

Overview of age-related changes in psychomotor and cognitive functions in a prosimian primate, the gray mouse lemur (*Microcebus murinus*): Recent advances in risk factors and antiaging interventions

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Abstract

Aging is not homogeneous in humans and the determinants leading to differences between subjects are not fully understood. Impaired glucose homeostasis is a major risk factor for cognitive decline in middle-aged humans, pointing at the existence of early markers of unhealthy aging. The gray mouse lemur (*Microcebus murinus*), a small lemuriform Malagasy primate, shows relatively slow aging with decreased psychomotor capacities at middle-age (around 5-year old). In some cases (~10%), it spontaneously leads to pathological aging. In this case, some age-related deficits, such as severe cognitive decline, brain atrophy, amyloidosis, and glucoregulatory imbalance are congruent with what is observed in humans. In the present review, we inventory the changes occurring in psychomotor and cognitive functions during healthy and pathological aging in mouse lemur. It includes a summary of the cerebral, metabolic, and cellular alterations that occur during aging and their relation to cognitive decline. As nutrition is one of the major nonpharmacological antiaging strategies with major potential effects on cognitive performances, we also discuss its role in brain functions and cognitive decline in this species. We show that the overall approach of aging studies in the gray mouse lemur offers promising ways of investigation for understanding, prevention, and treatments of pathological aging in humans.

KEYWORDS

aging, cognitive functions, gray mouse lemur (*Microcebus murinus*), psychomotor functions, neurodegeneration

1 | INTRODUCTION

Large brains are a defining feature of primates and the progressive encephalization of primates during evolution has had, among other parameters, profound behavioral, and cognitive consequences (Sansalone et al., 2020). It certainly procured a high adaptive value to primates with beneficial consequences for foraging, mating, social

interactions, or more general problem solving being discussed (Heesy, 2005; Roth & Dicke, 2019). Haplorhine primates (great apes, Old and New World monkeys) have long been considered to have strong cognitive peculiarities, but recent studies suggest that there is more continuity in primates' cognitive abilities. Thus, strepsirrhine primates (lemurs, lorises, and galagos) would share more abilities with haplorhines than previously thought (Fichtel et al., 2020; Kittler et al.,

2018). Ring-tailed lemurs, for example, share a common numerical processing mechanism with other primates (Cantlon & Brannon, 2006; D. Merritt et al., 2007; D. J. Merritt et al., 2011). Due to the benefits of advanced cognitive features, and since most of the studies focusing on cognitive abilities in primates were conducted in young adult animals, it is of major interest to address the impact of aging on such abilities. A few primate species are routinely used as models of human aging. This includes mainly macaques, squirrel monkeys, marmosets, and gray mouse lemurs (Austad & Fischer, 2011; Finch & Austad, 2012). The gray mouse lemur (*Microcebus murinus*) originates from Madagascar and belongs to the Strepsirrhini suborder and to the Cheirogaleidae family. From an evolutionary point of view, mouse lemurs may appear phylogenetically too far from humans to be considered a valuable model of human aging. However, they are positioned at about half the genetic distance between mice and humans (Ezran et al., 2017) and share very interesting common traits with both of them. In fact, they are small (body length of ~15 cm, mean body mass ~60–80 g in captivity), easy to breed and handle, they exhibit a fast development (animals are considered mature at 1-year old), and are among the most prolific primates in the world (~2 pups/mother/y. in captivity). From an aging research point of view, they share a very important trait with humans and other primates, a long lifespan (maximal longevity ~14 years in captivity) (Pifferi et al., 2019), with this an aging rate much more like that of humans than of rodents (Austad, 1993; Ezran et al., 2017). Gray mouse lemurs can be segregated between “young” and “aged” animals on the basis of the median survival time in captivity (at which half of the population has died). For instance, in the Brunoy colony, the median survival time is 4.9 years for females and 5.7 years for males. Thus, in this colony, animals are considered “aged” from the age of 5 (Languille et al., 2012b).

Mouse lemurs are omnivorous, nocturnal, arboreal solitary foragers. In the Malagasy forests where they live, the 6-month-long hot rainy season is characterized by elevated temperatures and abundant food resources. It corresponds to the birth season during which mouse lemurs exhibit high levels of activity and a high metabolic rate during the night. It alternates with 6 months of a cooler dry season characterized by lower food resources and temperatures during which their metabolism slows down until expressing daily phases of hypo-metabolism. In the wild, only 16% of the mouse lemurs (*Microcebus* sp.) are estimated to live beyond 4 years of age, the oldest animal captured being aged 8 years on the basis of teeth wear (Zohdy et al., 2014). In contrast, animals raised in captivity reached maximal observed longevity of approximately 14 years (Pifferi et al., 2019). This species thus represents a good compromise between practical breeding requirements and physiological and phylogenetic proximity to humans. In addition to the fact that their ecology, physiology, and behavior have been studied for decades (see Bons et al., 2006 for review), their genome is now fully assembled (Larsen et al., 2017), which is useful in the context of evolutionary studies (Hunnicut et al., 2019) and promising for translational research areas such as biomedical studies.

In addition, gray mouse lemurs express a spontaneous inter-individual variability in behavioral and cognitive performances

(Languille et al., 2012b) and spontaneous occurrence of pathologies, especially age-related neurodegenerative diseases, that constitutes in itself a research field. Indeed, aging is also not homogeneous in humans and the determinants leading to differences between subjects are not fully understood. As an example, impaired glucose homeostasis is a major risk factor for cognitive decline in middle-aged humans, pointing to the existence of early markers of unhealthy aging (Messier et al., 2003). Interestingly, mouse lemurs show relatively slow aging with decreased psychomotor capacities starting at middle-age (around 5-year old). In some cases (~10%; Bons et al., 2006; Languille et al., 2012b), pathological aging can be observed. In this case, some age-related deficits, such as cognitive decline, cerebral atrophy, and glucoregulatory imbalance are congruent with what is observed in humans (Djelti et al., 2016). Here, we show that aging studies in the gray mouse lemur offer promising ways for the investigation for both prevention and treatment of pathological aging in humans. The main findings that are discussed below are summarized in Table 1.

