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The impact of age on cerebral perfusion, oxygenation and metabolism during exercise in humans

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Abstract

Age is one of the most important risk factors for dementia and stroke. Examination of the cerebral circulatory responses to acute exercise in the elderly may help to pinpoint the mechanisms by which exercise training can reduce the risk of brain diseases, inform the optimisation of exercise training programmes and assist with the identification of age-related alterations in cerebral vascular function. During low-to-moderate intensity dynamic exercise, enhanced neuronal activity is accompanied by cerebral perfusion increases of ~10-30%. Beyond ~60-70% maximal oxygen uptake, cerebral metabolism remains elevated but perfusion in the anterior portion of the circulation returns towards baseline, substantively because of a hyperventilation-mediated reduction in the partial pressure of arterial carbon dioxide ($PaCO_2$) and cerebral vasoconstriction. Cerebral perfusion is lower in older individuals, both at rest and during incremental dynamic exercise. Nevertheless, the increase in the estimated cerebral metabolic rate for oxygen and the arterial-internal jugular venous differences for glucose and lactate are similar in young and older individuals exercising at the same relative exercise intensities. Correction for the age-related reduction in $PaCO_2$ during exercise by the provision of supplementary CO_2 is suggested to remove ~50% of the difference in cerebral perfusion between young and older individuals. A multitude of candidates could account for the remaining difference, including cerebral atrophy, enhanced vasoconstrictor and blunted vasodilatory pathways. In summary, age-related reductions in cerebral perfusion during exercise are partly associated with a lower $PaCO_2$ in exercising older individuals, nevertheless the cerebral extraction of glucose, lactate and oxygen appear to be preserved.

Abbreviations: $CMRO_2$, cerebral metabolic rate of oxygen; CO_2, carbon dioxide; CVCi, cerebral vascular conductance index; MCA, middle cerebral artery; NIRS, near-infrared spectroscopy; OCI, O_2–carbohydrate index; OGI, O_2–glucose index; $PaCO_2$, partial pressure of arterial carbon dioxide; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; V_{mean}, mean flow velocity; VO_2max, maximal oxygen consumption; W_{max}, maximal aerobic power.

Introduction

Public health interventions along with health care and education improvements over several decades, have led to an increase in life expectancy and global population ageing (Salomon *et al.*, 2012). Age is one of the most important risk factors for brain diseases such as dementia and stroke (Sacco *et al.*, 1997; Lindsay *et al.*, 2002), but even in 'healthy ageing' brain structure and function are altered (Scahill *et al.*, 2003; Burgmans *et al.*, 2011). Grey and white matter blood flow decreases by ~0.5% per year from early adulthood, and despite a small increase in oxygen extraction, the cerebral metabolic rate of oxygen ($CMRO_2$) is also decreased (Leenders *et al.*, 1990). Advancing age is associated with cerebral atrophy (particularly in frontal and temporal regions), altered neural signalling, and impairments in aspects of cognition (e.g., working memory and processing speed) (Martin *et al.*, 1991; Jagust, 2013).

Regular exercise can improve cerebral perfusion (Ainslie *et al.*, 2008), memory (Erickson *et al.*, 2011), mental health (Blumenthal *et al.*, 1999), and reduce age-related neurodegeneration (Kramer *et al.*, 1999; Colcombe *et al.*, 2006). However, the mechanisms by which exercise confers such beneficial effects remains incompletely understood. Examination of the cerebral responses to acute exercise in the elderly may aid the identification of age-related alterations in cerebral vascular function and inform the design of exercise training programmes by helping to pinpoint the mechanisms by which exercise training can improve cerebral vascular function (e.g., shear stress) and reduce the risk of brain diseases (Carter *et al.*, 2014; Lucas *et al.*, 2015). A disruption in the normal cerebral circulatory and metabolic responses to exercise has been implicated in fatigue (Secher *et al.*, 2008), therefore investigating the effects of ageing on cerebral haemodynamics may also further our understanding of the mechanisms underlying the well established age-related reductions in exercise tolerance (Fleg *et al.*, 1995).

In this article, we will outline the influence of age on cerebral perfusion, oxygenation and metabolism during exercise in humans, briefly review the underlying mechanisms and highlight important future directions for exploration. In most developed countries, an age of 65 years indicates the start of 'old age' (Roebuck, 1979). In view of the paucity of available data here we incorporate studies assessing the impact of age on the cerebral circulatory responses to exercise using an older cohort with a mean age of ≥57 years (Table 1).

How does cerebral blood flow respond to exercise?

The earliest direct measures of cerebral blood flow in non-anesthetized humans were made by Kety and Schmidt (1948b) using the nitrous oxide inhalation technique, and studies using this technique reported that global cerebral blood flow was unchanged during exercise (Scheinberg *et al.*, 1954; Kleinerman & Sancetta, 1955; Lambertsen *et al.*, 1959). However, a change in subject position from rest (supine) to exercise (upright), an associated change in the anatomy of cerebral drainage, confounding alterations in $PaCO_2$, and a reduced activation in some brain regions during exercise, may in part explain these observations (Secher *et al.*, 2008).

The administration of dissolved inert radioactive gases such as ^{133}Xenon and ^{85}Krypton via the common carotid artery and measurement of the emitted radiation by extracranial scintillation detectors permitted the earliest determination of regional cerebral blood flow responses to exercise (Hoedt-Rasmussen, 1965). Accordingly, Olesen (1971) observed a regional increase in perfusion of the cortical sensorimotor area corresponding to the hand during contractions with the contralateral hand. A ~10-30% increase cortical blood flow is also elicited by leg cycling, as determined with the ^{133}Xenon clearance initial slope index (Jorgensen *et al.*, 1992). This is paralleled by a comparable increase in middle cerebral artery (MCA) mean blood velocity (V_{mean}) (Jorgensen *et al.*, 1992) measured using the

transcranial Doppler technique introduced by Aaslid and colleagues (Aaslid *et al.*, 1982). In fact, leg cycling bilaterally increases V_{mean} in the MCA and anterior cerebral artery, whereas rhythmic handgrip exercise performed with the right hand principally increases the left MCA V_{mean}, and calf exercise performed with the right leg predominantly increases V_{mean} in the left anterior cerebral artery (Linkis *et al.*, 1995). Positron emission tomography and single-photon emission computed tomography have confirmed the exercise-induced regional increase in cerebral perfusion and activation in the sensorimotor and premotor regions, as well as the supplementary motor area, cerebellum and insular cortex (Williamson *et al.*, 1999; Hiura *et al.*, 2014), and highlights the coupling between regional cerebral activation and perfusion during exercise.

