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Regulation of intrinsic excitability: Roles for learning and memory, aging and Alzheimer's disease, and genetic diversity

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Abstract

Plasticity of intrinsic neuronal excitability facilitates learning and memory across multiple species, with aberrant modulation of this process being linked to the development of neurological symptoms in models of cognitive aging and Alzheimer's disease. Learning-related increases in intrinsic excitability of neurons occurs in a variety of brain regions, and is generally thought to promote information processing and storage through enhancement of synaptic throughput and induction of synaptic plasticity. Experience-dependent changes in intrinsic neuronal excitability rely on the activity-dependent gene expression patterns, which can be influenced by genetic and environmental factors, aging, and disease. Reductions in baseline intrinsic excitability, as well as aberrant plasticity of intrinsic neuronal excitability and in some cases pathological hyperexcitability, have been associated with cognitive deficits in animal models of both normal cognitive aging and Alzheimer's disease. Genetic factors that modulate plasticity of intrinsic excitability likely underlie individual differences in cognitive function and susceptibility to cognitive decline. Thus, targeting molecular mediators that either control baseline intrinsic neuronal excitability, subserve learning-related intrinsic neuronal plasticity, and/or promote resilience may be a promising therapeutic strategy for maintaining cognitive function in aging and disease. In this review, we discuss the complementary relationship between intrinsic excitability and learning, with a particular focus on how this relationship varies as a function of age, disease state, and genetic make-up, and how these targeting these factors may help to further elucidate our understanding of the role of intrinsic excitability in cognitive function and cognitive decline.

Keywords

aging; Alzheimer's disease; intrinsic excitability; hippocampus; learning and memory; genetic diversity

Introduction

Acquisition of various learning and memory paradigms is dependent on physical and chemical chemical changes in neurons within networks distributed throughout the brain. Long-term synaptic potentiation, or LTP, is a leading candidate mechanism underlying

learning and memory, as it results in the strengthening of synaptic connections to facilitate communication between neurons (Bliss and Lomo 1973). LTP has been most extensively characterized in the hippocampus—and within the hippocampus, at CA3-CA1 synapses (Kumar 2011). The hippocampus is critical to the acquisition and consolidation of episodic and spatial memories, and here LTP is generally thought to facilitate excitatory signal transmission (Wu, Chan et al. 2004). LTP is a strong candidate mechanism underlying learning and memory given that induction is synapse-specific and dependent on presynaptic transmitter release coincident with postsynaptic cell depolarization (Wigstrom and Gustafsson 1985). Functionally, CA3-CA1 glutamatergic NMDA-dependent LTP requires both activation of AMPA receptors and sufficient depolarization of the postsynaptic membrane to remove a magnesium block from NMDA receptors. The subsequent increase of intracellular calcium, primarily due to influx via NMDA receptors, activates protein kinases to initiate a cascade of changes in protein localization and activity (Herring and Nicoll 2016). In the hippocampus, changes associated with LTP, such as AMPA receptor insertion into the postsynaptic membrane, and the resultant enhancement of excitatory transmission, last on the order of hours to days when measured *ex vivo* or longer when measured *in vivo* (Abraham 2003). Subsequent changes in gene and protein expression help to maintain strengthened synaptic connections for longer durations. LTP occurs on a synapse-specific basis, and varied stimulation patterns and neuromodulators regulate the expression of LTP (Lynch, Dunwiddie et al. 1976, Luscher and Malenka 2012). LTP has been extensively described and reviewed on many occasions (Bliss and Lomo 1973, Lynch 2004, Kumar 2011, Herring and Nicoll 2016).

However, additional plasticity mechanisms beyond LTP are also thought to facilitate learning and memory. Since the intrinsic excitability of a neuron determines its likelihood of firing in response to the plethora of synaptic inputs it receives, plasticity of intrinsic excitability is thought to play a major role in learning and memory formation. While controlled by independent mechanisms, intrinsic and synaptic plasticity are tightly coupled, with increases in intrinsic neuronal excitability facilitating synaptic potentiation and strengthening of memory circuits (Sah and Bekkers 1996, Cohen, Cossens et al. 1999, Wu, Chan et al. 2004, Lin, Sim et al. 2010, Sim, Antolin et al. 2013, Gasselin, Inglebert et al. 2015, Joseph and Turrigiano 2017, Liu, Wang et al. 2017). Like synaptic plasticity, intrinsic plasticity in measures such as the post-burst afterhyperpolarization or firing rate occurs throughout the brain and has been most extensively studied in CA1 pyramidal neurons, where it modulates strength of several hippocampal-dependent associative and learning memory tasks (Disterhoft, Coulter et al. 1986, Disterhoft, Disterhoft, Golden et al. 1988, Moyer, Thompson et al. 1996, Weiss, Kronfrost-Collins et al. 1996, McEchron and Disterhoft 1997, McEchron, Tseng et al. 2003, Oh, Kuo et al. 2003, Matthews, Weible et al. 2008, Kaczorowski and Disterhoft 2009, McKay, Matthews et al. 2009, McKay, Oh et al. 2013, Neuner, Wilmott et al. 2015, Dunn, Neuner et al. 2018). Also like LTP, reports in the literature regarding learning-relating changes in intrinsic plasticity differ depending on both stimulation paradigm and recording paradigm, indices of neuronal excitability (e.g., firing rate versus post-spike afterhyperpolarization), genetic background, brain region, and cell type (Disterhoft, Coulter et al. 1986, Disterhoft, Golden et al. 1988, McEchron and Disterhoft 1997, McEchron, Tseng et al. 2003, Kaczorowski, Disterhoft et al. 2007,

