frontiers in
AGING NEUROSCIENCE

MINI REVIEW ARTICLE
published: 06 January 2015
doi: 10.3389/fnagi.2014.00337

# Dissecting mechanisms of brain aging by studying the intrinsic excitability of neurons

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Several studies using vertebrate and invertebrate animal models have shown aging associated changes in brain function. Importantly, changes in soma size, loss or regression of dendrites and dendritic spines and alterations in the expression of neurotransmitter receptors in specific neurons were described. Despite this understanding, how aging impacts intrinsic properties of individual neurons or circuits that govern a defined behavior is yet to be determined. Here we discuss current understanding of specific electrophysiological changes in individual neurons and circuits during aging.

**Keywords: aging, action potential, single neuron, synaptic transmission, electrophysiology**

## INTRODUCTION

Brain aging entails several changes in physiology and a progressive decline in cognitive functions (Burke and Barnes, 2006). However, cellular alterations related to this decline are not completely understood. Harold Brody (1955) postulated a decline in neuron number in all cortical layers during aging. Later investigations supported his work, showing a decline in cortical and subcortical neuron density (Ball, 1977; Coleman and Flood, 1987) of aging humans (Ball, 1977) and non-human primates (Brizzee and Knox, 1980). Nonetheless, in the 1980s, it was discovered that normal aging was not actually marked by neuronal death (West, 1993). Many studies showed that significant neuronal loss in the hippocampus (HP) and neocortex are not characteristics of normal aging in humans (West et al., 1994; Pakkenberg and Gundersen, 1997), non-human primates (Peters et al., 1994; Gazzaley et al., 1997; Merrill et al., 2000; Keuker et al., 2003) and rodents (Rapp and Gallagher, 1996; Rasmussen et al., 1996; Merrill et al., 2001).

Several studies support the hypothesis that cognitive deficits occurring in normal aging could be due to alterations in the intrinsic cellular properties of neurons (Driver et al., 2004; Chang et al., 2005; Wilson et al., 2005; Disterhoft and Oh, 2007; Luebke and Chang, 2007; Matthews et al., 2009). Investigations on the central nervous system (CNS) structures with crucial roles in cognitive processing have shown age-related alteration of intrinsic neuronal excitability (Landfield and Pitler, 1984; Disterhoft and Oh, 2007; Matthews et al., 2009; Oh et al., 2010; Wang et al., 2011). Consistent with this idea, aging neurons have been observed undergoing structural changes such as decreases in soma size (de Brabander et al., 1998; Wong et al., 2000; **Figure 1**), loss/regression of dendrites and loss of dendritic spines (Jacobs et al., 1997; Peters et al., 1998; Page et al., 2002; Duan et al., 2003; **Figure 1**), loss of synapses (Chen et al., 1995; Wong et al., 1998; **Figure 1**), alterations in neurotransmitter receptors (Post-Munson et al., 1994; Rosene and Nicholson, 1999; **Figure 1**) and/or decreased response to neurotransmitters (Fieber et al., 2010; Akhmedov et al., 2013; Kempsell and Fieber, 2014). Changes in neuronal physiology and structure lead to a less efficient transmission of information encoded in the form of action potentials (APs; Chang et al., 2005; Luebke and Chang, 2007) and impairment of the computational efficacy of the neuronal network (Randall et al., 2012). Taken together, these studies lead to three main questions: (1) Does normal aging impact electrophysiological properties of individual neurons? (2) Do morphological and molecular changes during aging correlate with electrophysiological changes? (3) Are these changes conserved across different species?

To address these questions, we should first understand whether and how aging affect the intrinsic electrophysiological properties of neurons and whether these changes affect neuronal communication and plasticity. We will first review our knowledge on changes in APs because APs play a central role in communication.

**Abbreviations:** HP, Hippocampus; CNS, Central Nervous System; APs, Action Potentials; S1-PC, Primary somatosensory cortex pyramidal cell; CA1, Cornus Ammonis 1; CA3, Cornus Ammonis 3; HP-CA1-PC, Hippocampal CA1 pyramidal cell; HP-CA3-PC, Hippocampal CA3 pyramidal cell; HP-CA3-IN, Hippocampal CA3 interneuron; HP-CA3-PlC, Hippocampal CA3 place cell; HP-CA1-PlC, Hippocampal CA1 place cell; PVC-SN, Ventral pleural ganglion sensory neuron; BSC-SN, Buccal ganglion sensory neuron; PFC-PC, Prefrontal cortex pyramidal cell; V1-PC, Visual cortex pyramidal cell; DGCL, Dentate granule cell layer; AHP, Afterhyperpolarization; fAHP, Fast Afterhyperpolarization; mAHP, Medium Afterhyperpolarization; sAHP, Slow Afterhyperpolarization; LTTC, L-type $Ca^{2+}$ channel; $Na_v$ channel, Voltage-gated $Na^+$ channel; SGNs, Spiral ganglion neurons.

