



The aging mouse brain: cognition, connectivity and calcium

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ABSTRACT

Aging is a complex process that differentially impacts multiple cognitive, sensory, neuronal and molecular processes. Technological innovations now allow for parallel investigation of neuronal circuit function, structure and molecular composition in the brain of awake behaving adult mice. Thus, mice have become a critical tool to better understand how aging impacts the brain. However, a more granular systems-based approach, which considers the impact of age on key features relating to neural processing, is required. Here, we review evidence probing the impact of age on the mouse brain. We focus on a range of processes relating to neuronal function, including cognitive abilities, sensory systems, synaptic plasticity and calcium regulation. Across many systems, we find evidence for prominent age-related dysregulation even before 12 months of age, suggesting that emerging age-related alterations can manifest by late adulthood. However, we also find reports suggesting that some processes are remarkably resilient to aging. The evidence suggests that aging does not drive a parallel, linear dysregulation of all systems, but instead impacts some processes earlier, and more severely, than others. We propose that capturing the more fine-scale emerging features of age-related vulnerability and resilience may provide better opportunities for the rejuvenation of the aged brain.

1. Introduction

Global life expectancy has grown at a rate of ~3 years per decade since the 1950s leading to an increased number of people suffering from age-related comorbidities and driving up the cost of healthcare for the elderly population [1–3]. According to the latest United Nations global population review, by 2050, one in four people living in Europe or the United States will be aged 65 or over, while the number of people over 80 will triple globally [4]. These statistics emphasise the pressing importance of understanding the impact of aging on molecular, cellular and systems level processes. Mice are a particularly convenient species to study aging as they are mammals with a relatively short lifespan and are amenable to targeted genetic manipulation. Furthermore, the inclusion of aged animals in preclinical studies is critical for translational validity [5]. Technological developments now allow for longitudinal imaging of neuronal activity in awake behaving animals [6,7], enabling better understanding of how age impacts neuronal circuit function [8]. Yet, there is still much to learn about how aging impacts the brain. For example, relatively little is currently known about how aging affects

different cell-types or synaptic plasticity processes [9–11].

The comparison of aging stages between mouse and human has been broadly agreed upon [12]. Numerous developmental studies have now established that mice up to 1 month of age are juvenile [13]; between 3 to 6 months mice are typically classified as young adults, while animals aged 14 to 24+ months are often pooled together in the single category of ‘old’ [12]. Most research on aging has focused on comparing ‘young’ and ‘old’ age groups, with far less interest given to finer timescales at which changes emerge across lifespan. This topic is an important issue since understanding the very earliest stages of senescence may allow for the development of targeted approaches that can slow the negative impact of aging, or even rejuvenate function [14,15]. Here, we argue for a more granular systems-based definition of aging in mice that considers the impact of age on key features relating to neural processing. Specifically, we have summarised the available evidence of age-dependent changes in behavioural, sensory, synaptic and molecular processes in mice (see Table 2). In this overview of age-related changes in typical inbred strains of laboratory mouse *Mus musculus*, we define mouse ages as follows: juvenile (up to 1 month of age); young adult (1–4 months);

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Table 1
Mouse age categories as defined in the current review.

Age bands (months)	Age categories
< 1 m	juvenile
1–4 m	young adult
4–10 m	mature adult
10–14 m	late adult
14–24 m	old
> 24 m	senescent

mature adult (4–10 months); late adult (10–14 months); old (14–24 months); senescent (over 24 months) (see Table 1). Throughout this review, we refer to our defined age categories, together with the exact age range of the mice used in the relevant study given in brackets.

2. Age-related changes in behaviour

Progressively increasing motor deficits and cognitive impairments are among the most evident indicators of aging in elderly individuals [16,17]. In humans, age-related mobility changes are reflected in slower walking speed, shorter steps, decreased stride length, and increased step and stride times [18]. Cognitive skills are characterised by distinct trajectories of age-related decline, and this decline is not universal between cognitive domains [19]. Processing speed, divided attention, spontaneous retrieval of information, and response inhibition are more severely affected, while recognition and procedural memory are more resilient [20,21]. In this section, we consider and compare the time scales of age-related changes in motor function and cognition in mice.

2.1. Motor functions

Age-related mobility deficits are a common feature in both humans and rodents [18]. Old mice (>18 m) of various strains (C57BL/6 J, DBA/2 J, A/J and 129/SvJ) have been shown to exhibit substantially lower levels of locomotor activity in the open field than young or mature adults (≤ 6 m) [22–30]. Several studies have detected the emergence of locomotor deficits by 6 to 12 months of age [31–35]. In contrast, others have reported a bell-shaped relationship between locomotor activity and age. Late/old adults (10.5–17 m) have been shown to travel longer distances in the open field compared to both young (3–5 m) and old/senescent (18–25 m) animals [36,37]. Interestingly, older mice travel shorter distances than young ones during the first 5 minutes of the test, with age-related differences becoming less pronounced across longer periods of testing (120 min) [35,38]. This suggests higher anxiety levels in older animals when initially exposed to a novel environment, rather than locomotion deficits [35]. Discrepancies in these findings may partly be explained by differences in analytical approaches used to interpret the data, for example, the time window over which behavioural performance was examined.

Gait analyses and rotarod tests have uncovered more robust age-related changes than open field behavioural measures. Mice have been shown to exhibit translational alterations of gait and posture by late adulthood (10 m) [39]. These include, decreased gait speed, cadence, stride length and swing speed in older age [39–42]. Balance and motor learning are traditionally measured using the rotarod test, where mice are placed on a rotating beam and must make co-ordinated steps to avoid falling. Thus, the rotarod test can identify age-related coordination deficits, hindered motor learning, or altered long-term retention of motor skills. Older mice show coordination deficits, such as shorter latency to fall and slower learning rates [23,33,35,43–46, although see 27, 47]. Some age-related deficits in motor learning are apparent at 11–13 months of age [38,45,46], or even earlier, at 4–8 months of age [33,35,44,47]. Altogether, these studies demonstrate that subtle age-related alterations in gait, balance and motor learning can be identified by mature and late adulthood.

2.2. Cognition

Several tests developed to assess cognitive abilities in rodents have been successfully employed in the evaluation of age-related effects [48, 49]. Two popular assays of cognition developed in the 1980s have since been used in numerous studies to examine avoidance memory retention, and spatial learning and memory. The passive avoidance test is used as a measure of associative hippocampal contextual memory and amygdala-dependent emotional memory [50]. In this test, mice are placed into an operant chamber with a lit and a dark compartment. During the training trial, mice receive a mild electric shock in the dark compartment. As a result, on the test trial their natural preference for the dark compartment is suppressed. The latency to the first entry in the dark compartment is used as a measure of memory retention [50]. Early studies have established that age negatively affects passive avoidance retention indicating a loss of memory of adverse experience. Deficits have been identified in several strains (C57BL/6 J, C57BL/6 J $\times$ C3H/J hybrids, NMRI and Swiss mice) starting from late adulthood (12–13 m), continuing across old age (23 m), and into senescence (31 m) [29,32,34, 51,52, although see 53]. However, more recent data have suggested that, while old female mice showed a decline in this type of retention memory, old male mice did not exhibit a similar deficit [36]. Notably, juvenile mice (< 1 m) have been shown to exhibit inferior retention to young adults (3.5 m), which may be attributed to insufficient neuronal maturity [54]. These findings suggest that avoidance memory develops from juvenility, peaking in young adulthood, after which it undergoes an age-related decline, the rate of which may be sex dependent.

Spatial learning skills in mice have often been examined using the Morris water maze (MWM) [55]. This test examines the ability of animals placed in a pool of opaque water to locate a hidden escape platform by using visual cues around the pool. Most studies that have explored the relationship between age and learning in the water maze have found spatial learning deficits in old and senescent mice when compared to young adult animals. Such impairments were reported in C57BL/6 [36, 37,56–60], 129/SvJ [26,61], NMRI [62], and CD1 mice [63]. The earliest deficits were described in late adulthood and the early stages of old age, at 11 months in NMRI mice [62], 13 months in CD1 mice [64], and 13–15 months in C57BL/6 J mice [57,58,65]. These lines of evidence suggest the presence of considerable deficits in spatial learning and memory retention in old and senescent mice. Some of these impairments have been shown to emerge as early as late adulthood (11–12 m), but it should be noted that very few studies examined performance between 5 and 10 months of age. Hence, it cannot be excluded that certain deficits may arise even earlier, as it has been identified for motor coordination learning [35,47].

