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Dissecting the age-related decline on spatial learning and memory tasks in rodent models: N-methyl-D-aspartate receptors and voltage-dependent Ca^{2+} channels in senescent synaptic plasticity

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Abstract

In humans, heterogeneity in the decline of hippocampal-dependent episodic memory is observed during aging. Rodents have been employed as models of age-related cognitive decline and the spatial water maze has been used to show variability in the emergence and extent of impaired hippocampal-dependent memory. Impairment in the consolidation of intermediate-term memory for rapidly acquired and flexible spatial information emerges early, in middle-age. As aging proceeds, deficits may broaden to include impaired incremental learning of a spatial reference memory. The extent and time course of impairment has been linked to senescence of calcium (Ca^{2+}) regulation and Ca^{2+} -dependent synaptic plasticity mechanisms in region CA1. Specifically, aging is associated with altered function of N-methyl-D-aspartate receptors (NMDARs), voltage-dependent Ca^{2+} channels (VDCCs), and ryanodine receptors (RyRs) linked to intracellular Ca^{2+} stores (ICS). In young animals, NMDAR activation induces long-term potentiation of synaptic transmission (NMDAR-LTP), which is thought to mediate the rapid consolidation of intermediate-term memory. Oxidative stress, starting in middle-age, reduces NMDAR function. In addition, VDCCs and ICS can actively inhibit NMDAR-dependent LTP and oxidative stress enhances the role of VDCC and RyR-ICS in regulating synaptic plasticity. Blockade of L-type VDCCs promotes NMDAR-LTP and memory in older animals. Interestingly, pharmacological or genetic manipulations to reduce hippocampal NMDAR function readily impair memory consolidation or rapid learning, generally leaving incremental learning intact. Finally, evidence is mounting to indicate a role for VDCC-dependent synaptic plasticity in associative learning and the consolidation of remote memories. Thus, VDCC-dependent synaptic plasticity and extrahippocampal systems may contribute to incremental learning deficits observed with advanced aging.

Keywords

episodic memory; incremental learning; long-term potentiation; aging

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1. Introduction

Animal models of age-related cognitive decline are employed to mimic features of human senescence in order to assist in identifying the molecular mechanisms and development of potential therapeutics. For each model, the appropriateness will depend on a number of factors including translational relevance, background genetics, availability of aged animals, and type of experimental manipulations involved. In order to enhance the translational relevance, it is important that the model has face validity, exhibiting similar symptoms relative to the human condition. Aging in humans is associated with a weakening of working memory, executive function, and processing speed; however, the most notable decline is observed as impaired episodic memory, including spatial memory (Kukolja *et al.*, 2009; Plancher *et al.*, 2010; Uttl and Graf, 1993). The impairment can be identified as a mild deficit in the rapid acquisition of flexible information and an increase in the rate of forgetting (Davis *et al.*, 2003; Hogge *et al.*, 2008; Huppert and Kopelman, 1989; Kral, 1962; Macdonald *et al.*, 2006; Mitchell *et al.*, 1990; Park *et al.*, 1988; Rajah *et al.*, 2010).

A second important aspect of age-related cognitive decline is that chronological age alone does not predict cognitive health. There is enormous variability in cognitive function across the life span from “successful” aging with little memory decline, through memory deficits associated with “unsuccessful” aging, to cognitive changes linked to dementia and neurodegeneration (Foster, 2006; Glisky, 2007). Notably, the deterioration of memory function in humans is progressive (Christensen *et al.*, 1999; Colsher and Wallace, 1991; Mungas *et al.*, 2010; Schonknecht *et al.*, 2005; Zelinski and Burnight, 1997) and an increase in forgetting may be an early sign of impaired synaptic transmission or an evolving neurodegeneration (Dierckx *et al.*, 2010; Gagnon and Belleville, 2010). Indeed, episodic memory deficits are symptomatic of impaired hippocampal function and the progressive decline in episodic memory is associated with a decrease in hippocampal volume (Kramer *et al.*, 2007; Mueller *et al.*, 2007; Mungas *et al.*, 2005; Reuter-Lorenz and Park, 2010; Sexton *et al.*, 2010; Stoub *et al.*, 2008). The question remains as to what mechanisms underlie different trajectories for memory decline and the heterogeneity in memory function in older individuals.

Rodents offer several benefits as models for investigation of the mechanisms and potential treatment of age-related cognitive decline. Similar to humans, information that requires hippocampal processing is particularly vulnerable to age. Furthermore, the memory deficit can be observed as a delay-dependent increase in the rate of forgetting (Dunnett *et al.*, 1988; Eichenbaum *et al.*, 2010; Forster and Lal, 1992; Lal *et al.*, 1973; Mabry *et al.*, 1996; Martinez *et al.*, 1988; Winocur, 1988; Zornetzer *et al.*, 1982). Importantly, rodents are not subject to neurodegenerative diseases, such that cognitive decline is thought to result from aging of physiological processes rather than cell death (Baxter and Gallagher, 1996; Foster, 2006; Rapp and Amaral, 1992). Finally, like humans, rodents exhibit wide-ranging heterogeneity in the extent of memory decline. This variability can be used to better define the process of cognitive senescence and investigate age-related changes in biological mechanisms critical to episodic memory.

In order to take full advantage of the translational relevance of animal models, consideration of the behavioral tasks employed is critical in characterizing the cognitive processes under consideration and limiting confounding influences or alternative hypotheses. In the absence of dementia, aged humans and rodents exhibit a preservation of non-hippocampal processes including incremental stimulus-response learning and procedural memory (Churchill *et al.*, 2003), as well as intact remote memories (Winocur *et al.*, 2008). Most studies in animals describe the probability of cognitive impairment with advancing age. However, it is unclear whether cognitive decline is progressive in rodents and there is a lack of longitudinal studies

tracking the course of altered cognitive function. Nevertheless, the existing literature provides a rich source from which to draw information for understanding the trajectory and extent of deficits in episodic memory. This literature provides evidence to indicate that the onset of memory decline emerges in middle-age. Furthermore, cognitive decline appears to be progressive, such that impairment in delay-dependent memory for rapidly acquired and flexible spatial information may advance to more severe deficits observed as impaired short-term memory and an inability to acquire a spatial reference memory through incremental learning.

The extent of age-related cognitive decline is highly variable. Therefore, behavioral tasks should be sensitive enough to detect mild deficits, identify the emergence of memory impairments in middle-age, and distinguish the severity of impairment in order to examine biological mechanisms. The sensitivity of the tasks for identifying age-related memory impairments will depend on the parameters of the task. Several hippocampal-dependent tasks can be designed in a manner that will permit the identification of memory deficits in middle-aged animals. Furthermore, many of these tasks suggest sex differences in the extent or the onset of cognitive decline. A short list of tasks would include olfactory memory (Roman et al., 1996; Taylor et al., 1999), contextual memory during fear conditioning (Kaczorowski and Disterhoft, 2009; Moyer and Brown, 2006), spatial working memory examined on the radial arm maze (Dellu-Hagedorn et al., 2004; Granholm et al., 2008; Sabolek et al., 2004) however see (Dellu et al., 1997; Jacobson et al., 2008; Oler and Markus, 1998), performance on various spatial mazes (Fouquet et al., 2009; Ingram, 1988; Kametani et al., 1989), and retention of inhibitory/passive avoidance (Benice et al., 2006; Moretti et al., 2011; Paris et al., 2010; Samorajski et al., 1985). Tests that examine recognition of novel objects or object locations have reported mixed results (Benice et al., 2006; Blalock et al., 2003; Fahlstrom et al., 2009; Paris et al., 2010), possibly due to procedures that render the task more or less hippocampal-dependent (Broadbent et al., 2009; Hammond et al., 2004). By far the most widely used task is the spatial version of the water escape task. Importantly, this task can be designed to identify deficits that emerge in middle-age (~12–14 months) and increase with advancing age (Adams et al., 2008; Bizon et al., 2009; Blalock et al., 2003; Davis et al., 1993; Driscoll et al., 2006; Foster et al., 2003; Francia et al., 2006; Granholm et al., 2008; Lindner, 1997).

