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RELATING MOTOR AND COGNITIVE INTERVENTIONS IN ANIMALS AND HUMANS

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Abstract

Cognition and motor performance are essential components of human functioning. Recent research has provided evidence that these two domains are more interrelated than previously thought. This is a potentially important area of research with many questions that warrant further exploration and have practical implications to the field of neurological rehabilitation. In this review of literature we included animals and humans in healthy conditions as well as pathological conditions affecting the central nervous system. Our primary goal was to comprehensively review the relevant basic science and clinical literature on the effects of motor interventions on cognitive function and vice versa. We found more evidence supporting positive effects of exercise on cognition than effects of cognitive training on motor function. In addition, we examined the extent to which findings from animal literature have been or can be translated to humans. We found that, with the exception of one study in monkeys, most animal studies which investigate rodents are somewhat challenging to translate to human studies, independent of the intervention employed. It is difficult to find a human parallel to exercise in rodents, because both the voluntary and forced exercise paradigms used in rodents happen in a different context than humans. In addition it is difficult to find an animal parallel to cognitive training in humans, because the environmental enrichment intervention cannot be considered "purely" cognitive stimulation as it also involves sensory, motor and social components. We conclude the review by suggesting avenues for future research and intervention strategies.

Keywords

• Neurological disorders • Exercise • Cognitive training • Movement • Cognition • Intervention • Animals • Humans

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Abbreviations:

TBI - traumatic brain injury;
MCI - mild cognitive impairment;
MS - multiple sclerosis;
PD - Parkinson's disease;
BDNF - brain-derived neurotrophic factor;
APOE-e4 - apolipoprotein E epsilon 4;
HD - Huntington's disease;
DG - dentate gyrus;
trkB - tyrosine kinase B;
cAMP - cyclic adenosine monophosphate;
CREB - cAMP response element-binding protein;
IGF-1 - insulin-like growth factor 1;
CXCL1 and 2 - chemokine (CXC motif) ligand 1 and 2;
VEGF - vascular endothelial growth factor;
FLK - fetal liver kinase-1;
CaM-K - calcium/calmodulin-dependent protein kinase;
MAP-K/ERK - mitogen-activated/extracellular signal-regulated protein kinase;
PKC - protein kinase C;
trkC - tyrosine kinase C receptor;
NMDA - N-methyl-D-aspartate receptor;
mRNA - messenger ribonucleic acid;
ADL - activities of daily living;
ECog - every day cognition scale;
EE - environmental enrichment;
SH - standard housing

Introduction

Cognition and motor performance are essential components of human functioning. Traditionally, the notion of a clear separation between motor and cognitive regions of the brain has been widely accepted. Yet, more recent research has provided evidence that these two domains are more interrelated than previously thought. A number of studies have provided evidence for links between motor and cognitive brain regions through neuroimaging or neuroanatomical studies [1,2]. It has also been shown that both motor and cognitive areas of the brain are co-activated during the performance of motor or cognitive tasks [1]. Furthermore, several studies have found that individuals with brain damage restricted to either motor or cognitive brain regions frequently demonstrate impairment in both skill areas [3] and there may be a trade-off between the recovery of cognitive and motor functions [4].

Arguably, the most compelling evidence for linkages between the motor and cognitive domains derives from studies on dual-tasking. The dual-task paradigm tests performance of two tasks (i.e., a motor and a cognitive task) simultaneously compared to performance of either single task. The introduction of a second task during cognitive or motor performance leads to a decline in performance in at least one of the tasks. This phenomenon can be observed in healthy individuals and, to a higher degree, in individuals with neurological disorders [5,6]. The main mechanism suggested to explain this phenomenon involves competition for

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available attentional resources [3] that can disrupt executive functioning [7].

In light of accumulating evidence of an inter-relatedness between motor and cognitive function a few studies have investigated the effects of interventions involving dual tasking in the elderly or neurological populations. Some findings support the use of dual task training (balance and/or walking plus cognitive task) to improve single task performance [8]. Others found that dual task training specifically improves dual task performance [9]. This is a potentially important area of translational research with many questions that warrant further exploration and have practical implications to the field of rehabilitation. One such question would be: what are the effects of interventions in one domain (i.e., motor or cognitive) upon the other?

The goals of this review were to: 1) comprehensively review the relevant basic science and clinical literature on the effects of motor interventions on cognitive function and vice versa; 2) to compare and contrast these findings, so as to examine the extent to which findings from animal literature have been or can be translated to humans; and 3) finally to explore avenues for future research and intervention strategies.

Methods

Inclusion and exclusion criteria

This review included animal and human studies. Humans were adults of age 18 or older. Studies with children were only included if they also enrolled adults (more than 50% of the sample). Studies on healthy individuals and/or those with a brain injury or pathology were included. Animal studies included healthy and those with brain injuries or other CNS pathology. All studies employed rodents, with the exception of one study using cynomolgus monkeys. Studies were excluded if: (1) interventions involved a pharmacologic component; (2) outcome measures were based solely on retrospective surveys; (3) interventions termed as "cognitive" had participants engaging in visualization such as motor imagery studies or concurrent practice of full body motor activity; (4) they included subsets of neurological patients with co-existing non-neurological conditions that could adversely affect motor performance (i.e., pulmonary or cardiac conditions); (5) animal studies that investigated the neuroprotection effects of exercise implementing an exercise routine before the lesion and not after (remediation effects); and (6) animal studies that used rotarod for exercise training.