Kaczorowski 2011, Moore, Throesch et al. 2011, Kaczorowski, Davis et al. 2012, Sehgal, Ehlers et al. 2014, Oh, Simkin et al. 2016, Neuner, Ding et al. 2019), though our understanding of how to integrate these disparate findings into a single working model of intrinsic plasticity is not yet complete. Finally, both reduced intrinsic excitability and impaired intrinsic plasticity in key brain regions such as CA1 of the hippocampus occur in aging and Alzheimer's disease (AD) and are associated with cognitive deficits (Knuttinen, Gamelli et al. 2001, McEchron, Weible et al. 2001, Power, Wu et al. 2002, Tombaugh, Rowe et al. 2005, Kaczorowski and Disterhoft 2009, Matthews, Linardakis et al. 2009, Oh and Disterhoft 2010, Kaczorowski, Sametsky et al. 2011, Eslamizade, Saffarzadeh et al. 2015, Neuner, Wilmott et al. 2015), though pathological hyperexcitability is also reported as a feature of AD (Amatniek, Hauser et al. 2006, Brown, Chin et al. 2011, Vossel, Beagle et al. 2013, Kerrigan, Brown et al. 2014, Scala, Fusco et al. 2015. Simkin, Hattori et al. 2015, Oh, Simkin et al. 2016, Haberman, Koh et al. 2017) This review addresses the history and recent developments in understanding intrinsic plasticity, with particular focus on how excitability is changed in learning and memory. in aging, in AD, and across genetic backgrounds.

1. The afterhyperpolarization (AHP) as an index of intrinsic excitability

Neuronal excitability can be thought of as a neuron's propensity to fire an action potential in response to an excitatory input, and is dependent on several membrane properties. Fundamentally, the membrane potential of a neuron dictates how much excitatory current is required to reach the action potential threshold, and neurons with more negative membrane potentials further from the threshold required to fire an action potential are generally less excitable. The membrane potential is regulated by the number, distribution and activity of a variety of ion channels distributed throughout the plasma membrane and resultant balance of intracellular and extracellular ion concentration. Prior studies found the resting membrane potential (RMP) to be altered as a function of age and disease state, with various studies finding that RMP may be hyperpolarized in aging (>36mo) rabbits and depolarized in mouse models of AD—(Power, Wu et al. 2002, Musial, Molina-Campos et al. 2018). However, such findings did not necessarily translate to altered intrinsic excitability by other measures (e.g., afterhyperpolarization), and have not been consistently replicated in AD or aged rodents (Tombaugh, Rowe et al. 2005, Kaczorowski, Sametsky et al. 2011, Tamagnini, Novelia et al. 2015), leading our group and others to hypothesize that other deficits in activity-dependent changes in intrinsic excitability (or induction of aberrant plasticity) underlie aging and AD-related learning and memory deficits (McEchron, Weible et al. 2001, Kaczorowski and Disterhoft 2009, Matthews, Linardakis et al. 2009, Kaczorowski, Sametsky et al 2011, Yu, Curlik et al. 2017); reviewed in (Wu, Oh et al. 2002, Disterhoft, Wu et al 2004, Disterrhoft and Oh 2006, Disterhoft and Oh 2007, Oh and Disterhoft 2010, Oh, Oliveira et al. 2010).

Activity-dependent changes in intrinsic excitability associated with learning and memory are many, with learning-related reductions in the post-burst afterhyperpolarization (AHP) arguably being the most reproducible and mechanistically well-understood form of intrinsic plasticity. The AHP is generated in response to a burst of action potentials that drives calcium (Ca^{2+}) influx and activation of calcium-activated outward potassium currents (Storm 1987, Storm 1989). The AHP results in the membrane potential temporarily

becoming more negative relative to RMP (Storm 1987, Storm 1989) and is critical in regulating neuronal excitability, with enhanced AHPs enabling spike-frequency adaptation, or slowing of the subsequent frequency of action potential firing. There are three main calcium-dependent components of the AHP: the fast AHP (fAHP) occurring within 2–5ms of a spike, the medium AHP (mAHP) occurring in the 50–100ms following a one or more spikes, and the slow AHP (sAHP) occurring more than one second following a spike burst (Madison and Nicoll 1986, Storm 1987, Storm 1989, Sah 1996, Stocker, Krause et al. 1999, Shah and Haylett 2000, Kaczorowski, Disterhoft et al. 2007). SK-type potassium currents are particularly important in establishing the fast and medium components of the AHP with alcium currents activating SK channels and allowing for an increase in potassium ion efflux and subsequent hyperpolarization of the membrane potential following a series of Action potentials (Sah and Faber 2002, Pedarzani, McCutcheon et al. 2005, McKay, Oh et al. 2012). Additional outward potassium currents occur via M-type K^+ channels or h-current via HCN cation channels to generate the medium component of the AHP (mAHP) and attenuate neuronal excitability (Gu, Vervaeke et al. 2005). The channels underlying the slow component of the afterhyperpolarization (sAHP) is a subject of debate (Villalobos, Shakkottai et al. 2004, Villalobos, Foehring et al. 2011, King, Rizwan et al. 2015, Turner, Asmara et al. 2016, Wang, Mateos-Aparicio et al. 2016, Tiwari, Mohan et al. 2018), but it is likely regulated by an as-yet unknown calcium-activated K^+ channel. A much slower, Na^+-dependent AHP also follows action potential trains by up to 20s (Schwindt, Spain et al. 1988, Schwindt, Spain et al. 1989, Kaczorowski 2006, Gulledge, Dasari et al. 2013). The mechanisms underlying each component of the AHP are distinct and have been reviewed extensively (Storm 1987, Storm 1989, Gu, Vervaeke et al. 2005, Kaczorowski, Disterhoft et al. 2007, Matthews, Linardakis et al. 2009, Kaczorowski 2011, McKay, Oh et al. 2012, Gulledge, Dasari et al. 2013, Mateos-Aparicio, Murphy et al. 2014). Plasticity of the AHP reflects regulation of the expression distribution, and ratio of various ion channels distributed throughout the plasma membrane.