With the development of new technologies, distinct types of learning and memory can be investigated by employing touchscreen devices in which mice interact with visual stimuli on a touch-sensitive screen in exchange for nutritional reward [66–69]. As this method is relatively new, evidence about age-related changes of performance in touchscreen tasks is scarce. However, one study using touchscreen testing has investigated the effects of aging on visual discrimination, spatial reversal, and automated searching [70]. This work has found that C57BL/6 J male mice become incrementally worse with age, with clear deficits evident at 17 m [70]. Touchscreen based testing can assess both executive function (such as working memory, pattern separation and cognitive flexibility), as well as long-term memory retention. Additionally, these tests have higher reliability and translational relevance from rodents and primates to humans, for example, they are similar to the human CANTAB (Cambridge Neuropsychological Test Automated Battery) tests [70–74]. Since touchscreen protocols are automated and standardised, open-access platforms, such as MouseBytes, could allow for future comparisons of multiple datasets across laboratories [75], and should help clarify the effects of age on various cognitive parameters.

Table 2

Age and direction of the earliest changes in physiological and biochemical parameters in older compared to young adult mice. Directions of significant changes in various physiological parameters are presented as ↓ (decrease) or ↑ (increase) compared to the respective values in young adult (1–4 months) mice. For studies where mice displayed alterations at multiple older ages, only one (the earliest) age at which statistically significant changes were reported is included below. Corresponding references are indicated in brackets.

Physiological parameter	Mature adult (4–10 m)	Late adult (10–14 m)	Old (14–24 m)	Senescent (>24 m)
Behaviour				
Locomotion	↓ [32,34,35]	↓ [30,31,33]; ↑ [36]	↓ [24,27,38,43,110]; ↑ [37]	↓ [23]
Gait coordination / balance	↓ [33,35,39,43,44,47]	↓ [38,46]	↓ [24,42]; ↑ [27]	↓ [23]
Passive avoidance latency	↓ [62]	↓ [34,51]	↓ [32,36,52,110]	
MWM latency / distance to platform	↑ [34]	↑ [57,62,65]	↑ [36,56,60,110]	
Touchscreen task (% correct)			↓ [70]	
Sensory				
Hearing (ABR threshold)	↑ [79–82]			
Vision (acuity / retinogram amplitude)	↓ [90]		↓ [85]	
Olfaction (odour discrimination)			↓ [99–101]	
Taste responsiveness			↓ [104]	↓ [106]
Touch (sensitivity)		↑ [31]	↑ [38]; ↓ [110,111]	
Neural circuitry				
Long-term potentiation	↓ [161]; ↑ [185]	↓ [154,162]	↓ [151,160]	↓ [163,164]
fEPSP amp / slope		↓ [154]	↑ [153]	↓ [164]
Paired-pulse ratio			↓ [151,153]	
GluN1/2B mRNA / protein	↓ [188]	↓ [189,195]; ↑ [196]		↓ [186,187,193,194,196]
AMPA receptor			↓ [205]	↓ [204]
Hyperexcitability		↑ [8,71]	↑ [149]	
PSD-95 expression		↓ [130]	↓ [205]	
Synaptophysin expression		↓ [196,283,284]		
Synapse density		↓ [130]	↓ [274]	
Synapse size		↑ [130]	↑ [274,279,280]	
Calcium				
Basal neuronal [Ca ²⁺] _i		↑ [221]		↑ [313]; ↓ [312,315,316]
Evoked neuronal [Ca ²⁺] _i transients			↓ [314,318]	↓ [312,313,316]
Evoked / spontaneous astrocyte [Ca ²⁺] _i transients	↓ [372]	↓ [370]		
Spontaneous microglia [Ca ²⁺] _i transients		↑ [378]		
Myelin fibres / internodes	↓ [65]		↓ [395]	
Inflammaging				
Inflammatory cytokines and reactive glia	↑ [258]		↑ [342,343]	

2.3. Summary

Studies on motor function and cognitive skills in mice have demonstrated distinct trajectories of age-related decline (see Table 2). Motor learning and balance are affected already in mature adult mice (4–8 m), whereas gait and posture begin to decline only from late adulthood (10 m) onwards (see Section 2.1). Classic assays of cognition have shown that both spatial learning and memory, and avoidance memory, begin to decline from late adulthood. Touchscreen testing, although in its infancy, is a promising tool to assess the impact of age on different cognitive domains (see Section 2.2).

3. Age-related changes in sensory functions

Mice develop a range of age-related sensory deficits across adulthood. The exact timeline over which these deficits arise, and their severity, vary between sensory modalities. Understanding the emergence of deficits within individual senses, as well as the interaction across sensory modalities, offers the potential to develop novel interventions for the rejuvenation of sensory systems in later life. Below, we summarise evidence for age-related changes in the five major senses in C57Bl/6 J mice and other commonly used laboratory mouse strains.

3.1. Hearing

With an estimated 900 million people in the world affected, hearing loss is the most common age-related sensory deficit in the elderly and the fourth highest cause of disability globally [76]. Mice are a popular animal model for studying the effects of aging on hearing [77]. Several mouse strains are susceptible to relatively early hearing loss, including the widely used C57Bl/6 J strain, which carries the hearing loss susceptibility allele *Cdh23*^{ah1} [78]. Measurements of the auditory brainstem response (ABR), an electrical activity pattern reflecting activation of auditory pathway components, have shown a gradual linear increase in the ABR threshold from 1 month up to around 8–9 months of age in C57Bl/6 J mice [79]. Additionally, impairments in hearing socially relevant vocalizations (>32 kHz) have been detected around 5 months of age [80]. From 8–9 months onward, hearing loss has been found to accelerate, suggesting a biphasic process of age-related hearing impairments in this strain [79,81,82]. The estimated transition point from the first gradual phase of hearing loss to the second accelerated phase varies from as early as 9 months to as late as 12 months [79]. Such inter-animal variability has been reported by others, making it challenging to map the fine-scale time-course of these changes [79,82]. However, taken together, the current work suggests that in C57Bl/6 J mice, a prominent phase of accelerated hearing deficits emerges around late adulthood, between 10–12 months of age [77,79,81,82]. In contrast to the relatively steep hearing loss observed in the C57Bl/6 J strain, the CBA strain retain good hearing up until 18 months of age: 1-, 6-, 12- and 18-month old mice were shown to have very similar ABR thresholds and hear sound frequencies below 16 kHz [82]. However, from 6 months of age, CBA mice displayed decreased sensitivity to high-frequency sounds (31.5 kHz), and from 18 months of age, sensitivity to all frequencies drops rapidly [82]. These observations suggest that CBA mice may be a better model of normal age-related hearing loss, as hearing deficits in this strain develop more gradually than in C57Bl/6 J mice, although in both strains, impairments in the sensitivity to high-frequency sounds (>10 kHz) precede more global hearing loss.

3.2. Vision

In humans, visual acuity is known to decline in later life [83]. Mice also experience age-related decline in visual functions, such as decreased acuity and impaired contrast sensitivity, which are driven by both deficits specific to the retina and changes in visual neuronal pathways [84]. Several studies have attempted to define the time-course

of age-related visual acuity changes in C57Bl/6 J mice. Measurements of the innate optomotor response to moving gratings found visual acuity was relatively stable up until 12 months of age, but showed a decline from that age onward [85]. An earlier decline in visual acuity, between 6 and 12 months, has been shown using a similar experimental approach in C57Bl/6 J and DBA/2 J mice, with larger impairments in the latter strain due to age-related glaucoma [86]. The discrepancy between the ages at which visual acuity deficits emerged in those two studies could be explained by a range of factors, including the potential for inter-animal variability, or plasticity relating to the individual experience of the animal. For example, rodent visual acuity has been shown to exhibit a degree of plasticity in response to training [87], and food restriction [88]. At the level of the retina, rod- and cone-mediated electroretinograms of young (1–2 m), mature adult (4–6 m) and late adult/old (12–17 m) C57Bl/6 J mice display similar shapes, but with progressively decreasing amplitudes [89–91]. These studies have concluded that the decline of electroretinogram $V_{\max}$ values could not be accounted for by comparable decreases in densities of rods and cones, or opsin gene transcription levels. Therefore, it is plausible that $V_{\max}$ decline could be mediated by age-related decreases in photoreceptor transduction efficiency [91]. Taken together, these results suggest that visual deficits in C57Bl/6 J mice begin to emerge between 6 and 12 months of age, becoming more pronounced during old age.