2 | AGE-RELATED COGNITIVE DEFICITS

2.1 | Conservation of procedural memory

Procedural memory is a type of long-term nondeclarative memory consisting of the implicit acquisition of motor abilities and reflexes. It can be assessed through discrimination tasks that have been considerably developed and adapted for mouse lemurs. Discrimination generally requires the animal to emit a motor response when triggered by a positive cue, and inhibit the response when triggered by a negative cue. The animal is then rewarded if it associated the stimulus with the correct behavior. Cues can involve several sensory modalities such as vision and olfaction. In some tasks, usually considered as “easier” to achieve, aged mouse lemurs show no deficit in associating the stimulus and the reward: they successfully learn the rule within the same number of trials as the young ones, showing a trend of conservation of procedural memory, that is, implicit acquisition of motor abilities, in aging (Joly et al., 2006; Picq, 2007). Such lack of impairment in this specific type of memory has been widely reported in rodents (Gilbert et al., 2009), other nonhuman primates (Rapp, 1990), and humans (Cohen & Squire, 1980; Squire, 1992). However, a newly designed touchscreen-based discrimination task found the impaired acquisition of the stimulus-reward association in aged lemurs (Joly et al., 2014; Schmidtke et al., 2018, 2020; Wittkowski et al., 2021). Actually, all tested animals succeeded in acquiring the visual discrimination but aged animals needed more trials to reach the task criterion of 80% correct responses in two consecutive daily sessions. Two aspects of the experimental design may have led the authors to these divergent results with respect to other studies. First, there are differences in the difficulty of the visual discrimination as the cues used by Picq (2007) were based on the illumination of corridors, whereas the visual cues used in the touchscreen study were based on different shapes of the same color. Second, the reward used in this study was appetitive (orange juice),

TABLE 1 Summary of the main cognitive, psychomotor, and cerebral modifications occurring during aging in *Microcebus murinus*

Age-related brain modifications	Effect	References
Cognitive modifications		
Procedural memory		
Implicit acquisition of motor abilities associated with a stimulus	=	Joly et al. (2006), Picq (2007), Picq et al. (2015)
Bias toward relative stimulus location and strategic conservatism	↘	Joly et al. (2014), Schmidtke et al. (2018), Schmidtke et al. (2020), Schmidtke (2021), Wittkowski et al. (2021)
	↗	Schmidtke (2021)
Working memory and executive functions		
Performance in visiting alternatively arms without repetition	↘	Languille et al. (2015), Picq (1993)
Repetitive errors	↗	Trouche et al. (2010)
Learning when introducing a delay between the stimulus and the reward	↘	Picq (1995)
Declarative memory		
Spatial memory and response to novelty		
Reference errors (three-panel runway maze)	↗	Trouche et al. (2010)
Remembering the task rule previously learned several months ago	↘	Joly et al. (2014), Picq et al. (1998, 2015)
Exploration of a new environment	↘	Languille et al. (2015), Picq and Dhenain (1998)
Cognitive flexibility: Ability to transfer the attention from a rule to another		
Intradimensional shift	=	Joly et al. (2006)
	↘	Picq (2007)
Extradimensional shifts	↘	Picq (2007)
Interindividual variability in performances	↗	Languille et al. (2015), Picq et al. (1998), Picq (2007)
Anxiety		
Latency of first movement in an open field or the first entry in a lit arm	↘	Languille et al. (2015)
Sensorimotor modifications		
Vision		
Age-depend lens opacity (cataract, nuclear sclerosis)	↗	Beltran et al. (2007), Dubicanac, Radespiel et al. (2017)
Glutathione-synthetase activity in the lens	↘	Rathbun and Holleschau (1992)
Glutathione-peroxidase activity in the lens	↗	Holleschau and Rathbun (1994)
Olfaction		
Olfactory-based behaviors of males and endocrine response	↘	Aujard and Némot-Bertholet (2004), Aujard and Perret (1998)
Threshold of odor discrimination	↗	Aujard and Némot-Bertholet (2004)
Olfactory memory	=	Joly et al. (2006)
Olfactory receptors' expression	=	Hohenbrink et al. (2014)
Fos expression in the main olfactory bulb	↘	Cayetanot et al. (2005)
Hearing		
Response threshold of the auditory brainstem neurons to stimuli	↗	Schopf et al. (2014)
Hearing range	↘	Schopf et al. (2014)
Frequency of best hearing	=	Schopf et al. (2014)
Amplitude of the peaks of the neurons' electric waves in response to stimuli	↘	Schopf et al. (2014)

(Continues)

TABLE 1 (Continued)

Age-related brain modifications	Effect	References
Motor abilities		
Pull strength and bite force	↘	Berthelot, Johnson et al. (2019), Marck et al. (2016), Thomas et al. (2015), Zablocki-Thomas et al. (2018)
Motor coordination	↘	Némoz-Bertholet and Aujard (2003)
Spontaneous locomotion such as jumps and difficult movements	↘	Némoz-Bertholet and Aujard (2003)
Cerebral and cellular alterations		
Cerebral atrophy (particularly in insular, parietal and occipital cortices, the hypothalamus, and the thalamus), neuron loss, and size of brain ventricles in animals aged >8 years	↗	Bons et al. (1992), Kraska et al. (2011), Nadkarni et al. (2019), Sawiak et al. (2014), Bons et al. (2006), Jallageas et al. (1998)
Senile plaques and amyloid deposits; neurofibrillary degeneration; gliosis	↗	Giannakopoulos et al. (1997), Mestre-Francés et al. (2000), Bons et al. (2006), Schmidtke et al. (2020)

Note: ↘, decrease during aging; ↗, increase during aging; =, conservation through aging.

and maybe more salient than the safety of the nestbox used as a reward by the previous studies. Nevertheless, this study helps to qualify better the modifications of procedural memory across aging by suggesting that, although there is well-described conservation of these abilities, procedural memory still undergoes an impairment—even a slight one—that more complex tasks reveal (Joly et al., 2014).

The same findings were reported more recently in a similar protocol, adding an analysis of the possible factors that may underlie this impairment (Schmidtke, 2021). Even though all the animals showed at least one type of bias (toward a type of stimulus of a spatial location) at the beginning of the training, the young animals showed reduced biases toward relative location than old animals. This suggests that old animals displayed more frequently a strategy based on relative stimulus position. Such a strategy would drive performance towards chance level (i.e., 50% of success) as both positions (left and right) were randomly rewarded across the test. This explanation is supported by evidence in humans that aged adults show higher strategic conservatism and strategy shifts in favor of scanning rather than a recall-based strategy in a similar task (Touron, 2006). A visual discrimination task based on ecological capabilities of mouse lemurs such as jumping did not show a difference in the number of trials needed for reaching the criterion of 80% correct responses between young and aged animals (Picq et al., 2015). These results can be explained by the task in itself, which is well adapted to the biology of the mouse lemur. It may be suggested, considering the tasks mouse lemurs face in their natural habitats, that even if a slight impairment in procedural memory occurs in aging, it may not interfere strongly with their day-to-day activities and thus their survival and fitness.

A very recent study aimed to assess procedural memory in mouse lemurs by using auditory cues (Ferreiro et al., 2020). Although this is itself a new paradigm as auditory discrimination has never been explored in mouse lemurs, the great innovation comes from the integration of sensory cues during self-motion. Indeed, the Sensory Island Task consists of an open field with particular areas (islands)

that can trigger the presentation of the auditory stimulus if the animal stays long enough in. Consequently, this task allows assessing the continuous processing of sensory cues while the animal is moving, reflecting ecologically relevant conditions that may undergo adaptive abilities. Yet, the task still has to be implemented in a larger number of animals to identify the basal performance of adult mouse lemurs. An interesting perspective then should be to assess the conservation of procedural memory across aging by using auditory cues such as in this study (Ferreiro et al., 2020).

