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# Influence of Aerobic Training and Combinations of Interventions on Cognition and Neuroplasticity after Stroke

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Stroke often aggravated age-related cognitive impairments that strongly affect several aspects of quality of life. However, few studies are, to date, focused on rehabilitation strategies that could improve cognition. Among possible interventions, aerobic training is well known to enhance cardiovascular and motor functions but may also induce beneficial effects on cognitive functions. To assess the effectiveness of aerobic training on cognition, it seems necessary to know whether training promotes the neuroplasticity in brain areas involved in cognitive functions. In the present review, we first explore in both human and animal how aerobic training could improve cognition after stroke by highlighting the neuroplasticity mechanisms. Then, we address the potential effect of combinations between aerobic training with other interventions, including resistance exercises and pharmacological treatments. In addition, we postulate that classic recommendations for aerobic training need to be reconsidered to target both cognition and motor recovery because the current guidelines are only focused on cardiovascular and motor recovery. Finally, methodological limitations of training programs and cognitive function assessment are also developed in this review to clarify their effectiveness in stroke patients.

**Keywords:** aging neuroscience, stroke rehabilitation, cerebral ischemia, angiogenesis, cognitive disorders, exercise intensity, neurotrophic factors, rat and human model

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## INTRODUCTION

Sedentary older adults are prone to cardiovascular diseases, such as stroke (Bherer et al., 2013), which occurs when blood flow is interrupted to a part of the brain. This trauma leads to severe motor dysfunctions and it may also aggravate cognitive impairments resulting from normal aging (Rafnsson et al., 2007, 2009; Deary et al., 2009; Waldstein and Wendell, 2010). Indeed, stroke survivors have more than twice the risk of subsequently developing dementia compared with people who have never had a stroke (Tatemichi et al., 1992; Patel et al., 2002). For instance, a stroke situated on the left hemisphere might disturb language and comprehension, which reduce the ability to communicate (Karbe et al., 1990; Pirmoradi et al., 2016). When the right hemisphere is affected, the intuitive thinking, reasoning, solving problems as well as the perception, judgment and the visual-spatial functions could be impaired (Tatemichi et al., 1994; Patel et al., 2002; Cumming et al., 2012; Sun et al., 2014b; Harris et al., 2015; Tiozzo et al., 2015; Save-Pédebos et al., 2016). It makes thus

difficult for patients to locate objects, walk up or down stairs or get dressed. Consequently, cognitive disorders are one of the strongest predictor of the inability to return to work, that contribute to the socioeconomic burden of stroke (Kauranen et al., 2013). However, stroke-induced cognitive disorders are often underestimated relative to motor impairments because they are confused with pre-existing symptoms of age-related mild cognitive impairments or Alzheimer's Disease (AD; Figure 1; Sun et al., 2014b; Corriveau et al., 2016). Furthermore, cognitive impairments are frequently associated with poor motor recovery (Patel et al., 2002; Lesniak et al., 2008; Rand et al., 2010). It suggests that stroke-induced cognitive dysfunctions and brain plasticity might also affect the stability, flexibility and learning of complex movements (e.g., locomotion, unimanual aiming, bimanual coordination), in which cognitive resources are highly involved as it was already observed in older adults (Temprado et al., 1999, 2013; Sleimen-Malkoun et al., 2012, 2013; Cohen et al., 2016).

It is thus of great importance to find effective interventions to induce both motor and cognitive improvement after stroke. In this respect, it is now widely established that aerobic training enhances cardiorespiratory fitness, muscular endurance and functional recovery of stroke patients resulting in a higher quality of life (Ivey et al., 2005; Macko et al., 2005; Marsden et al., 2013). Over the past few years, few studies have also shown that aerobic training could improve cognitive functions and promotes neuroplasticity in stroke patients (Quaney et al., 2009;

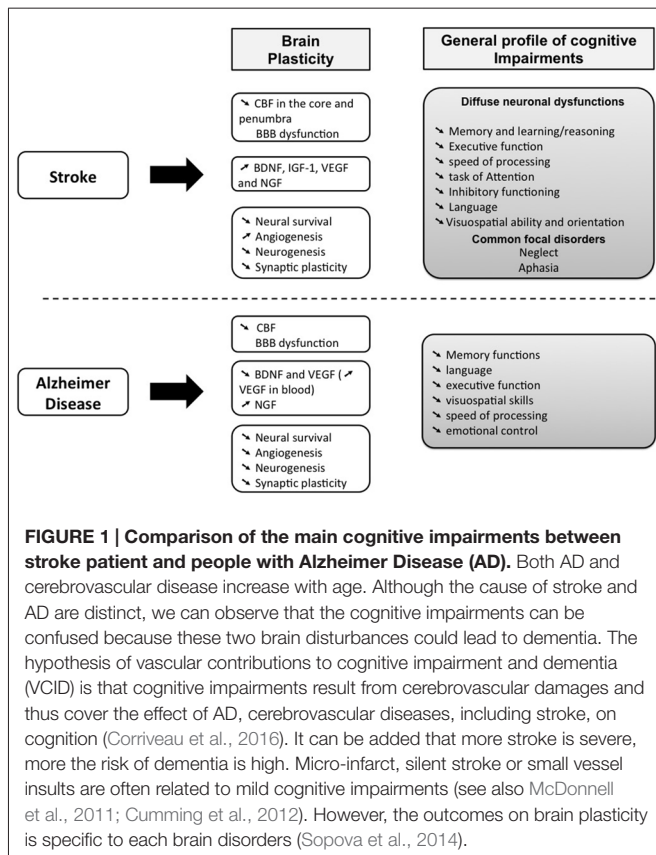
Rand et al., 2010; Wogensen et al., 2015). In support of these observations, animal studies have revealed that such training effects on cognitive functions might be partially mediated by the release of neurotrophic factors that promotes angiogenesis, neurogenesis, synaptogenesis and synthesis of neurotransmitters that could not be directly investigated at central level in humans (Churchill et al., 2002; Cotman et al., 2007; Lövdén et al., 2010). However, despite firm evidence supporting the use of aerobic exercise for stroke patients, the mechanisms underlying neuroplasticity that is at origin of cognitive and motor recovery in stroke patients remain unknown.

In the present review, we first examine how aerobic training might play a beneficial role on cognition after stroke. In particular, we highlight the influence of aerobic training on neuroplasticity in both human and animal. We also discuss whether additional rehabilitation strategies and/or pharmacological treatments could accentuate neuroplasticity and consequently, the recovery of cognitive functions. In addition, we present the different exercise parameters that should be taken into account in aerobic training, namely: intensity, duration, frequency (number of session per week) and types of exercise as well as timing of training initiation after stroke onset. Indeed, they might differ in their effectiveness to improve cognition and motor functions. Therefore, classic recommendations for aerobic exercise are reconsidered to target cognition as well as motor and cardiovascular functions. Finally, we discuss about the methodological limitations that may hamper the understanding of aerobic training effects on cognition both in human and animal studies.

## INFLUENCE OF AEROBIC TRAINING ON NEUROPLASTICITY AND COGNITIVE FUNCTIONS

Cognitive disorders (i.e., executive function and/or information processing speed), motor dysfunctions (i.e., locomotion, balance and strength impairments) and cardiorespiratory fitness weakness are frequently observed in both elderly and stroke people. However, the severity of these impairments is exacerbated due to ischemia in older stroke patients (Gordon et al., 2008; Billinger et al., 2012; Cumming et al., 2013; Harada et al., 2013). Moreover, some neural mechanisms involved in cognitive disorders appear to be close between aging and cerebral ischemia. Specifically, a decrease of neurotrophic factor release (Ang et al., 2003; Silhol et al., 2005; Chae and Kim, 2009) or an abnormal level of oxidative stress and inflammation in hippocampus have been observed in both population (Joseph et al., 2005; Wang et al., 2007). In addition, cerebral blood flow decreases in ischemic region (Cupini et al., 2001; Zhang et al., 2013a) while the reduced vessel density in aging brain leads to an overall reduced blood flow and oxygenation into the brain (Petcu et al., 2010). Therefore, promoting angiogenesis might be critical for these two populations.