Duplex Doppler ultrasound can be used to quantify arterial blood flow to the brain via the extracranial vessels (internal carotid and vertebral arteries) (Schoning *et al.*, 1994), because unlike the transcranial Doppler technique, both the diameter and V_{mean} of the extracranial vessels can be determined (see *Future directions* section below). In parallel with the increase in MCA V_{mean}, blood flow in the internal carotid and vertebral arteries increases by ~17% during moderate intensity leg cycling (Hellstrom *et al.*, 1996; Sato *et al.*, 2011). However, at exercise intensities above ~60% maximal oxygen uptake (VO_2max) MCA V_{mean} and internal carotid artery flow plateau and then return toward resting levels as exercise intensity increases, whereas in contrast vertebral artery flow continues to increase up to 80% VO_2max (Sato *et al.*, 2011; Smith *et al.*, 2014).

In summary, despite early reports that global cerebral blood flow is unchanged during dynamic exercise, it is now firmly established from studies in young healthy individuals that there is an increase in cerebral perfusion at low-to-moderate exercise intensities directed mainly to the activated brain structures, whereas during exercise at higher intensities perfusion in the anterior portion of the cerebral circulation returns towards resting levels.

126

127 **How does age impact the cerebral blood flow responses to exercise?**

128 An age-related reduction in cerebral blood flow was first shown over 50 years ago
129 (Kety, 1956). However, as summarised in Table 1, limited studies have investigated the
130 influence of age on the cerebral blood flow responses to exercise in older individuals.

131 Heckmann et al., (2003) were the first to employ exercise as means of assessing the
132 influence of age on cerebral circulatory regulation in humans. A more rapid increase in MCA
133 V_{mean} was observed at the onset of leg cycling in the older group compared to their younger
134 counterparts. In contrast, pulsatility index, a surrogate marker of cerebral vascular resistance,
135 increased more rapidly at the onset of exercise in the younger group. These findings suggest
136 that cerebral circulatory regulation is delayed at exercise onset in older individuals. However,
137 the precise workloads used in this study were not reported, and since maximal aerobic fitness
138 is reduced with age (Fleg *et al.*, 1995) it is possible that the older group were exercising at a
139 higher relative workload, and this may provide an alternative explanation for the findings.

140 Figure 1 summarises the results of studies that have investigated the impact of age on
141 the cerebral perfusion responses to incremental dynamic exercise. At matched relative
142 exercise intensities of 30% and 50% heart rate reserve (equivalent to low and moderate
143 intensity exercise, respectively) a similar MCA V_{mean} has been reported in young (24±3
144 years) and older middle-aged (57±7 years) individuals (Fisher et al., 2008). In contrast,
145 subsequent studies examining the MCA V_{mean} during incremental leg cycling exercise to
146 exhaustion reported that MCA V_{mean} was lower in an older individuals at any of the matched
147 relative (Marsden *et al.*, 2012; Fisher *et al.*, 2013; Flück *et al.*, 2014) or absolute exercise
148 intensities (Flück *et al.*, 2014) examined. These conflicting findings may relate to the smaller
149 age difference between the groups in Fisher *et al*., (2008) (33 years), compared to Marsden *et*
150 *al* (2012) (44 years), Fisher *et al* (2013) (44 years) and Flück *et al* (2014) (42 years). Indeed,

151 the normal age-related reduction in resting MCA V_{mean} was not observed in Fisher *et al*.,
152 (2008), but was evident in the other studies (Marsden *et al.*, 2012; Fisher *et al.*, 2013; Flück
153 *et al.*, 2014). Interestingly, no significant interaction between age and exercise intensity was
154 observed for MCA V_{mean} by Fisher *et al* (2013) and Flück *et al* (2014), meaning that the
155 magnitude of exercise-induced increase in MCA V_{mean} was not different between the young
156 and older groups. In contrast, Marsden *et al* (2012) observed that older adults had an
157 attenuated increase in MCA V_{mean} at low intensity exercise (28% young vs. 15% older). The
158 reason for these discrepancies is unclear, but may relate to the relatively small sample sizes
159 used and methodological issues surrounding the use of using the transcranial Doppler
160 technique as index of cerebral perfusion, as discussed in more detail below. Notably, a
161 blunted increase in cerebral vascular conductance index (CVCi, mean arterial pressure /
162 MCA V_{mean}) at low exercise workloads in older individuals has been noted, indicative of an
163 attenuated cerebral vasodilatory response (Fisher *et al.*, 2013). Moreover, an enhanced
164 cerebral vasoconstriction at moderate-to-high dynamic exercise workloads is reported in
165 older groups (Ogoh *et al.*, 2011; Fisher *et al.*, 2013). This altered cerebral vascular response
166 may represent a normal cerebral autoregulatory response given that blood pressure increases
167 during exercise are typically greater in older individuals, or alternatively it may be a
168 manifestation of a change in the balance between vasodilatory and vasoconstrictor pathways,
169 as discussed below.

170 In summary, the available evidence indicates that cerebral perfusion is lower both at
171 rest and during incremental maximal exercise with increased age, irrespective of whether
172 absolute or relative workloads are compared. The majority of the available evidence supports
173 the view that MCA V_{mean} increases to a similar extent in young and older individuals (~10-
174 30%) during low-to-moderate intensity dynamic exercise.
175

How does age impact cerebral metabolism and oxygenation during exercise?

The mass of the brain only accounts for ~2% of body mass but remarkably $CMRO_2$ is ~25% (~60 mL/min) of whole-body resting oxygen consumption (Kety & Schmidt, 1946). Although there is a small contribution from anaerobic glycolysis (~10%), the oxidation of glucose is the principal mechanism by which the energy demand of the brain is met during resting wakefulness. As such, the molar ratio between the cerebral consumption of oxygen and glucose (oxygen-glucose index: OGI) is slightly lower than 6:1 (~5.7) (Siesjö, 1978). Resting $CMRO_2$ is reported to be reduced with ageing in some (Kety, 1956; Pantano *et al.*, 1984), but not all studies (Burns & Tyrrell, 1992). Ageing also causes a reduction in cerebral metabolic rate for glucose (Nugent *et al.*, 2014), which is estimated to decline by ~6% per decade globally with most cerebral regions affected, except for the occipital cortex and cerebellum (Petit-Taboue *et al.*, 1998).