In addition to classical conductances underlying the AHP reviewed above, a wide-range of ion channels, receptors and neuromodulators have been identified that alter the amplitude and kinetics, making the ionic mechanisms of the AHP (and its plasticity) highly dynamic. Release of internal stores of calcium, in addition to influx of extracellular calcium, also contribute to an enhanced sAHP (Kumar and Foster 2004, van de Vrede, Fossier et al. 2007, Bodhinathan, Kumar et al. 2010). Ryanodine receptors (RyRs) are responsible for the release of intracellular calcium stores from the endoplasmic reticulum pharmacological blockade of RyRs ablates the sAHP, and activation of RyRs with caffeine or RyR agonists prolongs the sAHP and can impair performance on memory tasks such as the passive avoidance test, suggesting that this delayed release of Ca^{2+} from the endoplasmic reticulum is a significant contributor to the sAHP, at least in some neurons (Fujimoto, Yamamoto et al. 1980, Kawai and Watanabe 1989, Yusachev, Smigol et al. 1993. Berridge 1998, Galeotti, Quattrone et al. 2008).

Neuromodulatory transmitters and peptides also mediate intrinsic excitability and help to facilitate memory formation in a variety of brain regions and learning tasks. In general, monoamines such as serotonin, dopamine, and norepinephrine, as well as other excitatory neuromodulators such as PACAP increase intrinsic excitability by reducing postburst AHP

(Pedarzani and Storm 1993, Torres, Arfken et al. 1996, Satake, Mitani et al. 2008, Yi, Zhang et al. 2013, Zhang, Ouyang et al. 2013, Taylor, Madsen et al. 2014). Neurotransmitter activity that is classically important in learning and memory, such as cholinergic signaling via muscarinic receptors and glutamatergic signaling via kainate or metabotropic glutamate receptors, also promote reduced AHP and increased excitability (Pedarzani and Storm 1993, Mannaioni, Marino et al. 2001, Ireland, Guevremont et al. 2004, Brager and Johnston 2007, Santini, Sepulveda - Orengo et al. 2012, Chandra, Awasthi et al. 2019). Activation of muscarinic receptors with muscarine or carbachol reduces the M-current to dampen the AHP and facilitate learning on tasks such as auditory cued fear conditioning (Kawasaki and Avoli 1996, Santini, Sepulveda - Orengo et al. 2012, Lv, Dickerson et al. 2017); antagonizing these receptors with scopolamine has the opposite effects (Saar, Grossman et al. 2001).

Brain-derived neurotrophic factor (BDNF), likewise, has been associated with enhanced cognitive function and promotes synaptic plasticity (Yamada, Mizuno et al.2002, Lu, Christian et al. 2008, Leal, Bramham et al. 2017) and increases intrinsic excitability of cortical and hippocampal neurons *in vitro* (Desai, Rutherford et al. 1999, Bolton, Pittman et al. 2000). Underlying this enhanced synaptic plasticity induced by BDNF may be a reduction in the AHP, which has been shown to occur in CA1 (Kramar, Lin et al. 2004). In the hippocampal output neurons of the subiculum, BDNF has differential effects on intinsic excitability depending on cell type, with BDNF enhancing excitability in burst-spiking neurons and reducing excitability of regular-spiking neurons (Graves, Moore et al. 2006); this suggests that modulators of intrinsic plasticity may be cell-type specific, a concept covered in greater detail in the next section (2.1).

2. Learning-related enhancement in intrinsic neuronal excitability as targets for cognitive enhancement

The AHP is modulated by associative learning and aging, and this plasticity is a primary candidate mechanism for a non-synaptic basis for learning and memory. The relationship between AHP a.amplitude and learning efficiency has been documented in various cell types in several brain rejions including CA1 and CA3 of the hippocampus, the subiculum, the cortex, amygdala, and cerebellum (Disterhoft, Coulter et al. 1986, Disterhoft, Golden et al. 1988, Moyer, Thompson et al. 1996, Saar, Grossman et al. 2001, Saar and Barkai 2003, Matthews, Weible et al. 2008, Mahon and Charpier 2012, Sim, Antolin et al. 2013, Yi, Zhang et al. 2013, Sehgal, Ehlers et al. 2014, Song, Ehlers et al. 2015, Hamlet and Lu 2016, Soler-Cedeno, Cruz et al. 2016, Smithers, Terry et al. 2017, Dunn, Neuner et al. 2018, Chandra, Awasthi et al. 2019). Pharmacological and gene-therapy interventions that modulate the AHP have been shown to rescue cognitive deficits associated with aging, and enhancement of the AHP impairs learning (Disterhoft and Oh 2006, Matthews and Disterhoft 2009, Criado-Marrero, Santini et al. 2014, Neuner, Wilmott et al. 2015, Sun and Jacobs 2016, Yu, Curlik et al. 2017).

Work from our group and others has established a strong role of intrinsic plasticity as a cellular basis for learning and memory, particularly within the hippocampal formation. Learning of a hippocampal-dependent spatial task, such as the Morris water maze, is

sufficient to enhance intrinsic excitability within CA1 (Oh, Kuo et al. 2003). Hippocampal-dependent conditioning tasks such as trace or delayed eyeblink or fear conditioning remodel intrinsic plasticity and reduce the AHP, thereby reducing the threshold required to elicit subsequt action potentials (Moyer, Thompson et al. 1996, Weiss, Kronfrost-Collins et al. 1996, McEchron and Disterhoft 1997, McKay, Matthews et al. 2009, Kaczorowski 2011, McKay, oh et al. 2013). In addition to modulating hippocampal intrinsic excitability, those learning tasks that are dependent on intact fear circuitry, such as trace eyeblink conditioning or cued auditory fear conditioning (Phillips and LeDoux 1992, Kochli, Thompson et al. 2015) also induce enhanced excitability of neurons in the amygdala, cerebellum, and various parts of the cortex (Repa, Muller et al. 2001, Belmeguenai, Hosy et al. 2010, Sehgal, Ehlers, et al. 2014, Song, Ehlers et al. 2015). Within the amygdala, both fear learning (such as trace fear conditioning) and appetitive learning (e.g., “rule learning” to associate certain odors with reward) enhance intrinsic excitability (Saar, Grossman et al. 1998, Sehgal, Ehlers et al. 2014).