Search strategy

A literature search was performed using the PubMed, Web of Science, and Scopus databases. Records were limited to humans, animals, adults (18 years of age or older) and English language. The general search strategy for all databases was as follows: (cognitive OR cognition AND motor) AND (intervention OR training OR therapy) AND (neurological OR brain) AND (disorder OR injury OR aging) AND (rehabilitation OR recovery) AND function NOT spinal cord NOT (medication OR pharmacologic OR pharmacology OR drug) NOT (surgery OR neurosurgery). Following the literature search and acquisition of the sample of papers to be used in the review, references were examined for each article and additional relevant papers were selected. Please find detailed information about our search strategy in the flow chart (Fig. 1).

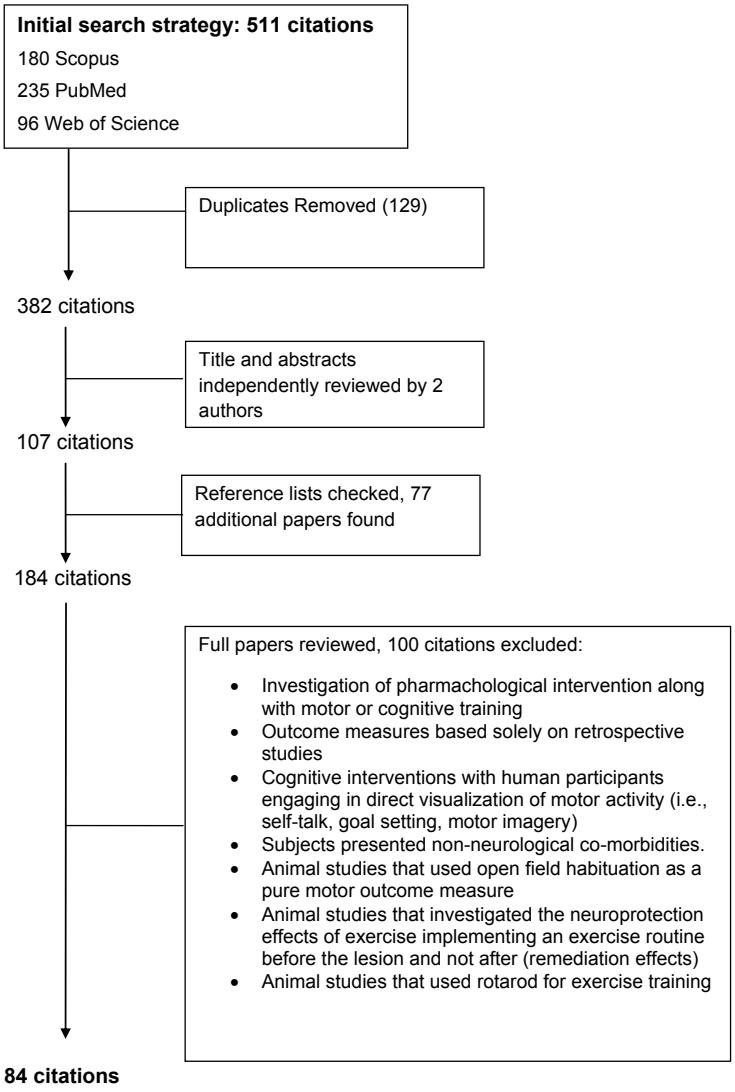

Figure 1. Flow chart of search strategy.

Results

Motor interventions effects on cognitive function in humans

A total of 33 studies pertaining to the effects of motor intervention on cognitive function were identified. Most studies focused on the elderly, with 24 of the 33 studies including individuals 65 years of age or older and most examined healthy volunteers, although in many cases the individuals were sedentary and/or at risk for disability. The most common neurological diagnoses were Alzheimer's disease (AD), dementia, or mild cognitive impairment (MCI) (6 studies), followed by depression (2 studies), and TBI, multiple sclerosis (MS), stroke and Parkinson's disease (PD) (1 study each). Aerobic exercise of medium to high intensity was the most common intervention, typically consisting of walking, jogging, sprinting, and/or cycle ergometry. Control interventions included yoga and stretching and/or toning.

Most exercise sessions were performed 2-4 times/week for 45-60 minutes/session, with total durations ranging from a single 30-minute bout of exercise to 3 years of training. The most common intervention duration was 24-27 weeks (9 studies). A wide variety of cognitive outcomes were utilized, many encompassing several different cognitive components in a single measure. In general, results were positive, with both healthy individuals and those with brain pathology demonstrating improvements in cognition following exercise.

In the healthy elderly without a neurological diagnosis, the most frequently reported cognitive domain found to improve with exercise was executive function. Several studies have compared aerobic training versus no exercise or non-aerobic training and have shown significant improvement in tests of executive function [10-15] as well as task-related activation in regions of prefrontal and parietal cortices involved in executive function [16]. In addition, improvements in executive function performance have been found to be associated with improvements in brain functional connectivity in response to vigorous walking [17]. Another area of the brain shown to respond to exercise is the cingulate cortex, which is thought to monitor conflicts in attention [16]. Other cognitive domains also reported to improve with exercise include short term memory and verbal learning [11,18,19] information processing ability, psychomotor speed, speed of processing, perceptual motor functioning [15,20-22] and attention [23]. In addition to cognition, parameters related to mood and psychological functioning [22], depressive symptoms [20] and self-concept/perceived locus of control [24] are also responsive to exercise.