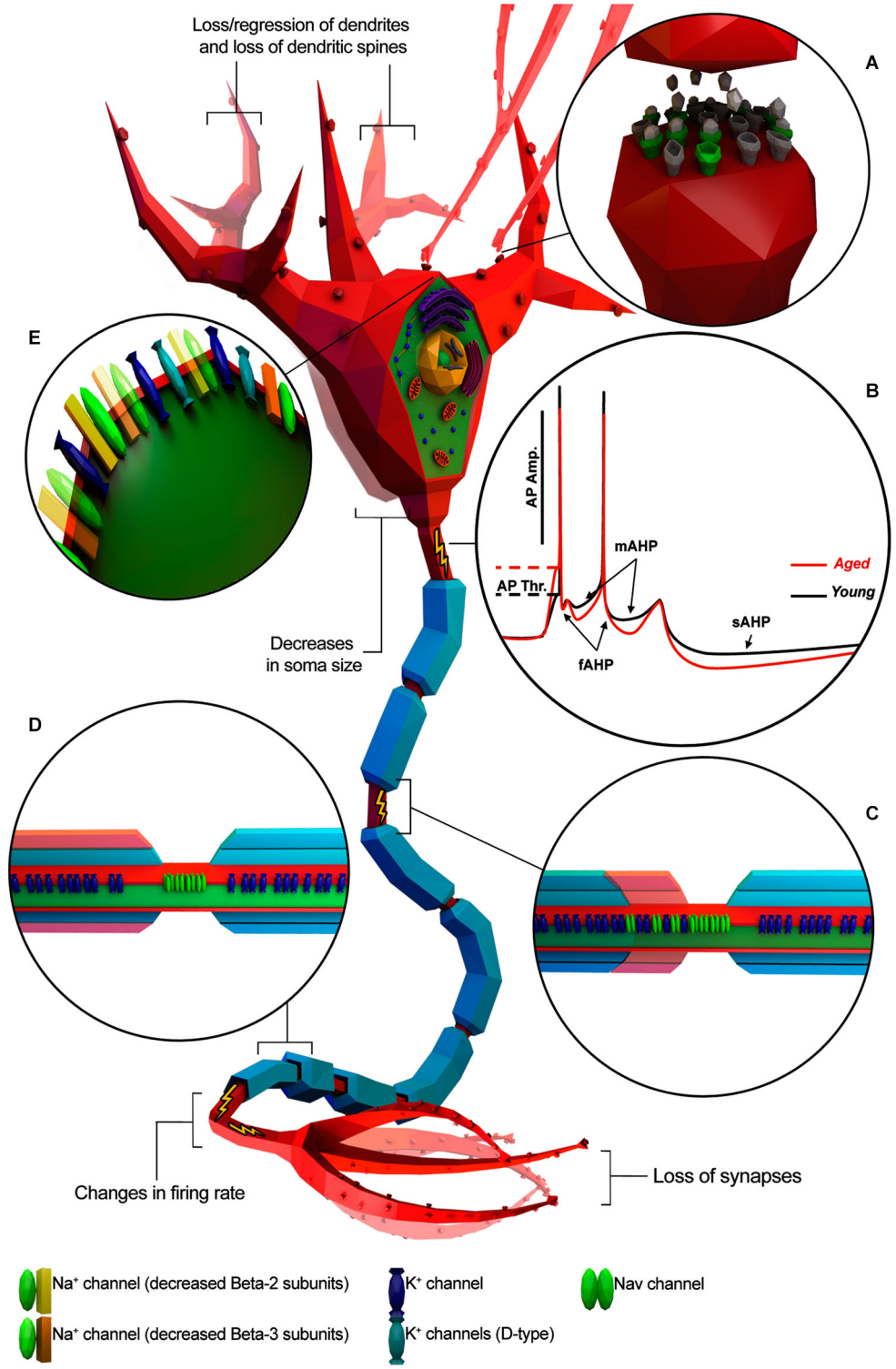


**FIGURE 1 | Known age-related electrophysiological and morphological changes in neurons**. Neuron is depicted as a generic myelinated neuron for simplicity, in order to summarize information from different animal models and neuronal cell type. **(A)** Age-related increase of altered neurotransmitter receptors (gray) and decreased expression of normal ones (green). **(B)** Representative AP traces of young and aged neuron. **(C)** Absence/disruption of paranodal ultrastructure (in red) leading $K^+$ channels to be relocated adjacent to "$Na_v$" clusters. **(D)** Depletion of myelin layers (in red) leading to an increase of the occurrence of redundant myelin sheaths exposing the enclosed axon. **(E)** Alterations in $Na^+$ and $K^+$ channel properties or subtype expression patterns. (Illustration was created using Autodesk 3Ds Max and Adobe Photoshop).

APs are short-lasting events characterized by the rapid rise and fall of electrical membrane potential, which play a central role in encoding information in the form of specific frequency and pattern. Hence we will discuss changes in various parameters of APs during aging (**Table 1**; **Figure 1**).

#### AP THRESHOLD

AP threshold is the critical level to which the membrane potential must be depolarized in order to initiate an AP and hence it is often used as a measure for neuron excitability. Recent studies have reported an age-related increase in the AP threshold of the rat hippocampal CA1 pyramidal cell (HP-CA1-PC; Matthews et al., 2009) and primary somatosensory cortex layer 3 pyramidal cell (S1-PC) (Hickmott and Dinse, 2013), mice (Randall et al., 2012) and rabbit HP-CA1-PC (Power et al., 2002) and also in the ventral pleural ganglion sensory neuron (PVC-SN) and buccal ganglion sensory neuron (BSC-SN) of aging *Aplysia* (Kempsell and Fieber, 2014). While the basis of this change has not yet been clarified, age-related depolarization of the AP threshold could likely be ascribed to alterations of voltage-gated $Na^+$ channel ($Na_v$ channel) activation properties or channel subtype expression patterns (Randall et al., 2012).

This age-related change in AP threshold dampens excitability of neurons and may affect neuronal activity by reducing transmission properties of neurons and their computing capability. Such an impairment of neuronal function in a brain region could constitute a functional lesion that may form the basis for cognitive decline during aging. Importantly, a direct correlation between the AP threshold and age-related learning or cognitive deficits is yet to be described (Matthews et al., 2009).