Plasticity in the AHP following learning peaks within about one day of learning and is transient, lasting about a week following learning (Moyer, Thompson et al. 1996, Thompson, Moyer et al. 1996), though others have observed changes in intrinsic excitability lasting between three days to multiple weeks (Saar, Grossman et al. 1998, Schreurs, Gusev et al. 1998), depending on. animal model, brain region, and conditioning paradigm. The lack of long-term persistence suggests that plasticity in intrinsic neuronal properties allows for longer-term changes to occur, such as synaptic strengthening and integration of the memory into neocortical areas that ultimately supports long-term storage of the learned memory (Davis and Squire 1984, Wiltgen, Brown et al. 2004, Costa-Mattioli, Sossin et al. 2009, Cohen-Matsliah, Motanis et al. 2010).

Across animals, learning is directly correlated with intrinsic plasticity. Learning-related changes in intrinsic excitability are absent both in animals that fail to learn a task (e.g., delayed eyeblink conditioning, Morris water maze), and in “pseudoconditioned” animals, which are control animals that underwent similar training to eyeblink conditioning but whose cue was unpaired with the stimulus (Disterhoft, Coulter et al. 1986, Disterhoft, Golden et al. 1988). Only those animals that successfully learn a task display plasticity in intrinsic excitability. Furthermore, animals that have lower baseline intrinsic excitability (i.e. hypoexcitability), such as that observed in aging or disease, likely explain why they are less able to learn tasks similarly to young, healthy animals (McEchron, Weible et al. 2001, Disterhoft, Wu et al. 2004, Disterhoft and Oh 2006, Disterhoft and Oh 2007, Kaczorowski and Disterhoft 2009, Oh, Oliveira et al. 2010, Kaczorowski, Sametsky et al. 2011). When aged animals are given extended training in order to acquire a fear memory to a similar level to young animals, they display similar plasticity in the AHP, suggesting that – to some degree – cognitive declin in aging may be related to a slower intrinsic excitability plasticity response in CA1 (Moyer 2010). Further details about age- and disease-related impairments in intrinsic plasticity are described below.

Finally, extracellular monitoring of CA1 neurons *in vivo* during learning has revealed further nuance to the relationship between intrinsic excitability and memory acquisition. During eyeblink conditioning acquisition, firing rate of CAI neurons is increased, suggesting that

enhanced excitability that has been consistently observed in whole-cell slice recordings corresponds to enhanced excitability *in vivo.* This increase in neuronal activity occurs on the day before and the first day of exhibition oi the conditioned response within 200ms of presentation of the conditioned stimulus. However this increase in firing declines in the days after learning has been established, and CAI firing rate is suppressed during the task as measured *in vivo* via extracellular recordings (McEchron and Disterhoft 1997). This may be indicative of a mechanism that enhances signal-to-noise ratio by preventing a learning response to extraneous or non-salient stimuli. This decrease in firing rate *in vivo* also corresponds to an increase of inhibitory input into CA1 following acquisition of the task that has been observed *ex vivo* (McKay, Oh et al. 2013), but is also coincident with increased intrinsic excitability of CA1 hippocampal neurons measured *ex vivo,* such as decreases in the AHP which persist up to several days following similar training. The mechanism/s underlying these apparently discrepant changes remain unclear, but may be attributed to differences inherent in each respective recording modality as discussed in more detail below in section 3.1.

2.1 Cellular heterogeneity in recruitment during learning tasks.

One of the particularly interesting features of intrinsic plasticity is the diversity in plasticity that is observed across cell types, brain regions, and individual animals. Not all neurons in a single brain region display intrinsic plasticity following successful learning. In cognitively intact, young adult animals, 25–57% of neurons exhibit learning-related modulation of intrinsic excitability. Within this range, *ex vivo* hippocampal slice recordings following trace conditioning have consistently found that between 30–50% CA1 neurons exhibit enhanced excitability following trace conditioning learning, where “responding” cells are generally defined as having postburst AHP amplitudes of one or two standard deviations. above the mean naïve animal AHP (Moyer, Thompson et al. 1996, Moyer, Power et al. 2000, Oh, McKay et al. 2009). *In vivo,* defining and reporting proportions of “responding” cells as measured by increased firing by extracellular recordings is more variable, representing the extremes of that range (Weiss, Kronfrost-Collins et al. 1996, McEchron, Tseng et al. 2003). A similar proportion (~30%) of lateral amygdala neurons display intrinsic plasticity in learning trace fear conditioning (Sehgal, Ehlers et al. 2014) when measured *ex vivo*. Interestingly, aged animals that require more extensive training to acquire tone fear conditioning compared to young animals may have a higher percentage of learning-participant neurons (89% in CA1), suggesting that acquiring long term-memories in aging requires greater neuronal participation than in young animals (Moyer, et al. 2000). This variation in the percent allocation of neurons within a given brain region during a learning task, particularly in young animals, hints at specialization of subsets of neurons for particular and simple. tasks such as fear conditioning. Neurons that are more excitable are more easily recruited. to formation of a memory engram, and more complex learning, or recall of more temporally distant memories, is thought to require a larger proportion of neurons to allow for the comprehensive encoding of a multifaceted context or problem (Lisman, Cooper et al. 2018, Rao-Ruiz, Yu et al. 2019).

Presumably, those neurons that participate in a learning event are most likely to display alterations in their intrinsic excitability (Han, Kushner et al. 2007, Reijmers, Perkins et al.