Early reports that global cerebral blood flow was unchanged during exercise, also suggested that cerebral metabolism was unaltered (Madsen *et al.*, 1993), and in fact it was even concluded that "*during vigorous physical exercise the brain behaved as a steady-state organ with little or no change in cerebral circulation or metabolism*" (Zobl *et al.*, 1965). However, cerebral activation with tactile stimulation increases regional cerebral blood flow and $CMRO_2$ (Fox & Raichle, 1986), and the same appears be true for $CMRO_2$ during exercise (Seifert *et al.*, 2009a; Smith *et al.*, 2014) although this has not been universally observed (Trangmar *et al.*, 2014). The cerebral metabolic rate for glucose and the OGI tend to be similar at rest and during exercise (Ide *et al.*, 2000b), although OGI can be reduced by very strenuous exercise, such as prolonged maximal exercise in the heat (Nybo *et al.*, 2003). Along with glucose, lactate also plays an important role as a substrate during exercise (Smith *et al.*, 2003), particularly when arterial lactate concentration is elevated such as during high intensity exercise. The combined uptake of glucose and lactate relative to oxygen remains

stable at low-to-moderate exercise intensities, but when exercise becomes more strenuous glucose and lactate uptake increase in excess of oxygen, in an intensity dependent manner. This means that the 'oxygen-to-carbohydrate consumption index' (OCI; O_2/[glucose +½ lactate]) is reduced, and during all-out rowing the OCI can decrease to <35% of the baseline value (Volianitis *et al.*, 2008). As the increase in cerebral uptake of lactate does not result in an accumulation of this substance in brain structures or in the cerebral spinal fluid it is seemingly metabolized by the brain during exercise (Dalsgaard *et al.*, 2004).

To date a single study has compared the arterial–jugular venous concentration differences for oxygen, glucose and lactate during exercise in young and elderly individuals (Fisher *et al.*, 2013). A discontinuous incremental exercise protocol was conducted to exhaustion and responses at relative workloads of 25%, 50%, 75% and 100% of maximal aerobic power (W_{max}) were compared. Despite reductions in the cerebral perfusion of the older group, increases estimated $CMRO_2$ and arterial-jugular venous differences for oxygen (rest vs. 100% W_{max}) and lactate (rest vs. 75% and 100% W_{max}) were observed. The arterial-jugular venous differences for glucose and OGI were unchanged, while the OCI was reduced similarly during exercise in young and older individuals (rest vs. 75% and 100% W_{max}). These findings suggest that the brain's ability to uptake glucose and lactate is preserved with healthy ageing.

Despite an age-related decline in maximal aerobic exercise capacity cerebral oxygenation falls to a similar extent in young and older individuals during exhaustive exercise, when indexed using estimates of either cerebral capillary oxygen saturation, capillary oxygen tension and mitochondrial oxygen tension derived using arterial-to-jugular venous differences (Fisher *et al.*, 2013), or frontal lobe oxygenation determined using near-infrared spectroscopy (NIRS) (Flück *et al.*, 2014). Such observations might imply the existence of a common centrally mediated element to fatigue. Rassmussen *et al.* (2010)

observed that reductions in cerebral mitochondrial oxygen tension induced by hypoxic exercise resulted in a reduction in the maximal volitional activation of the skeletal muscles (i.e., central fatigue). Intriguingly, despite maximal exercise capacity being increased by ~20% following exercise training, the reduction in cerebral mitochondrial oxygen tension at exhaustion was not different to the pre-training value (Seifert *et al.*, 2009a). Furthermore, at exhaustion the reduction in cerebral mitochondrial oxygen tension was similar before and after β-adrenergic blockade, despite blockade significantly reducing the maximal absolute workload performed (Seifert *et al.*, 2009b). However, administration of supplemental CO_2 to limit the exercise-induced fall in cerebral perfusion and oxygenation in young and older individuals fails to enhance exercise performance (Subudhi *et al.*, 2011; Flück *et al.*, 2014).

In summary, a preserved capacity for the cerebral extraction of glucose, lactate and oxygen has been observed in exercising healthy elderly individuals. Although reductions in cerebral oxygenation in young and older participants appear similar during exhaustive exercise, there is limited evidence to suggest that this limits exercise performance under normoxic conditions in healthy young and old individuals.

Age-related alterations in cerebral blood flow regulation during exercise

The regulation of cerebral blood flow in exercising humans is complex and incompletely understood, and as reviewed elsewhere, metabolic, chemical, autoregulatory, neurogenic, and systemic factors are among the likely contributors (Querido & Sheel, 2007; Secher *et al.*, 2008; Ainslie & Duffin, 2009). A brief discussion of the influence of ageing on these mechanisms follows and is summarised in Figure 2. Due to space constraints a focus will be placed on human studies where possible.

Metabolic: The molecular pathways involved in the coupling of regional cerebral activation and perfusion during exercise is incompletely understood. Among the substances

implicated in pial vessel dilatation and blood flow increases during cerebral activation are adenosine (Ko et al., 1990), the lactate/pyruvate ratio (Ido et al., 2001) and neuronal nitric oxide (Ma et al., 1996). Ageing impairs endothelial nitric oxide synthase, acetylcholine and ADP dependant cerebral vascular reactivity in aged rats (Mayhan *et al.*, 2008). In humans, alterations in several vasodilatory mechanisms (e.g., prostaglandins, ATP, nitric oxide) have been implicated in the age-related impairments in skeletal muscle vasculature regulation during exercise (Dinenno & Joyner, 2006). The use of pharmacological dissection to determine whether age-related alterations in the aforementioned molecular pathways occur within the human cerebral vasculature during exercise would greatly enhance our understanding of this topic.

