alberts et al., 2011.

Figure 1. Schematic depicting the proposed effect of ACT on central nervous system structure and function.

There are many atypical populations with movement deficits that cannot *voluntarily* exercise at a fast enough rate to produce the neurological changes that accompany improvements in motor control. Our research seeks to translate FE data found in animals into an effective and specific therapy for special populations. Our lab has recently examined the effect of Assisted Cycle Therapy (ACT) on motor and cognitive functions in adolescence with Down syndrome (DS) and Autism Spectrum Disorder (ASD).

ACT and Down Syndrome

Current interventions for persons with DS are not achieving the desired results of improving functional tasks. Much research has examined the effect of exercise on improving physical fitness in persons with DS, however, a recent meta-analysis concluded that there was insufficient evidence to demonstrate increased physical outcomes of aerobic exercise in persons with DS (Andriolo , El Dib, Ramos, Atallah, & da Silva, 2010). The DS population has physiological (e.g., low muscle tone, congenital heart conditions, etc.), (Cioni et al., 1994; Fernhall, Pitetti, Rimmer, & McCubbin, 1996) and psychosocial factors (e.g., low motivation, sedentary lifestyle, low exercise tolerance) (Jobling & Cuskelly, 2002) that limit their exercise capabilities such that they cannot exercise at the relatively high rate of typical populations. Adolescents with DS favor sedentary activities (e.g., 90% are sedentary) (Pastore et al., 2000) which translates into 43-95% obesity (Bell & Bhate, 1992; Melville, Cooper, McGrother, Thorp & Collacott 2005; Prasher, 1995). Furthermore, approximately 61% of persons with DS have been shown to have low exercise tolerance which will affect their voluntary exercise time and intensity and thereby limit the potential motor and cognitive benefits of exercise. Our recent single session data from nine adolescents with DS confirm this. In a 30 minute VE cycling session, the average cadence for adolescents with DS was 54.6 rpm, whereas in the 30 minute ACT session, the average cadence for adolescents with

DS was 81.5 rpm. Furthermore, it was only the ACT session that resulted in pre/post improvements in *motor and cognitive* functioning (Ringenbach et al., 2012), with no changes following VE or No Exercise (NE).

Specifically, as seen in Figure 2, our results showed greater improvements in manual dexterity as assessed by the Purdue Pegboard in ACT than the VE and NE sessions which did not show any improvements in manual dexterity. Our results are consistent with research in PD patients (Alberts et al., 2009) that found manual dexterity improvements following ACT, but not VE or NE sessions. What is similar about these populations is that both PD and DS have compromised CNS functioning, which leads to deficits in movement speed, force control, and coordination.

We also found improvements in cognitive function following ACT. As can be seen in Figure 3, in adolescents with DS, cognitive planning as assessed by the Tower of London improved following ACT, but did not show improvements after VE or NE. The Tower of London paradigm has been found to activate the dorsolateral prefrontal cortex, anterior cingulate cortex, caudate nucleus, (pre)cuneus, supramarginal and angular gyrus of the parietal lobe, and frontal opercular areas of the insula (Newman, Carpenter, Varma, & Just, 2003). This finding is in keeping with proposed effect of ACT on executive function as demonstrated by activation of the prefrontal cortex in PD patients found by Alberts and colleagues (Alberts et al., 2011). In addition, simple reaction time improved following ACT, but did not show any improvements after VE or NE in adolescents with DS. The prefrontal cortex continues to be indicated as a primary area responsible for various executive function tasks, reaction time included (Koechlin & Summerfield, 2007). These results are consistent with a proposed mechanism of up-regulation of neurotrophic proteins in the prefrontal cortex following AE (Alberts et al., 2011).