It is also important to consider that the above mentioned observations might not be universally true. For example, studies on age-related cognitive deficits in the Rhesus Monkey reported no change in the AP threshold in both layer 2/3 and 5 pyramidal cell of prefrontal cortex (PFC-PC; Luebke et al., 2013), layer 3 pyramidal cell of visual cortex 1 (V1-PC), dentate granule cell layer (DGCL; Luebke and Rosene, 2003), rat HP CA3 interneuron (HP-CA3-IN; Lu et al., 2011) and tail motoneuron (TMN) of aging *Aplysia* (Kempsell and Fieber, 2014). Taken together, these studies suggest that age-related changes in AP threshold may differentially affect species, neuron types, neuronal layers or sub regions of brain. Because of the lack of sufficient experimental data on the comparative analyses of changes in AP threshold in neurons from the different brain regions and correlation with specific functions, it is difficult to draw exhaustive conclusions of significance of the AP threshold during aging.

#### AP AMPLITUDE

The amplitude of the AP plays a crucial role in evoking $Ca^{2+}$ currents ($I_{Ca}$) and the amount of neurotransmitter released by the axon terminals. Investigations in primates reported an age-related decrease of AP amplitude of PFC-PC in layer 2/3 and 5 (Chang et al., 2005; Luebke and Chang, 2007; **Figure 1B**). Such alterations in amplitude could be explained by either a reduction of $Na^+$ channels and/or an increase in $K^+$ channels involved in a D-type current. Indeed, numerous lines of evidence have suggested that age-related changes in AP amplitude could result from altered expression of "$Na_v$" channel subunits, reduced expression of $Na^+$ channels or altered expression of $K^+$ channels involved in the $K^+$ currents $I_K$, $I_A$, and $I_D$ (Foehring and Surmeier, 1993; Korngreen and Sakmann, 2000; Chang et al., 2005; Luebke and Chang, 2007). Altered expression of voltage-gated delayed rectifier alpha Kv9.1 subunits seem to be particularly involved in age-related AP amplitude changes (Erraji-Benchekroun et al., 2005; Luebke and Chang, 2007), but further voltage-clamp studies would be required to gain a deeper insight.