Chemical: $PaCO_2$ is a major regulator of cerebral blood flow during exercise. $PaCO_2$ is generally well maintained or may increase slightly during low-to-moderate intensity exercise and may make a small contribution to the elevation of the cerebral perfusion at these workloads (Moraine *et al.*, 1993). At higher exercise intensities $PaCO_2$ is reduced due to hyperventilation and this restricts the exercise-induced increase in cerebral perfusion. Indeed, the provision of supplemental CO_2 during high intensity exercise in young healthy participants, in order to prevent the hyperventilation-mediated fall in $PaCO_2$ and maintain the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) at 50 mmHg, increases MCA V_{mean} by ~40% and cerebral oxygenation by ~15% (Subudhi *et al.*, 2011). Some studies have observed that elderly individuals have a reduced arterial, alveolar and $P_{ET}CO_2$ (Terman & Newton, 1964; Fisher *et al.*, 2013; Flück *et al.*, 2014). To assess influence of the age-related reduction in $PaCO_2$ on the cerebral circulatory responses to exercise, Flück *et al.* (2014) administered supplemental CO_2 to the inspired air (when $PaCO_2$ dropped below 40 mmHg) in order to prevent a hyperventilation-mediated reduction in $PaCO_2$ during incremental exhaustive leg cycling in healthy young and older individuals. Correction for the age-related difference in

276 $PaCO_2$ was suggested to account for ~50% of the reduction in cerebral perfusion during
277 exercise in elderly individuals. A lower cerebrovascular responsiveness to CO_2 could also
278 contribute to the lower cerebral perfusion during exercise in older individuals. However,
279 Murrell *et al*. (2013), observed that the cerebrovascular responsiveness to hypercapnia (5%
280 CO_2 added to the inspired air) was increased similarly from rest to sub-maximal exercise in
281 young and older individuals.

282 Of note, several studies mentioned above did not directly measure arterial blood
283 gases, and instead reported $P_{ET}CO_2$ or used $P_{ET}CO_2$ to calculate $PaCO_2$ (Fisher *et al.*, 2008;
284 Marsden *et al.*, 2012; Murrell *et al.*, 2013; Flück *et al.*, 2014). The use of $P_{ET}CO_2$ may lead to
285 an overestimation in changes of $PaCO_2$ during exercise (Robbins *et al.*, 1990; St Croix *et al.*,
286 1995), particularly when age-related changes in lung structure and function are present
287 (Miller & Tenney, 1956). However, a mathematical correction can facilitate the successful
288 estimation of $PaCO_2$ from $P_{ET}CO_2$ (Jones *et al.*, 1979) even in the elderly (St Croix *et al.*,
289 1995). A further point of note, is the observation that $PaCO_2$ vasodilates pial arterioles
290 principally as a consequence of local changes in extravascular pH (Kontos *et al.*, 1977a;
291 Kontos *et al.*, 1977b). Despite the observed reduction in baseline $PaCO_2$ with increased age,
292 arterial and arterialized pH were not altered (Fisher *et al.*, 2013; Flück *et al.*, 2014). However,
293 differences in extravascular pH, and thus a contribution to age-related alterations in cerebral
294 blood flow regulation, cannot be ruled out.

295 Along with $PaCO_2$, PaO_2 also modulates cerebral blood flow. The breathing of a
296 hypoxic gas evokes cerebral vasodilation *per se* (Kety & Schmidt, 1948a), however the
297 accompanying activation of the peripheral chemoreceptors causes hyperventilation, a
298 lowering of $PaCO_2$ and thus cerebral vasoconstriction. This phenomenon explains why during
299 acute hypoxia the exercise-induced change in MCA V_{mean} is similar to when breathing
300 normoxic air in young individuals (Ainslie *et al.*, 2007). Breathing a hyperoxic gas mixture at

rest, at least at sea level, also evokes cerebral vasoconstriction due to a chemoreflex mechanism (Floyd *et al.*, 2003). Interestingly, there is a notable regional heterogeneity in the cerebral perfusion response to hyperoxic exercise and that while changes from rest in MCA V_{mean} are unaffected a much greater response is seen in the posterior circulation (Smith *et al.*, 2012). Studies assessing the impact of hypoxia and hyperoxia on the cerebral blood flow responses to exercise in older individuals are needed to improve our understanding of the influence of arterial oxygen tension on cerebral perfusion in this population.

Blood pressure: The cerebral circulation has the intrinsic ability to maintain its flow relatively constant over a range of arterial blood pressure values (Paulson *et al.*, 1990). During dynamic exercise where pronounced intensity dependent increases in blood pressure occur, particularly in older individuals, cerebral autoregulation is likely important in order to restrict the increases in cerebral perfusion, which are modest and unlike blood pressure are greatest at low-to-moderate intensities, at least in the anterior portion of the circulation (Fisher *et al.*, 2008). Dynamic cerebral autoregulation, as determined from the linear transfer function analysis of blood pressure and MCA V_{mean}, appears to be maintained during exercise in young healthy individuals (Brys *et al.*, 2003). Similarly, the transfer function gain between mean arterial pressure and MCA V_{mean} in the very low and low frequency ranges, is not different between young and middle-aged individuals, suggesting that cerebral autoregulatory capacity is similar (Fisher *et al.*, 2008). However, the coherence between blood pressure and MCA V_{mean} noted in this study was relatively low which could have a bearing on the interpretation of these results, and carefully designed studies are required to examine whether the dynamic cerebral autoregulation of cerebral blood flow is altered in more elderly individuals during exercise.

Neurogenic: The adrenergic innervation of the cerebral vasculature has been long recognised (Lowe & Gilboe, 1971) but the nature of the sympathetic influence on the cerebral

circulation is still much debated (van Lieshout & Secher, 2008). Cerebral vasoconstriction is evoked by sympathetic nerves stimulation in animals (Auer *et al.*, 1983) and administration of α-adrenergic agonists and sympathoexcitatory manoeuvres in humans (Olesen, 1972; Micieli *et al.*, 1994). Heightened sympathetic nerve activity may serve to protect the cerebral arterioles from over-perfusion during a hypertensive insult (Bill & Linder, 1976). Therefore, a sympathetically–mediated cerebral vasoconstriction in older individuals may serve as an important mechanism to defend against the exaggerated-blood pressure response to exercise (Fisher *et al.*, 2008; Fisher *et al.*, 2013). An impairment of the normal metabolic modulation of sympathetic vasoconstrictor tone (i.e., functional sympatholysis) has been identified in the peripheral vasculature of elderly individuals (Dinenno *et al.*, 2005), although whether such a phenomenon is operative within the cerebral vasculature of elderly individuals remains to be examined. Along with the potential contribution of the sympathetic nervous system in the regulation of the cerebral blood vessels, a role for the parasympathetic system has also been suggested. Seifert *et al.* (2010) observed that the increases in MCA V_{mean} during incremental leg cycling exercise were abolished in young healthy individuals following administration of glycopyrrolate, a muscarinic cholinergic antagonist. An age-related reduction in cholinergic signalling has been identified in several tissues (e.g., heart, peripheral vasculature), and studies are needed to compare the cerebral blood flow responses to exercise in young and older participants following administration of a muscarinic cholinergic antagonist.