2.2 | Alteration of working memory and executive functions

Unlike procedural memory, working memory is a type of short-term memory allowing cognitive processing and manipulation of recently stored information, for instance, within a single trial (Olton, 1979). Working memory is often assessed in comparison with reference memory which is a type of long-term memory gradually acquired over trials. Both working and reference memories have first been tested in an eight-arm radial maze, consisting of four free arms and four blind arms. The mouse lemur had to explore the free arms before his nestbox becomes accessible when the last arm was visited. Visiting a free arm that had already been visited within the same trial was counted as a working memory error, whereas visiting a blind arm already known for never having given access to the nestbox throughout trials was counted for a reference memory error. All animals had no difficulty in memorizing the blind arms, but aged animals showed lowered performance in visiting alternatively the free arms without repetition, suggesting impaired working memory with aging (Picq, 1993). As discussed above, aged mouse lemurs had no difficulty in learning the association between the stimulus and the reward in discrimination tasks. However, their learning is impaired when a delay is introduced between the stimulus presentation and the motor response initiating the reward (Picq, 1995).

In a three-panel runway maze, the mouse lemurs must learn a sequence of consecutive gates that, when passed through, give access to the nestbox. After the learning session, various types of errors were assessed during a testing session. Among them, repetitive errors were defined as a reattempt to open an incorrect gate that has been already tested by the animal within the same trial. Aged mouse lemurs displayed a tendency for more repetitive errors compared to the young ones. Interestingly, even though aged animals attempted more often to open an incorrect gate already tried, this attempt was generally nonconsecutive. In contrast, young animals made more perseverative errors, defined as the repeated attempt to open the same incorrect gate consecutively (Trouche et al., 2010). A hypothesis that could explain the larger number of perseverative errors in young animals is that anxiety levels tend to decrease with aging. Indeed, anxiety tests such as the open field test or the light-dark plus-maze test reported that the latency of first movement or the latency of first entry in a lit arm of a maze, were significantly higher in young animals, suggesting greater anxiety (Languille et al., 2015).

Finally, a spontaneous alternation test showed for the first time in mouse lemurs a linear regression of the working memory performance. Animals, separated into three age categories young (2.5–4.2-year old), middle-aged (5–6.8-year old), and aged (7–9.5-year old), were placed in a cross-shaped maze with free exploration for 10 min. The internal walls of the four arms were covered with visual cues allowing recognition of the different arms. The expected spontaneous behavior is to explore arms that were not previously visited, leading to alternation of the four arms during the session test. The percentage of alternation decreases in case of working memory deficit since animals will tend to return more rapidly to already visited arms. A significant decline of the percentage of alternation with age has been shown (from around 40% at 2-year old to around 10% at 9-year old) (Languille et al., 2015).

Taken all together, these studies strongly corroborate the idea of an impaired working memory with aging in mouse lemurs, while reference memory seems to be relatively conserved. Age-related alterations of working memory have also been found in rodents (Bizon et al., 2012), nonhuman primates (Lacreuse et al., 2020; Rapp & Gallagher, 1997; Walker et al., 1988), and humans (Light & Anderson, 1985; Morris et al., 1988).

2.3 | Differential impairment of declarative memory

The ability to intentionally recollect previously stored factual information and experiences is associated with declarative (or explicit) memory (Ullman, 2004). In mouse lemur, like in rodents, declarative memory can be assessed using a spatial reference memory test. In the three-panel runway maze task described above, aged animals make more reference errors (i.e., first attempt to open a gate known for being incorrect during previous sessions) than young ones (Trouche et al., 2010). In the Barnes maze, the animal is introduced at the

center of a circular platform with 12 compartments identified by visual cues. During the training trials, all the compartments were closed excepting the compartment leading to the nestbox. During the test trials, all the compartments were opened and the animal had to remember which compartment leads to the nestbox. Long-term explicit memory was assessed 3 min and 24 h after the last training session. Linear regression showed that the number of errors increased with the age only for the session conducted 24 h after the last trial (Languille et al., 2015). The discrimination tests discussed above (Joly et al., 2014; Picq et al., 1998, 2015) allow to test declarative memory as well by starting the test again after a long period of rest (usually 6 months). These visual discrimination tasks have shown age-related deficits in remembering the rule previously learned several months ago, supporting the idea that aged animals acquired the rule as well as the young ones but have difficulties in its retention across time (Joly et al., 2014; Picq et al., 1998, 2015).

Declarative memory relies on (1) the ability to use the information previously stored and (2) the flexibility when facing a new context, leading either to the inhibition of a response, or the transfer the attention from an object or a task to another. These aspects of declarative memory can be assessed first with novel object recognition (NOR) tests. In an experimental enclosure containing various objects, the animals were allowed to explore the enclosure for three training sessions during a week to increase their familiarity with the environment and the objects. During the test sessions, new objects were added and the old objects previously presented during the training sessions were placed in a different location. Aged animals showed lower exploration of new objects than young ones. Moreover, aged animals showed no reaction to changes in the location of old objects (Picq & Dhenain, 1998). More recently, a comparable NOR experiment has been conducted using a T maze. The habituation session consisted in allowing access to the nestbox to the animal after it explored the two arms of the maze without any object inside. Then, during a first session, two symmetrical objects (A1 and A2, which were exactly the same) were added to each arm of the maze. Finally, during the second session, a triplicate of the previously presented objects (A3) and a new object (B) were presented. Different delays were introduced between the two tests (5 min, 1 h, or 24 h). Though no difference was found in new object exploration between young and aged animals, a downward trend in the discrimination ratio between the two objects in aged animals was found with an increased delay between the test sessions ($p = 0.057$) (Languille et al., 2015). Altogether these studies revealed that spatial memory and response to novelty, two abilities that rely on declarative memory, seemed to be altered in aged animals.

