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Effects of Aerobic and Resistance Exercise on Brain-Derived Neurotrophic Factor and Cognitive
Benefits in Alzheimer’s Disease

Stephanie Cullen

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24 **Abstract**

25 Cognitive function below age-matched controls is the hallmark of Alzheimer's disease.
26 Brain derived neurotrophic factor is a biochemical molecule that mediates neuronal survival, but
27 its expression is reduced in Alzheimer's disease, causing neurodegeneration. Exercise has been
28 shown to increase Brain-Derived Neurotrophic Factor, which mediates improvements in
29 cognition in Alzheimer's patients and slows cognitive decline. Evidence is presented to show
30 that aerobic exercise is well known to increase serum Brain-Derived Neurotrophic Factor, while
31 resistance training studies have not yet shown a conclusive effect. Increased Brain-Derived
32 Neurotrophic Factor from aerobic exercise has been shown to mediate improvements in
33 hippocampal volume and executive function. No clinical guidelines have been developed for
34 exercise to improve cognition in Alzheimer's patients, so clinicians are encouraged to follow the
35 Canadian Physical Activity guidelines and include both aerobic and resistance training in
36 exercise programs to achieve maximum cognitive benefits. Exercise prescription is especially
37 important for those at high risk of developing Alzheimer's disease, as they will greatly benefit
38 from the protective effects of Brain-Derived Neurotrophic Factor before converting and exercise
39 adherence is increased in Alzheimer's patients if they have found exercise they enjoy.

40 **Keywords:** Brain-Derived Neurotrophic Factor, Alzheimer's disease, aerobic exercise,
41 resistance training, cognition

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47 **Introduction**

48 As life expectancy increases, the proportion of older adults in the world's population also
49 increases, as well as the prevalence of age-related diseases, such as heart disease, diabetes and
50 dementia. This puts more pressure on research facilities to develop healthy aging strategies and
51 preventative interventions to prolong the healthy lifespan (Rizvi and Jha 2010). Cognitive
52 decline is a normal part of the aging process; however, cognitive decline can become more
53 severe in some older adults than their aged-matched controls, which is the manifestation of
54 clinical conditions such as mild cognitive impairment (MCI), dementia, and Alzheimer's disease
55 (AD). There is an increasing body of evidence that environmental factors can play a role in
56 healthy cognitive aging (Bherer et al. 2013). Three environmental factors have been described as
57 being the most important in later life for slowing cognitive decline and preventing against
58 dementia: an active social network, cognitively stimulating leisure activities, and physical
59 activity participation (Fratiglioni et al. 2004). Many reviews argue that physical activity is the
60 most important of these factors for maintaining cognitive function (Bherer et al. 2013; King and
61 Kitchener 2014).

62 Cognitive function is mediated by many biochemical factors in the brain, and as the aging
63 population grows, these molecules become more and more important for understanding the
64 decline in cognitive health. Brain-Derived Neurotrophic Factor (BDNF) is one of these
65 molecules, a protein that belongs to the neurotrophins family, which mediates the survival and
66 maintenance of neurons through binding with the receptor Tyrosine receptor kinase B (TrkB).
67 Both BDNF and TrkB are decreased in the brains of those with AD (Fumagalli et al. 2006).
68 Resistance training and aerobic exercise have been shown to affect serum levels of BDNF
69 (Coehlo et al., 2013), but in different magnitudes and methods, which may be the key to

70 understanding how exercise programs mediate improvements in cognitive function. This article
71 will focus on the role of BDNF in AD and current evidence to show that exercise may be a
72 valuable treatment for improving cognitive status in older adults through improving the
73 biochemical environment of the brain.

74

75 **BDNF Function in AD**

76 BDNF and TrkB are produced in the brain and throughout the central and peripheral
77 nervous systems. In early development, BDNF is produced to differentiate neurons from stem
78 cells and promote synapse formation. BDNF is continually produced throughout the life span in
79 low amounts, but even at low concentrations, it is highly effective at preventing neuronal cell
80 death. When BDNF binds to the TrkB receptor, a complex downstream signalling pathway is
81 turned on that leads to improved DNA damage repair in neurons and the production of proteins
82 involved in neuronal survival and plasticity (Marosi and Mattson 2014). BDNF expression is
83 controlled by many factors, such as sensory stimulation, bioelectric activity, pharmaceuticals,
84 and a wide array of neurotransmitters (Murer et al. 2001).