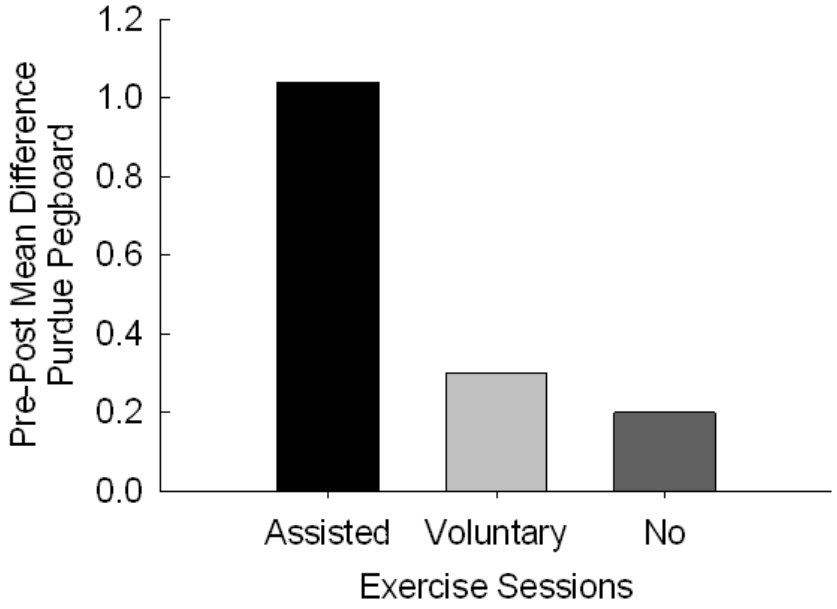


Figure 2. Pre-post difference of Purdue Pegboard as a function of exercise session in adolescents with DS.

An exciting finding for adolescents with DS is that, exercise perception improved following one ACT session and not the AE or VE sessions. We believe that during the ACT intervention, but not the VE intervention, when the participants were pedaling with the assistance of a mechanical motor, it made them feel like the exercise was less tiring, made them feel less sore, made their body feel good, and made them happier. Furthermore, because they were pedaling at such a fast rate, they perceived that they were more likely to get into shape, look better, improve their health and lose weight. Improvements in exercise perception are of particular benefit to DS populations, who typically have low motivation to exercise (Barr & Shields, 2011) and low exercise tolerance (Bell & Bhate, 1992).

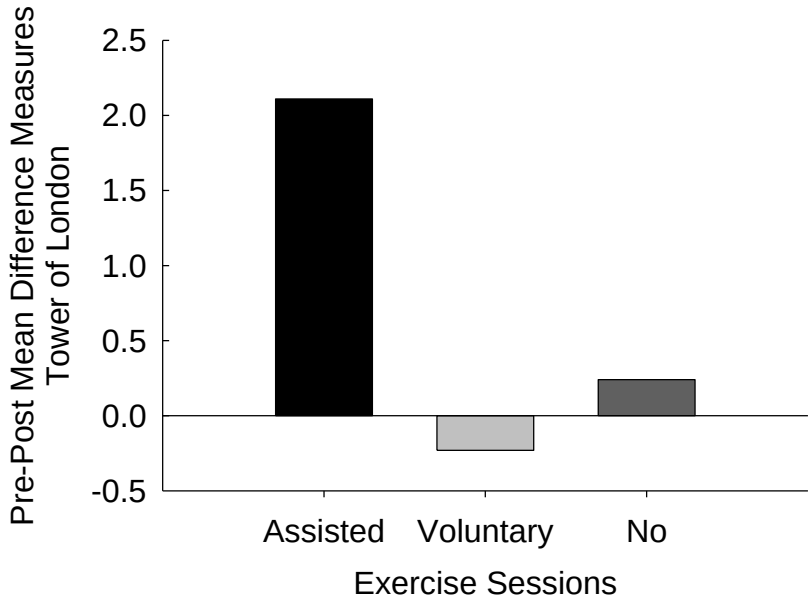


Figure 3. Pre-post difference of Tower of London as a function of exercise session in adolescents with DS.

Our results also found that after a single exercise session self-efficacy did not change. One explanation is that self-efficacy is thought to be a stable internal construct that is less influenced in short term interventions. Our previous research that found improvements in self-efficacy occurred following a cycling intervention, but not a stretching intervention, in typical participants after a seven week intervention period (Wipfli et al., 2011). Heller and colleagues found increases in performance self-efficacy following a 12 week intervention in persons with DS (Heller et al., 2004).