2007). Identification of learning-participant and leaming-nonparticipant cells, the characteristics that distinguish them, and their role in disease has been of recent interest (Denny, Kheirbek et al. 2014, Tonegawa, Liu et al. 2015, Grewe, Grundemann et al. 2017, Perusini, Cajigas et al. 2017, Butler, Wilson et al. 2018). Mechanistically, cAMP responsive element binding protein (CREB) expression appears to regulate allocation of cells to participate in learning within the amygdala and hippocampus, as higher CREB expression facilitates learning and cells with higher CREB expression are more excitable following conditioned or associative learning (Zhou, Won et al. 2009, Yiu, Rashid et al. 2011, Frankland and Josselyn 2015, Rogerson, Jayaprakash et al. 2016, Lisman, Cooper et al. 2018). CREB expression is triggered by increases in intracellular calcium concentration, and regulates gene transcription to support long-term memory formation and has long been associated with learning and memory (Silva, Kogan et al. 1998) thus CREB activation may be a key player in linking intrinsic plasticity in learning-participant neurons (and associated elevated intracellular calcium) to mechanisms underlying long-term memory stabilization and storage (Sehgal, Zhou et al. 2018). However, a full characterization of differences between neurons that do and do not display intrinsic plasticity, and how cells are recruited to participate in particular learning tasks, remains to be elucidated.

2.2 Region- and cell-specific differences in neuronal excitability underlie different modalities of information in complex learning and memory tasks.

Across brain regions and cell type, learning generally results in enhanced intrinsic plasticity, though there are notable exceptions. for example, the amygdala has region-specific plasticity following olfactory fear conch fining, with some regions (such as the BLA) displaying *reduced* excitability (enhanced spike adaptation) while the LA shows enhanced excitability (reduced AHP, spike adaptation) (Motanis, Maroun et al. 2014, Sehgal, Ehlers et al. 2014). Within the subiculum, our group has recently shown that neurons also undergo learning-related changes in plasticity, though this plasticity varies by cell type: burst-spiking neurons undergo an apparent conversion to regular spiking, and regular spiking neurons specifically display enhanced intrinsic excitability (Dunn, Neuner et al. 2018). Our and others' observations of a reduction in bursting, or burst-spiking cell-specific excitability is interesting and indicates that intrinsic plasticity is a complex and flexible process in various brain regions (Kaczorowski, Davis et al. 2012). In particular, this hints at mechanisms that carefully titrate excitability in various cell types, and that increased excitability may not be a universal solution to learning. More refined flexibility is required; reductions in excitability or bursting in one area or cell type may help to amplify the effects of increased excitability in other cells, thereby improving signal-to-noise output from the hippocampus. This cell-specific nature of intrinsic plasticity is reminiscent of the *synapse* specificity of LTP, where potentiation and strengthening at one synapse is associated with the weakening of nearby, non-participant synapses to—again—improve the signal-to-noise ratio of salient connections within a circuit.

3. Aging and Alzheimer's-disease induced changes in intrinsic excitability

Middle-aged and aged rodents, and particularly those that model AD, display deficits on hippocampal-dependent memory tasks relative to young and non-transgenic controls

(Knuttinen et al. 2001; Kaczorowski et al. 2009; Matthews et al., 2009, McEchron et al. 2001; Moyer et al 2000; Tombaugh 2005). These aging and AD-related cognitive deficits correspond to significant changes in intrinsic excitability in the hippocampal neurons measured *ex vivo* in brain slices.

Many studies have demonstrated age-related impairments in intrinsic excitability and/or plasticity in the hippocampus and elsewhere in the brain that correlate with impaired cognitive function. In hippocampal-dependent memory tasks--such as trace eyeblink conditioning, Morris water maze, or fear conditioning--animals that show impaired learning also have enhanced AHP and spike adaptation (Moyer, Power et al. 2000, Knuttinen, Gamelli et al. 2001, Tombaugh, Rowe et al. 2005, Moyer and Brown 2006, Kaczorowski and Disterhoft 2009, Matthews and Disterhoft 2009, Song, Detert et al. 2012) Matthews 2009, consistent with reduced intrinsic excitability. Baseline firing rate of CA1 neurons is also reduced in aging animals that display learning deficits (McEchron, Weible et al. 2001). Aging animals also show impairments in cognitive flexibility associated with extinction of fear conditioning prior to deficits in contextual fear conditioning. Underlying this is a reorganization of excitability in the medial prefrontal cortex (mPFC). Specifically, impaired fear extinction in aging is associated with increases in excitability in burst-spiking neurons in the prelimbic mPFC, but reduced excitability in the infralimbic mPFC (Kaczorowski, Davis et al. 2012). This suggests that a simple reduction in excitability in circuitry involved with cognitive decline in aging is not universal, and such reports should be considered as part of a more complex restructuring of neuronal excitability balance occurring throughout the aging process.

Animals with AD-associated cognitive decline also display deficits in intrinsic excitability similar to those typically observed in aging-related cognitive decline, as well as some changes that are specific to AD. In mouse models of AD, deficits in contextual fear conditioning are associated with deficits in intrinsic plasticity following learning, as well as a reduction in excitability at baseline that is not seen in normal aging (Kaczorowski, Sametsky et al. 2011).

Our lab and others have proposed other mechanisms by which aging may disrupt intrinsic plasticity and learning. First, intrinsic plasticity in CA1 is highly dependent on Ca^{2+} homeostasis, as regulation of the AHP is mediated by Ca^{2+}-dependent K^+ currents. Generally, these currents are initiated upon an increase in intracellular calcium following neuronal activity. However, in both normal aging and AD, Ca^{2+} homeostasis is disrupted and intracellular Ca^{2+} concentrations may be elevated (Khachaturian 1987, Landfield 1987, Thibault, Mazzanti et al. 1995, Hölscher 2005), particularly in cells that are in close proximity to amyloid plaques in AD (Kirischuk and Verkhratsky 1996, Hermes, Eichhoff et al. 2010). The precise mechanisms underlying Ca^{2+} dyshomeostasis in aging and AD have not been fully elucidated, though several components that maintain calcium homeostasis are disrupted. With aging comes an altered calcium buffering and increases in intracellular calcium following activity, and in AD, disease-related pathology, such as amyloid beta-induced disruption of calcium signaling pathways. Interestingly, calcium buffering may be *enhanced* in aging but become more quickly overwhelmed during high-frequency spiking, ultimately leading to increased cytosolic calcium concentrations (Oh 2013). Impaired RyR