Central command / exercise pressor reflex: Activation of feedforward signals from brain centres, that arise in parallel with the generation of motor signals to contracting skeletal muscles (i.e., central command), evoke an accompanying increase in MCA V_{mean} (Sato *et al.*, 2009) and cerebral lactate uptake, and decrease OGI (Dalsgaard *et al.*, 2002). In addition, feedback signals from stimulation of group III and IV afferents located within the exercising skeletal muscles (i.e., exercise pressor reflex) can increase MCA V_{mean} (Braz *et al.*, 2014),

increase cerebral lactate uptake and decrease OGI (Dalsgaard *et al.*, 2003). Age-related reductions in the strength of the exercise pressor reflex have been reported (Markel *et al.*, 2003) but the implication of this for cerebral perfusion and metabolism during exercise is not known.

Systemic: Attenuating the cardiac output response to exercise in young healthy individuals with the administration of a β_1-adrenergic receptor blocker reduces the magnitude of the normal MCA V_{mean} response (Ide *et al.*, 2000a). Furthermore, patients with atrial fibrillation in whom the cardiac output response to exercise is attenuated also demonstrate an attenuated MCA V_{mean} response (Ide *et al.*, 1999). Given the normal age-related decline in cardiac output during exercise (Hagberg *et al.*, 1985), the lower MCA V_{mean} observed during maximal exercise in elderly individuals may also relate to a lower cardiac output (increase of ≈200% young vs. ≈160% elderly) (Fisher *et al.*, 2013).

Aerobic fitness: Murrell *et al.* (2013) examined the MCA V_{mean} responses to incremental dynamic exercise before and after 12 weeks of aerobic exercise training which increased VO_2max from 24±4 to 26±4 ml·min^{-1}·kg^{-1} in older individuals (63±5 years). It was observed that the MCA V_{mean} responses to exercise were unchanged following training, and that cerebrovascular responsiveness to hypercapnia was augmented at rest but not during exercise. Using a cross-sectional study design, Flück *et al.* (2014) also observed that cardiorespiratory fitness did not influence on the MCA V_{mean} responses to incremental dynamic exercise in either young (VO_2max of trained vs. untrained; 66±1 vs. 50±2 ml·min^{-1}·kg^{-1}) or older (41±3 vs. 30±1 ml·min^{-1}·kg^{-1}) individuals. Seifert *et al.* (2009a) showed that 3 months of aerobic exercise training attenuates the normal reduction in OCI and the increase in $CMRO_2$ at a matched sub-maximal exercise workload. Whether exercise training impacts the cerebral metabolic responses to exercise in elderly individuals has not been examined.

375 *Sex*: Ovarian hormones can evoke a multitude of cerebrovascular effects (Duckles &
376 Krause, 2007). Oestrogen stimulates the production of prostacyclin and nitric oxide (Krause
377 *et al.*, 2006), and increases MCA V_{mean} in women undergoing hormone replacement therapy
378 (Bain *et al.*, 2004). In the three studies of the MCA V_{mean} responses to exercise that have
379 studied both young and older, men and women no significant interactions between age and
380 sex were noted (Table 1) (Heckmann *et al.*, 2003; Fisher *et al.*, 2008; Murrell *et al.*, 2013).
381 However, these studies were not specifically designed to determine how sex and ovarian
382 hormones impact the age-related changes in the cerebral circulatory responses to acute
383 exercise in humans.
384
385 **Future directions**
386 To date, all of the studies that have examined the impact of age on the cerebral
387 perfusion during exercise have relied upon the transcranial Doppler technique. This technique
388 is amenable for use during exercise at a range of intensities, has high temporal and spatial
389 resolution, and is relatively inexpensive. However, the major limitation of this technique is
390 that the V_{mean} is only proportional to flow if the arterial diameter remains constant (Ainslie &
391 Hoiland, 2014; Coverdale *et al.*, 2014; Verbree *et al.*, 2014). An alternative approach is the
392 use of duplex Doppler ultrasound to assess blood flow in the extracranial arteries (Hellstrom
393 *et al.*, 1996). This approach would also permit determination of whether ageing influences the
394 distribution of volumetric blood flow through the internal carotid and vertebral arteries during
395 incremental exercise, as has been performed in young individuals (Sato *et al.*, 2011). The
396 combination of such cerebral blood flow measures with arterial-jugular venous blood
397 sampling (Trangmar *et al.*, 2014) would also permit a more complete assessment of how age
398 affects cerebral perfusion and metabolic nutrient delivery/removal during exercise than has
399 been undertaken so far. In addition, studies employing a tracer dilution method are required

to determine the impact of age on cerebral lactate turnover, uptake and release, during exercise. Brain imaging techniques (e.g., functional magnetic resonance imaging) may provide an alternative approach to the assessment of cerebral perfusion, oxygenation and metabolism during exercise. Such approaches would also permit the normalisation of cerebral blood flow to cerebral mass and the consideration of regional responses with high spatial resolution. Cerebral atrophy and/or reduced neural activation might provide a potential explanation for the observed reduction in cerebral perfusion and maintained arterial-jugular venous difference for oxygen in exercising elderly individuals (Fisher *et al.*, 2013). Notably, the application of sophisticated brain imaging techniques during exercise is limited due to the incidence of movement artefacts during high intensity dynamic exercise.

At present there are no longitudinal studies assessing the impact of age on cerebral perfusion, oxygenation and metabolism during exercise in humans. Furthermore the cross-sectional studies that have been performed have utilized a single older cohort. To more completely elucidate how age impacts the cerebral response future studies should incorporate groups of individuals across a broader age range.

The vast majority of studies that have examined the impact of age on cerebral perfusion have utilized steady-state leg cycling. Although, the relative stability of the head position means that this is an attractive exercise mode to employ when assessing the cerebral vascular responses to exercise, the response profile is different to that observed during other exercise modes such as treadmill running (Lyngeraa *et al.*, 2013) and rowing (Pott *et al.*, 1997), where large fluctuations in blood pressure occur. Furthermore, the steady-state responses to exercise have predominantly been examined in young and older individuals, and carefully controlled studies investigating cerebrovascular kinetics at the onset and offset of exercise may provide important insights into the influence of age in cerebrovascular function.