3.3. Olfaction

Population studies have identified that olfactory dysfunction increases with age, and clinically healthy individuals with impaired olfaction are more likely to develop cognitive decline [92–94]. In mice, age-related changes in olfactory function have been assessed by measuring odour sensitivity, habituation and discrimination. Novel odour investigation behaviour and olfactory habituation were found not to substantially vary with age across multiple age points between 2 and 12 months in C57Bl/6 J mice [95], and between 3–4 and 21–29 months in C57Bl/6 J / SJL F1 mice [96]. In agreement with these results, no differences in the duration of novel odour exploration were noted between mature adult C57Bl/6 J mice (9 m), or late adult C57Bl/6 J $\times$ C3H F1 mice (13 m), and their young adult (3–4 m) counterparts [97,98]. The ability to discriminate between different odours was also relatively stable in mice across the period covering young (2–4 m) to late adulthood (12–13 m) in these studies [95,98]. These findings suggest that olfactory function is essentially intact in mice at least until late adulthood. However, the emergence of age-related olfactory deficits was described in older mice. For example, although, the sensitivity to odours was similar between mature (5 m), old (17 m) and senescent (25–26 m) C57Bl/6 NIA mice, the accuracy of odour discrimination in the two older groups was lower than in mature adult animals [37]. Breakdown of olfactory discrimination learning in senescence was demonstrated in another report that compared performance of 24-month-old C57Bl/6 J mice with young adult counterparts (4 m) in an olfactory learning task [99]. Other studies have revealed more subtle age-related alterations in olfaction. For example, old (18 m) and senescent (24 m) mice were found to be impaired in the ability to discriminate mixtures of two discrete odours, and struggle to differentiate between two similar odours upon repetitive exposure, when compared to young adults (2 m) [100,101]. However, odour habituation and basic discrimination were similar in these groups [100,101]. This suggests that sensory perceptual learning, rather than discrimination ability, may decline with age [101]. Several structural changes in the mouse olfactory system may underlie age-dependent alterations in olfaction. Morphometric measurements at several age points, from young adulthood (2 m) to old age (24 m) have demonstrated that the densities of projection neurons and interneurons in the olfactory bulb were stable, while total synapse density at the glomerular level declined linearly with age [102]. In addition, the density of various olfactory sensory neurons exhibited diverse lifespan trajectories depending on the type of olfactory

receptor they express. Age-related changes in olfaction may also be mediated by alterations in the piriform cortex [103]. In this region, spontaneous excitatory postsynaptic currents recorded *ex vivo* have been found to be smaller in neurons from senescent (24–28 m) compared to mature adult (6 m) C57Bl/6 J mice [103]. Overall, studies of mouse olfactory system have demonstrated that, despite some structural changes in the olfactory bulb, olfaction is not markedly affected before late adulthood (~12 m), and only begins to deteriorate in old age (>18 m). This resilience to age-related impairment is perhaps explained by the utmost importance of this sense for rodents.

3.4. Taste

Taste sensitivity in humans declines with age, although not as steeply as olfactory function [92]. An early report in mice has demonstrated that senescent (>26 m) animals discriminated sucrose and quinine solutions less efficiently than mature (5 m) animals [25]. More recent work has supported these early findings, and found that a change in the preference for sweet taste emerges in late adulthood, between 10–18 months of age, but this occurred in the absence of changes in other taste preferences [104]. Another study performed in young/mature (2–6 m) and senescent (30–35 m) C57Bl/6 J mice found decreased sensitivity to salty and bitter tastes in aged animals [105]. In contrast to these findings, a detailed set of experiments found age to have very little impact on the preference of C57Bl/6 J and 129 $\times$ 1/SvJ mice for solutions with five primary tastes (salty, sweet, bitter, sour, and umami), or ethanol [106]. Young adult mice (1 m) of both strains showed a relatively stronger preference for umami taste, whereas preference for the acidic and ethanol tastes were lower. However, after 1.5 months of age, there were no progressive, age-related changes in the preference for any taste until late adulthood (11–12 m) [106]. The only exception was senescent 129 $\times$ 1/SvJ mice (~29 m) that showed lower preference for umami-tasting inosine monophosphate [106]. These findings suggest that, except for subtle changes to sensitivity for certain tastes in senescent animals (>26 m), taste sensitivity in mice is generally resilient to aging.

3.5. Touch

Tactile sensitivity declines in the elderly due to skin thinning and a reduction in skin elasticity [107]. Age-related somatosensory findings in mice have been largely obtained from studies of cutaneous sensory thresholds to painful stimulation. Several studies have found heat and mechanical sensitivity remain fairly unchanged between 2 and 31 months of age in C57Bl/6 J mice [23,32,35,108]. A recent study comparing latency to paw lick, or foot shake, in the hot plate test across several age points, has found that young adults (3 m) responded with a longer latency than old (23 m) C57Bl/6 J mice, indicating augmented pain sensitivity with age [38]. Similar age-dependent increases in heat sensitivity were also observed between young (4 m), late adult (11 m), and senescent (24 m) 129 Sv/Ev mice [31], as well as between young (3 m), mature (5 m) and old (19–21 m) BALB/c mice [109]. In contrast, several studies have reported the opposite relationship, specifically lower heat sensitivity in old (>18 m) compared to young adult (1.5–2 m) mice [110,111]. In line with such observations, local pressure-induced vasodilation was lower in old (22–25 m) than in mature adult (6–7 m) C57Bl/6 J mice [112]. Disagreements regarding the direction of changes in sensory thresholds to adverse stimuli in mice resembles similar discrepancies in rat studies. A recent review of 25 rodent reports (predominantly on rats) published between 1981 and 2009 has indicated that pain sensitivity, gauged by reflex-based behavioural responses, showed decreased sensitivity (9/25), increased sensitivity (12/25), or no changes in sensitivity (4/25) with advancing age [113]. The likely factors contributing to these discrepancies are variations in the experimental protocols, housing conditions, species, strains and ages of the animals [108,113]. In such circumstances, establishing with certainty

the time-course of age-related changes in somatosensory sensitivity in mice is problematic. Perhaps future studies in mice may explore age-dependent aspects of whisker sensitivity [114], while drawing on the rich literature of approaches used to measure whisker discrimination capabilities in rats [115–118]. At present, the available body of evidence suggests that somatosensory sensitivity in mice does not exhibit a clear age-dependent decline.

3.6. Summary

Taken together, the findings discussed above reveal varying degrees and distinct trajectories of age-related changes across sensory modalities (see Table 2). Studies of the auditory, visual, olfactory and gustatory functions generally succeed in mapping emerging age-related changes in these sensory systems. However, much less is known about age-related changes in the somatosensory system. Further experiments are required to tie down the exact time-course of changes across multiple sensory modalities, however, the work summarised here suggests that emerging age-related deficits may be reliably detected by mature adulthood, between 6 and 12 months of age, in the auditory and visual systems, whilst gustation and olfaction appear to be more resilient up until late adulthood (~12 m).

4. Age-dependent changes in synaptic properties

The adult brain can dynamically adapt to a range of externally driven activity patterns during lifetime [119–123]. Distinguishing between natural age-related adaptive responses and heightened vulnerability *per se* is becoming increasingly important in a growing aging population [124]. Behavioural, cognitive and sensory decline linked to aging were thought to be associated with the loss of neurons and their processes, however, more recent stereological studies suggest this loss is minimal [125–127]. The focus has shifted instead to changes in the plasticity of synaptic contacts between neurons and the interaction with glial cells [127,128]. Synapses are highly dynamic and can adjust their molecular composition and structural configuration throughout their lifetime [129,130]. Synapses can be eliminated, or formed, thereby modifying neuronal circuit connectivity and potentially impacting memory formation, encoding, or consolidation [131,132,132–136]. The functional strength of synapses can be modulated through changes at the pre- and/or postsynaptic compartments [6,135,137–139]. In the broadest sense, synaptic plasticity is often considered to come in two flavours, Hebbian and homeostatic [139,140]. Hebbian plasticity is synapse-specific, modulated by correlated pre- and postsynaptic activity, and thought to underpin learning and memory [141,142]. In contrast, homeostatic plasticity occurs more broadly across populations of synapses and is thought to prevent extreme levels of neuronal hyper- or hypoactivity [140,143,144]. Multiple lines of evidence indicate that the expression of Hebbian-like synaptic plasticity changes with age, and this is often examined through the induction of long-term potentiation or depression (LTP/LTD), i.e. sustained increases or decreases in synaptic strength reported by measures of field excitatory postsynaptic potentials (fEPSPs), or excitatory postsynaptic currents/potentials (EPSC/Ps), following certain stimulation patterns [145–148]. In contrast, our understanding of age-related changes in homeostatic plasticity is less developed. However, a number of recent studies have found evidence for an age-related emergence of neuronal hyperactivity [8,149], suggesting that homeostatic control of neuronal firing rate may begin to fail in later life [143]. In the following section, we focus on studies that reveal age-related disturbances of Hebbian plasticity and glutamate receptors, the emergence of hyperexcitable networks, alterations in mechanisms that may affect homeostatic plasticity, and finally, changes at pre- and postsynaptic compartments in the aging mouse brain.