Furthermore, cognitive flexibility which is another aspect of declarative memory has been explored with set-shifting tasks which consist in testing the ability of the animal to transfer its attention from a task (or a rule) to another. Discrimination tests previously presented allow to assess first intradimensional shifts, by reversing the reward-stimulus association but with the same dimension (for instance, the lit corridor doesn't lead to the nestbox anymore but it is

the dark one, but the relevant dimension is the same: the lighting of the corridor). In this kind of intradimensional shifting task, different results were found. Although no differences were found in the reversal of an olfactory task between aged and young animals, high variability was reported in aged animals for this task with the lowest scores being held by animals belonging to the aged group (Joly et al., 2006). In contrast for a spatial discrimination task, while all the animals succeeded in reaching the criterion within the same number of trials, reversal of the stimulus-reward association showed that aged animals made a mean of 16 errors to reach the criterion, which is almost three times more than the number of errors of the young animals (Picq, 2007). Similar impairments in intradimensional shifts have been reported for more recent visual discrimination tasks (Joly et al., 2014). Extradimensional shifts have been explored by shifting from a lighting-based rule (the lit corridor led to the nestbox) to a spatial-based rule (the corridor on the right led to the nestbox regardless of the lighting). Again, performances in shifting from a rule to another are negatively impacted by age, with aged animals making a mean of 16 errors to criterion while the young animals made only a mean of 7 errors before reaching the criterion. However, it remains unclear if the animal had difficulties in getting rid of the old rule or acquiring a new rule (Picq, 2007). Altogether, these studies underline the lack of cognitive flexibility occurring with aging, which happens to be a key functionality of declarative memory. The fact that these findings are reported in rodents (Schoenbaum et al., 2006), rhesus monkeys (Voytko, 1999), and humans (Weiler et al., 2008) underline that such age-related impairments in cognitive flexibility and thus declarative memory may occur in the brain aging across mammals.

However, not all aged animals exhibit these alterations, or at least not all at the same degree of severity. Actually, a strong inter-individual variability in animals' performance has been found, which increases with age. A clustering of the animals according to their performances shows that some aged animals exhibit similar patterns of response as young ones (7/16 middle-aged and 7/12 old animals), and other aged animals exhibit deficits in declarative memory (7/16 middle-aged and 4/12 old animals). Regardless of the declarative memory-associated performances, most of the aged animals show deficits in working memory. This suggests that a distinction has to be made between deficits related to normal aging such as working memory, linked to cerebral atrophy in frontal and caudate regions of the brain occurring in all aged animals, and deficits related to pathological aging such as declarative memory alterations linked to cerebral atrophy in the hippocampus, entorhinal and cingulate cortices occurring in a subpopulation of aged animals (Languille et al., 2015; Picq, 2007; Picq et al., 1998). Interestingly, impairments in procedural memory described in the first section in the touchscreen-based discrimination task have been correlated with the accumulation of amyloid- β in the cortical regions of the brain, suggesting that impairments in procedural memory may be associated with pathological aging (Schmidtke et al., 2020). Such individual variability in declarative memory during aging has been reported previously in humans (Albert, 1993), monkeys (Rapp & Amaral, 1992), dogs (Salvin et al., 2011), and rats (see Gallagher, 1993 for review) as well.

3 | AGE-RELATED SENSORIMOTOR MODIFICATIONS

3.1 | Vision and aging

As the gray mouse lemur is a nocturnal species, the animals display a lot of visual adaptations improving the capture of light such as a large globe, a pear-shaped pupil, and a *tapetum lucidum*. However, this visual system can be altered across aging. Though the retina seems to be relatively preserved, the lens is the main structure that was shown to be affected by aging, with a high incidence of cataracts which amounts to nearly half of the old animals in the colonies that have been studied (Beltran et al., 2007; Dubicanac, Strueve, et al., 2017). More precisely, cataracts affected 100% of animals that were aged 8 years and more. Cataract-associated lesions such as hyphemia, posterior synechiae, pupil seclusion, corneal degradation, or buphthalmia were eventually observed. Various factors could lead to the formation of cataracts, for example, trauma, dietary and metabolic disorders, parasites, ocular inflammation, toxic substances, hereditary factors, UV light, and aging (Beltran et al., 2007). UV light is suggested to be a high-risk factor in the formation of cataracts in humans (Seddon et al., 1995), but a recent study did not find support for this hypothesis in mouse lemurs, as UV light intensities reached only around 0 W/m² in the tested colonies in captivity (Dubicanac, Strueve, et al., 2017). Genetic impacts as described in humans were not completely excluded in gray mouse lemurs even though no clear lineage dependency was found. In conclusion, aging remains one of the main risk factors (Dubicanac, Strueve, et al., 2017). Aging is partially caused by an imbalance between the production and degradation of reactive oxygen species, in favor of their production. This imbalance, called oxidative stress, may be caused by changes in the antioxidative system, such as the glutathione pathway. In mouse lemurs, as in humans, glutathione synthetase activity decreases and glutathione peroxidase activity increases with the age in the lens, leading probably to deficits in glutathione recycling and thus deficits in the efficiency of the antioxidative system (Holleschau & Rathbun, 1994; Rathbun & Holleschau, 1992).

Recent studies detected another major lens disease in mouse lemurs different from cataracts that affect the density of lens fibers in the lens core: nuclear sclerosis (Dubicanac, Strueve, et al., 2017). It was not detected in the study of Beltran et al. (2007) and was actually found as the first-age dependent lens opacity before cataract in the study of Dubicanac, Strueve et al. (2017), affecting 100% of the animals older than 6 years. A different genetic background could possibly be an explanation since both colonies tested in Beltran et al. (2007) and Dubicanac, Strueve et al. (2017) originated from different ancestors in Madagascar. However, no effect of lineage on nuclear sclerosis incidence (for instance, in its onset age) has been found. Age seems to be, as for cataracts, the major driver of nuclear sclerosis (Dubicanac, Strueve, et al., 2017). However, it appears that it is not the absolute number of years experienced by the gray mouse lemurs that increase the risk of developing nuclear sclerosis, but the number of seasonal cycles. When the animals were exposed to an accelerated

photoperiodic regime by a factor of 1.5, nuclear sclerosis was found earlier, at a chronological age corresponding actually to the normal number of seasonal cycles at which nuclear sclerosis should appear with a non-accelerated photoperiodic regime (Dubicanac, Strueve, et al., 2017). These results corroborate the idea that longevity and aging in gray mouse lemurs strongly depend on the number of experienced seasonal cycles rather than on a fixed chronological age (see Languille et al., 2012b; Zimmermann et al., 2016 for review).

3.2 | Olfaction and aging

Like vision, olfaction is a sensory modality highly adapted to the mouse lemur ecology. As foraging and communicating in dense forests by the night strongly rely on chemical signals, olfactory sensory organs are particularly developed. For instance, gray mouse lemurs display large olfactory bulbs that reach more than 2.6% of the cerebral mass, being then the greatest olfactory surface relative to other primates (Smith et al., 2007). Moreover, the gray mouse lemur is one of the few known species among the primates for which reproduction relies actively on pheromones, as evidenced by the existence of a functional vomeronasal organ (Schilling et al., 1984) and a large repertoire of vomeronasal receptors studied (Hohenbrink et al., 2014, 2012; Hunnicutt et al., 2019; Yoder et al., 2014).