Interestingly, normal aging has no effect on the AP properties of the aging monkey DGCL and layer 3 V1-PC (Luebke and Rosene, 2003; Luebke et al., 2013) suggesting different effects of aging on different populations of neurons (Luebke et al., 2004). This difference in findings is interesting since it could suggest that with regard to specific electrophysiological changes, specific populations of neurons might be more vulnerable to the effects of aging.

Similarly, no age-related change has been reported in the AP amplitude of the rat HP-CA1-PC and S1-PC (Gant et al., 2006; Matthews et al., 2009; Hickmott and Dinse, 2013), mice HP-CA1-PC and HP-CA3-IN (Lu et al., 2011; Randall et al., 2012) and *Aplysia* R15 neuron, PVC-SN, BSC-SN and TMN (Akhmedov et al., 2013; Kempsell and Fieber, 2014) suggesting that in these particular animal models the aging process may not be affecting normal resetting of "$Na_v$" channels and/or opening of voltage-gated $K^+$ channels. Interestingly, age-related change in AP amplitude does not seem to contribute to age-related cognitive decline or behavioral impairment (Luebke and Chang, 2007).

#### AFTER HYPERPOLARIZATION (AHP)

AHP is the hyperpolarizing phase of AP hindering the membrane potential from reaching the threshold for generating a new AP or continuing firing activity (Madison and Nicoll, 1984; Lancaster and Nicoll, 1987; Storm, 1990; Sah, 1996). AHP is responsible for the regulation of excitability and may be essential for normal integration of neurotransmission. An increase in AHP has been postulated to be a factor in age-related learning impairments (Disterhoft and Oh, 2006, 2007; Foster, 2007).

AHP has three components (**Figure 1B**): (1) fast AHP (fAHP), medium AHP (mAHP), and slow AHP (sAHP) and each component is individually related to different $K^+$ currents (Storm, 1990; Maccaferri et al., 1993; Sah, 1996; Stocker et al., 1999; Kumar and Foster, 2007). Indeed, studies on Kvβ1.1 mutant mice have suggested that age-related AHP increase and behavioral impairment could be a direct consequence of altered expression of specific $K^+$ -channel subunits (Giese et al., 1998; Need et al., 2003). fAHP occurs after single APs whereas mAHP and sAHP occur after a high frequency burst of APs as is typically observed in normal HP-CA1-PC during learning and memory.

fAHP is mediated by the $I_C$ $K^+$ current, which contributes to the repolarization of AP (Shao et al., 1999; Sesti et al., 2010) whereas mAHP is mediated by the $I_{AHP}$ $K^+$ current (Storm, 1990; Maccaferri et al., 1993; Sah, 1996; Stocker et al., 1999) and sAHP