In the elderly with or at risk for brain pathology, fewer studies have been identified than in the healthy elderly. Nevertheless, in females with MCI [25] and in females at risk for AD [26] the cognitive skills of selective attention, information processing, and executive function have been shown to improve with aerobic exercise. In a group including males and females at risk for AD, improvement in global cognitive ability [13] and general orientation [27] have been reported. In males with senile dementia, there have been improvements in attention and general orientation with aerobic exercise [28]. In addition, in individuals post stroke improvements in information processing speed have been reported [29].

In middle-aged and younger adults, one session of aerobic cycling exercise has been shown to improve executive function and information processing speed in both non-depressed individuals [30] and those with depression [31]. Brain event related potential measures, commonly used as indicators of decision-making components of executive function activity, have also been shown to improve after a single bout of exercise in healthy younger adults [30,32]. Reports of longer duration aerobic programs have also shown improvements in the brain's resting state functional efficiency in healthy individuals [17], improvements in verbal learning, visual learning and processing speed in those with mild to moderate TBI [33], and in memory and executive function in those with depression [34].

In addition to behavioral changes, changes in brain morphology and serum levels of brain-derived neurotrophic factor (BDNF) have also been investigated. BDNF is a protein that supports the survival, growth, and differentiation of neurons. In healthy elderly, aerobic exercise has been shown to promote increase in serum BDNF levels, which have been positively associated with improvements in memory and increases in the volume of the anterior hippocampus [35] and prefrontal and cingulate cortices [36]. In younger to middle-aged healthy adults, while one study found associations between increase in serum BDNF levels and improvement in learning [37] as a response to exercise, another study failed to demonstrate significant associations [38].

While aerobic exercise clearly shows benefits on cognition, improvements have also been found from less intense exercise regimes. Resistance training [39] has been shown to improve executive function in PD. Non-aerobic group training interventions, including stretching, balance and coordination activities performed in a game context have been shown to improve working memory in a group of nursing home residents with various diagnoses [40] and in AD [41]. Additionally, yoga has been found to improve selective attention in middle–aged individuals with multiple sclerosis (MS) [42].

Taken together, these studies provide compelling evidence that motor interventions have a positive impact on cognitive functioning in adult populations of various ages and health statuses. The type of exercise that has been most commonly shown to improve cognition was aerobic exercise, although a few studies employing non-aerobic interventions also demonstrated positive effects. Interestingly, several studies also used non-aerobic exercise as the control intervention. Executive function seems to be the cognitive skill that benefits the most. No ideal exercise program duration can be recommended, however, the great majority of the studies have investigated multiple rather than single session programs. Another consistent finding from these studies was that aerobic exercise lead to increased BDNF levels in the hippocampus, although the precise relationship between BDNF levels and exercise intensity was less clear.

Motor interventions effects on cognitive function in animals

A total of 33 studies pertaining to motor interventions to improve cognitive function

in animals were identified. Thirty studies used rodent models and one study used female cynomolgus monkeys [43]. The most common types of rodents used were Sprague-Dawley rats, and the most common age was 3 months, which is considered a mature adult [44]. For the primate study two age groups were studied: middle-aged (10-12 years old) and adults (15 and 17 years old). Healthy rodent models were used in 26 of the 33 studies, while the other 7 studies used those with focal ischemia [45,46], APOE-e4 [47], Huntington's disease (HD) [48], and aged mice [49-51].

The intervention most commonly used was voluntary aerobic exercise (20 studies) where animals had free access to a running wheel over a specified duration. Eight studies investigated forced exercise where animals had to run on a treadmill or a motorized wheel or swim. Two studies compared voluntary to forced exercise. In most of the voluntary exercise studies animals were not directly observed for the duration of the intervention since they often had continuous access to the running wheel for days to weeks. Most studies tracked wheel revolutions from mechanical counters to record distance. Interventions applied a wide range of durations: 1) voluntary exercise: wheels were either accessible at all times, accessible only overnight, or accessible for 60 minute timed sessions, with durations of sessions ranging from hour-long single to multiple sessions to 14 weeks of continuous access; 2) forced exercise: 30-60 minutes per day, with duration ranging from 5 days to 14 weeks. A wide variety of outcome measures were used, with the most frequent being biological markers requiring the animals to be sacrificed (e.g. neurotrophic and growth factors, synaptic plasticity and cell proliferation in memory-encoding regions of the brain). Only 12 out of 31 studies we found looked at the effects of exercise on behavioral outcomes [47-57].