regulation result in intracellular calcium stores within the endoplasmic reticulum “leaking” into the cytoplasm in aging and AD, thereby increasing cytoplasmic calcium concentration and contributing to neuron and cognitive dysfunction (Kumar and Foster 2004, Gant, Sama et al. 2006, Stutzmann, Smith et al. 2006, Del Prete, Checler et al. 2014); these finding, are supported by an increase in intracellular Ca^{2+} release pathway gene expression in the hippocampi of aged, cognitively impaired rats (Blalock, Chen et al. 2003). These data suggest that RyRs may be a promising target for the treatment of AD; in fact, blocking of RyRs has been shown to improve cognitive function in preclinical AD mouse models (Oules, Del Prete et al. 2012). Increased influx of calcium via L-type calcium channels, in part due to an increase in total channel number, enhances the sAHP underlying age- and AD-related cognitive deficits (Landfield and Pitler 1982, Thibault and Landfield 1996, Power, Wu et al. 2002). Blocking L-type calcium channels with nimodipine or nifedipine corrects both deficits in intrinsic plasticity and learning in aged animals (Quevedo, Vianna et al. 1998, Shah and Haylett 2000, Disterhoft and Oh 2006).

Second, given the importance of ion channels and receptors in mediating both synaptic and intrinsic plasticity, we have also hypothesized that targeted analysis of alterations in these proteins would provide further insight into specific changes underlying impaired intrinsic plasticity and learning in aging animals. Indeed, using a targeted proteomics approach, we identified TRPC3, a calcium channel, as a candidate protein regulating impaired intrinsic excitability and learning in middle-aged animals (Neuner, Wilmott et al. 2015). TRPC3 acts as a negative regulator of both neuron excitability and learning in adult mice, as we found that TRPC3 expression is downregulated following learning, and reductions in TRPC3 basal expression levels enhance performance on contextual fear memory tasks. In addition to this role in normal cognitive function in young animals, we have sine, identified a role for TRPC3 in cognitive aging and AD using multiple mouse models We also found that knockdown of hippocampal TRPC3 reduces amyloid burden and improves performance on both working memory and contextual fear conditioning (data in preparation and in (Neuner, Hohman et al. 2017)). These data suggest that such approaches (i.e., targeted proteomic analysis and quantitative trait mapping in diverse population of AD mice) will be powerful in identifying additional regulators of aging-related cognitive and excitability impairments.

3.1 Neuronal hyperexcitability in AD

Neuronal hyperexcitability is also commonly reported in human AD and animal AD models. This is particularly evident when considering the high incidence of seizure among patients with AD; in fact, seizure is one of the main clinical features of AD beyond cognitive decline (Amatniek, Hauser et al. 2006). Further, seizure activity is predictive of poorer cognitive function (Vossel, Beagle et al. 2013). Hippocampal neurons from AD models display hyperexcitability, increased firing rate, and elevated number of activated neurons, both within CA3 (Simkin, Hattori et al. 2015, Oh, Simkin et al. 2016, Haberman, Koh et al. 2017) and CA1 (Brown, Chin et al. 2011, Kerrigan, Brown et al. 2014, Scala, Fusco et al. 2015). In both mice and humans, this hippocampal neuron hyperexcitability correlates with impaired cognition (Roberson, Halabisky et al. 2011, Simkin, Hattori et al. 2015, Haberman, Koh et al. 2017). Reducing this hyperexcitability with the antiepileptic drug levetiracetam and its derivatives counter both cognitive deficits and synapse loss in human AD and mouse models

of the disease (Sze 2000, Cumbo and Ligori 2010, Bakker, Krauss et al. 2012, Robinson, Molina-Porcel et al. 2014, Sola, Aso et al. 2015, Loscher, Gillard et al. 2016).

Both tau and amyloid aggregates found in AD are directly associated with increases in neuronal excitability in both CA1 and CA3, with hyperexcitability being observed in particular in neurons in close proximity to plaques (Busche, Eichhoff et al. 2008, Tamagnini, Novelia et al. 2015), possibly in response to plaque-induced increases in intracellular caRiur concentrations (Kuchibhotla, Goldman et al. 2008). Such hyperexcitability likely contributes to increased incidence of seizure and epileptic activity seen in AD and mouse models of AD (Minkeviciene, Rheims et al. 2009). Interestingly, hyperexcitability has also been observed before plaque formation, suggesting that amyloid beta oligomers are also sufficient to induce hyperexcitability (Busche, Chen et al. 2012), and correcting such hyperexcitability in AD models can be achieved by immunizing against Aβ (Kazim, Chuang et al. 2017). Tau pathology also induces hyperexcitability and exacerbates amyloid-beta induces hyperexcitability (Roberson, Halabisky et al. 2011, Maeda, Djukic et al. 2016).

Mechanisms underlying the relationship between AD pathology-induced hyperexcitability, cognitive decline, and neurodegeneration have not been fully explored. Excitotoxicity of overactive neurons likely contributes to cell death, and aberrant activity within the memory engram impairs cognitive function (Palop and Mucke 2010). Neuronal activity induces DNA double-strand breaks, which are generally efficiently repaired in young mice. This DNA damage is heightened in aging and AD, and further accelerated in these mice following exposure to novel environments. Thus, aberrant excitability in AD may exacerbate the accumulation of this double stranded DNA breaks and increase vulnerability to neuron loss; correcting such hyperexcitability may reduce this effect (Suberbielle, Sanchez et al. 2013).