The evidence base for the benefits of exercise training and physical activity for the prevention of cerebrovascular disease is substantial. However, our understanding of the precise mechanisms whereby exercise confers such beneficial effects remains incompletely understood. Among the plethora of candidate mechanisms the importance of shear stress has been highlighted (Bolduc *et al.*, 2013; Lucas *et al.*, 2015) and it is notable that the greatest exercise-induced increases in cerebral perfusion occur at low-to-moderate intensities of dynamic exercise.

Conclusions

Ageing is associated with a lower cerebral perfusion at rest and during exercise. Nevertheless, cerebral extraction of glucose, lactate and oxygen appears to be preserved in exercising older individuals. An age-related reduction in $PaCO_2$ has been estimated to accounts for ~50% of the lower cerebral perfusion during exercise, and other metabolic, chemical, autoregulatory, neurogenic and systemic mechanisms likely contribute. Studies are required to better understand cerebrovascular regulation during exercise in elderly individuals, to explore the utility of exercise in identifying age-related alterations in cerebral vascular function, and to optimise exercise-training regimes to promote cerebral vascular function in health and disease.

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COMPETING INTERESTS

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TABLES

Table 1. Summary of studies assessing the impact of ageing on cerebral perfusion during exercise

Study	Participants	Protocol	Measurements	Cerebral perfusion	Other findings
Heckmann *et al.* (2002)	18 young (10♀, 29±5 yr), 18 older (12♀, 66±5 yr)	3 min leg cycling to ↑BP >10% and ↑HR >25%	Beat-by-beat radial NIBP, ECG, transcutaneous pCO_2, MCA V_{mean}, PI	Rest: ↔MCA V_{mean} Exercise: ↑MCA V_{mean} faster in older at exercise onset.	↔pCO_2, ↑PI delayed at exercise onset in the elderly
Fisher *et al.* (2008)	9 young (3♀, 24±3 yr), 10 older (4♀, 57±7 yr)	Steady-state leg cycling at 30% (low intensity) and 50% (moderate intensity) of HRR	Beat-by-beat finger NIBP, ECG, estimated $PaCO_2$, MCA V_{mean}, CVCi	Rest: ↔MCA V_{mean} Exercise: ↑MCA V_{mean} similar in young and older.	↔$PaCO_2$, ↔MAP and MCA V_{mean} transfer function gain and phase in young and older
Marsden *et al.* (2012)	20 young ♂ (23±4 yr), 14 older ♂ (71±10 yr)	Incremental leg cycling to volitional exhaustion	Intermittent brachial NIBP, ECG, $P_{ET}CO_2$, ventilation, VO_2, MCA V_{mean}	Rest: ↓MCA V_{mean} Exercise: ↑MCA V_{mean} lower in older at ≤50% VO_2peak.	Age: ↓$P_{ET}CO_2$. At VO_2peak, ↓hyperventilatory response, no hypocapnia and ↓cerebral vasoconstriction in older.
Murrell *et al.* (2013)	10 young (5♀, 23±5 yr) and 10 older (5♀, 63±5	Leg cycling at 30% and 70% HRR. Hypo- and hypercapnic challenge. Before and after 12	VO_2max, Beat-by-beat finger NIBP, ECG, $P_{ET}CO_2$, MCA V_{mean},	Rest: ↓MCA V_{mean} Exercise: ↑MCA V_{mean} lower (absolute) or similar	↔$P_{ET}CO_2$, ↔$CVRCO_2$ between groups at rest and exercise. Training:

	yr)	weeks of aerobic training	ventilation	(relative) in older. No change with training.	↑hypercapnic $CVRCO_2$ and work rate similarly in both groups
Fisher *et al.* (2013)	11 young ♂ (22±1 yr), 9 older ♂ (66±2 yr)	Discontinuous incremental leg cycling to volitional exhaustion	Intra-arterial BP, ECG, $PaCO_2$, MCA V_{mean}, CVCi, arterial-jugular venous differences of oxygen, glucose, lactate, OGI, OCI, $CMRO_2$.	Rest: ↓MCA V_{mean} Exercise: ↑MCA V_{mean} similar in young and older.	Age: ↓$PaCO_2$; ↔cerebral uptake of glucose, lactate, oxygen, OGI, OCI and $CMRO_2$ between groups.
Flück *et al.* (2014)	21 young ♂ (24±3 yr), 17 older ♂ (66±4 yr)	Incremental leg cycling to volitional exhaustion with and without supplemental CO_2	Beat-by-beat finger NIBP, HR monitor, estimated $PaCO_2$, MCA V_{mean}, CVCi, ventilation, cerebral oxygenation	Rest: ↓MCA V_{mean} Exercise: Supplemental CO_2 reduced age-related difference in MCA V_{mean} by ~50%.	Age: ↓$PaCO_2$, ↔hypercapnic $CVRCO_2$. Improved cerebral oxygenation with added CO_2 but ↔ performance.

$CMRO_2$, cerebral metabolic rate of oxygen; CO_2, carbon dioxide; CVCi, cerebral vascular conductance index; $CVRCO_2$, cerebral vascular reactivity to CO_2; MCA, middle cerebral artery; NIBP, non-invasive blood pressure; O, older; OCI, O_2–carbohydrate index; OGI, O_2–glucose index; $PaCO_2$, partial pressure of arterial carbon dioxide; V_{mean}, mean flow velocity; VO_2max, maximal oxygen consumption; ♀, women; ♂, men. ↑ denotes increase, ↓ denotes decrease, and ↔ denotes no difference.

FIGURE LEGENDS

Abstract figure: Putative mechanisms explaining the impact of age on the cerebral blood flow (CBF) responses to exercise.