85 There is a large body of evidence that shows that BDNF expression is decreased in the
86 brains of AD patients (Murer et al. 2001; Fumagalli et al. 2006). Most of this research is done in
87 the post-mortem brains of AD patients, as performing a brain biopsy on living patients is not
88 possible without severe damage to surrounding brain tissue; however, decreased serum BDNF
89 has also been measured in living patients with both early and late stage AD (Gezen-Ak et al.
90 2013). A detailed study of the various mRNA transcripts of BDNF showed that three of the
91 seven identified mRNA transcripts for BDNF were decreased in the parietal cortex of the post-
92 mortem AD brain compared to age-matched controls: transcripts 1 and 3 were decreased two-

93 fold, while transcript 2 was decreased five-fold compared to controls (Garzon et al. 2004).
94 Furthermore, in a study by Murer and colleagues (1999), chemical staining done of the brains of
95 deceased AD patients showed that those neurons that had large neurofibrillary tangles, a major
96 symptom of AD, did not contain BDNF. Most of the neurons that stained positive for BDNF did
97 not have the large degrading tangles in them.

98 In living patients, there has been evidence that high serum BDNF levels decreases risk
99 for developing dementia and AD. In a large longitudinal cohort of American adults, it was found
100 that for each standard-deviation increment increase in BDNF level, the ten-year risk for
101 developing dementia or AD was decreased by 23% in educated older women (Weinstein et al.
102 2014). Higher BDNF levels have also been associated with slower cognitive decline in AD
103 patients after one year follow-up, although further longitudinal studies are needed to corroborate
104 these findings (Laske et al. 2011).

105

106 **BDNF Response to Aerobic Exercise**

107 There is a large evidence base supporting the positive effect of aerobic exercise on BDNF
108 concentrations and its mechanism in maintaining cognitive health. A meta-analysis of 18 aerobic
109 exercise studies showed that BDNF concentrations in peripheral blood supply increased after
110 aerobic exercise interventions (Dinoff et al. 2016). Similar findings were also reported by Coelho
111 et al. (2013), Schmolesky et al. (2013), and Huang et al. (2013). These human studies are also
112 corroborated by many studies using rodent models (Hertzeg et al. 2008). Acute aerobic exercise
113 was shown to increase BDNF concentrations in both cognitively normal older adults and those
114 with AD (Coelho et al. 2014).

115 A randomized control trial of cognitively normal community-dwelling older adults by
116 Leckie et al. (2014) showed that increases in BDNF concentration after aerobic exercise also
117 mediated improvements in executive function. Those who completed the aerobic exercise
118 intervention showed improvements in their ability to switch between two tasks as a result of their
119 increased levels of BDNF. Executive function is the cognitive process used to plan, initiate and
120 regulate behaviour, and is impaired even in the early stages of AD (Farina et al. 2016). The effect
121 of exercise derived increases in BDNF on executive function may be important in understanding
122 the decline in executive function in AD patients and how it can be slowed using aerobic exercise
123 interventions.

124 Another study by Erickson et al. (2011) compared the effects of aerobic exercise and a
125 control stretching exercise program on serum BDNF concentrations and hippocampal volume in
126 older adults without previous cognitive impairment. Increases in BDNF concentrations
127 correlated with increased hippocampal volume only in the aerobic exercise group. The one year
128 aerobic exercise intervention was able to increase hippocampal volume by 2%, which is
129 equivalent to reversing the 1-2% deterioration per year normally seen in older adults without
130 dementia.

131 Aerobic exercise has been shown many times to improve multiple aspects of cognition in
132 both cognitively normal participants and those with AD. Many of these improvements are
133 mediated by BDNF level increases, which is important for understanding how aerobic exercise
134 improves cognition as a whole. While many of these studies give promising results, there are still
135 no defined guidelines for aerobic exercise programs specifically to slow cognitive decline,
136 whether through maximizing BDNF response or through other exercise mediated improvements.