In numerous studies, it was demonstrated that aerobic training could induce beneficial effects on brain plasticity and associated cognitive functions as well as motor and



229 cardiorespiratory functions in aging population (Patel et al.,  
230 2002; McAuley et al., 2004; Kramer and Erickson, 2007; Lesniak  
231 et al., 2008; Erickson and Kramer, 2009). Thus, it can be  
232 hypothesized that such training could lead to similar positive  
233 effects on cognitive functions in stroke patients. In the following,  
234 we present evidence supporting this hypothesis in both older  
235 adults and animal studies. Then, on the basis of the few available  
236 studies in the literature, we made an overview of the effects of  
237 aerobic training on cognitive functions in people and animal with  
238 cerebral ischemia.

## 240 **Studies on Healthy Older Adults**

241 It is now recognized that aerobic training stimulates the positive  
242 plasticity of the aging brain. Such exercise-related plasticity  
243 mediates the maintenance, or even the increase, of cognitive  
244 performance as indicated by the improvement of executive  
245 functions and long-term memory. Such enhancements were  
246 observed in spite of the heterogeneity of methods, subject  
247 characteristics, training parameters or cognitive tasks used in  
248 the related studies (Colcombe and Kramer, 2003). Thanks to  
249 the use of sophisticated brain imaging technologies, cerebral  
250 modifications induced by aerobic training has been observed  
251 at both structural (i.e., increase in white and gray matter  
252 volumes and changes in synaptic connections) and functional  
253 (i.e., changes in brain activation patterns) levels (Churchill et al.,  
254 2002; Cotman and Berchtold, 2002; Colcombe and Kramer,  
255 2003; Colcombe et al., 2004a,b, 2006; McAuley et al., 2004;  
256 Erickson and Kramer, 2009; Greenwood and Parasuraman, 2010;  
257 Voss et al., 2010a,b). For instance, using functional magnetic  
258 resonance imagery (fMRI), it was shown that elderly people  
259 aerobically trained displayed a higher activation of brain areas  
260 involved in attentional control and inhibitory functioning,  
261 while a reduced activation is observed in brain areas involved  
262 in behavioral conflict (Colcombe et al., 2004a). Additionally,  
263 12-week of both bike and treadmill aerobic training increases  
264 the hippocampal and anterior cingulate cortex cerebral blood  
265 flow and also an immediate and delayed verbal memory. Such  
266 increase is closely related to neuroregeneration (Petcu et al.,  
267 2010; Chapman et al., 2013; Duzel et al., 2016). This result  
268 was recently reinforced by showing with the use of gadolinium-  
269 based perfusion imaging (3 Tesla MRI) that aerobic fitness  
270 improvement in healthy older adults is correlated with changes in  
271 hippocampal perfusion and volume that were positively related  
272 to changes in recognition memory and early recall for complex  
273 spatial objects (Maass et al., 2015).

274 Circulating neurotrophic factor measurements such as brain-  
275 derived neurotrophic factor (BDNF), insulin-like growth factor-1  
276 (IGF-1) and vascular endothelial growth factor (VEGF; see  
277 below for details) might also explain the influence of aerobic  
278 training on neuroplasticity and cognition in Human but this  
279 point remains controversial (Cotman et al., 2007). In the one  
280 hand, few studies have observed an increase in serum BDNF level  
281 in older adults after 1-year of aerobic training that was correlated  
282 with an increase in hippocampal volume and improvement in  
283 spatial memory performance as well as in executive function  
284 (Erickson et al., 2012; Leckie et al., 2014). Specifically, Leckie et al.  
285 (2014), revealed that the oldest subjects exhibited the greatest

286 increase in circulating BDNF levels and improvement in task  
287 performance after training. This observation suggests that age  
288 affects BDNF serum levels (Leckie et al., 2014). On the other  
289 hand, numerous studies did not provide robust evidence for  
290 enhancement of these neurotrophic factors after several weeks  
291 of training in aging people (Voss et al., 2013; Maass et al.,  
292 2015). For instance, serum BDNF, VEGF and IGF-1 level did  
293 not increase after 12-month of aerobic or non-aerobic (stretching  
294 exercises) training despite an increase of connectivity in the  
295 temporal lobe between the bilateral parahippocampus and the  
296 bilateral middle temporal gyrus (Voss et al., 2013). Recently,  
297 Maass et al. (2015), confirmed these results by showing that no  
298 difference in changes of circulating BDNF, VEGF and IGF-1  
299 was observed after 3-month of treadmill (training group) or  
300 progressive-muscle relaxation/stretching (control group) despite  
301 an increase of hippocampal perfusion and volume (Maass et al.,  
302 2015). On the basis of these results, it was suggested that the  
303 training-related improvement of cerebral perfusion could lead to  
304 beneficial effects on neural function without any contribution of  
305 growth factors.

306 These contradictory findings might result from limitations  
307 associated with the circulating serum growth factor  
308 measurements and training protocols. For instance, nutritional  
309 status and changes in energy balance inducing by exercise  
310 interventions might affect growth factor levels (Monteleone et al.,  
311 2004). Moreover, as it was previously mentioned (Coelho et al.,  
312 2013), studies presented different training durations and exercise  
313 intensity and heterogeneous samples. Authors also included a  
314 different proportion of females and/or males in their studies.  
315 Such imbalance in gender composition of experimental groups  
316 could have an effect of baseline serum BDNF that might hide  
317 possible influence of aerobic training (Komulainen et al., 2008;  
318 Driscoll et al., 2012). It has also been suggested that the variable  
319 time-windows of circulating growth factor measurements and  
320 the analysis techniques used for quantifying blood growth  
321 factor levels could also affect the results and need to be clarified  
322 (Maass et al., 2015). Finally, data from circulating growth factor  
323 assessment should be interpreted with caution since no direct  
324 relationships between circulating and brain growth factor levels  
325 has been found in human. Studies on human only demonstrated  
326 that peripheral BDNF was associated with cognitive performance  
327 and cerebral structure integrity (Ventriglia et al., 2013). However,  
328 it was also established in animal model that BDNF, VEGF and  
329 IGF-1 might have the potential to cross the blood-brain barrier  
330 (BBB) in both directions in the central nervous system (CNS;  
331 Pan et al., 1998; Cotman et al., 2007). As an illustration, Karege  
332 et al. (2002), demonstrated that serum BDNF was positively  
333 correlated with cortical BDNF in rat model. In addition,  
334 blocking the peripheral IGF-1 or VEGF access to the brain  
335 impeded exercise-induced plasticity in the hippocampus (Karege  
336 et al., 2002; Cotman et al., 2007). However, other studies have  
337 shown in neurological disorders such as stroke and depression  
338 that changes in regional brain BDNF levels are not associated  
339 with changes of BDNF levels in peripheral blood (Elfvig et al.,  
340 2010; Béjot et al., 2011). To date, it thus remains difficult to  
341 clearly determine the real role of circulating growth factors on  
342 cognitive function in older subjects.