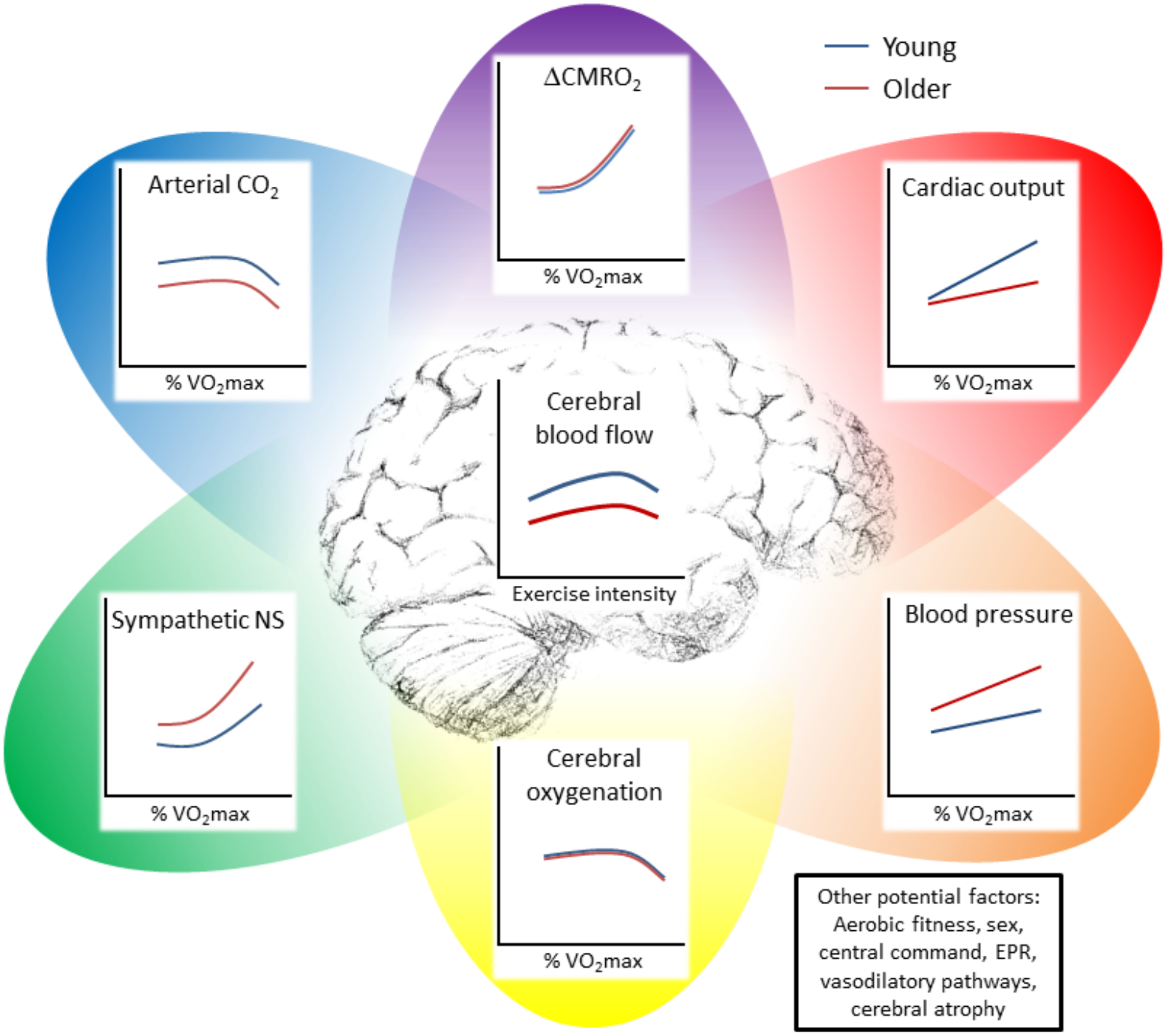
CO_2, carbon dioxide; $CMRO_2$, cerebral metabolic rate of oxygen; $\%VO_2max$, maximal oxygen consumption; NS, nervous system; EPR, exercise pressor reflex.

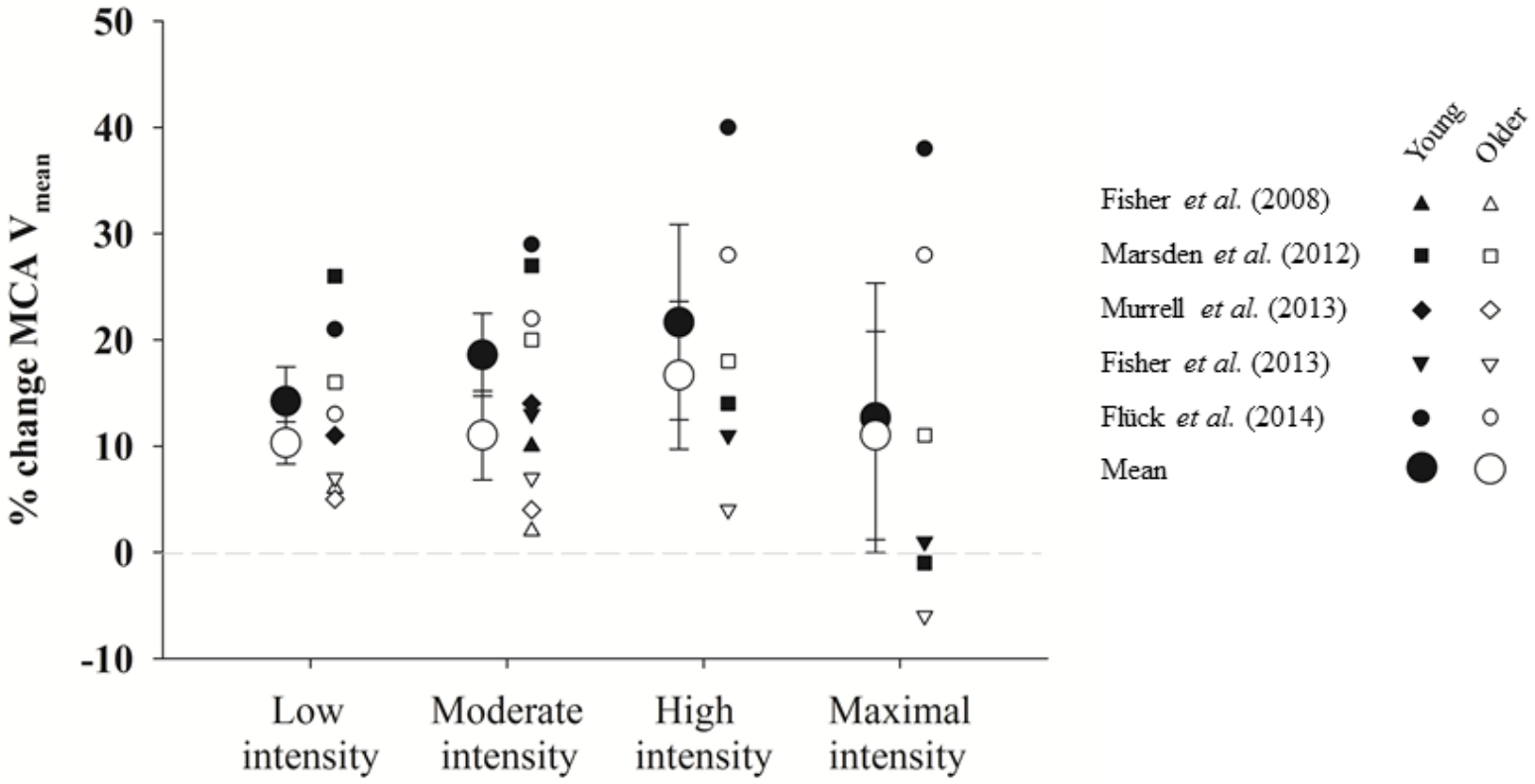
Figure 1. Percentage change from rest in middle cerebral artery mean blood velocity (MCA V_{mean}), during exercise at low (<50% VO_2max or HRR [heart rate reserve]), moderate (50-75% VO_2max or HRR), high (75-90% VO_2max) and maximal (90-100% VO_2max) intensities in young (closed symbols) and older (open symbols) individuals.