137

138 **BDNF Response to Resistance Training**

139 Evidence of the relationship between resistance training and BDNF concentrations is less
140 abundant and conclusive than that for aerobic exercise. A meta-analysis of twelve randomized
141 control trials using a resistance training intervention showed that BDNF levels in the blood did
142 not change significantly following the exercise protocols, which ranged in frequency, duration,
143 time and type (Dinoff et al. 2016). Walsh and colleagues (2016) also found that resistance
144 training had no effect on basal BDNF concentrations. Blood samples were taken in 20-minute
145 increments for two hours total, with time zero at the beginning of exercise, as well as under rest
146 conditions. The blood concentrations of BDNF did transiently increase during exercise, but
147 dropped back to baseline within two hours, and the rising and falling response of BDNF
148 concentrations to exercise was the same both before and after the eight-week exercise program.
149 This program consisted of four sets of eight to ten reps of three different lower body exercises,
150 increasing from 60% to 80% of 1-repetition maximum (1RM) over an eight-week period.

151 Alternatively, some resistance training programs have been shown to be effective in
152 increasing BDNF levels in older adults. In a study by Coelho et al. (2012), older female
153 participants completed three one-hour training sessions a week for ten weeks, consisting of three
154 sets of eight reps of various lower body exercises. The weight was set at 50% of participant's
155 1RM for the first two weeks and 75% of their 1RM for weeks two through ten, with a re-
156 evaluation of 1RM at weeks five and eight. Participants' BDNF levels were increased
157 significantly after the intervention. In another study by Church et al. (2016), participants were
158 randomized to either a high intensity/low volume (HI) or low intensity/high volume (HV)
159 resistance exercise protocol. The HI protocol included three to five reps at 90% 1RM, while the
160 HV protocol included ten to twelve reps at 70% 1RM, each four times a week for eight weeks.

161 Blood samples were collected at baseline and on the last day of exercises immediately following
162 the exercises, as well as thirty and sixty minutes after completion of the exercise session. Plasma
163 BDNF levels were significantly elevated after both protocols at all three post-exercise time-
164 points.

165 The effect of resistance training on BDNF levels varies across different experimental
166 designs and participant samples. Further research on this topic needs to be done before a
167 conclusive effect can be determined, and if there is a positive effect, which program design is
168 best for inciting this effect.

169

170 **Discussion and Clinical Implications**

171 The evidence discussed above shows that physical activity participation has many
172 positive effects on cognition through increasing BDNF concentrations. However, because no
173 guidelines have been set for exercise specifically to improve cognition, clinicians should focus
174 on having patients meet the Canadian Physical Activity guidelines for adults 65 and older, which
175 includes 150 minutes of aerobic activity per week, plus two days of strength training per week
176 and balance exercises as needed (Canadian Society for Exercise Physiology 2011). As less than
177 15% of adults aged 60-79 in Canada are meeting these guidelines (Statistics Canada 2015), this
178 is an important first step for clinicians until special programs to increase cognition are
179 developed.

180 Even though resistance training has not shown conclusive results in increasing BDNF
181 concentrations, this type of exercise is still important to include in exercise programs for older
182 adults for many reasons. Resistance training has been shown to improve cognition through
183 increasing other biochemical factors important for brain health, such as insulin-like growth

184 factor-1 (IGF-1) and homocysteine (Liu-Ambrose and Donaldson 2008). Also, exercise
185 programs that include both aerobic and resistance training exercise combined produce a greater
186 improvement in cognition than aerobic exercise alone (Colcombe and Kramer 2003). Finally,
187 strength training exercise programs have been shown to offset the decrease in physical capacity
188 to do activities of daily living (ADLs) in those with AD and to decrease falls risk, which
189 improves quality of life for AD patients (Santana-Sosa et al. 2008). Even though resistance
190 training has not been shown to increase BDNF conclusively, it is still important for increasing
191 cognition and overall physical health in both cognitively normal older adults and AD patients.