The imbalance and potential paradox of observed both hyper- and hypoexcitability in AD has also been an interesting point of discussion and investigation. Hyperexcitability in CA3 results in an increase in stimulation to CA1, which in turn may cause compensatory reductions in intrinsic excitability that have been commonly observed in CA1 (Oh, Simkin et al. 2016). One challenge in interpreting these data, though, is the variability in recording parameters across studies. *In vivo* recordings, both using extracellular electrophysiological recording electrodes and calcium imaging, have often reported hyperexcitability in the hippocampus of AD models; however, hypoexcitability has been extensively reported from *ex vivo* whole-cell electrophysiological recordings, particularly in CA1. *Ex vivo* activity using whole-cell recordings is intrinsically different from *in vivo* extracellular configurations, as these experiments disrupt and disconnect the recorded neurons from much of their larger circuitry. Furthermore, slice preparation methods (including anesthesia and decapitation) may themselves induce noradrenergic signaling that modulates intrinsic excitability (Zhang, Ouyang et al. 2013). Extracellular recordings *in vivo* cannot measure classical measures of intrinsic excitability such as AHP. Careful consideration of slice preparation for *ex vivo* recordings, or opting for *in vivo* extracellular recordings in awake, behaving animals reduces these potentially confounding effects of slice preparation. *Ex vivo* recording has been a highly valuable to understand mechanism underlying such changes, but in recent improvements in our ability to measure neuronal excitability *in vivo* may help to further elucidate physiological changes associated with aging, AD and learning. To better

harmonize the current discrepant findings, *in vivo* whole-cell patch-clamp experiments or the use of next-generation voltage sensing dyes to measure *changes* in AHP during and after learning and in disease will be particularly informative and may be achieved in the future (Lee and Brecht 2018); however, to our knowledge these experiments have not yet been completed.

4. Genetic background and intrinsic excitability

As described above, there is variability in how well individual animals learn, and these differences are often reflected in corresponding differences in intrinsic plasticity. For example, some aged rodents display significant impairment in cognitive function and hippocampal neuron plasticity, whereas other animals of the same age have cognitive and neuronal function similar to young, healthy animals. The mechanism underlying these differences is not well understood; however, this heterogeneity may be exploited to better understand how neuronal plasticity is differentially modulated—either by genetic or environmental factors, or stochastic changes in brain state—and how this contributes to cognitive function.

One potential opportunity for improved understanding of how intrinsic plasticity contributes to proper and pathological cognitive function is to identify genetically-regulated differences between species and strains of model animals. For example, cognitive function, susceptibility to disease-related cognitive decline, and synaptic and intrinsic plasticity are all related and vary across rodent strains. C57BL/6J and 129/SvEms strains show relatively robust long-term potentiation in response to a theta burst stimulation compared to DBA/2J and CBA/J mice (Nguyen 2006). However, C57BL/6J and 129/SvEms mice show distinct intrinsic plasticity: 129/S mice exhibit reduced postburst AHP in CA1 pyramidal neurons compared to C57BL/6J mice, with mice from the F2 generation of a cross between the two strains showing an intermediate AHP amplitude; these differences are in the absence of any major differences in cell morphology (Moore, Throesch et al. 2011).

Additionally, various common laboratory strains have widely differing seizure activity (Letts, Beyer et al. 2014), and these differences may correspond to variability in amyloid pathology in AD (Jackson, Onos et al. 2015). Within populations of mixed genetic backgrounds, some aged animals show baseline neuronal excitability and intrinsic plasticity resembling that of “young” animals (Kaczorowski, Sametsky et al. 2011). These differences correspond to differences in cognitive function and age-related cognitive decline. However, the mechanisms underlying these differences are not well understood—and these particular ocular populations are not well-suited to help identify the molecular or genetic mediators of these differences.

Complex strain crosses, particularly recombinant inbred populations, will allow us to exploit strain differences in neuronal excitability and learning capacity across the lifespan and systematically dissect out molecular mediators through refined genetic mapping and multi-omic analyses. Utilizing the recombinant inbred population of BXD mice, genetic variants underlying similar varied excitability have been explored (Jansen, Timmerman et al. 2011). As an example of this concept out group recently assessed cognitive aging in the BXD mice,

and performed quantitative trait locus analysis (QTL) to determine genetic variants underlying strain differences in intrinsic. excitability and cognitive function. We identified variants in the gene encoding heterochromatin protein 1 binding protein 3 (*Hplbp3)* as mediating cognitive decline in aging mice. Follow-up analyses confirmed that HP1BP3 modulates both intrinsic and synaptic plasticity, and is down regulated in cognitively impaired aged humans (Neuner, Garfinkel et al. 2016, Neuner, Ding et al. 2019). HP1BP3 regulates expression of genes in synapse and neuronal function, providing further support that neuronal excitability regulates cognitive function (Neuner, Garfinkel et al. 2016). Finally, our novel mouse model, which incorporates AD mutations into BXD strains (AD-BXDs) provides a powerful resource to identify mediators of susceptibility to specific AD-related changes in neuronal excitability and plasticity (Neuner, Heuer et al. 2018, Neuner, Heuer et al. 2019). Such investigations promise to elucidate additional molecular regulators of learning, memory, and cognitive decline with aging and AD, which will potentially reveal novel therapeutic targets to treat such dysfunction.

4.1 Changes in intrinsic excitability with environmental enrichment or stressors

In addition to genetic factors, environmental factors are known to modulate intrinsic plasticity, thereby regulating the relationship between neuron excitability and cognitive function. For example, environmental enrichment, which facilitates learning, is sufficient to enhance intrinsic excitability of hippocampal neurons (Kumar and Foster 2007, Malik and Chattarji 2012). Certain forms of acute stress also enhance hippocampal intrinsic excitability and potentiate learning (Weiss, Sametsky et al. 2005, Narayanan and Chattarji 2010), while social isolation stress inhibits both synaptic and intrinsic excitablity (Yamamuro, Yoshino et al. 2018). These data suggest that modulation of intrinsic excitablity via beneficial environmental exposures may confer enhanced learning and memory function, providing promise for the potential of pharmacological interventions that also enhance intrinsic excitability to be cognitive enhancers.

One unexplored domain is to understand how these environmental factors may interact with genetic factors to modulate intrinsic plasticity and cognitive function. For example, genetic factors may set a “baseline” of intrinsic excitability which is then modulated by an individual’s environmental exposure to enrichment or stressors. Learning a task occurs in the context of these varied genetic and environmental modulators and efficacy of learning, as well as vulnerability to age- and AD-related decay, likely depends on the interaction of all of these factors.