2. Sensitivity of the water maze task

2.1 Procedures

Several reviews have discussed the proper procedures for employing the Morris water maze (Brandeis et al., 1989; Vorhees and Williams, 2006) and factors that must be considered when examining aged animals including stress, fatigue, and sensory-motor deficits (Foster, 1999; van der Staay, 2002). Some measures, such as latency to find the platform, are poor indicators of cognitive function since latency can be influenced by an age-related decline in swim speed (Foster *et al.*, 2001; Norris and Foster, 1999). Normally, a cue discrimination task is used in order to identify sensory-motor or motivational deficits which would impede acquisition of a spatial search strategy. In addition to identifying animals with sensory-motor deficits, training on the cue discrimination task can insure that animals learn the procedural aspects of the task, including how to swim and the fact that the pool wall is not a route of escape (Vorhees and Williams, 2006). Consequently, animals may perform better on the spatial version of the task when they are first trained on the cue task. Similarly, when animals are initially trained on the spatial version of the task, they may perform relatively poorly due to a number of factors, but exhibit superior performance on subsequent cue training (Gerlai, 2001). Accordingly, extensive training on the spatial swim maze may mask differences in procedural learning. Alternatively, a correspondence between performance on the spatial swim task and cue discrimination task may indicate more global impairments and

correlations between the tasks have been used as an indication of the extent of pathology in mouse models of neurodegenerative disease (Arendash and King, 2002; Leighty et al., 2004).

Probe trials are employed to evaluate the acquisition and retention of a spatial search strategy. For the probe trial, the platform is removed from the pool and the animal is allowed to freely explore the maze for a set time (e.g. 60 sec). During the probe trial, the distance from the previous platform location is averaged or summed over the trial to obtain a proximity score (Carter *et al.*, 2009; Gallagher *et al.*, 1993; Maei *et al.*, 2009). In some cases, the number of times the animal crosses the previous location of the platform (platform crossings) is reported. However, this measure may be flawed for comparing across groups. A decrease in the number of platform crossings can result from differences in motor ability and young animals make quick sharp turns, while aged animals make more sweeping turns resulting in a reduction in the number of crossings and reduced variability of the measure (Clayton *et al.*, 2002; Devan *et al.*, 1996; Foster *et al.*, 2001).

Measures of the percent time searching the goal quadrant provide evidence for the use of a spatial search strategy. A probe trial delivered shortly after training is used to determine whether an animal has acquired information on the location of the escape platform, and a subsequent probe trial can be used to assess retention (e.g. 24 hr after the acquisition probe trial) (Foster *et al.*, 1991; Foster and Kumar, 2007; Foster *et al.*, 2003; Foster *et al.*, 2001; Norris and Foster, 1999). Animals are considered to have acquired or retained the spatial information if they spend greater than 25% (i.e. chance) of the time searching the goal quadrant. A discrimination index (DI score) can be calculated for probe trials using the time spent searching the goal and opposite quadrants according to the formula $DI = (\text{time in goal} - \text{time in opposite}) / (\text{time in goal} + \text{time in opposite})$. Since the DI score is dependent on discriminating two quadrants, it is less susceptible to influence of motor function. A larger DI score indicates better performance and a score near 0 indicates chance performance. Finally, it is possible that the animals change their search strategy within a probe trial. For example, after initially searching where the platform should be, the animals may then search other quadrants. Alternatively, during retention testing, it may take some time for the animal to find their directional bearings and begin to search the correct quadrant. In this case, the probe trial can be broken down into smaller time segments. Thus, one may want to separately examine the first and second 30 sec of a 60 sec probe trial.

2.2 Sensitivity of the water maze to hippocampal function

In considering the sensitivity of the spatial swim task in detecting impaired hippocampal function, it is important to note that the degree of impairment observed during aging is generally less severe than that observed following hippocampal lesions (Foster, 1999). Animals with damage to hippocampal circuits exhibit impairments in the retention of rapidly acquired spatial information (Martin and Clark, 2007; Morris *et al.*, 1990b; Ordry *et al.*, 1988; Steele and Morris, 1999). In contrast to hippocampal damage, most aged animals can acquire a spatial search strategy during one or a few training sessions and deficits surface as retention delays increase (Bizon *et al.*, 2009; Blalock *et al.*, 2003; Driscoll *et al.*, 2006; Foster *et al.*, 1991; Foster and Kumar, 2007; Foster *et al.*, 2003; Norris and Foster, 1999). Thus, memory deficits probably result from more subtle changes in memory processes such as storage or maintenance mechanisms (Foster, 1999).

Deficits in incremental learning of a spatial reference memory and impaired short-term memory are more common in the oldest animals (Bizon *et al.*, 2009; Frick *et al.*, 1995; Haberman *et al.*, 2009; Schulz *et al.*, 2002). The impairment in incremental learning in older animals may relate to aging of other brain regions. Animals impaired in incremental acquisition of a spatial reference memory are more reactive to novel stimuli (Collier *et al.*,

2004; Gallagher and Burwell, 1989; Rowe et al., 1998) and exhibit impaired olfactory learning (Frick et al., 2000; LaSarge et al., 2007; Matzel et al., 2008; Zyzak et al., 1995) suggesting involvement of neocortical systems and neuromodulatory input from the locus coeruleus. Older animals exhibit a severe decrease in catecholamine release (Del Arco *et al.*, 2001; Porras *et al.*, 1997) and a decline in cholinergic responsiveness (Ayyagari *et al.*, 1998; Narang *et al.*, 1996; Schwarz *et al.*, 1990). A decrease in neuromodulatory input, particularly to the prefrontal cortex, is associated with learning and memory deficits (Dunnett, 1990; Tanila *et al.*, 1994; Zhang *et al.*, 2007). However, age-related impairment of prefrontal function is linked to impaired skill or source information related to the task rather than increased forgetting of specific information (Eichenbaum *et al.*, 2010; Winocur and Moscovitch, 1990).

The use of multiple tasks, including cue discrimination, can provide important clues to the possible contribution of extrahippocampal regions. In one study examining Wistar rats, no relationship was observed between incremental acquisition of a spatial reference memory and other hippocampal-dependent cognitive tasks; however, rats impaired for incremental learning exhibited increased thigmotaxis on the cue discrimination swim task, indicating impaired acquisition of the procedural aspects of the task (Bergado et al., 2011). Similarly, for mouse models of Alzheimer's disease, the incremental acquisition of a spatial reference memory was correlated with performance on the cue discrimination task (Arendash and King, 2002; Leighty et al., 2004). Furthermore, performance was correlated with beta-amyloid deposition throughout the brain, indicating that deficits likely involved multiple systems.

It might be expected that individual differences would correlate across hippocampal-dependent tasks. However, there are several difficulties in relating performance across tasks including differential influences of sensory-motor processes or sensitivity of the task for cognitive processes linked to learning or memory. Even for tasks that appear to measure the same cognitive process, little relationship may be observed. For example, the ability to acquire a spatial reference memory is sensitive to age for both for the water maze and the Barnes maze; however, there is little predictability between tasks for individual animals (Arendash and King, 2002; Gallagher and Burwell, 1989; Leighty et al., 2004; Markowska et al., 1989).