4.1. Age-related alterations in Hebbian plasticity

Rodent aging is associated with alterations in both short- and long-term synaptic plasticity, with changes emerging in the hippocampus in mature and late adult (6–12 m) animals [150–154]. The hippocampal trisynaptic dentate gyrus (DG)-CA3-CA1 circuit and its connections with the entorhinal cortex (EC) play a key role in spatial navigation and episodic memory [155–157]. Normal and pathological aging affects the connectivity and integrity of these networks [150,155–158]. Several electrical stimulation protocols inducing hippocampal LTP in the young mouse were found to have less, or no efficacy in the aged mouse, suggesting age-dependent disruptions in multiple forms of LTP [153,154, 159–164]. The incidence and magnitude of evoked LTP in the CA1 region of the hippocampus was found to decrease with age when measured in young (2–3 m), mature (6 m), late adult (12 m), old (18 m) and senescent (30 m) mice [153,160]. In contrast, others reported evoked CA1 LTP to be similar in young/mature (3–6 m), old (22–24 m) and senescent (24–28 m) mice [165]. However, the latter study also found that aged mice may exhibit deficits in adrenergic and cholinergic facilitation of LTP [165]. Potential explanations for the contrasting results could be the stimulation of different CA3 Schaffer collaterals, known to be molecularly and functionally heterogeneous [166], or the application of different stimulation protocols. Another hippocampal pathway where LTP exhibits age-related alterations is the perforant path that connects the EC with the DG. This pathway has a key role in encoding, retrieval and discrimination of episodic memories [167–169]. The medial and lateral perforant path fibres to the DG originate from different parts of the EC and vary in the spatiotemporal information they carry. The medial path operates on the order of seconds and is associated with spatial encoding, while the lateral path is associated with slower and non-spatial information [167,169]. Deficits in LTP evoked by stimulation of the medial perforant path have been observed in mature and late adult (9–12 m) mice [154]. However, LTP evoked by stimulation of the lateral perforant path was preserved, with only a subtle decline emerging from late adulthood onwards (12–25 m) [151]. The observation that the medial path is affected at an earlier age compared to the lateral path is consistent with deficits in hippocampal-based spatial memory being an early feature of aging in mice [157]. Together, these findings suggest that long-term plasticity may show pathway-specific vulnerability to aging, with the earliest changes identified in late adults (9–12 m) in the EC-hippocampal circuits [153,154]. In humans, non-invasive methods have allowed some level of translation of Hebbian plasticity findings from rodents [170–172]. When compared to young adults, aged individuals were found to have decreased LTP-like response in the motor cortex [173,174], and an age-related shift in the threshold for LTP in the visual cortex [175]. Although some of these studies are consistent with findings from rodent experiments, the nature of the available experimental techniques limits access to deep brain regions that are closely linked to early decline during healthy and pathological aging. Future work may attempt to use non-invasive deep brain stimulation to probe the plasticity of deeper structures in the human [176].

4.2. Age-dependent changes in glutamate receptors

Induction and maintenance of LTP at hippocampal CA3-CA1 synapses requires the activation of N-methyl-D-aspartic acid receptor (NMDARs) and rapid recruitment of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) subunits [177–180]. Thus, some age-related changes in hippocampal plasticity might be explained by alterations in the expression, or trafficking of distinct NMDAR or AMPAR subunits [181–184]. For example, the magnitude of the late-phase NMDAR-dependent LTP has been found to increase in the CA1 of late adult and old (12–18 m) mice [185]. However, age-related alterations of glutamate receptors subunits are not specific to the hippocampus, and have also been identified in cortical, striatal and midbrain regions [186–189]. NMDARs are composed of subunits

belonging to three families (GluN1–3) [190], and represent a major route of Ca^{2+} entry into neurons [191,192]. The GluN2B subunit is the most affected by age in the mouse brain at both mRNA and protein levels [183]. GluN2B levels have been shown to decline in several cortical regions, the hippocampus, and the caudate nucleus in late adult (11 m) and old/senescent (24–30 m) mice [186–188,193–195]. The GluN1 subunit is also affected by aging, but at a later stage than GluN2B in some brain regions. Both mRNA and protein levels of GluN1 have been shown to decrease in the hippocampus, cortex and striatum of senescent (26–30 m) mice [186,187,196], while a decline in the inferior colliculus has been observed in late adult (11–15 m) mice [189]. However, in the frontal cortex GluN1 mRNA levels have been found to remain constant from juvenility to senescence [188,195, although see 186]. Some functional changes may accompany the age-related alterations in NMDAR expression. Although most NMDAR mediated synaptic current kinetics remained unchanged in both CA1 and cortical neurons [197–200], the rate of deactivation of these currents increased with aging [199], which is consistent with lower levels of GluN2B [183]. Specifically, deactivation rates of NMDAR evoked currents were faster in acutely isolated cortical neurons of late adult (10 m), and senescent (24 m) mice compared to young adult (3 m) mice [199]. These findings suggest that some NMDAR subunits are more susceptible to age-related changes than others, and the decline may emerge in late adulthood (10–15 m). Additional studies assessing NMDAR subunit interactions in the aging mouse brain are required to draw firm conclusions about their contribution to age-related changes in plasticity [193].

AMPA is a ligand-gated ion channel composed of a combination of four subunits (GluA1–4) [201–203]. Altered AMPAR expression or function could also contribute to age-related changes in Hebbian [182], but also homeostatic plasticity (see Section 4.4). Reduced AMPAR expression levels have been identified in senescent mice (25 m) in the CA1 region [204]. Old (17 m) mice showed a drastic decrease in AMPAR-GluA2 subunit expression in the hippocampus, as measured by both mRNA and protein assays, relative to that in mature adult (5 m) mice [205]. This reduction was accompanied by a decrease in the PDZ-domain scaffold protein, postsynaptic density protein 95 (PSD-95), and in the protein interacting with C-kinase 1 (PICK1), while levels of transmembrane regulatory protein, stargazin, increased in the old brain [205]. An imbalance in the levels of AMPAR stabilization and trafficking proteins may lead to impediments in LTP induction in aged animals [206]. Consistent with some findings in the hippocampus, the amplitude of AMPAR-mediated synaptic currents was reduced in the anterior piriform cortex of senescent mice (24–28 m), suggesting potential loss of synaptic AMPAR expression [103]. Altogether, studies investigating glutamate receptor subunit alterations with aging suggest the emergence of age-related decline in specific subunits in late adulthood (10–14 m) across several brain regions. An imbalance in these subunits could impact several forms of synaptic plasticity and stability, however, the underlying molecular mechanisms and age when these alterations may occur are currently unclear.

4.3. Increased hyperexcitability and reduced gamma oscillations power with aging

Normal and pathological aging have recently been associated with increased incidence of subclinical epileptiform activity in the aged human brain [207–209]. Increased hyperactivity, together with disturbed neuronal firing homeostasis, may be contributing factors in the early stages of Alzheimer's Disease (AD) progression [143, 210–212]. Age-related neuronal hyperexcitability has also been identified in cortical [8] and hippocampal neurons of the mouse brain [71, 149,213], as well as in the brain of other species [214–219]. Frequent large amplitude electroencephalogram (EEG) spike waveforms, suggestive of hyperexcitable networks, were present in hippocampal and cortical regions of old (16–18 m) mice [149]. The incidence of such large amplitude events gradually increased into senescence (24–28 m), while

similar waveforms were rare in young adult (3–5 m) animals [149]. *In vivo* Ca^{2+} imaging of excitatory layer 2/3 neurons in the frontal cortex identified a greater fraction of hyperactive cells in late adult (10–14 m) compared to mature adult (6 m) animals [8]. These studies suggest the emergence of hyperactivity in both cortical and hippocampal networks from 10 months of age. Age-dependent hyperexcitability could occur through Ca^{2+} dysregulation [8,220,221], or alterations of presynaptic processes involving glutamate release [71]. For example, intracellular Ca^{2+} stores, critical for proper compartmentalisation of dendritic Ca^{2+} signals, were shown to be dysfunctional specifically in hyperactive neurons [8].