As in rodents (Mobley et al., 2014; Schoenbaum et al., 2002), the gray mouse lemur's olfactory system appears to be altered by aging. First, olfactory-based behaviors are negatively impacted by aging: a decrease in the frequency of licking and sniffing of the genitalia of receptive females and a decrease in the frequency of scent marking behaviors have been reported in aged males (Aujard & Perret, 1998). These patterns were also found in adult males from which the vomeronasal organ (Aujard, 1997) or the olfactory bulb (Souza, 2003) was removed. Also, when stimulated with the volatile phase of urine from proestrus females, aged males failed to show the high increase in the plasmatic testosterone level that is observed in adult males (Aujard & Némot-Bertholet, 2004). Low levels of testosterone are again found in adult males from which the olfactory bulb has been removed (Schilling & Perret, 1993), associated with a loss of reproductive success (deficit in aggressivity and access to receptive females) (Perret, 1995). Whether the age-related alterations occur at a peripheral or a central level, however, is subject to an ongoing discussion.

Sensorial discrimination tasks may give some clues about the role of the peripheral and central levels in the impairment of olfactory functions with aging. In one of these tasks, the animals were isolated in a cage with two identical bowls containing the same quality and quantity of food (Aujard & Némot-Bertholet, 2004). One of the bowls was presented in a container filled with water, and the other one in a container filled with a repellent at different concentrations across the trials. The quantity of food consumed in each bowl was measured, and the threshold was defined as the highest dilution of repellent for which the mean difference in consumption between the two bowls is still significant. The animals typically exhibited repulsive behavior when the repellent was detected, associated with an immediate retraction from the area. This behavior was observed at lower concentrations of repellent in adult animals compared

to aged animals. There was furthermore a clear negative correlation between the threshold of discrimination and the age of the animals (Aujard & Némot-Bertholet, 2004). On the other hand, a discrimination task with two odors at high concentrations (strawberry and pear) showed no difference in the performance between adult and aged animals. However, the task rather tested the memory capabilities of the animals, suggesting that olfactory memory is not altered with age (Joly et al., 2006). Further studies at a central level found that exposure to the volatile phase of urine from proestrus females induced a higher level of Fos expression in the main olfactory bulb in adult mouse lemurs than in aged animals (Cayetanot et al., 2005). The only study that has investigated the expression of some olfactory receptors in the olfactory epithelium did not find age-related differences among the 6 animals that have been studied (age range: 10 days–11.9 years) (Hohenbrink et al., 2014). More studies involving more animals are needed to explore quantitatively the olfactory receptors and their functionality across aging in gray mouse lemurs. Indeed, studies in mice have shown a decrease in the density of olfactory receptor cells in the olfactory epithelium with aging (Nakayasu et al., 2000). Age-related sensory alterations are also found in humans when being tested with a suprathreshold detection task. The subjects showed a decrease in detection performance of an odorant with aging. Odor identification performance is also altered with aging. As identifying odors involves memory, such an impairment may support the hypothesis of an alteration of the olfactory system at a central level (Joussain et al., 2016). Interestingly, when comparing control and Alzheimer's disease (AD) groups, no difference in supraliminal detection was found, but the groups differed in the identification performance with a significant drop in the AD group (Rouby et al., 2011). These studies suggest that central alterations of the olfactory system may occur during pathological aging.

3.3 | Hearing and aging

Hearing is of prime importance in the ecology of gray mouse lemurs. They are very sensitive to high frequencies: their hearing range (750 Hz–44.9 kHz), and most particularly, their frequency of best hearing (7.9 kHz) (Schopf et al., 2014), overlap the frequencies of the vocalizations of some of their predators such as the Madagascar harrier-hawk (*Polyboroides radiatus*) (Fichtel & Kappeler, 2002).

So far, little investigation has been led on hearing in gray mouse lemurs in relation to aging. The auditory brainstem response has been studied on lemurs of different ages using a brainstem-evoked response audiometry technique (Schopf et al., 2014). After being anesthetized, the electric response to clicks and tone-pips was measured with silver chloride electrodes positioned subcutaneously. The measures were acquired for different levels of sound pressure (the level increased in 5-dB steps), and the threshold was defined as the first level at which a response was distinguished from the noise. First, the amplitude of the typical peaks of the electric wave was systematically lower in aged animals compared to the young ones. Several studies in humans and animals showed that the amplitude of the peaks is a direct function of the number of neurons, their synchronization, and the value of the endocochlear potential, suggesting that a decrease in this amplitude may be a symptom of

age-related neurodegeneration (Boettcher, 2002). Moreover, the mean thresholds for the range of frequencies tested were 12–27 dB higher for the aged animals. Thus, the hearing range, defined as the hearing thresholds below 60 dB, was shortened in aged animals. Interestingly, aging affected the upper and lower limits of hearing, but not the frequency of best hearing which remained unchanged. However, substantial interindividual variability in the thresholds of the old animals has been reported. Further investigations are needed to examine the effect of normal and pathological aging on these patterns of sensorial responses (Schopf et al., 2014).

3.4 | Age-related motor alterations

As behavior highly depends on motor abilities in animals, assessing cognitive functions in animals should always be accompanied by an evaluation of the motor capacities of a given individual. Indeed, like in humans, the age-performance relationship describes changes in the organism's structural and functional capabilities over the lifespan and concerns cognitive functions as well as motor functions (psychomotor functions) (Berthelot, Johnson, et al., 2019). Several studies found a decrease in motor abilities with age. Pull strength and bite force were altered in old animals, especially in females in which the performances tend to decrease more rapidly than in males (Berthelot, Bar-Hen, et al., 2019; Marck et al., 2016; Thomas et al., 2016; Zablocki-Thomas et al., 2018). Motor coordination was tested by measuring the time the animals remained on an accelerating rotating rod. The performance significantly decreased with aging, with 80% of the animals older than 6 years performing less than 60 s, while all the animals younger than 4 years performed more than 60 s. Regarding spontaneous locomotion, aged animals exhibited less jumps and difficult movements than the young ones. Interestingly, aged animals showed more exploratory behaviors in an open field than young animals, but these behaviors dropped with time in the open field while they tend to increase in young animals (Némoz-Berthelot & Aujard, 2003).