The lack of correlation between hippocampal-dependent tasks can result from differences in the sensitivity of the tasks and the degree of impairment. In this case the problem of sensitivity is compounded since it requires that both tasks are similarly sensitive to the extent of cognitive decline. There is evidence for a correspondence across tasks, when both tasks focus on retention or memory consolidation (Benice et al., 2006; Foster and Kumar, 2007; Gower and Lamberty, 1993; Paris et al., 2010). Inhibitory avoidance can be designed to be sensitive to the emergence of memory decline during aging (Gold et al., 1981; Martinez et al., 1988). In Lewis (24 month) and Sprague-Dawley (22–24 month) rats, no relationship was observed between impaired retention of inhibitory avoidance and incremental learning on the water maze (Blokland and Raaijmakers, 1993; Markowska *et al.*, 1989). In contrast, aged (26 month) Wistar rats exhibited deficits for retention of inhibitory avoidance and retention of a spatial reference memory, when retention was examined 6 days following the end of training (Miettinen *et al.*, 1993). As detailed below, the sensitivity of the water maze task to retention deficits can be increased by providing a single training session. Retention of inhibitory avoidance was related to retention of spatial memory examined 24 hr following a single training session on the water maze in aged (18–23 month) Fisher 344 (F344) rats (Foster and Kumar, 2007). For this study, retention on the inhibitory avoidance task was not correlated with acquisition of a spatial search strategy or performance on the cue task. In middle-age (14 month) and aged (24 month) F344 rats,

impaired retention 24 hr following a single day of water maze training was related to the 24 hr retention performance on a novel object recognition task (Blalock *et al.*, 2003). Retention impairments may emerge earlier in females. In a study of middle-age (12 month) Long-Evans female rats, declining reproductive function was associated with poor retention for the water maze, inhibitory avoidance, and object recognition (Paris *et al.*, 2010). In C57BL/6J mice, impairment on the water maze was related to age and gender, such that impairment for a probe trial delivered 1 hr after training, was greater for aged females (Benice *et al.*, 2006). In addition, this group of aged female mice also exhibited poorer retention of inhibitory avoidance. Again, it must be emphasized that in these cases, the inhibitory avoidance task is sensitive to milder deficits in aging, namely delay-dependent forgetting, and if designed correctly, can detect the emergence of impaired retention in middle-aged animals. However, the utility of the inhibitory avoidance task in detecting individual differences is limited due to ceiling effects and it is not as amendable to repeated training and testing. To differentiate early deficits in intermediate memory from deficits that develop over the course of aging requires a certain level of sophistication in terms of behavioral testing on the water maze.

2.3 Sensitivity and training schedules

2.3.1 Distributed training—Training schedules are important in determining the sensitivity of the swim task for detection of acquisition and retention deficits (Table 1). In general, training is massed into a single session or distributed across several days in order to examine rapid or incremental acquisition of a spatial search strategy, respectively (Fig 1). In mice the incremental learning paradigm is generally employed to examine age effects. However, recently researchers have developed versions of the water maze that focus on rapid acquisition in order to characterize more subtle changes associated with aging, age-related disease, the function of hippocampal subregions, and synaptic plasticity mechanisms (Gulinello *et al.*, 2009; Magnusson *et al.*, 2003; Malleret *et al.*, 2010; Nakashiba *et al.*, 2008).

Training distributed across several days may not be as sensitive to the emergence of deficits in middle-aged rats (Bizon *et al.*, 2009; Harati *et al.*, 2009; Jacobson *et al.*, 2008; Luparini *et al.*, 2000; Oliveira *et al.*, 2010; Wu *et al.*, 2004). For example, little or no difference in acquisition was observed between 6 and 25 month old F344 Brown Norway crossed (F344BN) rats for training distributed across multiple days (Hebda-Bauer *et al.*, 1999; Wu *et al.*, 2004); however, training within a single day was sensitive, revealing learning deficits between 12 and 25 month old F344BN rats (Carter *et al.*, 2009). One study employed distributed training for young, middle-aged, and aged F344 rats and probe trials, delivered at the end of training on alternate days, were used to determine the extent of learning (Bizon *et al.*, 2009). While a significant difference was observed for probe trial measures between young and middle-aged animals, this difference was mainly due to a subgroup of young animals with highly superior performance. If a cut-off was set using the performance in young animals, the vast majority of middle-aged animals exhibited learning measures within the range of young animals and these animals could be considered unimpaired (Fig 1D).

The number of days of training is an important factor in determining the sensitivity of distributed training (Fig 1C). In many cases, older animals can acquire a spatial reference memory following distributed training (Clayton *et al.*, 2002; Miyagawa *et al.*, 1998; Nyffeler *et al.*, 2010; Rapp *et al.*, 1987; van Groen *et al.*, 2002), such that acquisition deficits, that are apparent during the first couple of days of training, disappear after several days of repetitive training to the same location (Clayton *et al.*, 2002; Jacobson *et al.*, 2008; Luparini *et al.*, 2000). For aged (~24 months) Wistar rats, subgroups of impaired and unimpaired rats could be differentiated over the initial two to three days of training (2–6 trials/day) (Fontana *et al.*, 1995; Miyagawa *et al.*, 1998). However, differences were

diminished following further training. The diminished age differences with extended or repetitive training may be due to compensation, such that the animals may engage mechanisms involved in slower incremental acquisition of spatial information. Animals with hippocampal lesions can acquire a spatial reference memory following training distributed across several days, indicating extrahippocampal mechanisms involved in incremental learning of a spatial reference memory (Gerlai et al., 2002; Hannesson and Skelton, 1998; Martin and Clark, 2007; Morris et al., 1990b; Steele and Morris, 1999; Stoelzel et al., 2002; Whishaw et al., 1995). Furthermore, these other systems may be more resistant to aging.

The deficits observed early in distributed training may represent impaired memory consolidation processes mediated by the hippocampus (Fig 1C). We have noted that memory consolidation deficits could explain the characteristic saw-toothed pattern of behavior observed for aged rats (Foster, 1999). In this case, older rats exhibit improved performance across trials within a day and impairments are observed for the first trial on the following day (Aitken and Meaney, 1989; Diana et al., 1995; Driscoll et al., 2006; Gage et al., 1984; Mabry et al., 1996; Rapp et al., 1987). This pattern has also been reported to emerge in middle-age (12 month) Long-Evans rats (Aitken and Meaney, 1989), and a similar pattern may be observed for aged male mice (Benice et al., 2006). However, the saw-toothed pattern of memory deficits disappears with extended training, as aged animals incrementally acquire a spatial reference memory (Fig 1C).