An alternative explanation for age-related increases in network hyperexcitability could be alterations to the γ -aminobutyric acid (GABA)-ergic circuitry, with consequences on the excitatory to inhibitory (E:I) balance [222,223]. For example, the increased number of EEG spikes observed in old and senescent mice was suppressed by pharmacological enhancement of inhibition [149]. There is evidence for alterations in interneuron morphology and gene expression in the aging brain of humans and rodents, although findings are not consistent across brain regions and species [224–227]. Less equivocal evidence of age-related changes exists for parvalbumin (PV) expressing interneurons, which have a well-established role in modulating gamma oscillations [228–230]. Most cortical regions in late adult (12 m) mice showed decreased expression levels of PV [231], while senescent (24 m) mice had reduced Ca^{2+} signalling in PV perisomatic boutons and their targets [232]. Accompanying these changes, age-related reductions in gamma oscillation power have been found in the mouse CA3 region of the hippocampus and in layers 2–4 of the somatosensory cortex [232–234]. Interestingly, increasing gamma oscillations through genetic modification of Nav1.1 expression in PV cells reduced epileptiform activity in a mouse model of AD [235]. Understanding age-related changes in gamma oscillations is important, as reduced power of these oscillations has been found not only in aged and AD mouse models, but also in elderly humans and AD patients [235–241]. These recent studies suggest a connection between age-related alterations in neuronal network hyperactivity, interneuron function and gamma oscillations. One potential cause for this amalgam of disruptions could be failure of homeostatic control [210].

4.4. Age-related alterations that may affect homeostatic plasticity

Homeostatic regulation of neuronal firing rate is thought to prevent extreme levels of spiking activity and is, therefore, a critical feature of stable neuronal circuit function [140]. Despite accumulating evidence for hyperexcitable networks, during both normal and pathological aging (see Section 4.3), very little is known about age-associated effects on homeostatic control of neuronal firing rate. There is, however, some evidence of age-related alterations in processes which also play a role in homeostatic plasticity.

Synaptic scaling and maintenance of excitatory to inhibitory (E:I) balance are well-established homeostatic plasticity mechanisms in the young adult mouse [6,139,140,144,242,243]. Synaptic scaling involves alterations of synaptic strength by changes in postsynaptic AMPARs, including at the level of protein expression and interactions, subunit composition, and post-translational modifications [244–246]. PSD-95 is bidirectionally regulated during homeostatic scaling and plays a critical role in stabilizing AMPARs in mature neurons [247–249]. In the old (17–18 m) mouse brain, PSD-95 is downregulated [130,205,250], while knockdown of PSD-95 affects both synaptic up- and downscaling [251]. Thus, one possibility is that decreased PSD-95 levels in the old brain may impact bidirectional homeostatic scaling. Stargazin, an auxiliary AMPAR subunit, is also involved in the mediation of both synaptic up- and downscaling through phosphorylation and dephosphorylation, respectively [252,253]. In the young adult brain, increased stargazin expression and decreased PICK1 (a binding partner of the AMPAR-GluA2 subunit) activity are involved in the mediation of

synaptic upscaling [252,254,255]. However, in the old brain (17 m) stargazin is upregulated, while PICK1 is downregulated [205]. Hence, high basal levels of stargazin and low levels of PICK1 may lead to changes in AMPAR subunit composition and elevated basal AMPAR-mediated mEPSC amplitudes, obscuring the induction of upscaling [244,251]. Interestingly, synaptic upscaling is also reliant on the cytokine, tumour necrosis factor alpha (TNF- α) [242,256]. Normal aging leads to microglia and astrocyte reactivity, and is associated with a rise in the release of cytokines, such as TNF- α [257–261]. This heightened astrocyte-reactivity has been observed in the hippocampus in late adulthood (9.5 m), while the striatum and cortex only show increased reactivity in old age (24 m) [258]. Thus, altered cytokine release and increased levels of TNF- α may also potentially affect synaptic upscaling.

Downscaling-like effects involve downregulation of all AMPAR subunit protein levels, and reduced association with the PSD [244,247]. During downscaling, the removal and dephosphorylation of AMPAR subunits occurs via Homer1a-mGluR1/5 mediated signalling cascades [262–264]. In addition, increased neuronal activity triggers the Npas4-Homer1a signalling pathway, which is also thought to mediate homeostatic control mechanisms [265]. Aging affects both Homer1a protein expression levels [266] and *Npas4* transcript levels [267], which decrease in the old (24 m) compared to the mature (6 m) mouse brain. Diminished levels of Homer1a during aging may lead to increased coupling between G protein-coupled receptors and intracellular Ca²⁺ channels, and result in higher levels of intracellular Ca²⁺ release [266] (see also Section 5). Thus, alterations of Homer1a and *Npas4* expression may negatively impact synaptic downscaling in the aged brain, although this has not been directly demonstrated. In addition to these pathways, several other activity-induced genes and transcription factors, such as *Arc* [268,269], *Plk2* [270], and MeCP2 [271], have also been implicated in synaptic downscaling-like plasticity [272]. *Arc* transcript levels were found to be reduced in the hippocampus of memory impaired old (24 m) mice compared to mature adult (6 m) animals [267]. In the young adult brain, neuronal activity induction of *Arc* reduces AMPAR density and elevates the fraction of thin spines, preventing network hyperexcitability [273]. Thus, low levels of *Arc* expression, or alterations to other homeostasis-linked transcript factors may also contribute to age-related neuronal hyperactivity [8,71,149,213].

Regulation of the E:I synaptic balance is a critical homeostatic control mechanism [144]. Alterations in the E:I balance have been observed during aging in both human and rodent studies, although these were not directly linked to homeostatic control [274–276]. In the mouse brain, old age (24 m) was associated with loss of excitatory synapses, accompanied by an increase in the size of remaining excitatory synapses [274]. Inhibitory synapses were also lost in old age (24 m), but without a compensatory increase in size [274]. Interestingly, elevated levels of EEG spikes in old/senescent (16–18 and 24–28 m) mice occurred primarily during resting, or slow wave sleep, and were blocked by augmentation of inhibition [149]. Homeostatic plasticity was shown to occur over prolonged periods, as well as during sleep [242,243,263]. Thus, these studies support potential age-related disturbances in the E:I balance in the aged brain, with a shift towards greater excitation. Other mechanisms that may contribute to a modified E:I balance could be age-related alterations in inhibitory neurons (see Section 4.3), changes in transcription factors (see above), or modifications to the pre- and postsynaptic structures (see Section 4.5). However, the specific molecular, synaptic and network mechanisms that may contribute to the potential loss of neuronal firing homeostasis in the aged brain remain to be fully elucidated.

4.5. Age-related changes to pre- and postsynaptic structures

Robust evidence suggests that synaptic dysregulation may drive age-related cognitive decline [126,127]. Synaptic structural dynamics have been interpreted as a proxy marker of functional plasticity during learning, suggesting that their preservation is critical for healthy aging

[277,278]. Longitudinal *in vivo* two-photon imaging of the mouse somatosensory cortex has shown that *en passant* boutons (EPBs) exhibit an age-related increase in density between juvenility (< 1 month) and late adulthood (8–15 m), which stabilizes in old age (18–24 m) [279]. Despite stable density, the cortex of old (18–24 m) mice had a greater proportion of large EPBs [279], while turnover rates of EPBs almost doubled from young adulthood (4 m) to senescence (22–24 m) [280]. Age-related changes in turnover have been attributed to greater destabilization of synaptic structures, including the observed fluctuations in the size of persistent boutons [280]. In spite of the age-related increase in turnover, EPBs seem to retain the ability to form structurally normal synapses as measured by electron microscopy (EM) [279,280], and to persist long into adulthood [281]. Yet, although EPBs may be preserved at an ultrastructural level, alterations in the machinery of synaptic vesicle trafficking may have an impact on plasticity. For example, the presynaptic protein synaptophysin, which facilitates vesicle endocytosis [282], was downregulated by almost 30 % in several brain regions (somatosensory, occipital, frontal cortex and hippocampus) of late adult (10–12 m) compared to young adult (3 m) mice [196,283,284].