The most common outcome measure investigated was BDNF. Following exercise interventions, the highest concentrations of BDNF were most commonly found in the dentate gyrus (DG) of the hippocampus, a region of the brain implicated in learning and memory. Overall, the voluntary wheel-running intervention yielded overwhelmingly positive results for BDNF production seen in all studies [46,48,57-63]. One study using forced treadmill running found that low intensity exercise for a week resulted in significantly higher levels of BDNF in the hippocampus of healthy juvenile rats compared to high intensity exercise of the same duration [64]. Studies using voluntary wheel-running also reported positive effects on the BDNF tyrosine kinase B (trkB) signal transduction receptor [47,57,59,62,63]. Three studies specifically reported a positive correlation between distance run and BDNF mRNA or protein levels [60,61,65]. Only one study using Huntington's disease transgenic mice failed to find an increased concentration of BDNF in the hippocampus following exercise, instead finding an increased level of BDNF in the striatum [48].

Other outcome measures related to synaptic activity have also been investigated, albeit to a lesser extent. Several studies employing the voluntary wheel running intervention demonstrated a positive association between exercise over various durations of time and synapsin-1, a signal trafficking protein implicated in the regulation of neurotransmitter release at the synaptic level [47,57,59,62,66]. Yet, two studies using the voluntary wheel running exercise for a single 12-hour session failed to demonstrate positive effects [45,46] suggesting that increased synapsin-I levels may require greater wheel-running time. Levels of cAMP-response-element binding (CREB) protein, which has the ability to modify neuronal function through regulation of gene transcription and synaptic transmission, were also demonstrated to increase with voluntary [45,57,59,62,67] and forced wheel running [45]. For IGF-1, a factor implicated in plastic and neuroprotective functions in the brain, positive effects were demonstrated with forced fast-paced motorized wheel running, but not with forced moderate-paced or voluntary wheel running [45,46]. Finally, studies measuring levels of other neurotrophic factors including neurotrophin-3, nerve growth factor, glial-derived neurotrophic factor, and p75, failed to demonstrate positive effects following voluntary wheel running [60,63]. These findings suggest that overall, both voluntary and forced exercises seem to have positive effects on several measures of synaptic activity.

Cell proliferation in the hippocampus is an important surrogate measure of improved cognitive function. Voluntary wheel running has shown a strong positive effect on cell proliferation in the hippocampus of healthy rodents [51,68-72]. Other related effects have been observed, such as selective increases in cerebral blood volume which correlates with neurogenesis [70] and reduction in the age-dependent decline in cell proliferation in adult rats [69]. Another study, however, found no significant change in cell proliferation in the hippocampus with voluntary running in rats that had undergone a brief daily cold water swim; an effect presumably mediated by the negative effects of stress hormones on neurogenesis [71]. Forced exercise at slow speeds has been found to promote cell proliferation [46,51,56,64,66-71,73], whereas the effects of fast paced exercise were inconsistent, with one study showing positive results [74] and another study showing no changes [64]. Overall, there is more evidence for the positive effects of voluntary and forced slow-paced exercise to promote cell proliferation, than forced fast paced exercise. It may be the case that more aggressively trained animals tend to be less successful because they are more stressed.

Since many inflammatory mediators are believed to play a role in the pathogenesis of cognitive impairments, research has also examined the impact of exercise on inflammatory marker gene expression. CXCL 1 and CXCL 12 are two neuroprotective chemokines believed to be related to cognition. Levels of CXCL 1 and CXCL 12, which are typically decreased in early stages of Alzheimer's disease, have been found to increase markedly after wheel running exercise in a group of mice relative to a sedentary group and even be restored to age-matched healthy levels [50].

Several studies also investigated long-term potentiation as well as levels of Vascular Endothelial Growth Factor (VEGF) and its receptor, fetal liver kinase-1 (FLK-1). Voluntary running in healthy rodents has been shown to selectively increase hippocampus neuronal long-term potentiation [56,75], a long-lasting enhancement in signal transduction involved

in synaptic plasticity. Growth-associated protein, expressed at high levels during neuronal growth and phosphorylated after long-term potentiation, has also been found to increase following voluntary wheel running in healthy rodents [59]. On the other hand, levels of VEGF, known to exhibit neurogenic effects, were not significantly elevated following forced exercise at different intensities. Meanwhile, the VEGF receptor FLK-1 showed positive effects following forced slow-paced treadmill running, but not following moderate or fast-paced treadmill running [64].

Other studies assessed the effects of exercise on factors involved in signal transduction, components of the glutaminergic system, and on calcium and dopamine levels in the brain in healthy rodents. Signal transduction factors implicated in neurogenesis include calcium/calmodulin-dependent protein kinase II (CaM-K), mitogen-activated/extracellular signal-regulated protein kinase (MAP-K/ERK), protein kinase C (PKC), tyrosine kinase C receptor (trKC) and basic fibroblast growth factor (FGF). Voluntary running exercise showed positive effects for CAM-K, MAP-K/ERK, and hippocampal protein kinase C [66,67], while failing to show positive effects for the trKC receptor [63]. Voluntary running also caused a significant increase in glutamate receptor-5 and NMDA receptor, a component of the glutaminergic system involved in synaptic plasticity [50,51,66-75]. Forced exercise at slow and moderate-pace but not fast-pace had positive effects on NMDA receptors [64] while swimming promoted an increase in FGF mRNA levels [76]. Taken together these findings suggest that both voluntary and forced slow-pace exercise have positive effects on signal transduction with differential effects of forced fast-pace exercise on calcium and dopamine levels.