Similarly, we did not find improvement in digital memory span forwards (i.e., verbal short-term memory) or backwards (i.e., verbal working memory) or spatial memory span using both forwards (i.e., visual short-term memory) and backward (i.e., visual working memory) recall of Corsi Blocks. This is in keeping with recent literature that has also demonstrated the null effect of acute bouts of exercise on tests of short term memory span (Coles & Tomporowski, 2008; Ridgel, et al., 2009). However, the findings of Coles and Tomporowski (2008) demonstrated that acute bouts of exercise may facilitate the consolidation of information into long-term memory, further confounding the inconclusive

evidence of the effects of exercise on different measures of memory. Similarly, the effect of chronic exercise on measures of memory seems to be widely disputed. First, no significant improvement in a memory-search task was found following both chronic aerobic and anaerobic exercise interventions (Blumenthal & Madden, 1988). However, long-term fitness has been correlated to increased relational memory, but not item memory, in preadolescent children (Chaddock, Hillman, Buck, & Cohen, 2011). Also, it has been demonstrated in rat models that following a two week period of inactivity, chronic exercise pre-disposes animals to a rapid upregulation of BDNF in the hippocampus induced by a brief exercise bout, but animals with no previous exercise do not exhibit similar upregulation of BDNF (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005). Neurotrophic proteins are proposed to induce neuroplasticity, neurogenesis, and repair, which would explain the proposed effects of BDNF on cognitive functioning (Alberts et al., 2011; Cotman & Engesser-Cesar, 2002; Tajiri et al., 2009). This finding may be beneficial to humans given the sporadic exercise habits typical of many humans, and sedentary populations like DS. Recent fMRI data has also indicated greater hippocampal activation in measures of relational memory relative to item memory (Chaddock et al., 2010) and the hippocampus is another structure that is postulated to be influenced by ACT (Alberts et al., 2011). Given the seemingly inconclusive findings of previous research, it may be that some measures of memory are more sensitive to exercise induced changes in the hippocampus than others. We are currently conducting a three times per week for eight week exercise intervention in adolescents with DS in which we can examine the effect of a long-term ACT interventions on different measures of memory, self-efficacy, and Activities of Daily Living.

ACT and Autism Spectrum Disorder (ASD)

Recently we completed a similar experiment with ten adolescents with Autism Spectrum Disorder (ASD), which is the most common neurological disorder and developmental disability affecting 1 out of every 88 children (1 in every 54 boys and 1 in every 252 girls), and is increasing in prevalence (Centers for Disease Control, 2012). ASD is characterized by impaired social interaction and communication, repetitive and stereotyped behaviors, and delays or abnormal functioning before the age of three in either social interaction, language, or symbolic or imaginative play (American Psychiatric Association, 1994). While younger children with ASD have the same physical activity levels as typical children, as children with ASD age, their physical activity levels decline. The adolescent ASD population is limited in their exercise participation due to reduced physical activity during school, social cognitive or cultural differences in typical youth sports and noninclusion in Special Olympics or Paralympics unless diagnosed with an intellectual disorder (Pann & Frey, 2006). Thus, an appropriate exercise intervention specifically for children with ASD is needed.

Because a cardinal outcome in children with ASD is motor coordination deficits, finding an appropriate exercise intervention is challenging (Fournier, Hass, Naik, Lodha, Cauraugh, 2010). However, Assisted Cycle Therapy (ACT) will eliminate clumsiness, balance, and motor coordination deficits. Exercise on a stationary bicycle reduces the balance and coordination requirements of other exercises and the solitary nature is enjoyed by this population. The experimental procedure was similar to our recent study with adolescents with

DS comparing single sessions of ACT with VE and NE separated by at least one week, except that the session length was reduced to 20 minutes of exercise to accommodate their behavioral differences. In addition, we measured a few different outcomes specific to ASD that we thought would respond to ACT based on our previous research with adolescents with DS (Ringenbach et al., 2012), and other exercise research with adolescents with ASD (Anderson-Hanley, Turreck, & Schneiderman, 2011). Enhancing motor and cognitive functioning and reducing stereotypic behavior is critical to improving activities of daily living and fostering independence and improving quality of life for persons with ASD.

As can be seen in Figure 3, inhibitory behavior as assessed by a Stroop task ($p=.034$) and to some extent set-switching ($p=.118$) and cognitive planning ($p=.071$) improved after ACT but did not change after VE or NE. Because inhibitory control and cognitive planning are both prefrontal tasks, this finding is in keeping with the proposed effect of ACT on executive function as demonstrated by activation of the prefrontal cortex in PD patients found by Alberts and colleagues (Alberts et al., 2011).