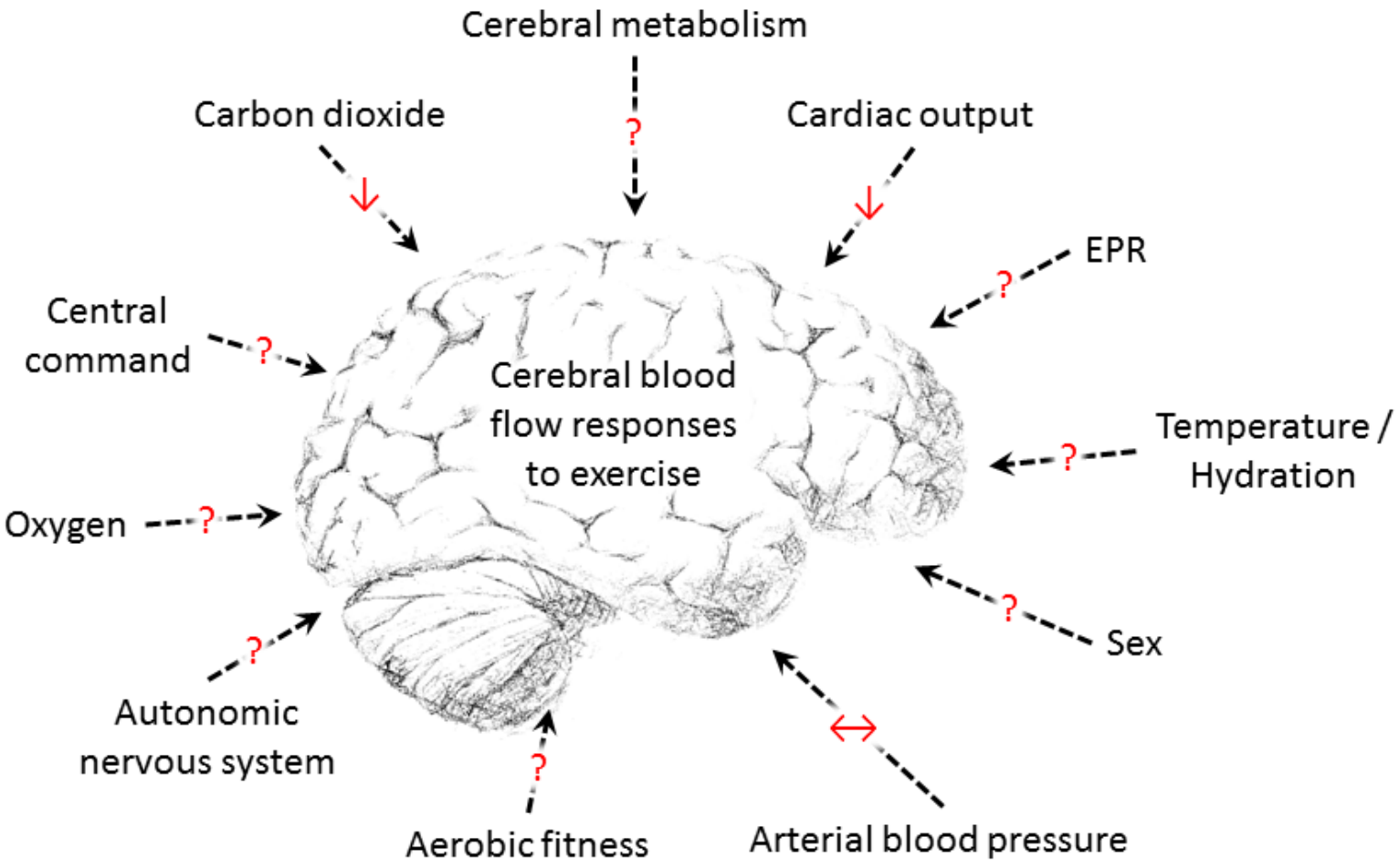
Mean values are shown for the 5 studies that have examined the impact of age on cerebral perfusion responses to incremental dynamic exercise in humans. In instances where VO_2max was not determined, HRR has been used.

Figure 2. Summary of the mechanisms whereby age may impact the cerebral blood flow responses to exercise in humans.

Red arrows denote how age modifies the contribution of a specified mechanism to the cerebral blood flow to exercise (e.g., age reduces cardiac output during exercise which likely contributes to a lower cerebral perfusion). A '?' indicates where the impact of age is presently unknown.


Young
Older
ΔCMRO2
% VO2max
Arterial CO2
% VO2max
Cardiac output
% VO2max
Cerebral blood flow
Exercise intensity
Sympathetic NS
% VO2max
Blood pressure
% VO2max
Cerebral oxygenation
% VO2max
Other potential factors: Aerobic fitness, sex, central command, EPR, vasodilatory pathways, cerebral atrophy


50
40
30
20
10
0
-10
% change MCA V mean
Low intensity
Moderate intensity
High intensity
Maximal intensity
Young
Older
Fisher et al. (2008)
Marsden et al. (2012)
Murrell et al. (2013)
Fisher et al. (2013)
Flück et al. (2014)
Mean


Cerebral metabolism
?
Carbon dioxide
↓
Cardiac output
↓
EPR
?
Central
command
?
Cerebral blood
flow responses
to exercise
Temperature /
Hydration
?
Oxygen
?
?
Sex
?
Autonomic
nervous system
?
Aerobic fitness
↔
Arterial blood pressure