5. Plasticity in the subiculum as a potential target for AD

Targeting intrinsic plasticity in aging and AD may be a promising therapeutic strategy to preserve cognitive function and neuronal integrity. Understanding how intrinsic excitability affects the memory engram or across the memory circuitry will be important for maximizing success of such therapies. For example, though much of our understanding of intrinsic plasticity has been focused in CA1, it will be valuable to explore the consequences of manipulating intrinsic excitability in other relevant brain regions. The subiculum may be of particular interest, as it is the main output region of the hippocampus, and one of the first

brain regions to exhibit AD-related pathology and atrophy in humans and animal models of AD (Carlesimo, Piras et al. 2015, Heggland, Storkaas et al. 2015, Lindberg, Martensson et al. 2017). Lesions (experimentally- or disease-induced) in the subiculum are associated with impaired memory (Maren 1999, Lindberg, Martensson et al. 2017). The subiculum is also unique within the greater hippocampal formation in its pyramidal cell heterogeneity: about half of the cells in the subiculum are bursting cells and fire multiple action potentials upon a stimulus pulse (Staff, Jung et al. 2000). We recently established that pyramidal neurons within the subiculum undergo unique learning-related and cell-type specific plasticity (Dunn, Neuner et al. 2018). Specifically, we observed reduced excitability and downregulation of burst-spiking activity, and enhanced excitability of regular spiking neurons following learning in young mice. Though aging- and AD-related changes in intrinsic excitability have been extensively investigated in CA1 and CA3 of the hippocampus, much less attention has been directed toward age-related changes in the subiculum. However, given its early vulnerablity to disease processes, as well as its critical role in integrating all hippocampal signal output, the subiculum may prove to be an ideal target for AD therapeutics.

6. Future directions

The majority of work on modulation of intrinsic excitability has focused on the primary pyramidal neurons in CA1 and CA3 of the hippocampus during associative learning, along with brain regions associated circuitry. Our understanding of how learning, aging and disease affect intrinsic excitability is incomplete, though recent technological developments will allow us to address some of the outstanding questions.

One of the initial questions may be to characterize plasticity specifically in learning-participant/memory engram neurons both *ex vivo* and *in vivo* using neuronal activity reporter models. There is significant variability among populations of neurons within a given structure that display plasticity in intrinsic properties following learning. Understanding how plasticity occurs in context of greater circuitry, and how intrinsic plasticity modifies activity of downstream targets will perhaps give us a better idea of which neurons are participating in learning, and whether propensity to plasticity differs across neurons. Additionally, the mechanisms underlying the “choice” (i.e. allocation) of neurons that participate in learning, and how plasticity is specifically and transiently induced in these neurons, have been largely unexplored. For example, transcriptomic and/or epigenetic mechanisms that likely contribute to these specific and transient changes (such as those observed as mediating synaptic plasticity (Campbell and Wood 2019)) could be identified using neuronal activity markers separate learning-participant vs non-active neurons; this could be followed by single-cell sequencing to identify differences between these two populations of neurons, similarly to recent approaches to characterize distinct cell populations within discrete brain regions such as the subiculum (Cembrowski, Wang et al. 2018).

Next, much of our understanding of intrinsic plasticity has been derived from largely correlative studies. *In vivo* monitoring and manipulation of activity or plasticity may directly address which changes in intrinsic plasticity may be most important in augmenting learning. For example, *in vivo* whole-cell patch clamp in the cortex may address whether observed

impaired and aberrant intrinsic plasticity in AD (as measured in slices) is truly reflective of *in vivo* changes when the cell is recorded in the context of its larger circuitry. *In vivo* calcium imaging to monitor cellular activity also allows for direct single-cell monitoring of neuronal activity; though it would not be able to contribute to further understanding of how intrinsic membrane properties change, this technique has already shed considerable light on the regional variability and imbalance of excitability changes in the hippocampus, particularly in AD and surrounding AD pathology. Finally, controlling neuronal function optogenetically to manipulate plasticity and learning will provide clues to the causative relationship between intrinsic plasticity in learning, aging and disease (Liu, Ramirez et al. 2012). For example, CA1 neurons display reduced excitability with age, though as described earlier this has been postulated to occur as a compensatory downregulation of activity in response to CA3 hyperactivity. Manipulating CA3 activity *in vivo* may change the intrinsic plasticity output we observe in CA1 both *in vivo* and *ex vivo.* Ultimately, a better understanding of these mechanisms may lead us to novel treatments of cognitive decline in aging.

Finally, recent efforts in AD research have demonstrated the utility and necessity of integrating multi-scale data, from genes to behavior, in order to build a working model of complex processes occurring in the disease (Sancesario and Bernardini 2018). High-throughput methods have been established at many levels, including molecular ‘omics and behavior, and the required computational modeling has advanced alongside; however, we do not yet have the ability to examine electrophysiological properties of neurons at a similar scale in order to fully understand the upstream and downstream factors influencing plasticity and its functional outcome. A common theme in this review is the heterogeneity of electrophysiological outputs relating to neuronal excitability reported in the literature, across animal models, brain regions, cell types, and recording paradigms—with a lack of satisfying harmonization of the data into a well-defined model of single-neuron plasticity and its role in learning, aging, and disease. Improving the throughput of electrophysiology, both *in vivo* and *ex vivo* will allow us to incorporate such measures into our advancing models of memory circuit function and molecular and behavioral changes in disease.

7. Conclusions

Intrinsic plasticity is critical to learning throughout the brain, and particularly in CA1 during learning of hippocampal-dependent tasks. Aging and AD alter intrinsic excitability, but restoring this plasticity can rescue cognitive deficits. Further work should focus on *in vivo* dissection of regional and cell-type differences in excitability changes during learning, aging and disease in order to better target potential cognitive enhancers/disease therapeutics.

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Highlights:

- Plasticity of intrinsic excitability underlies hippocampal learning and memory
- Impaired intrinsic plasticity is a feature of aging and Alzheimer's disease (AD)
- We have an incomplete understanding intrinsic plasticity in memory, aging and AD
- Future studies may facilitate therapeutically targeting intrinsic excitability