4 | AGE-RELATED CEREBRAL, METABOLIC, AND CELLULAR ALTERATIONS, AND COGNITIVE DECLINE

About 30 years ago, the first descriptions of cerebral alterations in aged gray mouse lemurs were documented. For example, Bons et al. (1992) observed that mouse lemurs older than 8 years exhibited cerebral atrophy associated with the increased size of the cerebral ventricles. Such atrophy was already linked to the presence of senile plaques and amyloid deposits partly comparable to those observed in humans and associated with cognitive decline (Bons et al., 1992). These early studies paved the way to further research addressing the link between cellular and anatomic alterations, cognition, and aging. Among them, several magnetic resonance imaging (MRI)-based studies suggested that aged mouse lemurs show similar cerebral alterations to those observed in aged humans (Bertrand et al., 2013;

Dhenain et al., 1998). Recent technical and analytical ameliorations allowed to produce three-dimensional-based morphometric analysis and confirmed, with better resolution and more detailed brain regions, that age-related cerebral atrophy occurred in a similar way as other primates including humans. The age-associated atrophy particularly affects the insular, parietal, and occipital cortices (according to Nadkarni et al., most of the cortical regions display some atrophy with age) and the thalamus and hypothalamus (Fritz, Zimmermann, Picq, et al., 2020; Nadkarni et al., 2019; Sawiak et al., 2014). MRI-based studies have also been complemented with histology studies that show an association between age-related cerebral atrophy and neurodegenerative pathologies accompanied by cognitive deficits in a subset of aged individuals. These aged animals exhibit several cerebral alterations among which brain atrophy (Kraska et al., 2011), neuron loss (Bons et al., 2006; Jallageas et al., 1998), amyloidosis (Bons et al., 1994; Schmidtke et al., 2020), neurofibrillary degeneration (Giannakopoulos et al., 1997), and gliosis (Bons et al., 2006; Mestre-Francés et al., 2000), that translates into behavioral alterations and severe cognitive decline (Fritz, Zimmermann, Meier, et al., 2020). This neurodegenerative pattern is, at least partly, comparable to humans and has been described as the *Microcebus age-associated neurodegeneration* (Bons et al., 2006). In addition to the above-mentioned observations, one needs to consider that the gray mouse lemur also has essential singularities regarding its metabolism, in particular the existence of a seasonal, facultative, daily torpor expression that impacts its physiology. This might be the main limitation for a systematic extrapolation of observations made in mouse lemurs to humans. As an example, it has been described that hypometabolism can affect the phosphorylation and dephosphorylation of tau proteins in the brain of several heterotherm mammals, obligate hibernators (arctic ground squirrels and black bears) as well as permissive hibernators (Syrian hamsters) (Stieler et al., 2011). Such a phenomenon could also exist in mouse lemurs since the mechanisms of their hypometabolism is similar to other heterotherms (Biggar et al., 2015). It might provide them some protection against the accumulation of tau proteins in the brain. Although different from humans, it is nonetheless interesting to explore such potentially protective pathways from a mechanistic and therapeutic perspective, and thus constitutes in itself a promising research topic (Chiocchetti et al., 2021; Luppi et al., 2019).

Interestingly, cognitive decline in older human adults has been related to both brain atrophy and type 2 diabetes (Buss et al., 2018; Geijselaers et al., 2015; Weinstein et al., 2015). Similarly, middle-aged mouse lemurs exhibit impaired fasting blood glucose that correlates well to cognitive decline and brain atrophy (with regional specificities that were linked to the cognitive functions tested). In particular, these animals had lower spatial memory performance together with the lower hippocampus and septum volumes (Djelti et al., 2016). It confirms the link between impaired glucose homeostasis, brain atrophy, and cognitive processes, and the role of energy metabolism in long-term proper brain functioning. In addition, brain functions are also known to highly depend on the constant energy supply (Chi & Roberts, 2003; Nehlig, 1997).

5 | NUTRITIONAL ANTI-AGING STRATEGIES

5.1 | General introduction

Optimal nutrition is one of the most effective and least expensive ways to decrease risk factors (mostly obesity and vascular disorders) associated with noncommunicable diseases, primarily heart diseases, cancers, and diabetes (Ohlhorst et al., 2013; WHO, 2014). Among dietary interventions that have proven their efficacy against some of these risk factors are the equilibrated intake of polyunsaturated fatty acids (PUFAs) (Abdelhamid et al., 2018; Joffre et al., 2014; Kones et al., 2018; Watanabe & Tatsuno, 2020; Weiser et al., 2016), optimal energy balance (equilibrating the caloric intake with energy expense) (Fontana et al., 2010; Le Bourg, 2018; Redman et al., 2018; Romieu et al., 2017), and, to a lesser extent, the optimal intake of micro-nutrients (such as vitamins, minerals, or plant-derived compounds such as polyphenols) (Liu et al., 2019; Lorenzo-López et al., 2017; Martin et al., 2013; Rutjes et al., 2018). The gray mouse lemur presents specific features that make it an appropriate model for nutrition studies. In addition to the fact that it is easy to raise and handle (Languille et al., 2012b) it has an omnivorous diet based on the consumption of fruits, flowers, gum, arthropods, and small vertebrates (Dammhahn & Kappeler, 2008) with a relatively long lifespan that allows long-term, but still feasible nutritional interventions (Pifferi et al., 2019, 2018).

5.2 | Effect of n-3 PUFAs supplementation

The brain is known to be the organ with the second-highest lipid concentration after the adipose tissue (Alessandri et al., 2004; Pifferi et al., 2012), most of which are fatty acids (Sastry, 1985), suggesting their importance in cerebral functions. Among fatty acids, n-3 PUFAs have been found to play a key role in brain development. n-3 PUFAs achieve several functions in the brain, such as increasing membrane cell fluidity which is essential for communication and signal transduction, or ensuring tissue integrity by modulating the inflammatory status. Large quantities of n-3 PUFAs can be found in marine animal tissue such as tuna or in some plant oils such as colza oil, which exhibits in particular high quantities of docosahexaenoic acid (DHA), one of the major n-3 PUFAs (for review, see Alessandri et al., 2004; Dyall, 2015).

The impacts of n-3 PUFAs on cognitive functions have been assessed by supplementing animals with two isoenergetic diets, tuna oil-based diet (rich in long-chain n-3 PUFAs) and olive oil-based diet (rich in monounsaturated acids but poor in n-3 PUFAs) (Vinot et al., 2011). The tuna oil-based diet was designed to ensure that the French national recommendations about DHA intake were achieved (namely, that the DHA intake should reach 0.3% of the total energy intake) (Martin, 2001). Increases in plasmatic DHA levels (and thus the decrease in n-6/n-3 ratio) were assumed to be good biomarkers of DHA assimilation, in particular into brain membranes. In adult gray