Several labs have characterized a subgroup of aged rats that exhibit impaired incremental acquisition of a spatial reference memory. The impairment is particularly evident in the oldest animals (28–30 month) or when training consists of one to two trials per day (Bergado et al., 2011; Bizon et al., 2009; Collier et al., 2004; Frick et al., 1995; Gallagher and Burwell, 1989; Ivy et al., 1994; Lindner, 1997; Rowe et al., 1998; Schulz et al., 2002; Yamazaki et al., 1995). The ability to detect memory deficits during aging is enhanced by using a single training event or minimal training massed into a single session (Lal et al., 1973; Vasquez et al., 1983). As such, the sensitivity of distributed training in detecting age differences can be increased by reducing the number of training trials per day. When the number of trials was reduced to one trial per day for 10 days, the majority of F344 rats, 12 months or older, exhibited impaired acquisition, relative to 2 month old animals (Lindner, 1997). In contrast, when the training consisted of 6 trials per day for 5 days, F344 rats 4 to 17 months of age performed similarly after 5 days of training and deficits were only readily apparent for 24 month old rats (Frick et al., 1995). Studies that have employed multiple training trials (usually 4–8 trials per day) have provided evidence that the age at which incremental learning deficits emerge is strain sensitive. For Sprague-Dawley and F344 rats, the proportion of animals classified as impaired increases with advancing age and group differences were readily apparent by ~22–24 months of age (Bizon et al., 2009; Fischer et al., 1992). In contrast, F344BN rats exhibit either minimal impairment or a subgroup exhibit impaired incremental learning at ~24 months and notable deficits are not observed until ~31 months (Barrientos et al., 2006; Hebda-Bauer et al., 1999; Markowska and Savonenko, 2002; Wu et al., 2004). The appearance of deficits at divergent ages across rat strains may be related to differences in life span, which varies from ~25 months for F344 and ~34 months for F344BN rats. Thus, impairment in the ability to gradually acquire spatial knowledge becomes prominent when animals reach ~90% of their average life span (LaSarge and Nicolle, 2009).

As noted above, animals that exhibit impaired incremental learning may exhibit other behavioral differences including reactivity to novel stimuli (Collier et al., 2004; Gallagher and Burwell, 1989; Rowe et al., 1998) and impaired associative learning (Bergado et al., 2011; Frick et al., 2000; LaSarge et al., 2007; Matzel et al., 2008; Schulz et al., 2002; Zyzak et al., 1995) suggesting involvement of extrahippocampal systems. Certainly, for mouse

models of Alzheimer's disease, impaired incremental acquisition of a spatial reference memory is correlated with impairment in several behavioral domains as well as the extent of brain beta-amyloid deposition (Arendash and King, 2002; Leighty et al., 2004). The results suggest that the inability to acquire a spatial reference memory following extensive training may portend robust hippocampal dysfunction and/or more global changes which preclude incremental learning (Cho and Jaffard, 1995; Moffat et al., 2007). As such, impaired incremental acquisition of a spatial reference memory following distributed training may be a good model of severe cognitive deficits associated with dementia.

2.3.2 Massed training—Due to the fact that learning and/or memory deficits on the water maze are more pronounced during the initial training period, some studies have massed training into a single session in order to increase the sensitivity of the task (Table 1).

Memory following massed training is not as strong as memory acquired following distributed training (Commins et al., 2003; Dash et al., 2002; Spreng et al., 2002) and depends more on the hippocampus (Bouffard and Jarrard, 1988). Furthermore, massed training schedules make use of distinct molecular memory mechanisms that are sensitive to aging (Foster et al., 2001; Genoux et al., 2002; Malleret et al., 2001). Again, aged animals may exhibit slower learning during training (Fig 1E). Acquisition of a spatial search strategy following a single training session can be confirmed by a probe trial and calculating the discrimination index or measuring the portion of time spent searching in the quadrant that originally held the escape platform (Fig 1F). This probe trial can be used to detect age-related impairment in the acquisition of a spatial search strategy. Once it is clear that an animal has acquired a spatial search strategy, a subsequent probe trial may be delivered at more distant time points in order to evaluate retention (Fig 1F). Work from our lab and others indicates that a subset of middle-age animals exhibit memory deficits examined 24 hr after acquisition and the probability of memory impairment increases with advancing age (Aitken and Meaney, 1989; Blalock et al., 2003; Driscoll et al., 2006; Foster et al., 1991; Foster and Kumar, 2007; Foster et al., 2003; Mabry et al., 1996; Norris and Foster, 1999).

Virtual environments, including versions of the water maze, have been used to examine spatial learning and memory in amnesic and elderly humans. In general, training is massed into a single session and the research confirms that damage to the hippocampus results in impaired spatial navigation (Astur et al., 2002; Bartsch et al.,; Bohbot et al., 2004; Goodrich-Hunsaker et al.,; Skelton et al., 2000). Furthermore, elderly individuals exhibit deficits involving increased path length during acquisition and impaired performance on probe trials (Driscoll et al., 2003; Moffat et al., 2007; Moffat and Resnick, 2002; Moffat et al., 2001). While all age groups exhibit acquisition on a virtual environment maze, middle-aged and aged subjects were slower to learn and exhibited increased spatial memory errors (Driscoll et al., 2003; Driscoll et al., 2005; Jansen et al., 2010; Moffat et al., 2001; Thomas et al., 1999). Similar to animal studies, deficits were apparent following a single training session, and with continued training, older subjects performed in a manner that was not different from younger individuals (Jansen et al., 2010). Again, the initial learning and asymptotic level of performance in virtual environments may depend on different brain systems (Bohbot et al., 2007; Etchamendy and Bohbot, 2007; Etchamendy et al., 2011; Hartley and Burgess, 2005). The results suggest that training massed into a single session is sensitive in detecting the emergence of deficits in intermediate-term memory for rapidly acquired spatial information during middle-age in rodents and humans.

2.3.3 Repeated acquisition/matching-to-sample training—Repeated acquisition training provides another version of massed training, which is designed to specifically examine rapid flexible learning and can be adapted to examine retention or forgetting (Table 1). For this task, the escape location is changed across sessions such that the animal must repeatedly learn new escape locations (Fig 2A). This task usually involves only one or two

days of training to each location. Deficits in the rapid acquisition of a spatial memory emerge by ~12 months of age in spontaneously hypertensive rats; however, most rat strains exhibit deficits by 18 months of age (Driscoll *et al.*, 2006; Markowska and Savonenko, 2002; van der Staay and de Jonge, 1993; Wyss *et al.*, 2000) (Fig 2B). Moreover, studies that directly compare incremental learning using distributed training and repeated acquisition in which the escape platform is changed each day indicate that repeated acquisition testing is more sensitive in detecting the emergence of age-related cognitive decline (Bizon *et al.*, 2009; Markowska and Savonenko, 2002; Miyagawa *et al.*, 1998; Nyffeler *et al.*, 2010). In these cases, animals that exhibited impairments on the repeated acquisition version of the task could still acquire a spatial reference memory with training distributed across several days, consistent with the idea that impairments in rapid acquisition precede impaired incremental learning.

Memory deficits can be characterized using the repeated acquisition training and delayed matching-to-sample testing to examining the savings from trial to trial. In this case, deficits are observed as a decrease in savings as the inter-trial interval is increased (Fig 2C). Interestingly, there is evidence to indicate that the extent of the memory impairment increases with advancing age. Compared to young rats, middle-aged animals exhibit a similar level of performance during acquisition training (8 trials/day) and impaired retention is observed on the first trial examined on day 2, 24 hr after the initial training (Driscoll *et al.*, 2006). Furthermore, the extent of impairment increases with advancing age (Driscoll *et al.*, 2006). Indeed, following a single training trial, young rats exhibit retention for up to 6 hr; middle-aged animals begin to exhibit retention deficits as the delay is increased to 2 hr and aged animals exhibit deficits for delays greater than ~1 hr (Bizon *et al.*, 2009; Means and Kennard, 1991) (Fig 2C).