A few studies have measured behavioral outcomes after exercise in animals. The most commonly used tests were the Morris, the radial arm, the T maze and Y-mazes, which evaluate spatial learning and memory. In healthy rodents improvement in learning and memory has been reported after voluntary [51,56-58] and forced running [52-54]. Similar improvements have been observed following voluntary running in APOE-e447 and aged mice [49,50]. Besides learning and memory, voluntary running has also been shown to improve exploratory behavior and motor coordination in HD transgenic mice [48]. Together these studies provide some evidence that both voluntary and forced exercise improves cognition in rodents.

Three studies have compared the effects of forced versus voluntary exercise in ischemic [45,46] and healthy rodents [55]. However, only one of them carefully controlled for equivalent amounts of exercise between groups by matching the distance, duration and intensity of exercise [55]. This study showed that forced exercise promoted more hippocampal neurogenesis but also significantly increased anxiety-like behaviors compared to voluntary exercise, which in turn was more effective in enhancing learning performance. The other two studies found that voluntary running for 12 hours promoted longer lasting BDNF production than forced running for 60 minutes [45], but on the other hand forced walking for 30 min produced more BDNF in the sensoriomotor cortex than voluntary running for 12 hours [46]. In summary it seems that voluntary and forced exercise have differential effects in the brain and on behavior but it is still unclear which type of exercise is superior.

We identified only one other animal study in primates that investigated the effects of exercise on cognition [43]. The study was a randomized control trial showing that forced treadmill running for 1 hour/day, 5 days/week for 5 months produced significant improvements in executive function, fitness levels and blood flow to the motor cortex of monkeys at ages ranging from middle to mature adult. After the end of the exercise program, monkeys were assessed again after a 3 month sedentary period and showed no retention of the benefits, indicating that regular exercise is needed to maintain changes in cognition, fitness levels and brain vascular density. This study provides evidence that exercise improves cognition and brain vascularity in an animal species more similar to humans than rodents.

Overall, the literature on exercise interventions in rodents has shown convincing positive effects for both biologically and performance based outcome measures of cognition. However, biologically based measures were far more frequently investigated than behavioral measures. Taken together the research in rodents seems to indicate that the voluntary wheel running most commonly leads to positive effects followed by forced slow-pace and finally forced fast-pace exercises also leading to positive changes but to a lesser extent. However, it is difficult to estimate the equivalence of exercise programs used in rodents as to how they might apply to humans. Therefore, the findings from the study on primates are particularly encouraging because they confirm the findings in rodents at least in part and are more translatable to the human species.

Cognitive interventions effects on motor function in humans

A total of 10 studies on the effect of cognitive interventions on motor function in humans were identified. The ages of participants in the studies ranged from 40-94 years. Three of the studies included individuals with AD and/or mild cognitive impairment (MCI), 2 studies included individuals post-stroke, 2 MS, and the remaining 3 healthy volunteers.

A wide range of cognitive interventions were utilized, including general cognitive rehabilitation and targeted training on memory, speed of processing, and attention. Overall, interventions aimed at improving memory were the most prevalent. Studies not meeting criteria for purely cognitive (i.e. motor imagery) and studies combining cognitive and motor function (i.e., dual tasking, virtual reality physical training) were excluded. Intervention durations ranged from 3 weeks to 28 weeks and frequency typically consisted of 2-4 sessions of 40-60 minutes.

The most common motor-related outcome measure assessed was activities of daily living (ADL) performance. These measures describe daily self-care activities and are primarily used to assess disabled and elderly populations. Although ADL incorporates various motor-related components such as bathing, eating, and personal hygiene, we have designated functional mobility components of ADL as having the most direct relevance to what

would be considered motor-related outcome measures. Some studies applied the extended ADL measure, which incorporates an additional sub-scale specifically for mobility including activities such as walking, climbing and lifting.

In individuals with or at risk for brain pathology, studies are inconsistent in demonstrating positive effects of cognitive training on motor function. In patients with AD, while one study showed no significant improvements in ADLs after a period of 4 to 6 weeks of computerized memory and attention training [77], another investigation found significant improvements in the Functional Living Skills Assessment in patients who received either a general memory training program or an individualized cognitive training program [78]. The latter study also assessed ADLs pre and post intervention but found no significant changes, which could alternatively be indicative of the fact that ADL measures are of low sensitivity to detect small changes at the functional level. In elderly with MCI a 6-week training program led to no improvement in ADLs but results approached significance in the E-Cog, which is a measure designed to assess higher-order ADLs in MCI [79]. In patients post-stroke, a 3-week period of visual scanning, visual spatial perception, and time-judgment skills training failed to improve mobility-related measures of the Barthel Index of daily functioning assessment [80]. Also in patients post-stroke, a 3-month program involving a general practitioner-directed cognitive rehabilitation program failed to demonstrate improvements on an extended ADL measure [81]. In patients with MS, while one study demonstrated improvement on a self-rating inventory for daily function following 4 weeks of computer-based attention training [82], the other study showed no improvements on an extended ADL measure following 6 months of specialized cognitive training [83].