## 343 Studies on Healthy Animals

344 Animal experiments could provide information about  
 345 neuroplasticity mechanisms at cellular level in brain areas  
 346 involved in cognitive functions. To date, three main  
 347 neurotrophic factors have been identified to contribute to  
 348 increase neuroplasticity after aerobic training: (i) the VEGF,  
 349 which is a protein whose main role is to stimulate angiogenesis;  
 350 (ii) the BDNF, which is a critical protein involved in brain  
 351 plasticity. Indeed, this neurotrophin mediates numerous  
 352 proteins expressions and molecular pathways, i.e., synapsin-I  
 353 and synpatophysin, both involved in synaptic transmission and  
 354 neurotransmitter release, C-AMP response element-binding  
 355 protein (CREB) and beta calcium/calmodulinedependent kinase  
 356 II ( $\beta$ -CaMKII) both contributing in long-term potentiation  
 357 (LTP). BDNF thus promotes synaptic plasticity, neurogenesis  
 358 and neuronal survival within the hippocampus (Vaynman et al.,  
 359 2004; Cassilhas et al., 2012); and (iii) the IGF-1, which is a  
 360 peptide that crosses the BBB and stimulates neurogenesis and  
 361 angiogenesis. These growth factors act together to promote  
 362 training-related benefits in brain plasticity and associated  
 363 cognitive functions.

364 It was found in adult rats that aerobic training induced-  
 365 angiogenesis is associated with an increase in brain VEGF mRNA  
 366 and protein (Ding et al., 2006; Cotman et al., 2007). Moreover,  
 367 Swain et al. (2003), have proved that prolonged voluntary  
 368 exercise induced an increase of blood volume in the motor  
 369 cortex of 19% greater than control animals (Swain et al., 2003).  
 370 Angiogenesis needs to be promoted because some animal studies  
 371 have suggested that angiogenesis was closely linked to adult  
 372 neurogenesis and other neuroplasticity mechanisms (Pereira  
 373 et al., 2007).

374 It was demonstrated that 8-week of aerobic training on  
 375 treadmill induced an improvement in learning speed and  
 376 spatial learning. Authors suggested that these results could be  
 377 explained by an increase of hippocampal BDNF and IGF-1  
 378 and more precisely by the activation of BDNF/TrkB/ $\beta$ -CaMKII  
 379 pathway and to a lesser extent to IGF-1/IGF-1R/Akt pathway  
 380 (Cassilhas et al., 2012). Radák et al. (2001, 2006), indicated  
 381 that short- and long-term memory was improved after 8  
 382 weeks of regular swimming exercise in middle-aged rats (14-  
 383 month-old). BDNF and nerve growth factor (NGF) expressions  
 384 were up-regulated as well as a reduction of accumulation  
 385 of reactive carbonyl derivatives that are known to damage  
 386 proteins, nucleic acids and lipids (Radák et al., 2001, 2006).  
 387 Similarly, one study on aging rat model, induced by D-galactose  
 388 injection, has shown that 8-week of moderate aerobic training  
 389 treadmill could importantly increase both level of NGF and his  
 390 receptor, the tyrosine kinase A (TrkA) in the hippocampus.  
 391 NGF/TrkA activates the phosphoinositide 3-kinase (PI3-K)/Akt  
 392 pathway that decreases apoptosis (Wiesmann and de Vos, 2001;  
 393 Chae and Kim, 2009). Excessive reactive oxygen species (ROS)  
 394 production can also trigger apoptosis in brain areas such as  
 395 the hippocampus that contribute to neurodegenerative disorders  
 396 and cognitive function impairments in aging people. However,  
 397 moderate intensity training on treadmill (18 m/min, 30 min/day  
 398 during 15 weeks) in middle-age female rats (12-month-old)  
 399 could enhance antioxidant defense system and thus induced a

neuroprotective effect in the hippocampus (Marosi et al., 2012).  
 Training also facilitated the release of metabolic proteins in  
 the hippocampus such as mitochondrial precursor of ornithine  
 aminotransferase and isocitrate dehydrogenase subunit alpha.  
 However, these results remain difficult to interpret because  
 authors suggested that alteration of mitochondrial proteins may  
 be either reflecting mitochondrial damage or adaptation to  
 mitochondrial dysfunction (Kirchner et al., 2008).

## 400 Studies on Stroke Patients

401 Only three studies investigated the role of aerobic training on  
 402 cognition in stroke patients (Table 1). Two of them indicated  
 403 that aerobic training might reduce cognitive disorders by  
 404 improving functional outcomes as well as motor learning by the  
 405 increase of information processing speed and implicit memory  
 406 while executive functions remain affected (Quaney et al., 2009;  
 407 El-Tamawy et al., 2014). However, patients did not preserve  
 408 long-term beneficial effects 8 weeks after the end of aerobic  
 409 training (Quaney et al., 2009). Contrary to what was observed in  
 410 healthy subject, an acute and short aerobic exercise on treadmill  
 411 (20 min; 70% of the heart rate reserve) did not induce cognitive  
 412 improvement in stroke patient while a slightly improvement of  
 413 the movement of upper-extremity was observed (Ploughman  
 414 et al., 2008).

## 420 Studies on Animal with Cerebral Ischemia

421 Consistent with healthy older animals, neuroplasticity can be  
 422 partially promoted by aerobic training through up-regulation  
 423 of the expression of BDNF, synapsin-I and post-synaptic  
 424 density protein 95 (PSD-95), also involved in LTP within  
 425 hippocampus (dentate gyrus, CA1 and CA3 areas) and by  
 426 increase of both CREB phosphorylation and newborn cell  
 427 survival (Luo et al., 2007; Shih et al., 2013). The beneficial  
 428 effect of training was reinforced when the activation of the  
 429 high affinity BDNF receptor, the TrkB, was blocked because  
 430 the function of BDNF was reduced and the exercise-induced  
 431 spatial learning enhancement was impeded (Griesbach et al.,  
 432 2009). Thus, consistent with data collected within aging rodents,  
 433 it is supposed that BDNF-mediated pathway contributed to  
 434 explain the improvement of spatial memory performances after  
 435 cerebral ischemia. Furthermore, spatial memory performances  
 436 were positively correlated with an increase of both newborn  
 437 cell survival in bilateral dentate gyrus and restored microtubule-  
 438 associated protein 2 (MAP2) density after cerebral ischemia  
 439 (Luo et al., 2007; Shimada et al., 2013). Treadmill training  
 440 might also protect against cognitive impairments in rats with  
 441 bilateral common carotid artery occlusion (CCAO) by reducing  
 442 the lipoperoxidation in the hippocampus through an increase  
 443 of antioxidant capacity and by improving the acquisition of a  
 444 spatial task as well as the performance for both retention and  
 445 working memory (Figure 2; Cechetti et al., 2012). In addition,  
 446 few weeks of treadmill training in rat with cerebral ischemia  
 447 increases the VEGF, and its regulatory protein, caveolin-1, and  
 448 improves the cerebral blood flow in ischemic region (Zhang et al.,  
 449 2013a; Gao et al., 2014). However, no study has directly shown  
 450 that vascular changes could contribute to explaining the cognitive  
 451 disorders.