2.4 Reliability

One distinguishing feature of the swim task is that it is amenable to multiple testing sessions in order to examine the reliability of acquisition and retention deficits, as well as the success of treatments (Fontana *et al.*, 1995; Markowska *et al.*, 1994). However, it is important to recognize that there are carry-over effects of multiple testing sessions. Furthermore, testing on the water maze increases the release of stress hormones (Engelmann *et al.*, 2006) and the stress of extended water maze training can influence hippocampal neurogenesis (Namestkova *et al.*, 2005) and may have enduring effects on hippocampal function, particularly in learning impaired animals in which water maze training may be analogous to a being exposed to an uncontrollable swim stress (Foster and Kumar, 2007). On the other hand, training may act as cognitive stimulation and promote skills needed to solve the water maze. Animals that are trained on the maze during young adulthood or middle-age exhibit an advantage in re-learning when tested during aging (Hansalik *et al.*, 2006; Vallee *et al.*, 1999; van Groen *et al.*, 2002; Vicens *et al.*, 2002). As noted above, procedural memory is relatively intact during aging such that animals likely acquire a procedural strategy for how to find a hidden platform across multiple testing sessions. However, individual differences are observed such that heterogeneity in performance is consistently observed between individual subjects. Tests of repeated acquisition in the same environment indicate a slower rate of acquisition for aged animals, while performance of middle-aged animals is similar to young (Driscoll *et al.*, 2006; Frick *et al.*, 1995; Wyss *et al.*, 2000). Nevertheless, middle-aged animals continue to exhibit retention deficits relative to young (Bizon *et al.*, 2009; Driscoll *et al.*, 2006; Means and Kennard, 1991). Similarly, for incremental learning across days of repetitive training, some aged animals consistently perform more poorly than young (Fontana *et al.*, 1995; Lindner, 1997). When the acquisition of a spatial reference memory is retested using a new environment, carry-over effects are observed such that young and aged animals exhibited more rapid learning relative to the

initial environment; however, aged animals that exhibited the poorest initial performance also exhibited poorer performance in the new environment (Colombo and Gallagher, 2002).

2.5 Aging of hippocampal subregions and the trajectory of cognitive decline

Little is known concerning the trajectory of cognitive decline during aging in rodents. The preceding review of the literature, focused on the water maze, supports the idea that cognitive decline is progressive and can be tracked using different water maze training procedures. Middle-age is associated with impairment of rapid spatial learning/memory and intact gradual acquisition of spatial knowledge. Tests involving a single training session or delayed matching-to-sample provide sensitive measures for deficits in intermediated-term memory as an early marker of cognitive decline. Repeated acquisition training can detect impairments in rapid, flexible spatial learning as animals move from middle-age to old age. Furthermore, the propensity for acquisition and memory deficits increases with advanced age. Finally, a subset of the oldest animals will exhibit profound learning deficits such that they will not be able to acquire a spatial reference memory, even with distributed training to the same location.

The cognitive changes observed with advancing age suggest a progression in the senescence of biological mechanisms of memory. Cognitive deficits are not associated with obvious hippocampal pathology involving cell death (Gallagher *et al.*, 1996). Rather, memory deficits probably result from more subtle changes in memory processes for storage or maintenance mechanisms (Foster, 1999). All hippocampal subregions; dentate gyrus, CA3, and CA1, show some form of age-related change, which is likely to contribute to impaired cognition (Burke and Barnes, 2011; Rosenzweig and Barnes, 2003; Small *et al.*, 2011; Wilson *et al.*, 2006). Furthermore, these subregions are differentially susceptible to diseases of age including effects of stress, Alzheimer's disease, and cell death due to ischemia.

Importantly, the subregions differentially contribute to different phases or aspects of episodic memory (Daumas *et al.*, 2005; Kesner and Hunsaker, 2010; Kesner *et al.*, 2004), suggesting that aging of subregions could uniquely modify performance on the water maze. As such, aging of different subregions or senescence of different mechanisms may account for early deficits in memory consolidation relative to later deficits in rapid acquisition, and finally impaired incremental learning. For example, the dentate gyrus is involved in spatial pattern separation (Gilbert *et al.*, 2001; McHugh *et al.*, 2007). Pattern separation declines during aging in humans and is associated with altered activity in the dentate gyrus (Small *et al.*, 2011; Yassa *et al.*, 2011). Neurogenesis is a notable form of neuroplasticity observed in the dentate gyrus, which declines during aging (Cameron and McKay, 1999; Kempermann *et al.*, 1998; Kuhn *et al.*, 1996; Nacher *et al.*, 2003). The exact role of neurogenesis in memory function is currently a subject of intense research. However, it is interesting to note that variability in neurogenesis in aged animals is correlated with the rapid acquisition of spatial information observed during the early phases of spatial learning (Drapeau *et al.*, 2003; Drapeau *et al.*, 2007; Driscoll *et al.*, 2006) and is not associated with impaired incremental learning (Bizon and Gallagher, 2003; Bizon *et al.*, 2004; Merrill *et al.*, 2003).

Region CA3 is thought to be involved in rapidly encoding and pattern completion for spatial information and the modifiability of CA3 cell activity is reduced with age (Wilson *et al.*, 2005). Behavioral stress induces dendritic structural changes in region CA3 and susceptibility to stress effects increases with age (Christian *et al.*, 2011; Cohen *et al.*, 2011; Gartside *et al.*, 2003; McEwen, 2001; Shoji and Mizoguchi, 2010). Gene changes in this region during aging indicate that preservation of CA3 function is maintained by neurotrophic mechanisms that permit adaptation to stress (Zeier *et al.*, 2010) and failure to enlist these adaptation mechanisms is associated with impaired learning (Haberman *et al.*, 2009). N-methyl-D-aspartate receptors (NMDARs) contribute to CA3 function in rapid

encoding and mutant mice with a deletion of NMDARs, specific to CA3, exhibit normal incremental learning and impaired performance on repeated acquisition training (McHugh *et al.*, 2007; Nakazawa *et al.*, 2002). In addition, the stress mediated dendrite changes require activation of CA3 NMDARs (Christian *et al.*, 2011). Aging and learning impairment are associated with changes in CA3 synaptic markers, including NMDARs (Adams *et al.*, 2001; Smith *et al.*, 2000). However, the decline in CA3 NMDAR markers have been associated with learning deficits (Adams *et al.*, 2001), no change in learning (Nicolle *et al.*, 1996), or better performance (Le Jeune *et al.*, 1996), suggesting that loss of NMDAR may mediate deficits or may act as a compensatory mechanism to protect cells from stress.

Region CA1 of aged animals exhibits gene changes related to increased susceptibility to inflammation, oxidative stress, Ca^{2+} dysregulation, and a decline in neurotrophic support (Blalock *et al.*, 2003; Jackson and Foster, 2009; Jackson *et al.*, 2010; Wang and Michaelis, 2010; Zeier *et al.*, 2010). In turn, changes in these processes are thought to contribute to the propensity for region CA1 to exhibit increased susceptibility to Alzheimer's disease and increased cell loss following ischemia, as well as impaired memory and synaptic plasticity during aging (Blalock *et al.*, 2003; Zeier *et al.*, 2010). Region CA1 is involved in consolidation of an intermediate or long-term form of memory (Dudai, 2004; Kesner and Hunsaker, 2010; Kesner *et al.*, 2004; Lee and Kesner, 2002; Morris *et al.*, 2003; Rawlins and Tsaltas, 1983), and as discussed above, disruption of memory consolidation is an early behavioral marker of cognitive aging. As such, the age-related disruption in Ca^{2+} regulation and synaptic plasticity is thought to contribute to the emergence of memory consolidation deficits (Foster, 2007; Foster and Norris, 1997; Kumar *et al.*, 2009).