**Table 1 | Aging associated changes in action potentials (APs).**

| Species | AP Threshold | AP Amplitude | AHP | AP Conduction | AP Firing | References |
|---|---|---|---|---|---|---|
| **Monkey** | –No change in Layer 2/3 PFC-PC;<br>–No change in Layer 5 PFC-PC;<br>–No change in Layer 3 V1-PC;<br>–No change in DGCL | –Decrease in layer 2/3 PFC-PC;<br>–Decrease in Layer 5 PFC-PC;<br>–No change in Layer 3 V1-PC;<br>–No change in DGCL | –Increase in Layer 2/3 PFC-PC;<br>–Increase in Layer 5 PFC-PC;<br>–No change in Layer 3 V1-PC;<br>–No change in DGCL | na | –Increase in Layer 2/3 PFC-PC;<br>–Increase in Layer 5 PFC-PC;<br>–Increase in layer 3 V1-PC | Schmolesky et al. (2000), Leventhal et al. (2003), Luebke and Rosene (2003), Chang et al. (2005), Luebke and Chang (2007), Luebke et al. (2013) |
| **Rat** | –Increase in HP-CA1-PC;<br>–Increase in Layer 3 S1-PC; | –No change in HP-CA1-PC;<br>–No change in Layer 3 S1-PC | –Increase in HP-CA1-PC;<br>–No change in Layer 3 S1-PC; | –Decrease in Nucleus Basal is cortical afferent cholinergic neurons;<br>–Decrease in Parallel fiber Purkinje cell circuitry | –Increase in HP-CA3-PIC;<br>–No change in HP-CA1-PIC | Rogers et al. (1981), Landfield and Pitler (1984), Aston-Jones et al. (1985), Kerr et al. (1989), Hsu et al. (2002), Kumar and Foster (2004), Wilson et al. (2005), Gant et al. (2006), Matthews et al. (2009), Hickmott and Dinse (2013) |
| **Mouse** | –Increase in HP-CA1-PC;<br>–No change on HP-CA3-IN; | –No change in HP-CA1-PC;<br>–No change in HP-CA3-IN | –Increase in HP-CA1-PC;<br>–No change in HP-CA3-IN | na | –Decrease in HP-CA1-PC<br>–Increase in HP-CA1-PIC | Lu et al. (2011), Randall et al. (2012) |
| **Rabbit** | –Increase in HP-CA1-PC | na | –Increase in HP-CA1-PC;<br>–No change in HP-CA3-IN | na | –Decrease in HP-CA1-PC | Moyer et al. (1992), Disterhoft et al. (1996); Moyer et al. (2000), Power et al. (2002), Disterhoft and Oh (2006, 2007) |
| **Aplysia** | –Increase in PVC-SN;<br>–Increase in BSC-SN;<br>–No change in TMN;<br>–No data on R15; | –Increase in PVC-SN;<br>–Increase in BSC-SN;<br>–No change in TMN;<br>–No change in R15 | na | –Decrease in R2 | –Decrease in PVC-SN<br>–Decrease in BSC-SN<br>–No change in TMN<br>–No change in R15 | Harley (1975), Akhmedov et al. (2013), Kempsell and Fieber (2014) |
| **Cat** | na | na | na | –Decrease in spinal cord motoneurons;<br>–Decrease in Pyramidal tract neurons | -Increase in cat V1-PC | Chase et al. (1985), Morales et al. (1987), Xi et al. (1999) |

is mediated by $I_{AHP}$ $K^+$ current (Lancaster and Adams, 1986; Sah, 1996; Stocker et al., 1999; Sah and Faber, 2002; Bond et al., 2004).

In general, several pieces of evidence have reported an increase in AHP amplitude and duration in HP-CA1-PC of rat (Landfield and Pitler, 1984; Kerr et al., 1989; Hsu et al., 2002; Kumar and Foster, 2004; Gant et al., 2006) and rabbit (Moyer et al., 1992, 2000; Disterhoft et al., 1996; Power et al., 2002) as well as in monkey Layer 2/3 and 5 PFC-PC during aging (Chang et al., 2005; Luebke and Chang, 2007; **Figure 1B**). Conversely, no change has been observed in AHP properties of the aging monkey DGCL (Luebke and Rosene, 2003) and layer 3 V1-PC (Luebke et al., 2013), in mice HP-CA3-IN (Lu et al., 2011) and rat S1-PC (Hickmott and Dinse, 2013) suggesting that alteration of the $K^+$ currents may occur during aging in specific populations of neurons. Unfortunately, data on non-vertebrate animal models is not yet available for comparisons.

Examinations of the fAHP in aged animals revealed that alteration of this component is not common (Kumar and Foster, 2007; Matthews et al., 2009; Oh et al., 2010) whereas alteration of either mAHP or sAHP or both appear to be quite frequent during normal aging (Disterhoft and Oh, 2006; Kumar and Foster, 2007; Oh et al., 2010). Interestingly, simultaneous age-related change of both mAHP and sAHP has been observed in the rat (Gant et al., 2006) and rabbit HP-CA1-PC (Power et al., 2002) while Layer 2/3 and 5 PFC-PC of aged monkey show changes only in sAHP (Chang et al., 2005; Luebke and Chang, 2007).