In healthy elderly we identified two studies that were part of a large cognitive intervention trial (ACTIVE trial) aimed at improving independence in older adults [84]. In the trial, nearly 3,000 participants were randomly assigned to either 10 sessions of training in memory, reasoning, speed of processing or to a control group. Although the group who underwent training showed significant improvements in individual components of cognition and slower decline in quality of life [85], no improvements in ADL measures were observed [86].

In general, there were more studies showing no effects than studies showing positive effects of cognitive rehabilitation on motor function among the studies we identified. Interestingly, 3 out of 4 studies that reported some positive effect used other measures of daily function rather than ADL scales, e.g. Functional Living Skills Assessment [78], ECog [79], self-rating inventory for daily function [82]. A common theme discussed in all papers identified was that even though there were cognitive improvements they tended not to translate into detectable improvements in daily functioning as measured with ADL scales.

Cognitive interventions effects on motor function in animals

A total of 8 studies pertaining to more purely cognitive interventions to improve motor function in rodent models were identified. The animals studied were all late adolescent or adult (> 3 months), males and mostly of the type Sprague-Dawley. In contrast to studies examining the impact of motor interventions on cognitive function, where most of the animals tested were healthy, all of the animals in these studies received an experimentally-induced neurological injury including TBI (4 studies) and stroke (3 studies). Outcome measures related to motor function included the beam walk (time to cross a narrow, elevated beam), beam balance, rotating pole and inclined plane (time the animal is able to remain on those surfaces), limb placement (assesses proprioception and motor integration), prehensile traction (evaluates muscle strength and equilibrium when the animal's forepaws are placed on a rope) and climbing test (time it takes animals to climb a ladder).

Environmental enrichment (EE) was the primary cognitive intervention used in all of these studies. EE is believed to enhance cognition by increasing hippocampal neurogenesis, synaptogenesis, and growth factor levels [87]. The impact of EE on motor function has been less frequently examined. Typically, EE involves exposing animals to physical and sensory stimuli with increased cage space and opportunities for play and exploration (e.g., increased cage space, balls, blocks, and tubes), social stimulation with animals housed in groups, and the presence of nesting materials. However, whether EE can be considered a purely cognitive intervention is controversial because it provides animals with opportunities for physical exploration and activity. Some studies promoted voluntary exercise as part of physical stimulation by exposing the animals to running wheels in the EE cages. We excluded those studies from this review in an attempt to separate as much as possible EE from exercise interventions.

A few important questions have been discussed in the literature related to the effects of EE intervention: 1. Is EE more effective in improving motor recovery after a brain injury than standard housing (SH)? (SH consists of keeping animals in single cages with only food, water and nesting materials). 2. Does exposure to EE pre-injury play a neuroprotective role on the motor recovery after a brain injury compared to exposure to EE post-injury? 3. What aspect of EE is responsible for the recovery after injury: cage space, social interaction or opportunities for play and exploration? 4. What is the ideal dose or treatment duration with EE to promote optimal recovery? 5. How soon after injury should EE treatment start? 6. How does EE compare to exercise as an intervention to promote motor recovery after brain injury?

Regarding question 1, we have identified a number of articles showing that EE is more effective than SH to improve motor recovery after a brain injury. All 7 studies identified in this review included a comparison between EE and SH and showed that rats exposed to EE performed significantly better on the beam walke [88-92], beam balance [88,93], limb placement [90,92,94], rotating pole [92,94], inclined plane [90], prehensile traction [94] and climbing tests [90,92].

Regarding question 2, we identified one study showing that being exposed to EE before injury does not confer any benefits to motor recovery compared to being exposed to EE only after injury [92]. This study compared three groups of rats with stroke: 1) rats exposed to SH before and after surgical injury; 2) Rats exposed

to SH before but transferred to EE 24 hours after injury, and 3) Rats exposed to EE before and after injury. The duration of exposure to the respective cage conditions before injury was 4 weeks and after surgery was 10 weeks. Rats transferred to EE after surgery (groups 2 and 3) performed significantly better on limb placement, beam walking, rotating pole and climbing tests than rats in group 1. In addition, there were no significant differences in motor performance between groups 2 and 3 confirming that exposure to EE pre-injury did not play a neuroprotective role on motor recovery after a brain injury.

Regarding question 3, we identified one study that investigated the components of the EE paradigm separately to determine which component may be most responsible for its effects on motor recovery [93]. This study grouped rats with TBI for 21 days as follows: 1) EE (large cage with ladders, toys and materials for nesting), 2) EE without the social component (only 2 animals per cage at a time), 3) EE without the stimuli (no toys in cage), 4) SH (small wire mesh cage, 2 rats per cage) and 5) SH with stimuli (small wire mesh cage with toys). Results showed that group 1 had significantly improved motor performance compared to group 2 which only lacked the "full" social component as well as group 4 which limited all aspects. These results seem to support the idea that the social aspect of EE plays a prominent role on motor recovery, but the basis for why this is effective is not yet well-understood

Regarding question 4, one study compared different doses of EE exposure per day for a period of 19 days post TBI injury [88]. The groups were EE continuous, EE 2 hours/day, EE 4 hours/day, EE 6 hours/day, or SH continuous. The group of rats exposed to EE 6 hours/day performed significantly better on beam walking and beam balance than groups with less or no EE time and was not significantly different than the continuous EE group. These results indicate that it may be possible to achieve the same motor recovery with a smaller dose of EE. These findings are encouraging in terms of supporting clinical rehabilitation because in real life exposure to therapy is limited and obviously more realistic than continuous exposure.