3. NMDAR-dependent and VDCC-dependent plasticity during aging

The general view is that synaptic plasticity mechanisms represent the biological substrate for memory and learning and the weight of evidence indicates a link between synaptic plasticity and spatial memory (McNaughton *et al.*, 1986; Morris *et al.*, 1986; Moser *et al.*, 1998). Considering the prominence of synaptic plasticity as a model of memory storage, it is not surprising that a number of studies have examined age-related changes in two major forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD). LTP is an increase in synaptic transmission, induced by pattern stimulation of afferent fibers and is proposed as a cellular mechanism for the kind of rapid and flexible intermediate-term memory that is disrupted early in the course of cognitive senescence (Dudai, 2004; Morris *et al.*, 2003). LTD is a decrease in synaptic strength, which may contribute to loss of synaptic contacts and increased forgetting during aging (Foster, 1999, 2007; Shinoda *et al.*, 2005; Zhou *et al.*, 2004). Age-related changes in LTP and LTD suggest the functional significance of altered synaptic plasticity for cognitive function (Foster, 1999, 2002; Foster and Norris, 1997).

While age-related changes in synaptic plasticity have been reported for all regions of the hippocampus, the majority of work has focused on perforant path to dentate gyrus and CA3 to CA1 synapses. For the dentate gyrus, the evidence indicates that impaired induction of LTP during aging results from neuroinflammatory changes, oxidative stress, and a decrease in NMDAR function (Lynch, 2009; Rosenzweig and Barnes, 2003). Undoubtedly, synaptic contacts between CA3 and CA1 pyramidal cells have received the most attention in terms of age-related changes in synaptic plasticity and this synapse is the focus of the current review. In general, no difference is observed in the expression mechanisms or the asymptotic amplitude of LTP and LTD, rather there is a shift in the mechanisms that regulate the threshold for induction of synaptic plasticity (for a review see Foster, 1999). Thus, age differences are likely to be observed for a given stimulation paradigm, particularly if the pattern of stimulation is close to the threshold for induction of synaptic plasticity. The

threshold for induction of LTP increases with age such that higher stimulation frequencies or more induction sessions are required in older animals in order to achieve the same level of LTP. Similarly, the threshold for induction of LTD is lowered in aged animals, facilitating induction of LTD. Thus, an important question concerns differences in the mechanisms that regulate the induction of synaptic plasticity.

Induction of LTP involves released of glutamate from the presynaptic terminals. The glutamate binds to postsynaptic NMDARs and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Fig 3). The activation of AMPA receptors depolarizes of the postsynaptic membrane. The depolarization is critical in removing the Mg^{2+} block of the NMDAR channel and provoking a brief, large magnitude rise in postsynaptic Ca^{2+} . The large rise in intracellular Ca^{2+} activates kinases including protein kinase C (PKC), Ca^{2+} -calmodulin kinase II (CaMKII), and protein kinase A (PKA). The kinases phosphorylate proteins, increasing the function of AMPA receptors, resulting in an increase in synaptic transmission (Fig 3A). Induction of LTD is achieved by prolonged low frequency pattern stimulation to produce a modest and prolonged rise in intracellular Ca^{2+} . A modest rise in Ca^{2+} activates phosphatase cascades, calcineurin (CaN) and protein phosphatase 1 (PP1), dephosphorylating proteins to decrease synaptic responses (Fig 3B). Thus, both LTP and LTD depend on a rise in intracellular Ca^{2+} , and the degree and direction of altered synaptic function is determined by the level and duration of the Ca^{2+} rise.

The rise in intracellular Ca^{2+} levels is a function of the stimulation pattern, and the stimulation pattern influences the source of intracellular Ca^{2+} . There are three main Ca^{2+} sources for induction of synaptic plasticity, NMDARs, voltage-dependent Ca^{2+} channels (VDCCs), and intracellular Ca^{2+} stores (ICS) (Fig 3). During aging, NMDAR function decreases and Ca^{2+} from VDCCs-ICS increases in region CA1. This shift in Ca^{2+} sources contributes to modifications in the threshold for induction of synaptic plasticity, leading to the proposed Ca^{2+} dysregulation hypothesis for age-related changes in synaptic plasticity (Foster, 1999; Foster and Norris, 1997).

3.1 LTP

Electrophysiological and pharmacological data indicate that at CA3-CA1 synapses, there are at least two forms of LTP that differ in terms of induction mechanisms. It should be emphasized that all Ca^{2+} sources normally contribute to LTP induction in the absence of specific antagonists. Nevertheless, depending on the stimulation pattern, LTP induction is mainly due to NMDAR activity (NMDAR-LTP) or can include NMDAR-independent and VDCC-dependent mechanisms (VDCC-LTP). In young animals, high frequency stimulation (HFS 25–100 Hz) or stimulation patterns near the threshold for LTP-induction, including brief episodes of theta burst stimulation (TBS) induce a rise in intracellular Ca^{2+} mainly through activation of NMDARs (Fig 3A). The shift in LTP mechanisms during aging can be observed as a decrease in the LTP magnitude for weak or threshold stimulation that largely activates NMDARs (Barnes, 1979; Foster, 1999, 2002, 2007; Landfield *et al.*, 1978) and no age-related difference is observed when strong stimulation is used (Kumar *et al.*, 2007). Higher frequency stimulation (200 Hz) can induce LTP independent of NMDARs, due to increased Ca^{2+} from VDCCs, particularly L-channels (Cavus and Teyler, 1996; Grover and Teyler, 1990). The Ca^{2+} from L-channels binds to ryanodine receptors (RyRs) to release Ca^{2+} from ICS, resulting in a further increase in intracellular Ca^{2+} (Fig 3). In addition, glutamate binding to metabotropic glutamate receptors (mGluRs) can increase release of Ca^{2+} through inositol trisphosphate receptor (IP3R) activation on ICS. Unlike NMDAR-LTP, VDCC-LTP tends to be greater in older animals (Boric *et al.*, 2008; Robillard *et al.*, 2011; Shankar *et al.*, 1998).

There are two mechanisms that mediate the age-related decrease in NMDAR-LTP, one involves a reduction in NMDAR function and the other involves active inhibition of NMDARs through VDCCs and ICS (Fig 4). Electrophysiological studies consistently show a decrease in the NMDAR component of the synaptic transmission in region CA1 during aging (Barnes et al., 1997; Billard and Rouaud, 2007; Bodhinathan et al., 2010a; Tombaugh et al., 2002). The weight of evidence indicates that NMDAR binding declines in a number of brain regions, including the hippocampus (Magnusson et al., 2010). However, the level of receptor binding does not readily match the levels of protein or RNA expression, suggesting that changes in the functional state of the receptors or regulation of receptor activity contribute to the decrease in agonist/antagonist binding and the decrease in NMDAR function (Magnusson et al., 2010).