mAHPs result from the activation of several $K^+$ channels such as M-channels, H-channels, and Small conductance $Ca^{2+}$-activated $K^+$ channels (SK channels) (Stocker et al., 1999; Bond et al., 2004; Villalobos et al., 2004; Gu et al., 2005). Intriguingly, age-related upregulation of SK-channels in HP-CA1-PC have been observed to cause memory loss in mice (Dodge and Cooley, 1973) suggesting a direct involvement of this specific ion channel in age-related memory impairment. It remains to be determined whether age-related memory deficits may directly stem from changes in mAHP caused by altered expression of specific SK channels. On the other hand, age-related increase in sAHPs seems to be mediated by voltage-gated L-type $Ca^{2+}$ channel (LTTC) and increased LTTC activity could be directly related to cognitive impairment since L-type calcium channel blockers has been demonstrated to ameliorate the age-related learning deficits, along with a reduction of AHP amplitude in aging rabbits (Disterhoft and Oh, 2006, 2007). It is likely that the increase in LTCC function underlying sAHP increased amplitude may be relatively specific to HP-CA1-PC since increased LTTC currents have only been observed in aged rat HP-CA1-PC (Campbell et al., 1996; Thibault and Landfield, 1996; Thibault et al., 2001; Brewer et al., 2009) while no age-related change in LTTC expression or activity within the cortex has been observed (Tanaka and Ando, 2001; Iwamoto et al., 2004).

## AP AXONAL CONDUCTION VELOCITY

The flow of information within the nervous system relies on the AP conduction rate, which is determined by the passive and active flow of current. Several studies describe age-related decreases in axon conduction velocity in rat Nucleus Basalis cortical afferent cholinergic neurons (Aston-Jones et al., 1985) and parallel fiber Purkinje cell circuitry (Rogers et al., 1981) as well as in cat spinal cord motoneurons (Chase et al., 1985; Morales et al., 1987) and pyramidal neurons (Xi et al., 1999). Such age-related change in CNS seems to occur only in myelinated neurons since similar phenomena has not been reported in unmyelinated neurons in vertebrate or invertebrate animal models. Indeed, changes in the myelin sheath organization occurring in normal aging have been suggested as major contributors to age-related decrease in AP conduction (Peters et al., 1996; Peters, 2002). Interestingly such changes has been postulated in a study on the *Aplysia* R2 motoneuron (Harley, 1975).

Several studies have suggested that changes in myelin structure may affect conduction velocity by altering the location of specific ion channels on the axon (**Figures 1C,D**). For example, Hinman et al. (2006) have found that aging is associated with increased paranode disorganization, abnormalities in paranodal-juxtaparanodal junctions maintenance, and variation in paranodal ultrastructure (Hinman et al., 2006) resulting in an increased expression of $K_v1.2$ channels in paranodal regions of the axon of both the monkey and rat optic nerve. These mislocalized $K_v$ channels may compromise axonal function (Hinman et al., 2006) by stabilizing the membrane voltage (Rasband, 2004), thus impeding AP axonal conduction (Chiu, 1991). Also, changes in myelin ultrastructure increase the occurrence of redundant myelin sheaths exposing the enclosed axon (Peters et al., 2001; Peters, 2002) in the end reducing or interrupting saltatory AP axonal conduction (Hinman et al., 2006).

Alternatively, changes in myelin sheath organization seen in aging may also affect the expression of $Na_v$ channels. Indeed, it has been demonstrated that lack of compact myelin structures in Shiverer mouse optic nerve leads to a diffuse expression of $Na_v1.2$ channels and lower expression of $Na_v1.5$ channels (Boiko et al., 2001). However, age-related alteration of axonal $Na_v^+$ channel localization in nodal structure and the putative consequences on AP axonal conduction velocity are not known.

Age-related changes in myelin structure and composition have been found in the rat corpus callosum (Sugiyama et al., 2002), in mice spiral ganglion neurons (SGNs; Xing et al., 2012), human (Albert, 1993), and non-human primate (Peters, 2002; Sloane et al., 2003). Even though age-related cognitive decline has been suggested to be a consequence of an alteration of the integrity of myelinated axons (Peters et al., 1996; Peters, 2002), whether they also correlate with a reduction in axonal conduction velocity is still unknown.

## FIRING RATE

Information in the nervous system is encoded and transmitted in the form of a specific pattern of APs. Neurons build these patterns by changing the firing rate of their APs. Several lines of evidence have reported age-related alteration of the AP firing rate in different animal models and a direct correlation between age-related alterations of AP firing rate and decline of cognitive functions or behavioral impairment (Chang et al., 2005; Wilson et al., 2005; Burke and Barnes, 2006; Caetano et al., 2012; Branch

et al., 2014). Intriguingly, in monkeys differential aging process have been observed in layers 2/3 of PFC-PC that undergoes an increase in the AP firing rate (Chang et al., 2005) while layer 5 PFC-PC does not show any age-related changes in firing rate (Luebke and Chang, 2007).