However, our results do not support the hypothesis that ACT showed greater improvements in manual dexterity, as assessed by the Purdue Pegboard than the VE and NE sessions. In fact, for adolescents with ASD, there were improvements in manual dexterity but only after the VE session and not the ACT or NE sessions. It is important to note that in both ACT and VE, the participants are exercising at the same intensity. One explanation is that their upper limb motor control did not improve following ACT is that adolescents with ASD were afraid of cycling with the motor. One of the characteristics of children with ASD is that they exhibit reduced fear in dangerous situations (e.g., snakes, running into the street) and heightened fear in harmless or new situations (e,g., ACT, interacting with other people) (American Psychiatric Association, 1994). Furthermore, Sagaspe, Schwartz and Vuilleumier (2011) suggested that the amygdala may modulate brain circuits involved in motor control by emotional signals. It can be presumed that the brain activity in the motor areas may be lower during ACT in adolescents with ASD because their movements were accompanied by a fearful emotion, relative to VE. It is hypothesized that this is caused by a dysfunction of the amygdala and its related genes in persons with ASD (Baron-Cohen et. al., 1999). As seen in Alberts and colleagues (2011) proposed model (Figure 1) ACT may improve functioning of the amygdala through increased BDNF response which may lead to improvements in social and coping behavior.

Opposite to our results with adolescents with DS, but consistent with our explanation of increased fear with ACT, exercise perception only improved following the VE session and not the ACT session in adolescents with ASD. However, adolescents with ASD do enjoy exercise as was seen with their enhanced exercise perception after the VE session. Again, we believe this stems from an increased sense of fear in uncontrollable situations such as in the ACT session due to amygdala dysfunction. Because the amygdala is one structure proposed to be influenced by ACT in Alberts et al. (2011) model we believe that over time, ACT may enhance amygdala function. Understanding exercise perception may be of particular benefit to ASD populations, who typically have poor social skills which limit their physical activity choices (Pann & Frey, 2006). Thus, future research will investigate if chronic ACT sessions can improve functioning of the amygdala and have a positive effect on social behaviors in persons with ASD.

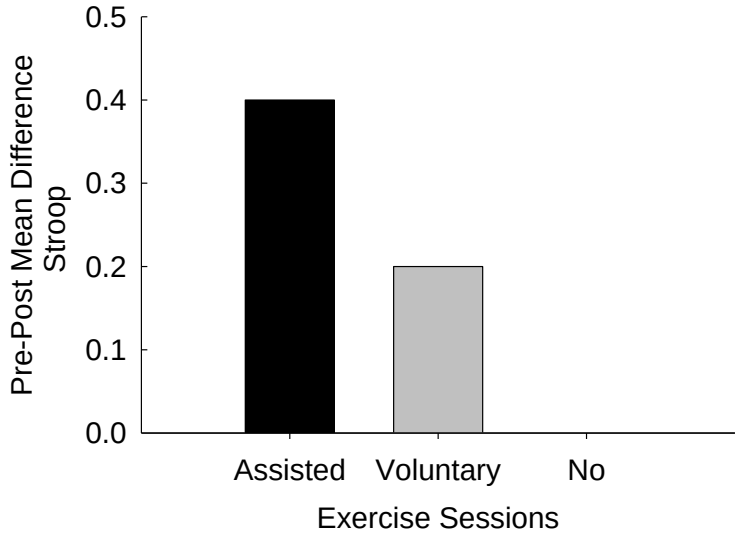


Figure 4. Pre-post difference of Stroop Pegboard as a function of exercise session in adolescents with ASD.

Conclusion

Enhancing motor and cognitive functioning is critical to improving activities of daily living and fostering independence and improving quality of life for special populations. Assisted Cycle Therapy (ACT) is a method of intervention that has had positive effects on motor and cognitive functioning in clinical populations with compromised CNS, poor motor function, low exercise motivation, and reduced cognition. Our results with several special populations reveal that positive results from this project have potential to change clinical practice, which may improve motor and cognitive functioning, as well as attitudes towards exercise for populations with neurologic disorders that inhibit movement rate. Future research will continue to examine the mechanisms responsible for improvements in global motor functioning following ACT interventions.

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