Several lines of evidence have indicated an age-related increase in synapse size at pre-synaptic (axonal boutons) and post-synaptic (dendritic spine) structures [130,274,280]. However, findings related to synapse density are relatively mixed. The density of synapses in the somatosensory cortex and CA1 region of the hippocampus has been found to either decrease [130,274], or to remain fairly stable in the old mouse brain [159,162,279,285]. More recent studies using serial EM reconstruction [274] and synaptome mapping [130] have found an inverse relationship between synapse density and size, suggesting possible engagement of compensatory mechanisms in the aging brain. In the somatosensory cortex of old (24 m) mice, the loss of excitatory synapses was accompanied by an increase in the size of remaining excitatory synapses, suggesting total synaptic surface per unit volume of neuropil was maintained during aging [274]. Synaptome mapping has also shown that the density of PSD-95 and SAP102-positive synaptic puncta was greatly reduced by 18 months of age and this was concomitant with increased puncta size in multiple regions of the mouse brain [130]. Similar compensatory changes in synaptic size have been reported in younger mice following plasticity induction paradigms in the hippocampus [286] and cortex [242]. In the cortex of young adult mice, longitudinal *in vivo* measurements of dendritic spine size were anti-correlated with local dendritic spine loss at both excitatory layer 5 and inhibitory layer 2/3 neurons [242]. Besides changes in synapse size, another potential age-related compensatory mechanism recently identified in older animals involved an increase in the percentage of multi-innervated spines [159]. Taken together these reports suggest that synapse loss may result in a compensatory increase in the size of remaining synapses both during plasticity and in response to aging [130, 242,274,286].

Aging has an impact not only on axonal bouton dynamics, but also on spine stability. In the young/mature adult (2–6 m) mouse cortex the percentage of mature stable spines varies across studies, but has been reported to be between 75 % and 95 % [278,287–289]. In contrast, by mid-late adulthood (8–15 m) 53 % of mature spines have been found to be stable, decreasing further to 41 % by old age (18–24 m) [279]. Most mature stable spines in the adult brain contain PSD-95, while transient spines generally contain other membrane-associated guanylate kinases (MAGUKs) scaffolding proteins, such as synapse-associated protein (SAP) 102, SAP97 or PSD-93 [290–292]. MAGUKs express regional diversity and have distinct roles in different types of learning in the adult mouse brain [293,294]. PSD-95, required for spine stabilization [290, 295], was reduced in density in multiple brain regions between 6 and 24 months of age, with most of the loss occurring prior to 18 months [130,205,250]. Therefore, this reduction in PSD-95 may contribute to the diminished spine stability observed with aging *in vivo*. In the young adult brain, newly formed spines, mostly lacking PSD-95, have been suggested to underlie the majority of spine dynamics during learning

[291,296]. These typically thin spines create transient connections and are stabilized in the short-term by SAP102, SAP97 and PSD-93 [132,288,292,295,297]. Senescent (25 m) mice preferentially lose transient spines at CA1 pyramidal cells [298]. Hence, expression levels of MAGUKs, such as SAP102, also vulnerable to the aging process, may affect transient spine dynamics [130,291,292]. Consistent with findings in the mouse brain, studies of human *post-mortem* brain tissue have also demonstrated downregulation and reduced trafficking of MAGUKs in the hippocampus of healthy aged and AD individuals [299–301]. However, to our knowledge, no studies have thoroughly investigated the relationship between MAGUKs dynamics and spine formation, and stabilization during aging *in vivo*. Furthermore, the exact age-dependent molecular and functional processes that affect the stabilization mechanisms of newly formed spines, or those that disrupt already mature and stable spines, are currently unknown.

4.6. Summary

Several age-related changes in synaptic plasticity and structure have now been identified in the adult mouse brain, however, the finer time-scales at which these changes emerge are still unclear. Hebbian plasticity has mainly been explored in the aging rat brain, while studies of age-related changes in homeostatic plasticity are scarce. Some evidence suggests alterations in Hebbian plasticity in the mouse brain by late adulthood. Although the mechanisms behind these changes are unclear, several contributing factors, such as modifications in glutamatergic receptor expression or trafficking (see Section 4.2), or impairments in Ca^{2+} homeostasis have been identified (see Section 5). Neuronal hyperactivity and hyperexcitable networks have now been demonstrated in the late adult mouse cortex and hippocampus by several groups, while age-related findings linked to disruptions to GABAergic interneurons and inhibitory synaptic circuitry are only beginning to emerge (see Sections 4.3 and 4.4). Surprisingly, however, no study to date has investigated age-related changes in neuronal firing rate homeostasis, although abnormalities could be inferred from how mechanisms and pathways involved in this type of plasticity are affected by age. These include modifications at the level of AMPARs, and other postsynaptic components, elevated glial-related cytokine release, or alterations of activity-induced genes and transcription factors (see Sections 4.4 and 4.5). In contrast, several studies have now identified multiple age-related changes affecting the structure, composition and dynamics of dendritic spines before late adulthood (8–14 m) in the mouse brain, emphasising the age-related vulnerability of these synaptic features (Fig. 1, Table 2). Future studies need to explore the mechanisms underlying the balance between plasticity and stability and find potential targets to preserve this balance into old age.

5. Dysregulation of intracellular calcium homeostasis

5.1. Age-related impairments to neuronal Ca^{2+} homeostasis

Ca^{2+} ions perform important signalling functions, and therefore their intracellular concentration is tightly regulated at rest at ~50–100 nM [302,303]. One long-standing hypothesis proposes that altered homeostasis of neuronal intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) plays a critical role in brain aging [304–307]. Evidence in favour of this hypothesis has been obtained largely from studies in rats and includes data on increased $[\text{Ca}^{2+}]_i$ [308], increased Ca^{2+} entry through voltage-gated Ca^{2+} channels [309], decreased activity of Ca^{2+} -ATPase [310], and augmented Ca^{2+} -induced Ca^{2+} -release from intracellular stores [311] in neurons from aged animals. Most of these studies argue that aging is accompanied by an increase in $[\text{Ca}^{2+}]_i$ (although see [312] for alternative data), which results in pathological disruption of several cellular processes. In the following section, we review existing experimental evidence relating to the calcium hypothesis of aging obtained specifically in the mouse brain.

If the main tenets of the calcium hypothesis (based on the observations in rats) also apply to mice, then basal $[\text{Ca}^{2+}]_i$ should be increased in neurons of aged mice. Indeed, recent data have shown that basal $[\text{Ca}^{2+}]_i$, measured in the aged brain by intracellular Ca^{2+} -selective microelectrodes was increased both in cortical neurons *in vivo* and in hippocampal pyramidal neurons *ex vivo* [221]. In these experiments, basal $[\text{Ca}^{2+}]_i$ was elevated in late adult (12–14 m) and senescent (24–26 m) compared to that in young adult (3–4 m) C57Bl/6 J mice [221]. Similarly, an age-related elevation in resting $[\text{Ca}^{2+}]_i$ has been found by *ex vivo* fura-2-based imaging in cerebellar granule cells of senescent (28–30 m) compared to young (1 m) CBA mice [313]. However, others have shown similar levels of $[\text{Ca}^{2+}]_i$ in cerebellar granule cells (1.5, 11, 18 vs 24 m) and Purkinje neurons (6 vs 24 m) *ex vivo* in C57Bl/6 J mice [314]. Findings in interneurons of the CA3 hippocampal area also suggest similar resting $[\text{Ca}^{2+}]_i$ levels in young adult (3–5 m) and old/senescent (22–28 m) C57Bl/6 J mice [233]. In contradiction to the notion of Ca^{2+} overload with aging, experiments performed in suspensions of total forebrain cells have noted basal $[\text{Ca}^{2+}]_i$ to be lower in senescent (20–24 m) compared to young adult (3–4 m) mice [312,315,316]. The differences between the conditions in which basal $[\text{Ca}^{2+}]_i$ was recorded likely explain the discrepancies in these studies. Taken together, the available evidence in mice does not yield a uniform picture of age-related changes in basal $[\text{Ca}^{2+}]_i$. This resembles the lack of agreement in studies involving rats (cf. [308,312,317]). However, recent data suggests that Ca^{2+} homeostasis impairments might emerge in late adult animals (~12 m), before the conventional definition of old age [221]. Thus, $[\text{Ca}^{2+}]_i$ may rise with age in mice, although these increases could be specific to strain, brain region or neuronal type [221, 233,313,314].