Recent work demonstrates that the decrease in NMDAR function is related to oxidative stress and a shift in the intracellular oxidation-reduction (redox) state (Bodhinathan et al., 2010a). The nervous system is highly sensitive to oxidative stress (Halliwell, 1992). Irreversible damage to lipids, DNA, and proteins results from the production of the oxygen radical, superoxide. To protect tissue from irreversible damage, superoxide dismutase converts superoxide in to the nonradical hydrogen peroxide. Hydrogen peroxide per se does not induce irreversible oxidative damage (Catala, 2010; Leutner *et al.*, 2001; Linden *et al.*, 2008; Shacter, 2000). The relatively milder hydrogen peroxide induces the reversible formation of disulfide bonds between pairs of cysteine residues in proteins, shifting protein structure and function, and influencing multiple signaling cascades including Ca^{2+} signaling (Foster, 2007). The redox state of cysteine residues on the extracellular portion of the NMDAR have been implicated in regulating NMDAR function in cell cultures and neonatal animals (Aizenman *et al.*, 1990; Aizenman *et al.*, 1989; Bernard *et al.*, 1997; Choi and Lipton, 2000), suggesting that altered redox state of these extracellular cysteine residues could mediate the decline in NMDAR function during aging. Indeed, application of the cysteine specific reducing agent, dithiothreitol, selectively increased the NMDAR component of the synaptic response and the magnitude of LTP in hippocampal slices from older rodents (Bodhinathan et al., 2010a). The membrane-impermeable reducing agent, L-glutathione, failed to increase the NMDAR response when applied to the slice; however, an increase in the NMDAR response was observed by intracellular delivery of L-glutathione through the intracellular recording pipette. The results indicate that intracellular redox state, rather than disulfide bonds of extracellular cysteine residues, mediates the suppression of NMDAR responses and impaired LTP. The decline in NMDAR function during aging, mediated by intracellular redox state, has recently been confirmed by other labs (Robillard *et al.*, 2011; Yang *et al.*, 2010). Finally, the dithiothreitol mediated growth of the NMDAR response was blocked by inhibition of CaMKII, but not by inhibition of PKC, PP1, or CaN. Furthermore, CaMKII activity of aged animals could be enhanced by dithiothreitol treatment, indicating that the effect was specific to CaMKII activity (Bodhinathan *et al.*, 2010a).

The other mechanism for decreasing NMDAR-LTP in aged animals is mediated by VDCCs and ICS. VDCCs and ICS regulate NMDAR-dependent LTP by influencing the membrane potential (Fig 4). NMDAR activation requires depolarization of the postsynaptic membrane (Fig 3A). Release of Ca^{2+} from ICS or influx through VDCCs activates Ca^{2+} -dependent SK potassium (K^+) channels to hyperpolarize dendrites (Faber, 2010) and inhibition of Ca^{2+} release from ICS increases the NMDAR response in older animals (Kumar and Foster, 2004), suggesting a direct connection between ICS and NMDAR function. The membrane potential is also regulated by another well-characterized biomarker of age-related memory impairment; the Ca^{2+} -dependent, K^+ mediated slow afterhyperpolarization (sAHP). In this case, action potentials activate VDCCs, the influx of Ca^{2+} stimulates RyRs to release Ca^{2+} from ICS and the rise in intracellular Ca^{2+} opens K^+ channels to hyperpolarize the

membrane (Fig 4). In aged animals, increased Ca^{2+} from VDCCs and ICS enhance the magnitude and duration of the sAHP (Bodhinathan *et al.*, 2010b; Kumar *et al.*, 2009; Kumar and Foster, 2004; Oh *et al.*, 2010; Thibault and Landfield, 1996). The sAHP represents a window of time after cell discharge activity, with a peak at ~200 ms (Fig 5A), in which the hyperpolarization disrupts the integration of depolarizing postsynaptic potentials. This disruption is evident for stimulation patterns near the theta frequency (i.e. 5 Hz with a 200 ms interval between stimulation episodes), including TBS (Diamond *et al.*, 1988; Fuenzalida *et al.*, 2007; Kramar *et al.*, 2004; Moore *et al.*, 1993).

The effect of the larger sAHP on the threshold for induction of LTP can be observed by plotting the change in synaptic strength as a result of different stimulation frequencies (Fig 5B). For young animals, the threshold frequency for induction of LTP is near 5 Hz and the level of LTP increases as stimulation frequency increases. The frequency response function for CA3-CA1 synapses in older animals is marked by a plateau region in which no LTP occurs for intermediate stimulation frequencies (~5–25 Hz), resulting in an increased threshold frequency required for induction of LTP (Foster, 1999; Hsu *et al.*, 2002; Kumar and Foster, 2007b). An important observation is that treatments that reduce the sAHP drastically decreased the LTP threshold for aged animals; unmasking NMDAR-LTP for stimulation patterns as low as 5 Hz (Fig 5B). Treatments to reduce the sAHP and promote LTP include blockade of Ca^{2+} release from intracellular stores, blockade of SK channels, and L-channel antagonists (Bodhinathan *et al.*, 2010a; Kumar and Foster, 2004; Norris *et al.*, 1998). The results emphasize that VDCCs, RyRs, and ICS regulate synaptic plasticity not only by supplying intracellular Ca^{2+} for induction of VDCC-dependent synaptic plasticity, but also by regulating the membrane potential to dynamically inhibit NMDAR activation. Thus, increased Ca^{2+} from VDCCs and ICS facilitates LTP for higher frequency stimulation (i.e. 200 Hz) and actively inhibits NMDAR-LTP in older animals.

Recent work has emphasized oxidation of RyRs and increased release of Ca^{2+} from ICS in mediating age-related changes in the sAHP and synaptic plasticity. Blockade of L-channels reduces the sAHP to a similar extent (~30%) in young and aged animals (Bodhinathan *et al.*, 2010b; Disterhoft *et al.*, 2004; Norris *et al.*, 1998; Power *et al.*, 2002). In contrast, treatments to reduce the release of Ca^{2+} from ICS has greater effect in aged animals, reducing the sAHP by ~50%, such that the amplitude approximates that normally observed in young animals (Bodhinathan *et al.*, 2010b; Kumar and Foster, 2004). RyRs are redox sensitive such that release of Ca^{2+} from ICS is increased under conditions of mild oxidative stress (Bodhinathan *et al.*, 2010b; Hidalgo *et al.*, 2004). Application of cysteine specific reducing agents decreased the amplitude of the sAHP specifically in aged animals (Bodhinathan *et al.*, 2010b). The antioxidant mediated reduction in the sAHP could be blocked by depletion of Ca^{2+} from ICS or blockade of RyRs, but not through blockade of VDCCs. The results indicate that redox state of RyRs is the major contributor to the age-related increase in the sAHP. In addition, RyR involvement in the age-related growth of the sAHP appears to emerge in middle-age (Gant *et al.*, 2006). Finally, the shift in redox state and increased release of Ca^{2+} from ICS may underlie the age-related shift from NMDAR-LTP to VDCC-LTP. As noted above, Ca^{2+} release from ICS decreases the NMDAR response in older animals (Kumar and Foster, 2004), suggesting a direct connection between ICS and NMDAR function.

The disruption of Ca^{2+} regulation and impaired learning and memory are hypothesized to result from a shift in the level of hydrogen peroxide and reversible redox state of proteins, rather than irreversible oxidative damage associated with superoxide. Application of hydrogen peroxide to hippocampal slices from young animals decreases CaMKII activity (Shetty *et al.*, 2008), decreases NMDAR responses (Bodhinathan *et al.*, 2010a), and impairs LTP (Kamsler and Segal, 2003; Pellmar *et al.*, 1991). Furthermore, hydrogen peroxide can

enhance VDCC-LTP, possible through increased RyR activation (Huddleston *et al.*, 2008; Kamsler and Segal, 2003). Virus mediated over expression of individual antioxidant enzymes in the hippocampus decreased the level of lipid and DNA oxidative damage without improving learning on the water maze (Lee *et al.*, 2011). In fact, expression of superoxide dismutase-1 in older animals enhanced impairments of learning on the water maze. The effect of superoxide dismutase-1 is thought to result from an increase in the production of hydrogen peroxide. In support of this idea, deficits due to over expression of superoxide dismutase-1, as well as age-related deficits on the water maze, were ameliorated by co-expression of superoxide dismutase-1 and catalase. Together, the results establish a mechanism that links general theories of aging (i.e. oxidative stress and redox state) with altered Ca^{2+} homeostasis and senescent physiology, thought to under lie cognitive decline (Foster, 2007; Kumar *et al.*, 2009).