**Q5 TABLE 1 | Summary of aerobic training protocols with or without combination (pharmacological agents or other types of exercise) and their effects on cognition in stroke patient.**

Studies	Participants	Aerobic training	Combination	Cognitive assessments	Results
Ploughman et al., 2008	n = 21; (61.4 ± 10.2 years old); 6 months to 5 years post-stroke.	- AEX: single bout of 20 min on BWSST at 70% of THR or 13 on The Borg RPE Scale. - Control condition: 20 min review of home exercises.	none	- TMT-A and B - Symbol digit substitution test - Paced auditory serial addition test	No significant improvement observed No relationship between exercise intensity and cognitive tests.
Quaney et al., 2009	n = 38 (68.96 ± 14.68 and 64.10 ± 12.30 years old); > 6 months post-stroke.	- AEX: 45 min on cyclo-ergometer 3 times/week for 8 weeks at 70% HRmax (n = 19). - Control group: Upper- and lower-extremities stretching activities 45 min on cyclo-ergometer 3 times/week for 8 weeks at home (n = 19).	none	- WCST - Stroop task - TMT-A and B - SRTT test - PGFM	↗ VO <sub>2peak</sub> ↗ Complex motor learning tasks No significant improvement observed of executive function measures
Rand et al., 2010	n = 11 (67 ± 10.8 years old); > 4 years post-stroke.	AEX: 1 h composed of stretching, balance, task specific exercises and 20 min of moderate exercise on The Borg RPE Scale (somewhat hard), 2 times/week for 6 months.	1 h of recreation time, 2 times/week for 6 months.	- Digit backwards - TMT - RAVLT - WWT - Digit symbol - Stroop test	↗ Dual task, response inhibition and memory at 3 months ↗ Executive functions ↗ Response inhibition at 6 months ↗ VO <sub>2</sub> max at 3 and 6 months
Kluding et al., 2011	n = 9 (63.7 ± 9.1 years old); > 6 months post-stroke.	AEX: 1 h on TBRS, 3 times/week for 12 weeks.	Lower extremity muscle strengthening exercises: 1 h, 3 times/week for 12 weeks.	- Digit span backwards task - Flanker test - Memory component of the SIS	↗ Digit span backwards task ↗ SIS total score (including memory subscale) Significant relationship between improvement of aerobic and Flanker tests

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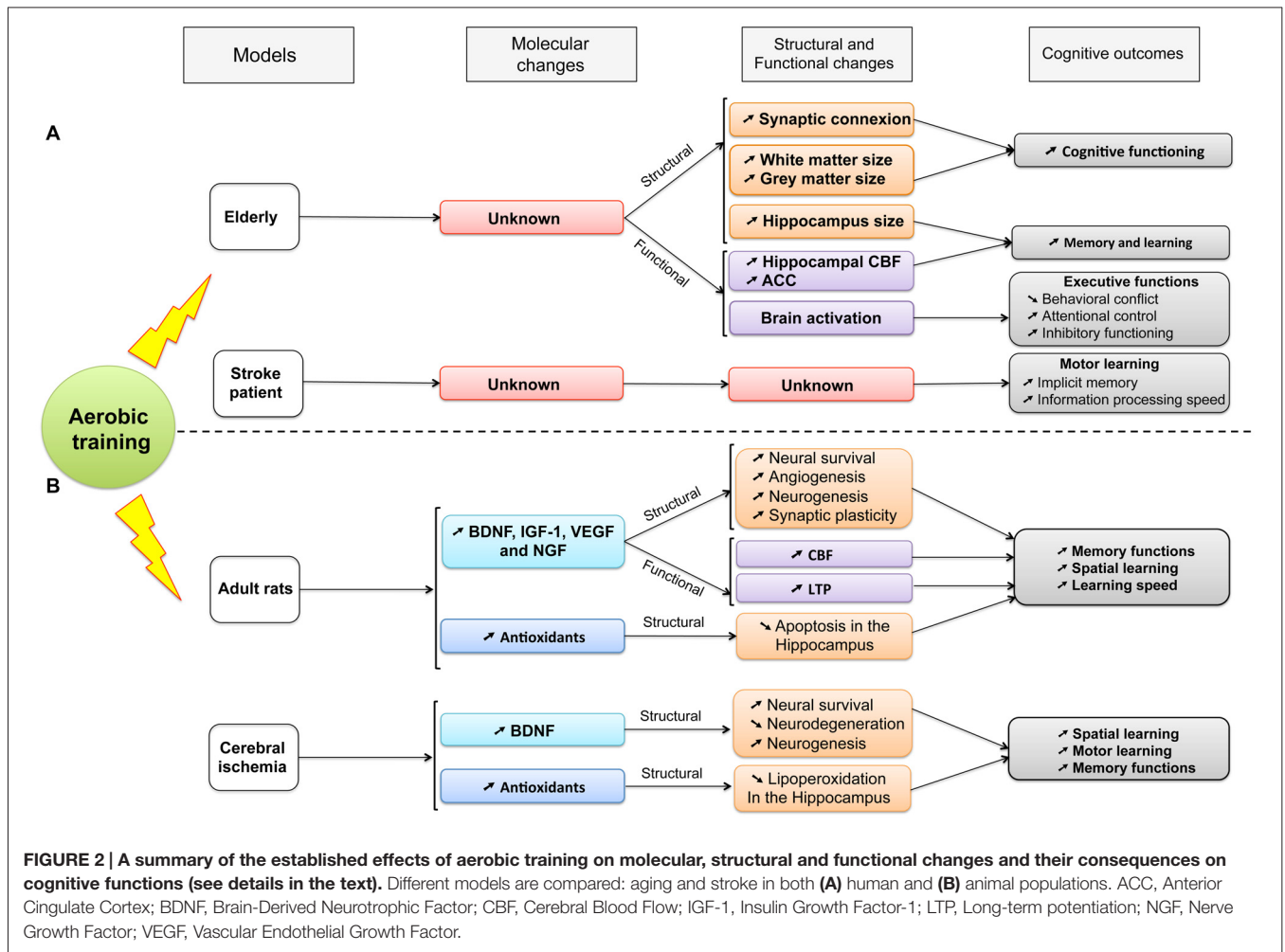
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TABLE 1 | (Continued).

Studies	Participants	Aerobic training	Combination	Cognitive assessments	Results
Marzolini et al., 2012	n = 41 (63.6 ± 13.5 years old); 10 weeks post-stroke (74 ± 135 days).	AEX: treadmill or cyclo-ergometer depending on patient ability, 20–60 min, 5 times/week for 6 months at 40–70% of HRR or VO <sub>2peak</sub> , HR achieved at the ATge and/or 11–6 on the RPE of the Borg Scale. Intensity was progressively increased.	Resistance training during 6 months: - 50% to 60% of 1RM for non-affected limb; - ≥ 50% of 1RM and/or 13–14 RPE on the last repetition on the affected limb. - Intensity from 10–15 repetitions.	MoCA (7 different cognitive domains): - Visuo-spatial and executive function - Attention and concentration - Language - Delayed recall - Orientation - Abstraction - Naming	<ul style="list-style-type: none"> <li>↗ VO<sub>2peak</sub></li> <li>↗ VO<sub>2</sub> at the ATge</li> <li>↗ Upper- and lower-muscular strength</li> <li>↗ Attention and concentration</li> <li>↗ Visuo-spatial and executive function</li> </ul>
El-Tamawy et al., 2014	n = 30 (49.67 ± 6.98 and 48.4 ± 6.39 years old); 3–18 months post-stroke.	AEX: 30 min, 3 times/week for 8 weeks of physiotherapy program + 45 min cyclo-ergometer Control group: 30 min, 3 times/week for 8 weeks of physiotherapy program	none	- ACER test	<ul style="list-style-type: none"> <li>↗ serum BDNF level</li> <li>↗ ACER for AEX group</li> <li>Significant correlation between changes in serum BDNF level and in ACER test</li> </ul>
Bartolo et al., 2015	n = 47 (64.5–67 years old); Within the previous 2 weeks post-stroke.	L-deprenyl (n = 23) Placebo group (n = 24) Both group: 1 h of physiotherapy (6 days/week) + 30 min of cyclo/arm-ergometer training (5 days/week) + 1 h of occupational therapy (3 days/week) during 6 weeks.	L-deprenyl: 10 mg/day once day during 6 weeks.	<ul style="list-style-type: none"> <li>- TMFA and B</li> <li>- MoCA and RAVLT</li> <li>- Logical memory</li> <li>- Digit Span</li> <li>- Corsi's test</li> <li>- Attentive matrices</li> <li>- Stroop test</li> <li>- Symbol digit</li> <li>- PM-47 and FAB</li> <li>- Phonological fluency</li> <li>- Semantic fluency</li> </ul>	<ul style="list-style-type: none"> <li>↗ Logical memory</li> <li>↗ Attentive matrices</li> <li>↗ TMFA and B</li> <li>↗ PM-47</li> <li>↗ MoCA</li> <li>↗ Digit Span</li> <li>↗ Stroop test</li> </ul>