Although the relationship between age and resting $[\text{Ca}^{2+}]_i$ in mouse neurons is somewhat variable, the majority of studies agree that aging negatively affects the absolute amplitude of the $[\text{Ca}^{2+}]_i$ signal in response to stimulation. In particular, recordings from both isolated neurons and neurons in slices showed that KCl-evoked depolarisation and/or caffeine stimulation evoked smaller Ca^{2+} responses in aged cells [313,315,316]. In prefrontal cortex pyramidal neurons, smaller Ca^{2+} transients in response to stimulation with inositol triphosphate have been observed in old (18 m) compared to young (1.5 m) and mature adult (6 m) mice [318]. In cerebellar granule neurons, although peak Ca^{2+} responses to KCl stimulation were similar in young adult (1–1.5 m) and old (20–24 m) mice, ~15 % of cells from aged animals showed almost no responses [314]. These responses were often accompanied by delayed, irreversible $[\text{Ca}^{2+}]_i$ increase after KCl withdrawal [314]. In addition, it has also been found that, when cerebellar slices were maintained *in vitro* for up to 6 h, resting $[\text{Ca}^{2+}]_i$ increased at a higher rate in granule neurons from old mice than in slices from young animals [314]. These findings, and observations of the slower rate of $[\text{Ca}^{2+}]_i$ recovery following external stimulation [313,314], suggest neurons in aged mice are compromised in their ability to mobilise $[\text{Ca}^{2+}]_i$ and maintain it at a low level following stimulation, or when exposed to stressful conditions.

5.2. Age-related alterations in VGCCs

Several mechanisms could be responsible for dysregulation of Ca^{2+} signalling in the aged brain. Voltage-gated Ca^{2+} -permeable channels (VGCCs) represent a major route of Ca^{2+} entry into neurons [319,320]. Studies in rats have provided evidence for augmented L-type Ca^{2+} channel expression and activity in hippocampal neurons of aged animals [309,321–323]. In the aged mouse brain, upregulation of L-type VGCCs in hippocampal neurons has been inferred indirectly, from evidence of increased slow afterhyperpolarisation (sAHP) following single or multiple action potentials. sAHP is mediated by Ca^{2+} -dependent K^+ channels and the source of Ca^{2+} was assumed to be predominantly L-type VGCCs [324]. However, electrophysiology data and findings on Cav1.2 and Cav1.3 pore-forming subunits, which largely define the

characteristics of L-type Ca^{2+} currents, have failed to provide substantial evidence for an increase in L-type Ca^{2+} channel activity in the aged mouse brain [200,325–327]. Furthermore, sAHP does not depend solely on the activation of L-type VGCCs [328]. Therefore, at least in the mouse brain, the hypothesis about the relationship between aging and L-type VGCC function remains unconfirmed. Other types of VGCCs are also unlikely to provide the main route of excess Ca^{2+} entry. Studies that examined, the relationship between age and P/Q-, N- and T-type VGCCs, in different neuronal types and brain regions, have mostly reported attenuated or unchanged levels and function [325,329–334]. Overall, these studies suggest that augmented VGCC function are unlikely to be the predominant source of potential Ca^{2+} overload in the aged mouse brain.

5.3. Inflammation and glial cells

Research over the last couple of decades has identified that aging is characterised by low-grade, controlled and mostly asymptomatic inflammation, a process termed ‘inflammaging’ [335,336]. Although the mechanisms that control inflammaging are complex and feature multifactorial and multiorgan processes, an association has been suggested between an increased inflammatory state, chronic stress and the microbiota-gut-brain axis [336–338]. Multiple lines of evidence indicate that the dominant processes that promote inflammaging involve failure to dispose cellular debris and accumulation of misplaced, or misfolded self-molecules [337]. In proliferating cells, dysfunctional proteins and end-products of metabolism or catabolism become diluted over the proliferation process, however, in nonproliferating cells, such as neurons, these by-products accumulate over time, causing damage and cell death [339]. Several studies have now shown that brain aging involves increased activation and notable changes in glial cell profiles [258, 340–344]. Augmented activation was found to increase the release of both pro- and anti-inflammatory molecules in aged compared to young mice [259,345–349]. Recent RNA-sequencing data from the aged mouse brain showed that the population of microglia enriched for inflammatory signals, such as interleukin (IL)-1 β and TNF- α , is relatively small, however, their signals can be highly damaging and lead to neurotoxicity [342,350]. Others have suggested that only certain microglia populations may exhibit dysfunctional properties with aging, and these may show regional variability [343,351,352]. For example, in old (18 m) mice, lipid-droplet-accumulating microglia released increased levels of cytokines, including IL-6, and the chemokines MIP1- α /CCL3 and CXCL10 [343]. High levels of microglia-secreted molecules during aging can alter homeostasis and trigger increased reactivity in other glial cells. Specifically, microglia in old age mice (18–24 m) uniquely express certain proteins, such as CD22, which regulate phagocytosis, and may alter neuronal homeostasis and functioning [353]. Additionally, in several brain regions of late adult (9.5 m) and old age mice (24 m), increased levels of microglia-secreted cytokines, such as IL-1 α , TNF- α or complement component subunit 1q (C1q), triggered increased reactivity in astrocytes [258]. In line with studies in mice, human studies suggest a more active inflammatory system during aging. Inflammaging in humans may not simply reflect an increase in pro-inflammatory cytokines, but simultaneous changes in both pro- and anti-inflammatory cytokines such as soluble TNF-receptors (STNF-RI, STNF-RII), TNF- α , interleukins (IL-6, IL-18 and IL-1 RA), and high-sensitive C-reactive protein (hsCRP) [354]. Such studies emphasise the importance of validating robust markers for various glial types and states in order to allow tracking and distinguishing between physiological activation, inflammation, and contribution to, or protection from disease progression.

5.4. Age-related impairments to glial Ca^{2+} homeostasis

In addition to glial-related increased activation and changes in glial states during brain aging, several lines of evidence also show glial dystrophy and functional alterations. For example, astrocytes have been

shown to become smaller with age, exhibiting reduced synaptic coverage [355,356], microglial cells have been reported to become dystrophic [357–359], while oligodendrocyte precursor cells (OPCs) have been suggested they reduce the generation of new myelinating oligodendrocytes [128,360,361]. Age-related changes in glial cells may occur through dysfunction of $[\text{Ca}^{2+}]_i$ signalling pathways [128,355, 356,360,362–366]. Alternatively, age-related morphological changes may drive altered glial function resulting in modified Ca^{2+} signalling. For example, astrocyte morphology and function are closely linked [367], thus the reduction in astrocytic processes with age can modify their proximity to synapses, and may result in disrupted Ca^{2+} signalling and synaptic function [368,369]. Previous work has suggested that age-related changes in astrocytic Ca^{2+} signalling shares a similar trajectory to that of Ca^{2+} signalling in neurons [128,370,371]. Specifically, the frequency and amplitude of spontaneous Ca^{2+} transients in cortical astrocytes were either stable or increased from young (1–1.5 m) to mature adulthood (3–6 m), and began to decrease from mature/late adulthood (8–12 m) into old age/senescence (16–28 m) [370]. Similarly, the amplitude of synaptically evoked $[\text{Ca}^{2+}]_i$ transients followed the same pattern [370,372]. In contrast, others have found no changes in spontaneous or evoked astrocytic $[\text{Ca}^{2+}]_i$ signals recorded in aged cortical, or hippocampal slices [368,373]. Instead, these studies reported differences in the spatiotemporal organization of Ca^{2+} events, finding evidence for more rigid microdomains in old (20–24 m) compared to late adult mice (9–12 m) [368]. Age-related changes in astrocytes are likely to have consequences for neuronal function and play a role in disease-related dysfunction. For example, Ca^{2+} imaging and patch clamp recordings have identified impaired glutamate clearance by astrocytes in both healthy and pathological aging [368,374], which may contribute to the emergence of neuronal hyperactivity in the aged brain (see Section 4.3). Astrocyte Ca^{2+} signalling is also directly linked to reactive astrogliosis [375], failure of which can exacerbate pathology in neurodegenerative diseases such as AD [375,376].