mouse lemurs, n-3 PUFA supplementation has been associated with greater cognitive performances in memory tasks such as the circular platform task testing the spatial reference memory, and the visual discrimination task testing procedural memory, in comparison to the animals that underwent the olive-based diet. Simultaneously, n-3 PUFA supplementation helped to decrease the anxiety levels of animals as demonstrated by the decrease in the latency of the first movement and the increase in exploratory behavior in an open field task (Royo et al., 2018; Vinot et al., 2011). Actually, these two findings seem to be highly correlated since diminished levels of anxiety should enhance motivation in animals, and thus their success in cognitive tasks. These results suggest, as demonstrated in rodents, an anxiolytic effect of n-3 PUFAs in the gray mouse lemur (Carrié et al., 2000; Takeuchi et al., 2003). Further investigations established a link between n-3 PUFA supplementation, cognitive improvement, and increased brain uptake of glucose by using positron-emitting tomography (Pifferi et al., 2015). Moreover, in recent studies, n-3 PUFA supplementation has been associated with increases in cortical electrical activity using electroencephalography techniques (Royo et al., 2018). Increases in the power of alpha and beta waves for instance have been associated with improvements in recovery of long-term stored memories and with decision-making, such capacities involved in the cognitive tasks implemented in the previous studies. These results corroborate the findings in rodents, suggesting that n-3 PUFAs help supply glucose to the brain, which delivers the energy needed for neuronal communication (Gerbi et al., 1993). Indeed, the Na/K ATPase pump alone consumes up to 50% of the brain ATP to maintain the membrane potential (Leybaert et al., 2007). Enhanced neurotransmission may emerge from this mechanism, or from the increased fluidity of the cell membrane, and may cause the observed changes in cortical electrical activity. Finally, n-3 PUFA supplementation has also been associated with increased neurogenesis in some brain areas involved in memory such as the dentate gyrus and the olfactory bulb by using BrdU and NeuN labeling (Royo et al., 2018). Similarly, aging has been associated in humans with deficits in brain glucose uptake and thus with brain hypometabolism that may lead to mild cognitive impairment. Similar patterns were found in n-3 deficient rodents (Gerbi et al., 1993; Hennebelle et al., 2015; Ximenes da Silva et al., 2002). These deficits are even more pronounced in patients with AD. In vitro and in vivo investigations in rodents showed that n-3 PUFA supplementation may help restore brain glucose uptake, brain glucose metabolism and prevent cognitive decline with aging (Freemantle et al., 2006; Kitajka et al., 2002; Pifferi et al., 2007, 2010). However, studies led in humans demonstrated controversial results, most of the time failing to demonstrate a protective effect of n-3 PUFA supplementation (Cunnane et al., 2009; Plourde et al., 2007). This highlights the importance of the use of a nonhuman primate model for understanding the mechanisms of n-3 PUFA supplementation during aging.

To our knowledge, only one study aimed to assess the antiaging potential of n-3 PUFAs in gray mouse lemurs (the above-mentioned studies were conducted in young adult animals) (Languille et al., 2012a). Twelve aged females were tested with cognitive tasks before

being divided into the two diets previously described. After 14 weeks of supplementation, the animals underwent the same cognitive tasks again. Unlike what Vinot et al. (2011) demonstrated, and against expectations, cognitive performances did not differ significantly between the two groups, and latency of the first movement in the open field task even increased in animals fed with the tuna oil-based diet. In addition, no differences were found between the two groups in the latency of first entry in the light arm in the light/dark plus-maze task. This parameter is highly correlated with anxiety level, which suggests that the differences in exploratory behavior in the open field task may not have been associated with increased anxiety but possibly with changes in motivation. The effects of the n-3 PUFA supplementation seemed to be dependent on the age at which it occurs, with memory improvement and anxiolytic effects in young adults that were not found in aged animals. These differential effects were also found in rodents and may arise from age-related changes in physiology, such as a longer retaining of the ingested DHA in the blood of older animals, exposing it to higher risks of beta-oxidation and reconversion than in young adults (Plourde et al., 2011). Further investigations are needed to quantify the long-term effects of n-3 PUFA supplementation in aged gray mouse lemurs on cognitive functions, brain glucose metabolism, and brain inflammatory status in relation to neurodegenerative diseases.

5.3 | Effect of caloric restriction

Caloric restriction (CR) is defined as a decrease in energy intake without malnutrition (Yamada et al., 2018). Yet, it is the only non-genetic manipulation that has been proven to extend lifespan and delay age-related pathologies in various species (for review, see Spindler, 2010). In short-lifespan species such as rodents, CR has increased the lifespan by almost 50% while improving health (McCay et al., 1935). Similar results have also been reported in long-lifespan species such as Rhesus monkeys, with also reduction in cerebral atrophy (Colman et al., 2009, 2014; Mattison et al., 2017, 2012). However, the effects on cognition and the underlying mechanisms remain unclear and contradictory. Indeed, CR has improved cognitive performances in mice (Means et al., 1993) while it failed in providing protection against age-related cognitive impairment in rats (Markowska, 1999). Moreover, a CR throughout life even led to cognitive impairments in a spatial discrimination test in aged rats (Yanai et al., 2004), while short-term CRs suppressed the age-related inflammation and oxidative stress increases (10 days) (Jung et al., 2009) and improved memory and learning (6 months) (Fontán-Lozano et al., 2007).

The gray mouse lemur appears to be an interesting model to study the effects of CR on lifespan and cognition since its lifespan (median survival time: 6.4 years) allows longitudinal studies easier than in rhesus monkeys while still being phylogenetically closed to humans (Ezran et al., 2017). In 2006, a large calorie restriction program called *RESTRIKAL* has been initiated on 34 males gray mouse lemurs initially aged 3 years. Calorie-restricted animals were fed 30% fewer calories than their control counterparts with

the same daily mixture and fresh fruits (for detailed protocol see Dal-Pan, Terrien, et al., 2011). This CR has been reflected in the body mass of the animals, stabilizing after 4 years at 28% of the initial body mass in restricted animals. Cognitive, motor performances and metabolic parameters have been investigated all along with the protocol until all the animals died spontaneously. The last gray mouse lemur died in 2017, more than 10 years after the beginning of the program.

CR had a great effect on the survival of the animals. The median survival time (the time at which half of the animals have died) increased by 50% in the restricted group (9.6 vs. 6.4 years in the control group). When all the control animals died, 26% of the restricted animals were still alive. A record in longevity has been reported, since seven restricted animals reached 13 years, while the maximum longevity previously ever reported in the colony was 12 years (Pifferi et al., 2018). The last calorie-restricted animal died at the age of 13.8 years (Pifferi et al., 2019). The investigation of the causes of death showed a lower incidence of cancer and chronic nephritis in restricted animals, which were associated with only 33.3% of the deaths versus 73.3% for the control animals (Pifferi et al., 2018). Such improvements of health associated with CR may be partly explained by a better glucoregulatory function. Indeed, restricted animals after 33 months of treatment displayed faster fasting responses to a glucose load, which was correlated with lower levels of insulinemia, insulin resistance index, and resting metabolic rate (Marchal et al., 2012). Similar results are reported in rodents (Cartee et al., 1994; Masoro, 2000; Reaven et al., 1983), rhesus monkeys (Bodkin et al., 1995; Kemnitz et al., 1994), and humans (Heilbronn et al., 2006).