↗ indicate an increase, ↘ a decrease respectively; BWSTT: Body-Weight-Supported Treadmill Training; THR: Target Heart Rates; RPE: Rating of Perceived Exertion; TMT: Trail making tests parts A and B; AEX: Aerobic Exercise; HRR: Heart Rate Reserve; HFImax: Heart Rate Maximal; WCST: Wisconsin Card Sorting test; SRTT: Serial Reaction Time Task; PGFM: Predictive Grip Force Modulation; RAVLT: Rey Auditory Verbal Learning Test; WWT: Walking While Talking; SIS: Stroke Impact Scale; ATge: Gas Exchange Anaerobic threshold; ACER: Addenbrooke's cognitive examination-revised; TBRS: Total Body Recumbent Stepper; MoCA: Montreal Cognitive Assessment ; PM-47: Raven's Coloured Progressive Matrices 47; FAB: Frontal Assessment Battery; BDNF: Brain Derived Neurotrophic Factor.



## IS THE COMBINATION OF AEROBIC TRAINING WITH OTHER TYPES OF THERAPIES EFFECTIVE FOR IMPROVING COGNITION RECOVERY AFTER STROKE?

### Combination with Other Rehabilitation Exercises

The question arises of whether different types of exercise could be combined to improve the effects that they could have separately. As reviewed by Chang et al. (2012), resistance exercise alone could positively impact selective cognitive functions in older adult such as information-processing speed, attention and several aspects of memory and executive functions (Chang et al., 2012). It was postulated that the main potential underlying mechanism for these benefits is based on resistance training-induced IGF-1 both in brain and blood circulation. Moreover, growing evidence have shown that the combination of aerobic and resistance training induced superior beneficial effect on cognition than aerobic exercise alone in aging population (Colcombe and Kramer, 2003). In this way, the association between resistance and aerobic training might be a potential strategy to further facilitate the

cognitive function recovery in stroke population. However, few studies have been conducted to test this attractive hypothesis (Rand et al., 2010; Kluding et al., 2011; Marzolini et al., 2013). Results indicated that combination of aerobic training and lower extremity muscle strengthening improved executive functions, attention and voluntary motor control (Kluding et al., 2011). This is consistent with the study carried out by Marzolini et al. (2013), in which 6 months of both aerobic training at moderate intensity associated with resistance exercises induced improvements in the Montreal Cognitive Assessment (MoCA) scores in subdomain of attention/concentration and visuospatial/executive functioning (Marzolini et al., 2013). Another study on chronic stroke patients combining aerobic training with stretching, balance and task-specific exercises as well as sessions of recreation time has shown an improvement in verbal memory and cognitive flexibility but did not promote executive function (Rand et al., 2010). However, since the isolated effects of resistance and aerobic training were not compared with the combination of both of them, it remains difficult to ensure that such combination induces superior beneficial effects on cognition than aerobic intervention alone after stroke. It should also be noticed that the neuroplasticity associated with cognition

799 recovery after combination of aerobic and other rehabilitation  
800 strategies has not been investigated in both human and animal  
801 stroke studies.

802  
803

## 804 **Combination of Aerobic Training** 805 **with Pharmacological Treatments**

806 Currently, both aerobic and behavioral training have been  
807 shown to improve cognition on stroke patient but it remains  
808 insufficient to induce total recovery (Quaney et al., 2009;  
809 Cherry et al., 2014). Thus, it seems crucial to find new  
810 strategy combinations including aerobic exercise to amplify  
811 the effects on cognition. Many pharmacological treatments are  
812 possible candidates to improve cognitive function after stroke by  
813 stimulating brain plasticity. For instance, the drug memantine,  
814 used for the treatment of moderate to severe dementia of the  
815 Alzheimer's type, could increase synaptic plasticity and LTP and  
816 decrease overactivation of N-methyl-D-aspartate-type glutamate  
817 receptors (NMDA-r) in order to limit excitotoxic neuronal  
818 death (Martin and Wang, 2010; Berthier et al., 2011). Other  
819 substances, like citicoline, an intermediate in the generation of  
820 phosphatidylcholine from choline, could increase the level of  
821 acetylcholine and dopamine as well as decrease infarct volume in  
822 animal model with cerebral ischemia (Alvarez-Sabín and Román,  
823 2011).

824 To date, only the intravenous (IV) recombinant tissue  
825 plasminogen activator (rt-PA) was approved by the USA Food  
826 and Drug Administration for the treatment of acute ischemic  
827 stroke in human (Marshall, 2015). The rt-PA is focused on  
828 thrombolytic events and could reduce the infarct volume (Nys  
829 et al., 2006) by restoring cerebral blood flow and oxygen supply to  
830 ischemic brain tissue (Thompson and Ronaldson, 2014). When  
831 rt-PA is administered within the first 3 h after stroke, it could  
832 improve clinical outcomes and activities of daily life from 3,  
833 6 and 12 months (Kwiatkowski et al., 1999; Nys et al., 2006;  
834 Murao et al., 2014). However, the effects of rt-PA administration  
835 during the first 24 h on cognitive functions are limited to aphasia  
836 that is explained by the reperfusion of language areas (only  
837 for one-third of patient; Nys et al., 2006; Hajjar et al., 2013;  
838 Kremer et al., 2013). Only one study used rt-PA in combination  
839 with physical activity during leisure-time. Results showed that  
840 combination of the 2 strategies did not accentuate the cognitive  
841 and physical improvements compared to rt-PA alone after  
842 3 months (Decourcelle et al., 2015).

843 In preclinical study, L-deprenyl is a pharmacological  
844 treatment used to decrease ROS known to contribute to  
845 neuronal cell death in the ischemic core following permanent  
846 middle cerebral artery occlusion in mice (Unal et al., 2001).  
847 This substance has already shown the clinical effectiveness on  
848 cognitive functions in the elderly human with AD (Wilcock  
849 et al., 2002). L-deprenyl generates an amphetamine-like effect  
850 by acting on the release of dopamine and hampering its  
851 reuptake that contribute to the modulation of both attention and  
852 executive functions (Table 1; Bartolo et al., 2015). After stroke,  
853 combination of both L-deprenyl and standard rehabilitation  
854 including physiotherapy, cycle arm-ergometer training and  
855 occupational therapy during 6 weeks showed an improvement

of logical memory, visual selective attention and non-verbal  
reasoning (Bartolo et al., 2015). However, this study did not  
compare the effect of such combination with the L-deprenyl  
treatment effect or the standard rehabilitation alone. Therefore,  
it remains difficult to postulate that the combination of  
these two strategies reinforced the cognitive recovery. In rat  
model, D-amphetamine administration combined to locomotor  
training enhances locomotor recovery after cortical injury  
(Feeney et al., 1982; Ramic et al., 2006). Moreover, other  
study assessed the effect of D-amphetamine administration  
combined with functional rehabilitation and physical therapy  
alone on cognitive memory performance and motor recovery  
after embolic stroke. Results showed that D-amphetamine with  
functional rehabilitation was more effective to improve cognitive  
performance than training alone, especially for memory, but  
the latter could improve fine motor performance (Rasmussen  
et al., 2006). By contrast, it was found in stroke patient that the  
combination of unique training session of—lower-extremity  
stability platform task, upper-extremity simulated feeding  
task and declarative learning—with D-cycloserine treatment  
did not accentuate the effect of motor and cognitive training  
(Cherry et al., 2014). This agent is already known to improve  
both motor and cognitive functions through increasing LTP in  
the hippocampus by regulating NMDA-r (Yaka et al., 2007).  
Cherry et al. (2014) postulated that an unique training session  
is not enough to amplify pharmacological treatment and that  
D-cycloserine could not act on the reduced NMDA-r function,  
and thus, on the motor task learning after stroke.