In contrast to findings in astrocytes, studies in microglia suggest a more complex trajectory for Ca^{2+} signalling alterations with aging. Specifically, the fraction of spontaneously active microglia progressively increases with age (2–21 m), yet Ca^{2+} transient frequency and amplitude in individual cells, as measured using *in vivo* two-photon imaging, exhibit a bell-shaped distribution over the same timeframe [377,378]. Interestingly, in young adult mice, the vast majority of microglia show no spontaneous $[\text{Ca}^{2+}]_i$ transients, even in conditions of elevated neuronal activity, however, such transients are generated, with a short delay, in response to damage to a neighbouring neuron [379]. Therefore, the apparent contrast between the direction of age-related changes in Ca^{2+} signalling in microglia, versus neurons and astrocytes, may be explained by the different functions of these cells: microglia respond to cellular damage, whereas neurons participate in synaptic transmission, and astrocytes regulate synaptic formation/function and provide metabolic support. However, several lines of evidence suggest that both microglia and astrocytes play a critical role in both modulating neuronal activity and coordinating neural circuit plasticity, suggesting that the age-related changes in these cell-types are likely to be linked to a variety of processes [380–382].

Oligodendrocyte lineage cells, including OPCs and myelinating oligodendrocytes, can also experience increases in $[\text{Ca}^{2+}]_i$ through several pathways [363]. Ca^{2+} regulation of the oligodendroglia lineage and myelin formation operates at much slower timescales compared to neurons [363]. OPCs can respond to increased neuronal firing, and may also be able to tune activity, while myelin sheaths contain Ca^{2+} permeable channels and exhibit microdomain Ca^{2+} transients [360,363, 383–386]. OPCs retain the ability to proliferate throughout adult life and can migrate to specific sites where they differentiate into oligodendrocytes that myelinate axons [387]. This process can happen both as a result of axonal demyelination, or in response to environmental changes, or learning experiences [388–391]. Recent data suggests that in the aged environment, OPCs exhibit Ca^{2+} activity, but their

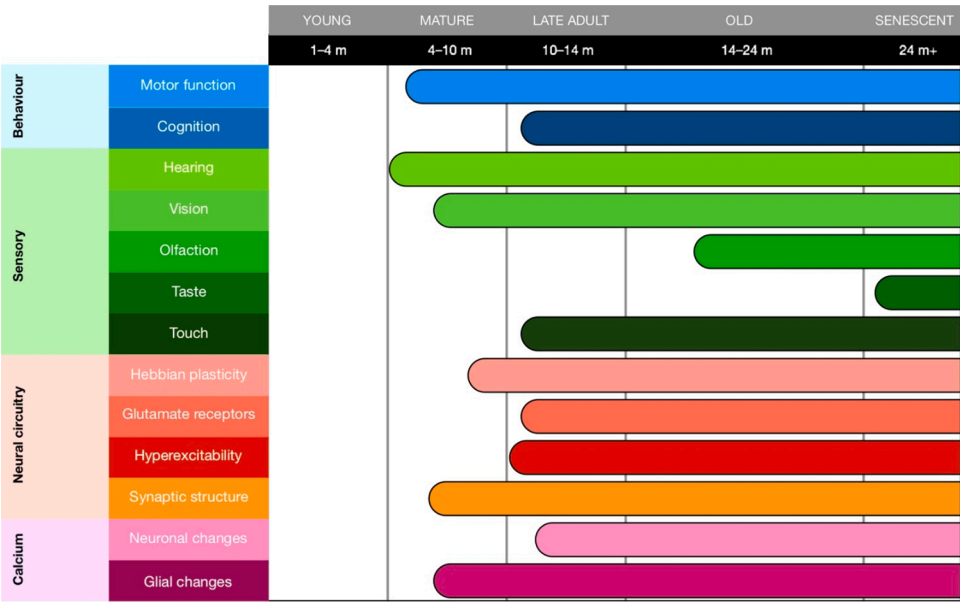


Fig. 1. Timeline of age-related alterations across multiple functions. Functional categories include behavioural and sensory systems, neural circuitry plasticity and structure, and calcium regulation. Mouse ages are defined as follows: juvenile (up to 1 month of age); young adult (1–4 months); mature adult (4–10 months); late adult (10–14 months); old (14–24 months); senescent (over 24 months). Timeline for each category depicts the earliest identified changes in studies covered in this review.

proliferation decreases, however, when the mechanosensitive Ca^{2+} channel Piezo1 is knocked down in 18 months old mice, the proliferation levels of OPCs increase again [392]. Moreover, evidence of abnormal myelination [393], reduced myelin regeneration capacity [394], myelin internode loss [395], and decline in myelinated fibres were found in the cortex of mature adult (6 – 10 m), late adult (13–14 m) and old mice (18–24 m) [65], while enhancing endogenous myelination improved spatial memory function in older animals [65]. Furthermore, as animals age there is an increase of myelin debris in microglia, suggesting a failure of debris clearance by these cells and a contribution of myelination breakdown to inflammaging [128,395,396]. Another possible cause for decreased OPC proliferation and differentiation, and altered myelination with aging, involves impaired glutamate signalling, potentially due to altered receptors and transporters [360]. Although the specific effects of aging on OPCs and myelinating oligodendrocytes Ca^{2+} signalling currently remain unclear, recent studies begin to elucidate the important role of these types of glial cells in preserving the aging brain.

5.5. Summary

The available evidence in the aged mouse brain offers partial support to the calcium hypothesis (see Table 2). Increased levels of basal $[\text{Ca}^{2+}]_i$ have not been consistently identified with aging, although both neuronal and glial cells show altered Ca^{2+} signalling. Neurons become progressively impaired in the ability to generate spontaneous or evoked $[\text{Ca}^{2+}]_i$ transients and show a deficit in the capacity to return transients to resting $[\text{Ca}^{2+}]_i$. Furthermore, augmented VGCC function, or changes to Ca^{2+} -permeable NMDARs (see Section 4.3), are unlikely to be the predominant source of potential Ca^{2+} overload in mice. Findings suggest that expression levels and activity of these voltage- and ligand-gated channels are generally either unaffected, or decreased, in the aged mouse brain. Aging studies investigating Ca^{2+} signalling in glial cells, which operates at different timescales compared to neurons, are still scarce. In addition, the process of inflammaging, involving notable changes in glial cell states and increased activation during aging, may contribute to alterations in both glial cell function and Ca^{2+} signalling. However, alternative mechanisms of Ca^{2+} dysregulation in old age may also include changes in activity of other ligand-gated Ca^{2+} -permeable channels [397], mitochondrial status [314], activity of plasma membrane and endoplasmic reticulum Ca^{2+} -ATPases [310,317], expression levels of Ca^{2+} -binding proteins [398–400], or intracellular Ca^{2+} store

dynamics (see also Section 4.3) [8,311,401]. Further work will be required to evaluate the importance of Ca^{2+} homeostasis in the mouse brain, and to delineate the earliest ages at which this process begins to become dysregulated.

6. Conclusion

Aging is a complex process, differentially impacting multiple cognitive, sensory, neuronal and molecular systems. Mice are a widely used model to study adult neuronal circuit function, plasticity, and related molecular mechanisms, as well as consequences for cognition and sensory processing. A growing number of studies have been using the mouse as a model to determine the impact of aging on these systems [9,11,15,125,306,401]. Here, we reviewed the available reports investigating how aging impacts processes related to neuronal function in mice (see Table 2). Across many systems we found evidence for prominent age-related dysregulation even before 12 months of age, suggesting that emerging age-related deficits can manifest in early stages of late adulthood. However, we also found that some processes are remarkably resilient to aging. For example, while emerging age-related deficits in the auditory and visual systems may be reliably detected in the transition period between mature and late adulthood (6–12 m), gustation and olfaction appear to be more resilient up until late adulthood (~12 m). Classic assays of cognition find that both spatial learning and memory, and avoidance memory, begin to decline from late adulthood onward (11–13 m). Furthermore, several age-related changes in synaptic plasticity and structure have been shown to occur from 10–12 months of age in the adult brain. At the molecular level, increases in basal $[\text{Ca}^{2+}]_i$ are not consistently identified with aging, although both neuronal and glial cells show altered Ca^{2+} signalling in early stages of late adulthood (8–12 m). Together, these lines of evidence suggest that more fine-scale mapping of the transition from mature to late adulthood is required to capture the onset of emerging age-related deficits involving neuronal circuit function (Fig. 1). A better understanding of emerging age-related deficits is a critical first step on the road to developing novel intervention strategies for rejuvenation of the aged brain.

Declaration of Competing Interest

The authors report no declarations of interest.

CRediT authorship contribution statement

Carola I. Radulescu: Conceptualization, Writing - original draft. **Veronika Cerar:** Conceptualization, Writing - original draft. **Peter Haslehurst:** Conceptualization, Writing - original draft. **Maksym Kopanitsa:** Conceptualization, Writing - original draft. **Samuel J. Barnes:** Conceptualization, Writing - original draft, Supervision, Project administration, Funding acquisition.

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