192 Exercise prescription is especially important for those at high risk of converting to AD,
193 such as those with family history of AD or patients with MCI. Once converted to AD, retention
194 rates of exercise programs vary much more than in programs for cognitively normal older adults
195 (Yu 2013). Participants with lower scores on cognitive tests, meaning those further along in
196 cognitive decline, are also more likely to drop out of aerobic exercise programs (McCurry et al.
197 2010). However, one of the major barriers to exercise cited by AD patients and their caregivers is
198 the patient's dislike of structured exercise (Suttanon et al. 2012). If patients can find a type of
199 exercise they like before converting to AD, participation in exercise may slow their cognitive
200 decline through increased BDNF, with the additional effect of increasing adherence to the liked
201 program if they do eventually convert.

202 Increasing BDNF concentrations through exercise is an emerging therapy for
203 neurodegeneration caused by AD. While this relationship has been proven for aerobic exercise,
204 more research is needed into the effects of strength training and combined programs before
205 guidelines can be set for exercise prescription. The current Canadian Physical Activity
206 Guidelines for adults 65 and older should be used for all older patients, but especially those at

207 risk for cognitive decline, as the positive relationship between exercise, cognition, and overall
208 health has been proven in many different mechanisms, not just increased BDNF concentrations.

209

210 **Take Home Points**

- 211 • BDNF is a small protein in the neurotrophins family that improves the growth and
212 survival of neurons and is decreased in the brains of AD patients.
- 213 • BDNF concentrations have been shown to be increased by aerobic exercise, which
214 mediates improvements in hippocampal volume and executive function.
- 215 • Resistance training programs may increase BDNF concentrations, but further research is
216 needed before a conclusion can be made.
- 217 • No specific exercise guidelines have been established yet to improve cognitive function.
218 The current Canadian Physical Activity Guidelines for older adults should be used for
219 exercise prescription, as they suggest combined aerobic and resistance training exercise,
220 which has the greatest positive effect on cognition.
- 221 • Exercise prescription is especially important for those at high risk for AD, as increasing
222 BDNF concentrations may slow their cognitive decline and prior exercise may increase
223 adherence if they do convert to AD.

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230 References

- 231 Bherer L, Erickson KI & Liu-Ambrose T. (2013) A review of the effects of physical activity and
232 exercise on cognitive and brain functions in older adults. *Journal of Aging Research*,
233 657508. doi:10.1155/2013/657508.
- 234 Canadian Society for Exercise Physiology (2011). *Canadian Physical Activity Guidelines for*
235 *Older Adults 65 years and older*. Retrieved from
236 http://www.csep.ca/CMFiles/Guidelines/CSEP_PAGuidelines_older-adults_en.pdf
- 237 Church, D. D., Hoffman, J. R., Mangine, G. T., Jajtner, A. R., Townsend, J. R., Beyer, K. S., et
238 al. (2016). Comparison of high-intensity vs. high-volume resistance training on the
239 BDNF response to exercise. *J Appl Physiol*,121(1), 123-128.
240 doi:10.1152/jappphysiol.00233.2016
- 241 Coelho, F. M., Pereira, D. S., Lustosa, L. P., Silva, J. P., Dias, J. M., Dias, R. C., et al. (2012).
242 Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor
243 (BDNF) levels in non-frail and pre-frail elderly women. *Arch Gerontol Geriatr*,54(3),
244 415-420. doi:10.1016/j.archger.2011.05.014
- 245 Coelho, F. G., Gobbi, S., Andreatto, C. A., Corazza, D. I., Pedroso, R. V., & Santos-Galduróz, R.
246 F. (2013). Physical exercise modulates peripheral levels of brain-derived neurotrophic
247 factor (BDNF): A systematic review of experimental studies in the elderly. *Arch*
248 *Gerontol Geriatr*,56(1), 10-15. doi:10.1016/j.archger.2012.06.003
- 249 Coelho, F. G., Vital, T. H., Stein, A. M., Arantes, F. J., Rueda, A. V., Camarini, R., et al. (2014).
250 Acute Aerobic Exercise Increases Brain-Derived Neurotrophic Factor Levels in Elderly
251 with Alzheimer's Disease. *J Alzheimers Dis*,39, 401-408. doi:10.3233/JAD-131073