Finally, the review of literature suggests that no efficient  
combination between pharmacological treatments and training  
has yet found to improve recovery on cognitive functions.  
However, several combinations of pharmacological treatments  
and aerobic training have proven effectiveness on motor  
recovery after cerebral ischemia (Pin-Barre and Laurin, 2015).  
For example, the combination of both S-nitrosoglutathione  
and training accentuated neuroplasticity (reduce excitotoxicity,  
inflammation and protect BBB integrity) and motor recovery  
(Sakakima et al., 2012). Future studies should investigate  
the effects of these types of associations on cognitive  
recovery.

## 856 **MOTOR VS. COGNITIVE FUNCTION** 857 **RECOVERY: CAN AEROBIC TRAINING** 858 **SIMILARLY FACILITATE BOTH?**

859 Currently, the recommendations for the use of aerobic  
860 training after stroke were only established according to the  
861 effectiveness of endurance programs on cardiovascular and  
862 motor functions (Pang et al., 2013; Billinger et al., 2014).  
863 The cognitive outcomes are thus not taken into account  
864 for prescribing physical exercise. However, several findings  
865 arising from rodent studies indicate that the most appropriate  
866 intensity, the optimal timing to initiate training and the exercise  
867 mode (type of exercise) for improving motor performance  
868 might be different to improve cognitive function and motor  
869 recovery.

## Cognitive Performance Improvement by Aerobic Training

### Exercise Intensity

Low-intensity aerobic training seems to be more effective than high-intensity training to promote cognitive health. Indeed, animal studies have shown that low-intensity training induced superior positive effects on spatial learning task in a water maze test and on both object recognition and location tasks than intense training (Shih et al., 2013; Shimada et al., 2013). Such cognitive task improvements were concomitant with an increase in plasticity-related proteins such as the increase of hippocampal BDNF level, synapsin-I as well as the number of dendritic spines and the number of neurons in the ipsilateral dentate gyrus (Shen et al., 2013; Shih et al., 2013; Shimada et al., 2013). It was mainly explained by the fact that, compared to low-intensity exercise, the high-intensity exercise induced higher levels of stress-hormone, which might downregulate BDNF level in hippocampus (Schaaf et al., 1999; Soya et al., 2007). Nevertheless, caution is required concerning the chosen running intensity. Indeed, the speed, fixed to 20–22 m/min, was considered as “high” intensity in Shih and Shimada’s studies (Shih et al., 2013; Shimada et al., 2013) while others have classified such range of speed as moderate intensity (Sun et al., 2008; Ni et al., 2012). Therefore, the real influence of exercise intensity based on physiological parameters (for example, lactate threshold or  $VO_{2peak}$ ) on cognitive recovery remains to be further investigated (see “Methodological Considerations” Section).

### Timing of Training Initiation

Late exercise, beginning after the first week post-brain injury, is more effective than early exercise (starting during the first week) to improve cognitive functions. Indeed, spatial learning and retention were better improved with the late training and was associated with the upregulation of BDNF (Griesbach et al., 2004; Clark et al., 2008). Voluntary running wheel training, starting 1 week after transient focal cerebral ischemia in mice, promoted neurogenesis in the adult dentate gyrus and spatial memory rebuilding (Luo et al., 2007). Interestingly, the Schmidt meta-analysis indicated that a start of skilled forelimb training from days 1 to 5 post-injury was more effective to improve cognitive function compared to late training (Bland et al., 2000; Wurm et al., 2007; Schmidt et al., 2014). It might be suggested that motor skilled training might start before aerobic training to improve cognitive functions.

### Forced vs. Voluntary Training

The training mode might also influence the neuroplasticity underlying cognitive performance. Some studies have recently demonstrated that involuntary exercise (functional electrical stimulation), forced (treadmill) and voluntary (running wheel) training have similar beneficial effects on cognitive function after cerebral ischemia as indicated by improvement of both object recognition and location tests (Lin et al., 2015). Moreover, these three training regimens enhanced the levels of synapsin I, synaptophysin, PSD-95, MAP-2 and Tau protein in the hippocampus. It was confirmed by a previous study on

healthy rats where 6 weeks of forced swimming or voluntary running resulted in similar increase of hippocampal BDNF level and in similar effect on learning capabilities and short/long term memories (Alomari et al., 2013). Nevertheless, other studies indicated divergent results. On one side, Hayes et al. (2008), demonstrated that, after 2-h of middle cerebral artery occlusion, forced treadmill training reduced infarct volume and increased the gene expression of heat shock proteins (Hsp), in particular the 27 kDa Hsp and the 70 kDa Hsp mRNA than voluntary exercise despite higher corticosterone level. The Hsp acts in the brain as molecular chaperones with neuroprotective activities (Hayes et al., 2008). Other authors indicated that 12 weeks of forced treadmill training could protect against cognitive and biochemical impairments caused by CCAO in rat (Cechetti et al., 2012). Similar results were found after whole-brain irradiation where forced running training reduced the neurocognitive deficits but also the hippocampal neurogenesis impairments, i.e., the down-regulation of BDNF-mediated pathway (including TrkB receptors, protein kinase B (Akt) and CREB, for example; Ji et al., 2014). On other side, some authors indicated that voluntary exercise is the most effective training in up-regulating the hippocampal BDNF level (Luo et al., 2007; Ke et al., 2011). Indeed, Ke et al. (2011), compared the effect of voluntary, involuntary and forced training after cerebral ischemia in rat. Results indicated that 7-day intervention of voluntary training induced higher level of BDNF in the hippocampus than the other modes (Ke et al., 2011). Such divergent results might be attributable to variable experimental designs.

## Motor Performance Improvement by Aerobic Training

### Exercise Intensity

To date, post-stroke guidelines recommend moderate-intensity continuous aerobic training to improve aerobic capacity and motor recovery (40–80% of the maximum heart rate reserve; 3–5 sessions/week; 20–60 min/session). However, it was demonstrated that high-intensity exercise could improve aerobic fitness by increasing the peak oxygen uptake ( $VO_{2peak}$ ) and 6-min walk performances, that remained higher 1 year after the end of training compared with baseline value (Globas et al., 2012). In addition, it has been found that the high-intensity interval training (HIT) could promote superior beneficial cardiovascular and muscular adaptations among persons with different cardiorespiratory disorders (Rognmo et al., 2004; Wisløff et al., 2007). HIT is defined as repeated series of brief and intense exercise separated by active or passive rest periods. This type of intense training is also well known to be a time-efficient strategy to promote metabolic adaptations because the total session duration is strongly reduced compared to traditional moderate-intensity continuous aerobic training (Sun et al., 2014b). Such finding is important given that “lack of time” remains the most cited barrier to regular aerobic exercise participation.

It was observed that HIT is well accepted for ambulatory chronic stroke and could induce encouraging improvements of



1027 quality of life as observed by improvements of  $VO_{2peak}$  and work  
 1028 economy (Gjellesvik et al., 2012; Boyne et al., 2013; Mattlage et al.,  
 1029 2013). Recently, only one study has compared HIT (series of 30 s  
 1030 at maximum tolerated treadmill speed separated by 30–60 s rest  
 1031 periods) and traditional moderate-intensity continuous aerobic  
 1032 training (Boyne et al., 2016). Authors indicated that no clear  
 1033 difference between HIT and moderate-intensity continuous  
 1034 aerobic training was observed because of a small sample size.  
 1035 Nevertheless, this type of training seems to be feasible and safe  
 1036 because no adverse events occurred.