Regarding question 5, a few studies have addressed how soon after injury EE exposure should start for optimal results [89,91,94]. One study on rats post stroke showed significantly better motor performance in a group of rats that started EE 2 weeks after injury compared to SH [94], indicating that a start after 2 weeks is superior to SH on promoting motor recovery. However, this study failed to compare early versus delayed start EE. Another study on rats with TBI was more comprehensive and included four groups of comparisons: 1) Rats exposed to EE immediately after injury for 1 week and then transferred to SH for 2 weeks (early EE), 2) Rats exposed to SH immediately after injury for 1 week and then transferred to EE for 2 weeks (delayed EE), 3) Rats exposed to EE immediately after injury for 3 weeks (continuous EE) and 4) Rats exposed to SH immediately after injury for 3 weeks (continuous SH). Results showed that, when compared to delayed EE or SH, early and continuous EE are equally superior in promoting motor recovery [89]. Another study using similar comparison groups showed similar findings, with faster beam walk performance in the groups that received early EE [91].

Regarding question 6, we identified one study that compared 13 weeks of EE, versus exercise (small individual cage with running wheel), versus social interaction (large cage with no equipment) in rats with stroke [90]. The EE group demonstrated the best overall performance in numerous outcome measures (beam walking, limb placement, rotating pole, inclined plane, ladder climbing), followed by social interaction, which was also superior to wheel-running alone. These results support the idea that EE is more effective than exercise alone in improving motor recovery after stroke. In addition the social interaction component of EE seems to be a strong factor in improving motor function in animals. However it is not possible to completely isolate the social from the motor component of EE as rats were still moving around during EE; although the animals were not given access to an a wheel, they were given access to toys and other objects that stimulate motor function and larger areas to explore and interact with other animals.

Overall, the EE paradigm demonstrated convincing positive effects on motor function in brain-injured animal models with significant promise for, as well as challenges in, its potential application in humans. For rodents evidence indicates that EE is more effective on improving motor recovery after a brain injury than SH and exercise. Previous exposure to EE does not seem to play a neuroprotective role on the motor recovery after a brain injury compared to exposure to EE post-injury. Regarding the ideal starting time of EE therapy post injury it seems sooner rather than later is the best approach. Regarding the dose that should be recommended for EE therapy, it seems that higher doses (6 hours/daily) are as effective as continuous EE and superior to lower doses (2 or 4 hours/daily) to improve motor function. Finally, considering the different aspects of EE, the studies we identified seem to support the notion that social interaction may play a more critical role in improving overall performance on motor tasks than the other components of EE. However, the extent to which social stimulation alone may increase motor activity has not been well-documented and should be investigated further.

Discussion

Summarizing current evidence for positive effects of motor interventions on cognitive outcomes and cognitive interventions on motor outcomes

Two of our specific interests in conducting this review were, first, to determine the amount and consistency of both the basic science and clinical evidence that has emerged in recent years supporting positive effects of motor interventions on cognitive functioning and vice versa. To this end, we aimed to include only those studies that provided clearly only one type of intervention, with the one possible exception being the inclusion of environmental enrichment paradigms in animals which provides other types of stimulation in addition to cognitive. As anticipated, we identified a far greater number of papers on motor interventions affecting cognitive function compared to those on cognitive interventions affecting motor function.

Our findings concerning the effects of motor interventions on cognitive function concur with other reviews that there is compelling evidence supporting a positive effect [95,96]. In humans, exercise seems to be strongly beneficial for cognition in the areas of speed of processing, attention, memory but most of all in the area of executive control. Cognitive improvements are accompanied by increases in blood levels of biomarkers considered key in the process of neural protection and neural plasticity, such as BDNF. In animals, results are very similar, with the addition of positive brain structural findings which show specific areas that are more susceptible to plasticity such as the hippocampus. The preponderance of the evidence in humans is based on aerobic exercise protocols versus variably- or self-paced exercise in animals which may or may not be at an aerobic threshold. The effects of more moderate exercise regimens on cognitive outcomes, preferably at a range of speeds, warrants more study in humans, as well as perhaps the effects of anaerobic exercise. The confounding issues of social versus individual exercise as well as stress on outcomes, particularly on more vulnerable subjects, also needs greater scientific clarity. An intriguing unanswered question is whether motor interventions may be superior to or more efficient than existing cognitive interventions for improving selected cognitive outcomes.

Our findings concerning the effects of cognitive interventions on motor function show positive but limited evidence derived more heavily from animal studies than humans. In animals, exposure to EE seems to play a critical role on motor recovery; although not purely cognitive the social interaction of EE seems to be the most important component. In humans our findings are limited and inconsistent with another review, which has reported some positive effects [97]. In the prior review, cognitive intervention was reported to be somewhat beneficial for motor function, although strong conclusions were limited by heterogeneity and methodological issues. In our review, there was more evidence of no effects than positive effects. A possible explanation for this difference may be our selection criteria, which were more stringent and focused on purely cognitive interventions excluding cognitive-motor (i.e., dual tasking) or motor imagery interventions. Methodological issues also need to be considered because most studies identified in our review utilized ADLs as the main outcome measure which are not purely motor but have a strong cognitive and social component as well. Before more definitive conclusions can be made, this question needs to be addressed more directly by applying more definite motor tasks as outcome measures rather than general assessments of daily function.