- 252 Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults:
253 A Meta-Analytic study. *Psychol Sci*,*14*(2), 125-130. doi:10.1111/1467-9280.t01-1-01430
- 254 Dinoff, A., Herrmann, N., Swardfager, W., Liu, C. S., Sherman, C., Chan, S., & Lanctôt, K. L.
255 (2016). The Effect of Exercise Training on Resting Concentrations of Peripheral Brain-
256 Derived Neurotrophic Factor (BDNF): A Meta-Analysis. *Plos One*,*11*(9).
257 doi:10.1371/journal.pone.0163037
- 258 Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011).
259 Exercise training increases size of hippocampus and improves memory. *Proceedings of*
260 *the National Academy of Sciences*,*108*(7), 3017-3022. doi:10.1073/pnas.1015950108
- 261 Farina, N., Tabet, N., & Rusted, J. (2016). The relationship between habitual physical activity
262 status and executive function in individuals with Alzheimer's disease: a longitudinal,
263 cross-lagged panel analysis. *Aging, Neuropsychology, and Cognition*,*23*(2), 234-252.
264 doi:10.1080/13825585.2015.1080213
- 265 Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated
266 lifestyle in late life might protect against dementia. *Lancet Neurol*,*3*(6), 343-353.
267 doi:10.1016/s1474-4422(04)00767-7
- 268 Fumagalli, F., Racagni, G., & Riva, M. A. (2006). The expanding role of BDNF: a therapeutic
269 target for Alzheimer's disease? *Pharmacogenomics J*,*6*(1), 8-15.
270 doi:10.1038/sj.tpj.6500337
- 271 Garzon, D., Yu, G., & Fahnstock, M. (2004). A new brain-derived neurotrophic factor transcript
272 and decrease in brain-derived neurotrophic factor transcripts 1, 2 and 3 in Alzheimer's
273 disease parietal cortex. *J Neurochem*,*82*(5), 1058-1064. doi:10.1046/j.1471-
274 4159.2002.01030.x

- 275 Gezen-Ak, D., Dursun, E., Hanagasi, H., Bilgic, B., Lohman, E., Araz, O. S., et al. (2013).
276 BDNF, TNF α , HSP90, CFH, and IL-10 Serum Levels in Patients with Early or Late
277 Onset Alzheimer's Disease or Mild Cognitive Impairment. *Journal of Alzheimer's*
278 *Disease*,37, 185-195. doi:10.3233/JAD-130497
- 279 Hertzog, C., Kramer, A. F., Wilson, R. S., & Lindenberger, U. (2008). Enrichment Effects on
280 Adult Cognitive Development. *Psychol Sci Public Interest*,9(1), 1-65.
281 doi:10.1111/j.1539-6053.2009.01034.x
- 282 Huang, T., Larsen, K. T., Ried-Larsen, M., Møller, N. C., & Andersen, L. (2013). The effects of
283 physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A
284 review. *Scand J Med Sci Sports*,24(1), 1-10. doi:10.1111/sms.12069
- 285 King, P. M., & Kitchener, K. S. (2014). Cognitive Development in the Emerging Adult. *Oxford*
286 *Handbooks Online*,9(1), 1-65. doi:10.1093/oxfordhb/9780199795574.013.14
- 287 Laske, C., Stellos, K., Hoffmann, N., Stransky, E., Straten, G., Eschweiler, G. W., & Leyhe, T.
288 (2011). Higher BDNF serum levels predict slower cognitive decline in Alzheimer's
289 disease patients. *Int J Neuropsychopharmacol*,14(03), 399-404.
290 doi:10.1017/s1461145710001008
- 291 Leckie, R. L., Oberlin, L. E., Voss, M. W., Prakash, R. S., Szabo-Reed, A., Chaddock-Heyman,
292 L., et al. (2014). BDNF mediates improvements in executive function following a 1-year
293 exercise intervention. *Frontiers in Human Neuroscience*,8, 985.
294 doi:10.3389/fnhum.2014.00985
- 295 Liu-Ambrose, T., & Donaldson, M. G. (2008). Exercise and cognition in older adults: is there a
296 role for resistance training programmes? *Br J Sports Med*,43(1), 25-27.
297 doi:10.1136/bjism.2008.055616