### 1037 **Timing of Training Initiation**

1038 It was postulated in human studies that starting rehabilitation  
 1039 program in the acute-subacute phase after stroke could  
 1040 prevent complications relating to prolonged inactivity (i.e.,  
 1041 deconditioning period) and presented a low relative risk for  
 1042 adverse effects (Musicco et al., 2003). Numerous studies in  
 1043 rodents with cerebral ischemia have also observed that an early  
 1044 starting aerobic exercise (from days 1 to 5) was more effective  
 1045 to improve the running performance and to reduce the infarct  
 1046 volume compared to late training (Bland et al., 2000; Luo et al.,  
 1047 2007; Schmidt et al., 2014). For example, Park et al. (2010),  
 1048 indicated that early treadmill training could better improve the  
 1049 motor performance, using the Rotarod test, than late treadmill  
 1050 training after hemorrhagic stroke (Park et al., 2010). Such early  
 1051 training did not increase the infarct volume or brain edema  
 1052 in accordance to other studies (Matsuda et al., 2011; Zhang  
 1053 et al., 2013b). Likewise, an early treadmill exercise increased the  
 1054 cellular expression levels of some neurotrophic factors, promoted  
 1055 cell growth and reduced the expression of apoptosis markers  
 1056 (Mizutani et al., 2010; Matsuda et al., 2011). Moreover, an early  
 1057 endurance exercise improved blood flow in the ischemic region  
 1058 and promoted angiogenesis (Zhang et al., 2013b). We may also  
 1059 add that sensorimotor deficits and cortical infarct volume were  
 1060 aggravated on a longer-term when training started too soon i.e.,  
 1061 before 24 h post-ischemia (Kozłowski et al., 1996; Risedal et al.,  
 1062 1999; Bland et al., 2000; DeBow et al., 2004; Schmidt et al.,  
 1063 2014).

### 1064 **Forced vs. Voluntary Training**

1065 Numerous studies highlighted that forced treadmill training is  
 1066 more effective than all the other types of exercise, included  
 1067 voluntary exercise, to improve running function, aerobic fitness  
 1068 and to reduce infarct volume (Takamatsu et al., 2010, 2016;  
 1069 Schmidt et al., 2014). However, some authors indicated that  
 1070 voluntary exercise is more effective to improve motor recovery  
 1071 using the De Ryck's behavioral test (Ke et al., 2011). These  
 1072 controversial results might be explained by the use of different  
 1073 motor behavioral tests between studies as well as by a  
 1074 different training protocol (variable speed and timing of training  
 1075 initiation).

### 1076 **Concomitant Improvement of Cognitive and Motor 1077 Functions Induced by Aerobic Exercise**

1078 Interestingly, Sun et al. (2014), might find a compromise in rats  
 1079 by proving that training with gradually increased intensity on  
 1080 treadmill (from 5 to 26 m/min) could better improve motor  
 1081

1082 function and produce higher hippocampal BDNF with lower  
 1083 stress compared to both stably low and high intensity training  
 1084 (Sun et al., 2014a). These results were in accordance with  
 1085 Zhang et al. (2012), study in which both motor performance  
 1086 (forelimb placing, stepping coordination) and spatial memory  
 1087 in rats with middle cerebral artery occlusion-reperfusion were  
 1088 improved after progressive intensity aerobic training (Zhang  
 1089 et al., 2012).

1090 On the basis of these findings, it appears that training might  
 1091 alternate between high- and low-intensity sessions or might  
 1092 progressively reach high-intensity to accentuate improvement of  
 1093 either cognitive or motor performance. It also suggested that  
 1094 treadmill training might be appropriate for improving these two  
 1095 functions. However, it is more difficult to find a compromise  
 1096 for the timing of training initiation. Indeed, an early training  
 1097 seems to be more appropriate to promote motor recovery while  
 1098 cognitive performances were improved when aerobic training  
 1099 started later. Therefore, the influence of aerobic training on  
 1100 cognitive deficits might be considered to complete the actual  
 1101 exercise recommendations.

## 1102 **METHODOLOGICAL CONSIDERATIONS**

1103 Although it is currently admitted that aerobic training  
 1104 positively affects neuro-cognitive impairments, available  
 1105 studies reveal a great heterogeneity in the methods used  
 1106 and for some, weaknesses, which make results difficult to  
 1107 compare (Cumming et al., 2012). These methodological  
 1108 limitations, which are either specific or common to human  
 1109 and animal models, need to be considered before interpreting  
 1110 results.

### 1111 **Methodological Considerations 1112 Concerning Exercise Parameters 1113 in both Animal and Human Studies**

1114 Available studies strongly differ in the parameters related to  
 1115 exercise during aerobic training: duration, intensity, frequency,  
 1116 mode and timing of rehabilitation initiation. In particular,  
 1117 exercise intensity, which is a critical parameter of aerobic  
 1118 training effectiveness, deserves to be questioned (Pin-Barre and  
 1119 Laurin, 2015). For both human and animal models, intensity is  
 1120 frequently based on empirical speed/power (Ploughman et al.,  
 1121 2008; Kluding et al., 2011; Pählman et al., 2012; Shih et al., 2013;  
 1122 Shimada et al., 2013). In some human studies, the intensity was  
 1123 determined from subjective parameters such as level of exertion  
 1124 perceived by the patient (Ploughman et al., 2008; Kluding  
 1125 et al., 2011; Pählman et al., 2012). In these conditions, exercise  
 1126 intensity (moderate, intense and severe) could not be precisely  
 1127 determined because no physiological markers were recorded (Xu  
 1128 and Rhodes, 1999). Therefore, a given absolute intensity was  
 1129 considered as moderate for some authors but as severe for others.  
 1130 When training intensity was based on physiological markers,  
 1131 percentages of maximal heart rate or the maximal oxygen uptake  
 1132 ( $VO_{2peak}$ ) were the most frequently used parameters (Ploughman  
 1133 et al., 2008; Quaney et al., 2009; Kluding et al., 2011; El-Tamawy  
 1134 et al., 2014). However, these methods are insufficiently reliable  
 1135