Similarly, aging associated alteration of the HP AP firing rate has been observed to be sub region specific given that rat HP-CA3 place cell (HP-CA3-PlC) undergoes an increase of the AP firing rate during aging whereas HP-CA1-PlC does not (Wilson et al., 2005). Interestingly, age-related decrease in the AP firing rate has been reported in mouse HP-CA1-PC (Randall et al., 2012) whereas in mouse HP-CA1-PlC increase its AP firing rate during aging (Yan et al., 2003). Intriguingly, the *Aplysia* R15 neuron do not change their firing properties during aging (Akhmedov et al., 2013) while PVC-SN and BSC-SN decrease their AP firing rate (Kempsell and Fieber, 2014). These findings suggest that the aging process could differentially affect AP firing properties at the single neuron level.

Interestingly, other studies suggest conservation of mechanisms of aging in analogous brain regions of different animal models. For example, V1-PC show increased firing rate in both aged monkeys (Schmolesky et al., 2000; Leventhal et al., 2003; Chang et al., 2005) and cat (Hua et al., 2006) suggesting that some mechanisms could be shared by different species. Several of the age-related factors discussed in this review could have a direct impact on a neuron's firing rate. For example, the change in neuron's AP axonal conduction observed in aged monkeys and rat optic nerve (Hinman et al., 2006) could likely affect a neuron's AP firing rate as well. Firing rate could also be altered by AHP whose age-related changes prolong the repolarization phase of APs and lengthen the period of time that neurons cannot fire new APs (Kumar and Foster, 2007; Sesti et al., 2010). For example, as discussed above increased $Ca^{2+}$ influx via LTTC may cause an increase in the amplitude of sAHPs in rat HP-CA1-PC neurons (Kumar and Foster, 2007; Kumar et al., 2009) leading to a prolonged period of quiescence between AP bursts (Sesti et al., 2010). Importantly, a similar age-related increased $Ca^{2+}$ influx could have the opposite effect on the AP firing rate in different brain regions. In fact, a recent study by Hickmott and Dinse (2013) have found that age-related increase in T-type $Ca^{2+}$ currents in rat S1-PC is able to switch firing patterns to burst firing.

## CONCLUSION

We have discussed our current understanding of electrophysiological changes in individual neurons associated with aging (**Table 1**; **Figure 1**). We have also compared evidence from studies using different animal models wherever possible. It is important to note that aging affects fundamental properties of neurons, such as phases of APs, AP firing pattern and AP conduction velocity, leading to specific changes in neuronal communication and plasticity. However, age-related alterations of the intrinsic excitability of neurons might reflect secondary consequences of aging while others might be compensatory mechanisms to such changes. For example, the decrease in excitatory synaptic transmission and increase in inhibitory synaptic transmission in layer 2/3 PFC-PC (Luebke et al., 2004) seen in aged monkeys could, hypothetically, represent a compensatory response to significantly increased AP firing rates observed in layer 2/3 PFC-PC of the aged monkey (Chang et al., 2005). Consistent with the gene expression data on single neurons (Moroz and Kohn, 2010; Kadakkuzha et al., 2013) aging associated changes in electrophysiological properties are mostly specific to species, brain region and neuronal type. It remains to be shown whether specific electrophysiological changes in neurons directly lead to a behavioral deficit during aging. Further integrated approaches that combine behavioral, electrophysiological and genomic analysis of individual neurons and circuits might help solve this challenging problem. Lower organisms such as the snail *Aplysia* where fewer neurons regulate specific behavior such as gill withdrawal reflex is ideally suited for the gain of function experiments to address this challenge.

## ACKNOWLEDGMENTS

We sincerely thank the Whitehall Foundation and The Scripps Research Institute for their funding support that helped us to carry out our research.

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**Conflict of Interest Statement**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Received: 08 September 2014; accepted: 29 November 2014; published online: 06 January 2015.*

*Citation: Rizzo V, Richman J and Puthanveettil SV (2015) Dissecting mechanisms of brain aging by studying the intrinsic excitability of neurons. Front. Aging Neurosci. **6**:337. doi: 10.3389/fnagi.2014.00337*

*This article was submitted to the journal Frontiers in Aging Neuroscience.*