- 298 Marosi, K., & Mattson, M. P. (2014). BDNF mediates adaptive brain and body responses to
299 energetic challenges. *Trends Endocrinol Metab*,25(2), 89-98.
300 doi:10.1016/j.tem.2013.10.006
- 301 McCurry, S. M., Pike, K. C., Logsdon, R. G., Vitiello, M. V., Larson, E. B., & Teri, L. (2010).
302 Predictors of Short- and Long-Term Adherence to a Daily Walking Program in Persons
303 With Alzheimer's Disease. *Am J Alzheimers Dis Other Demen*,25(6), 505-512.
304 doi:10.1177/1533317510376173
- 305 Murer, M., Boissiere, F., Yan, Q., Hunot, S., Villares, J., Faucheux, B., et al. (1999). An
306 immunohistochemical study of the distribution of brain-derived neurotrophic factor in the
307 adult human brain, with particular reference to Alzheimer's disease. *Neuroscience*,88(4),
308 1015-1032. doi:10.1016/s0306-4522(98)00219-x
- 309 Murer, M., Yan, Q., & Raisman-Vozari, R. (2001). Brain-derived neurotrophic factor in the
310 control human brain, and in Alzheimer's disease and Parkinson's disease. *Prog*
311 *Neurobiol*,63(1), 71-124. doi:10.1016/s0301-0082(00)00014-9
- 312 Rizvi, S. I., & Jha, R. (2010). Strategies for the discovery of anti-aging compounds. *Expert*
313 *Opin Drug Discov*,6(1), 89-102. doi:10.1517/17460441.2011.533653
- 314 Santana-Sosa, E., Barriopedro, M. I., López-Mojares, L. M., Pérez, M., & Lucia, A. (2008).
315 Exercise Training is Beneficial for Alzheimer's Patients. *Int J Sports Med*,29(10), 845-
316 850. doi:10.1055/s-2008-1038432
- 317 Schmolesky, M. T., Webb, D. L., & Hansen, R. A. (2013). The effects of aerobic exercise
318 intensity and duration on levels of brain-derived neurotrophic factor in healthy men. *J*
319 *Sports Sci Med*,12(3), 502-511.

- 320 Statistics Canada. (2015). Directly measured physical activity of Canadian adults, 2012 and
321 2013. *Health Fact Sheet*. Statistics Canada Catalogue no. 82-625-X.
322 <http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14135-eng.htm>
- 323 Suttanon, P., Hill, K. D., Said, C. M., Byrne, K. N., & Dodd, K. J. (2012). Factors influencing
324 commencement and adherence to a home-based balance exercise program for reducing
325 risk of falls: perceptions of people with Alzheimer's disease and their caregivers. *Int*
326 *Psychogeriatr*,24(7), 1172-1182. doi:10.1017/S1041610211002729
- 327 Walsh, J. J., Scribbans, T. D., Bentley, R. F., Kellawan, J. M., Gurd, B., & Tschakovsky, M. E.
328 (2016). Neurotrophic growth factor responses to lower body resistance training in older
329 adults. *Appl Physiol Nutr Metab*,41(3), 315-323. doi:10.1139/apnm-2015-0410
- 330 Weinstein, G., Beiser, A. S., Choi, S. H., Preis, S. R., Chen, T. C., Vorgas, D., et al. (2014).
331 Serum Brain-Derived Neurotrophic Factor and the Risk for Dementia. *JAMA*
332 *Neurol*,71(1), 55-61. doi:10.1001/jamaneurol.2013.4781
- 333 Yu, F. (2013). Improving recruitment, retention, and adherence to 6-month cycling in
334 Alzheimer's disease. *Geriatr Nurs*,34(3), 181-186. doi:10.1016/j.gerinurse.2012.12.014