Regarding the cognitive and motor performances, the results mostly showed no difference between the two diet groups in gray mouse lemurs for this chronic CR. Long-term spatial memory using the Barnes maze task and working memory using the spontaneous alternation task was assessed. The first years of treatment led to a selective enhancement of certain cognitive tasks (working memory was improved after 2 years of CR (Dal-Pan, Pifferi, et al., 2011). In the very long term (up to 6 years of treatment, the time at which the very limited number of control animals did not allow adequate statistical analysis) we observed no effect of CR on cognitive performances (Pifferi et al., 2018). This finding brings some light on the effects of CR on cognitive performances as controversial results were found in various species, from improvements in mice (Means et al., 1993) to impairments in rats (Yanai et al., 2004) and in humans (Dirks & Leeuwenburgh, 2006). The *RESTRIKAL* program demonstrated no alteration of cognitive performances with CR, but no improvement neither. Similarly, no difference was found in long-term motor performances by using the rotating rod task, which is promising with regard to the increased risk of frailty during aging (Le Bourg, 2018; Yamada et al., 2018).

As it has been described in the part entitled “cerebral alterations, metabolism and cellular risk factors of age-related cognitive decline,” aging in gray mouse lemurs has been associated with cerebral atrophy and cognitive impairments (Picq et al., 2012). Similar patterns are

found in other nonhuman primates such as in rhesus monkeys (Shamy et al., 2011), and in humans (Chetelat et al., 2003). However, this atrophy was shown to be reduced in rhesus monkeys under CR, for either gray or white matter. MRI studies along the RESTRIKAL program have led to different results. CR gray mouse lemurs displayed gray matter atrophy for the temporal area and the entorhinal cortex and increased gray matter atrophy in areas that already endure marginal, but significant, age-related atrophy such as the hippocampus (Pifferi et al., 2018). Only very few areas, like the septum and the amygdala, went through gray matter atrophy in control animals. Although temporal area and entorhinal cortex were widely associated with learning and executive functions (Squire et al., 2004), none of these gray matter atrophies are associated with cognitive impairments in this study. Besides, restricted gray mouse lemurs underwent lower white matter atrophy than control animals in the genu, splenium, and corpus callosum. Positive effects of CR on the white matter were similar to those found in mice and rhesus monkeys (Bendlin et al., 2011; Guo et al., 2015).

It might be noted that these effects have been shown for a chronic (over 10 years) and relatively moderate (30%) CR. Among CR studies, the effects vary a lot depending on these two parameters. For instance, an acute (over 19 days) and more severe CR (40%) has been investigated in gray mouse lemurs (Villain et al., 2016). Loss of body mass appeared as soon as the 4th day of treatment and reached a 14.6% loss at the end of the 19th day of treatment. It showed that this energetic challenge led to a general and significantly lower learning performance while the effects on memory recall depended on the metabolism of the individual. Indeed, during the memory test, CR animals showed a particularly high level of interindividual performance variability. It was linked to a significant negative correlation between weight loss and success rate: the individuals with the greatest weight loss (>20% of their initial body weight) were the ones who recalled the worst. It suggests that, if learning is negatively affected by lowered energy supply, long-term memory recall (that reposes on a phase of consolidation; Rasch & Born, 2013) depends more on the individual metabolic capacity to resist food shortage. It has already been suggested that hypoglycemic in rats might induce damages in the hippocampus, a structure involved in the storage and recall of memories (Auer et al., 1984; Won et al., 2012).

CR has been also investigated in humans. Most studies converge on the effects of CR on metabolic health (Heilbronn et al., 2006) supporting what has already been found in animals. However, the effects of CR on cognitive performance are widely disputed. This nutritional intervention may be risky to implement in humans since the long-term effects and underlying mechanisms are quite unclear (Le Bourg & Redman, 2018). It might be even counterproductive in the elderly because of the high incidence of frailty in this population for whom unintentional weight loss could be deleterious (Yamada et al., 2018). CR should be seen as a potential early life intervention to prevent metabolic disorders that occur during aging, in particular, in light of the high prevalence of worldwide obesity which has nearly tripled since 1975 (WHO, 2021). Indeed, a clear link has been established between body mass index in young adults and longevity

and life quality during aging (Stenholm et al., 2017) suggesting that handling the process much earlier in life might be the most relevant way to healthy aging.

5.4 | Maternal effects

Concerning the nutritional antiaging strategies, recent and increasing attention has been given to the long-term effects of the early life features, such as maternal effects, on adult health and longevity. A lot of studies have already assessed the positive impacts of an appropriate maternal uptake of DHA (a long-chain n-3 PUFA) during pregnancy and lactation on infant neurodevelopment, by affecting neurogenesis, brain cells and vascular maturation, glucose uptake, and preventing from oxidative injury and stress in the neural tissues (see Basak et al., 2020 for review). These effects may arise from epigenetic mechanisms such as DNA methylation, histones acetylation, or micro RNA silencing (Indrio et al., 2017; Verduci et al., 2014). However, both the clear mechanisms and the effects of DHA during aging have not been resolved. In addition, the long-term impact of maternal nutrient supplementation on the health and longevity of infants has not been studied so far. In gray mouse lemurs, some studies have been conducted on the heritability of some behavioral and physiological traits (Zablocki-Thomas et al., 2018). The results have brought to light a maternal effect for some of these traits, such as radius length, growth rate, or emergence latencies (the time spent by an animal to come back to its own cage from a wooden box placed in front of it). These traits are susceptible to change with aging, which is called “temporal plasticity” (Zablocki-Thomas et al., 2019). These effects might both be explained by genetics or environment like maternal investment during reproduction and lactation. Yet, to our knowledge, there is no data available on the impact of nutritional strategies implemented during pregnancy as a maternal effect on aging, adult health, and cognitive status in the gray mouse lemur. Further investigations are needed to assess the efficiency of such potential nutritional antiaging strategies.

6 | CONCLUSIONS AND PERSPECTIVES

Besides the interesting notions provided for ecological and evolutionary fields from an adaptative point of view, all the knowledge accumulated on mouse lemur brain aging sheds light on the very striking similarities between human and gray mouse lemur aging processes. Indeed, both species seem to display very similar patterns of age-related cognitive impairments and the brain alterations associated with (Bertrand et al., 2013; Dhenain et al., 1998). More interestingly, they share the large individual variability found for many alterations with aging (Joly et al., 2014, 2006; Picq, 2007; Valdois et al., 1990; Ylikoski, 1999), that might help differentiate mild cognitive impairments during normal aging from severe cognitive impairments associated with pathological aging. Investigating such a differential path might help to identify behavioral, cellular, and

molecular biomarkers of pathological aging, and the associated risk factors. Understanding why a given nutritional antiaging strategy seems to work only for some categories of individuals, or for a specific time frame, will help to decipher some aging pathways that are still undiscovered or unsolved.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Yohann Chaudron: Conceptualization (supporting); writing original draft (lead); writing—review and editing (supporting). **Fabien Pifferi:** Conceptualization (equal); writing original draft (supporting); writing—review and editing (supporting). **Fabienne Aujard:** Conceptualization (equal); writing original draft (supporting); writing—review and editing (lead).

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