Examining the extent to which findings from animal literature have been or can be translated to humans

Another goal was to determine the extent to which findings in the animal literature have been or can be translated to humans. We found that rodent studies are somewhat challenging to translate to human studies, independent of the intervention employed. For instance, most motor interventions employing exercise in rats are voluntary so the animals are allowed to run as much as they want and in general rats tend to be very active; the parallel to humans is not the same because humans tend to be inactive, especially in the presence of injury. In animal studies that force the animal to exercise there is a stress component (e.g. electrical shock) that is different from forcing humans to exercise as in therapy. Nevertheless, some authors believe in a more simplistic comparison and consider voluntary wheel running to be the human parallel to exercise [98]. The only primate study identified in this review seems to provide a better translation from animals to humans because the methodology is more directly applicable. Animal studies employing the EE intervention, which is supposedly a counterpart to the cognitive interventions for humans, cannot make strong inferences about the role of a pure cognitive intervention to improve motor function because EE cannot be considered a purely cognitive intervention. This is in large part due to the increased cage space and the presence of physical activity devices (i.e., toys, tunnels, climbing ladders). In animals it is difficult to separate the effects of the social interaction aspect of EE from the opportunities to exercise, such as the extent to which group interaction may affect the amount and type of motor activity.

Exploring avenues for future research and intervention

A final goal of this review is to suggest future directions for clinical rehabilitation and related research. One issue which limits conclusions on optimal exercise parameters to achieve specific outcomes, is that exercise intensity may not be comparable across animal and human studies, specifically the pace of the activity and the aerobic level. In animals, the effect of intensity of exercise is confounded by potential stress induced by faster-paced forced exercise. Notably, voluntary exercise and forced slow-paced exercise consistently led to positive effects on neurotrophic factors such as BDNF. On the other hand, forced moderate-fast paced exercise yielded inconsistent results, which seems to be related to the countering effects of stress on BDNF production. It has been shown that higher-intensity exercise causes elevated levels of corticosterone, a stress hormone that is widely believed to have an adverse effect on BDNF levels [99].

It is also unknown whether animals when self-paced are exercising aerobically even though that is the presumption. In humans, aerobic exercise was shown to be more effective than non-aerobic exercise in all studies comparing the two, but some studies on elderly individuals with AD demonstrated that non-aerobic exercise (i.e., movement therapy) may have more of an effect on cognition than no exercise [40,41]. Obviously, studies using healthy adults were more likely of higher intensity exercise and studies involving the elderly and/or neurologically-disabled patients were more likely to use lower-intensity or non-aerobic exercise. However, they may have similar relative intensities in more impaired or fragile individuals, but this is not typically reported in many studies. Greater characterization of the aerobic intensity and pace for all exercise programs in both animal and human research would go far to better inform treatment recommendations.

Prolonged exercise has been demonstrated to evoke sustained increases in neurotrophic

factors [96] and the cognitive effects of exercise were not shown to be sustained after the exercise was discontinued, so the answer to the optimal duration may be determined by how long one wants the designed cognitive effects to persist. This is similar to the physical effects of exercise on muscle size or cardiorespiratory capacity which must also be sustained to maintain benefits.

Arguably, the EE paradigm so prevalent in the animal literature seems the most challenging to implement in humans. Janssen *et al*. [100] made the claim that many rehabilitation settings may be environmentally-deprived compared to a typical human environment. They suggested that rearranging ward set-ups, altering ward routines, and including additional equipment may prove to be beneficial for rehabilitation. Other studies propose possible ways to implement EE for improvement of cognition in humans as well. Arendash *et al*. [87] found that long-term EE of an aged mouse model of AD resulted significant improvement in cognitive function and suggested that this long-term stimulation could yield positive effects in humans. Once again, further studies are needed to more precisely determine the "active" ingredients in EE for producing behavioral changes in motor or cognitive performance, or improving emotional well-being.

Future research should further explore the effects of pure cognitive training on motor function. The available literature in humans is limited in numbers and in the adequacy of available studies to answer this question. The available literature in animals cannot be directly extrapolated to humans. It is possible that cognitive interventions work indirectly to improve motor function by improving resources in the brain that allow for motor functions to be executed more automatically and effectively. However, this idea can only be confirmed when studies employ better methodological control. Including brain imaging and blood biomarkers in those investigations is crucial in order to explain the neural mechanisms involved in this dynamics.

Another potential avenue for future research and intervention is the use of exercise to potentiate the effects of cognitive interventions. Given that exercise has specific effects on increasing levels of BDNF which has been related to learning and attention among other cognitive functions, the idea would be to use exercise in adjunction to or as a primer for cognitive interventions. The question to be answered is whether or not better cognitive outcomes can be reached when combining exercise with cognitive therapy versus cognitive therapy alone.

Conflict of Interest

The authors in this paper declare no conflict of interest.

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