1141 to distinguish between high and moderate training intensities.  
 1142 Indeed, patients barely reach their maximal aerobic capabilities  
 1143 during an incremental test. Recently, submaximal parameters  
 1144 such as ventilatory or lactic threshold have been recognized  
 1145 to be more suitable than  $VO_{2peak}$  to induce a higher inter-  
 1146 individual reproducibility in physiological response to exercise  
 1147 (Faude et al., 2009; Marzolini et al., 2013; Bosch et al., 2015).  
 1148 It is noticeable however that there is no consensus on the  
 1149 methods used to measure these physiological parameters from  
 1150 an incremental exercise test (Bentley et al., 2007). Indeed,  
 1151 depending on the type of incremental test, the performance  
 1152 and the related physiological parameters could be altered. The  
 1153 chosen ergometer (ergocycle or treadmill), stage duration as well  
 1154 as the magnitude of intensity increment between each stage are  
 1155 known to affect the performance (for review see, Bentley et al.,  
 1156 2007). Moreover, the progressive increase of exercise intensity  
 1157 on treadmill could be induced either by an elevation of speed  
 1158 (m/s) and/or inclination (percentage). The speed increment  
 1159 is not systematically reported in literature but some authors  
 1160 indicated that the grade increment was increased of 2% every  
 1161 2 min with a constant (high) walking speed (Voss et al., 2013).  
 1162 Increase in the slope of the treadmill needs to be considered to  
 1163 improve the validity and the relevance of the chosen incremental  
 1164 test on treadmill for aging subjects. Indeed, the increment  
 1165 of treadmill inclination seems to be more appropriate for  
 1166 aging people and/or for the individuals for whom running is  
 1167 impossible or difficult. For instance, a lower running/walking  
 1168 speed on treadmill could reduce the perceived exertion of the  
 1169 exercise for some individuals and thus might reach highest  
 1170 intensities (Ehlen et al., 2011). Moreover, it was reported on  
 1171 obese persons that faster walking speeds might increase the risk  
 1172 of musculoskeletal injuries because of higher reaction forces and  
 1173 loading rates (Ehlen et al., 2011) in lower extremities tendons,  
 1174 joints and ligaments (Puga et al., 2012). Finally, most authors  
 1175 frequently used a stationary cycle ergometer for aging people  
 1176 (Maass et al., 2015) because measurements of physiological  
 1177 parameters during the test are more stable using this device  
 1178 compared to treadmill. The risk of falls is also lower on  
 1179 cycle ergometer. For the rodent model, some studies have  
 1180 proposed different treadmill protocol in order to reach the  
 1181 highest  $VO_{2peak}$  by modifying the treadmill inclination. It has  
 1182 been found in both rats and mice that the highest  $VO_{2peak}$  was  
 1183 reached at 25° because a distinct leveling-off of  $VO_2$  was mainly  
 1184 observed at this inclination (Wisløff et al., 2001; Kemi et al.,  
 1185 2002).

1186 In addition, among different studies, intensities are  
 1187 rarely individualized, especially in rodents, while training  
 1188 individualization is one of the most important recommendations  
 1189 of stroke rehabilitation (Pang et al., 2013; Schmidt et al.,  
 1190 2014). This limitation might attenuate the “real” effectiveness  
 1191 of aerobic training. Finally, it is commonly considered in  
 1192 exercise physiology studies that energy expenditure needs to  
 1193 be equivalent between exercise types in order to compare the  
 1194 different effects of a specific training parameter (such as intensity  
 1195 or duration). In this way, all the experimental groups have the  
 1196 same energy expenditure and thus only the influence of a tested  
 1197 exercise parameter is assessed (Rognmo et al., 2004; Wisløff

et al., 2007). However, it has never been applied in animal as well  
 as in human stroke studies.

## Specific Methodological Considerations in Human

Inter-individual differences in cerebral ischemia location and/or aerobic fitness level may affect, positively or negatively, cognitive impairments. However, they remain difficult to counteract (Tang et al., 2013; Sun et al., 2014b). For example, it was found that patients with infarction located within cortical regions, middle cerebral artery territory and/or on left hemisphere were more prone to cognitive impairments (Sun et al., 2014b).

Otherwise, using a cognitive test that did not detect the specific cognitive impairments of a patient might hide some potential effect of a training intervention (McDonnell et al., 2011; Cumming et al., 2012). For instance, cognitive measurements are frequently limited to clinical tests, as functional independence measures (FIM), that are not enough sensitive. Likewise, mini-mental state examination (MMSE) may underestimate stroke-related cognitive deficits because it presents a lack of sensitivity for identifying disorders of visual perception and of high-order executive functions (Nys et al., 2006; Pendlebury et al., 2010; Cumming et al., 2012). This might be problematic given that these latter cognitive functions are frequently affected by stroke (Sun et al., 2014b; Tiozzo et al., 2015). In this respect, the MoCA can assess numerous cognitive impairments such as executive function, attention and delayed recall disorders that appear to be more suitable for stroke patient (Pendlebury et al., 2010). Some studies have also used specific neuropsychological tests such as Trail-making part A and B, Symbol digit test, Stroop test, Digit backward test, which allow to better detect cognitive deficits induced by stroke (Ploughman et al., 2008; Quaney et al., 2009; Rand et al., 2010; Kluding et al., 2011).

To ensure that cognitive performance improvements are related to aerobic training effectiveness, an increase of aerobic fitness needs to be observed at the end of the intervention. However, change in cardiorespiratory fitness after aerobic training is not systematically reported in the different studies. Thus, caution is often required when it is claimed that cognitive improvements are associated with aerobic training rather than other interventions or environmental factors.

The issue of cognitive-motor interactions in stroke patients also deserves to be considered. Indeed, cognitive and motor processes are classically considered as functionally independent and then, explored separately in the literature. However, the control and learning of complex goal-directed movements require a close cooperation between sensorimotor control processes and higher cognitive functions. This is even more marked in older adults, for which cognitive and motor processes become less differentiated by virtue of functional reorganization of brain activation patterns. Thus, change in cognitive-motor interplay expresses an important facet of age-related intrinsic plasticity of brain and cognition. Strategic variations might be thus analyzed to assess behavioral adaptability in cognitive (Lemaire and Hinault, 2014) and sensorimotor tasks (Poletti et al., 2015, 2016).

## Specific Methodological Considerations in Animal Models

Animal experiments can provide information about underlying mechanisms of neuroplasticity that could not be investigated in human. However, several drawbacks are often observed in some studies. For instance, it is impossible to investigate the large range of cognitive functions identified in human, such as verbal learning and memory for example (Voss et al., 2013). Cognitive dysfunctions after cerebral ischemia are limited to spatial and working memory, recognition and motor learning skills (Morris water maze, passive avoidance test, object recognition or location test; Luo et al., 2007; Griesbach et al., 2009; Cechetti et al., 2012; Shih et al., 2013; Shimada et al., 2013).

In addition, exercise-induced neuroplasticity are mainly explored within hippocampus (CA1 and CA3 areas and dentate gyrus), which is related to memory and learning (Vaynman et al., 2003). However, other areas such as basal ganglia, prefrontal cortex, thalamus and cerebellum are also involved in learning and memory processes, executive functions and motor control (Graybiel, 1995; Doya, 2000; Johnson and Ojemann, 2000). Except the hippocampus, other regions, remote away from the lesion zone, are connected to the affected structures and thus might also be disturbed after stroke (i.e., diaschisis effect and synaptic inhibition). For example, inflammatory responses could be observed within thalamus or substantia nigra after cortical brain injury that might partially contribute to explain the cognitive deficits (Block et al., 2005). It could be relevant to investigate the effect of aerobic training on the cognitive functions of these cerebral areas (Carmichael et al., 2004).

## CONCLUSION

This present article provides an overview of the positive effect of aerobic training on cognitive functions. It seems that training could increase the release of the same neurotrophic

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factors (BDNF and VEGF) in both elderly and stroke people that mediate beneficial neuroplasticity in brain areas involved in cognitive functions. We also identify some methodological limitations in both human and animal studies such as the standardization procedure of aerobic exercise intensity and the chosen cognitive tests, depending on the target population, that remain one of the most important concerns. Moreover, our review article suggests that the combination of aerobic training with other exercises/therapies or treatments represent a promising strategy with strong clinical perspectives. Importantly, this review highlights the lack of a firm guideline for exercise recommendations targeting recovery of cognition in stroke patient. Therefore, no standard aerobic protocol has yet been established as a commonly accepted reference regarding intensity, timing of training initiation and exercise type. It also appears that investigating changes in cognitive-motor interplay are critical to develop appropriate rehabilitation to improve both cognition and motor control after stroke.

## AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct, and intellectual contribution to the work, and approved its final version for publication. JL and J-JT: conceived the review focus, conducted literature review, summarized, and finalized the manuscript. PD: summarized, and finalized the manuscript. AC, CP-B and JL: reviewed literature, wrote first draft, and finalized the manuscript. All authors approved final version of manuscript.

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