3.2 LTD

Relative to LTP, induction of LTD requires a modest rise in Ca^{2+} , which is usually induced by 1–3 Hz low frequency stimulation (LFS) or paired-pulse LFS (PP-LFS) using a 50 ms interval between pulse pairs (Fig 3B). In the hippocampal CA1 region, several mechanisms for induction of LTD have been characterized and these mechanisms involve different Ca^{2+} sources. Again it must be emphasized that in the absence of specific blockers, all sources are likely to contribute to the induction of LTD. The dysregulation of Ca^{2+} homeostasis during aging results in an increased susceptibility to LTD induction (Foster and Kumar, 2007; Foy *et al.*, 2008; Hsu *et al.*, 2002; Norris *et al.*, 1996), in the absence of a change in the maximum LTD amplitude (Kumar *et al.*, 2007). Due to the age-related shift in Ca^{2+} sources, NMDARs appear to contribute less to LTD with advanced age. Thus, NMDAR antagonists reduce but do not block induction of LTD in older animals (Ahmed *et al.*, 2011; Norris *et al.*, 1996) and there is an increased reliance on VDCCs (Norris *et al.*, 1996) and ICS (Kumar and Foster, 2005) for LTD induction. Another form of LTD can be induced by activation of mGluRs (Oliet *et al.*, 1997; Palmer *et al.*, 1997) and the susceptibility to this form of LTD also increases with age (Kumar and Foster, 2007c).

The characterization of age-related modifications in Ca^{2+} homeostasis has provided a deeper level of understanding concerning the interaction of the cellular and molecular components that regulate LTP and LTD. The next section discusses the potential role of NMDARs and VDCCs in mediating deficits in consolidation of rapidly acquired memory in middle-age and impairments in incremental learning with advanced age.

4 Age-related deficits in consolidation of rapidly acquired memories: Relation to NMDAR function

Consolidation of memory from a short-term form, lasting seconds, to an intermediate-term form lasting hours is thought to depend on NMDAR activity (Jerusalinsky *et al.*, 1992; Kim *et al.*, 1992; Newcomer and Krystal, 2001; Packard and Teather, 1997; Roberts and Shapiro, 2002; Rossato *et al.*, 2004; Shimizu *et al.*, 2000; Steele and Morris, 1999). Early on, it was recognized that treatment with NMDAR antagonists impaired spatial memory (Butcher *et al.*, 1990; Handelman *et al.*, 1987; McLamb *et al.*, 1990; Mondadori *et al.*, 1989; Morris, 1989; Morris *et al.*, 1986; Morris *et al.*, 1990a). Later research provided evidence that NMDAR blockade can result in an initial disruption in the acquisition of spatial information; however, this initial impairment may not be observed with continued training (Bannerman *et al.*, 1995; Kesner *et al.*, 2004; Steele and Morris, 1999). Rather, a certain level of NMDAR activity is required for the rapid consolidation of flexible spatial information (Jerusalinsky *et al.*, 1992; Lee and Kesner, 2002; Steele and Morris, 1999). Furthermore, the role of NMDARs in acquisition and retention of spatial information appears to be region specific.

Blockade of CA3 NMDARs contributes to the initial impairment in spatial working memory as the environment or task demands change (Kesner *et al.*, 2004). Importantly, improved performance is observed with continued training suggesting non-NMDAR dependent plasticity mechanisms may compensate for loss of NMDAR function in CA3 to reorganize or store spatial information. In contrast, blockade of NMDARs in region CA1 results in impairment of intermediate-term spatial memory (Kesner *et al.*, 2004). Unlike the recovery of the initial learning impairment, the intermediate memory deficit did not improve with continued training, indicating that other plasticity mechanism cannot compensate for a loss of CA1 NMDARs to rescue memory consolidation.

Comparison of water maze performance during NMDAR blockade and aging supports the idea that a decline in NMDAR function could mediate the memory consolidation deficits which are an early indication of cognitive decline. An effect of NMDAR blockade on retention can be demonstrated by measuring the savings in latency to find a hidden platform on the second (i.e. retention) trial during repeated acquisition training. When the inter-trial interval is short (15 sec), rats treated with the NMDAR blocker AP5 exhibit acquisition similar to saline treated animals, decreasing the latency to find a hidden platform on the second training trial. Similar to older animals (Bizon *et al.*, 2009), this savings is reduced if the inter-trial interval is increased (Steele and Morris, 1999). It may be important to point out that, for these studies, the spatial representations were established by prior training. It appears that aging and NMDAR blockade do not influence the ability to use or reorganize established representations; rather there is impaired maintenance of newly acquired information.

Intact acquisition and impaired memory consolidation during NMDAR blockade is apparent when the initial training is massed into a single day. In this case, repeated trials with relatively short inter-trial intervals permit rats to acquire a spatial search strategy in a novel environment under NMDA receptor blockade. However, like aged animals (Blalock *et al.*, 2003; Foster *et al.*, 1991; Foster and Kumar, 2007; Norris and Foster, 1999), impaired retention was observed over a 24 hr period after training (Ge *et al.*, 2010; Holahan *et al.*, 2005; Kesner and Dakis, 1995; McDonald *et al.*, 2005). Together, the results indicate that aged animals and animals under NMDAR blockade can acquire novel spatial information; however, consolidation deficits are evident if this information needs to be maintained.

The effect of NMDAR blockade on distributed training depends on the same factors that influence performance in aged animals, including sensory-motor function, prior training, and the number of training trials per day. Prior training facilitates incremental learning in aged animals (Colombo and Gallagher, 2002; Hansalik *et al.*, 2006; van Groen *et al.*, 2002) and during NMDAR blockade (Bannerman *et al.*, 1995; Saucier *et al.*, 1996). Similar to aged animals (Lindner, 1997), animals under NMDAR blockade fail to acquire a spatial search strategy when the number of training trials is reduced to one trial per day (Bannerman *et al.*, 1995). This deficit may be overcome to a certain extent by increasing the number of trials per day. In studies using four to six trials per day, the antagonist AP5 resulted in a dose dependent impairment in acquisition performance (Davis *et al.*, 1992; Uekita and Okaichi, 2009). The highest doses completely blocked learning; however, higher doses also resulted in sensory-motor disturbances and thigmotaxic behavior. Similar dose dependent effects on learning and sensory-motor function are observed for other NMDAR antagonists (Ahlander *et al.*, 1999; Saucier *et al.*, 1996). For doses within the range that normally block the induction of LTP, some impairment in learning was observed; nevertheless, a probe trial at the end of training indicated that search behavior was focused on the goal quadrant (Davis *et al.*, 1992). Treatment with ifenprodil, which is a specific antagonist for the NR2B subunit of the NMDAR, did not block incremental acquisition of spatial learning over eight days of training (Ma *et al.*, 2010). However, treatment for three days following training was

associated with impaired memory consolidation (Ma *et al.*, 2010). Thus, similar to aged animals that exhibit impaired incremental learning, is associated with sensory-motor impairment, suggesting the involvement of other brain regions. For lower doses that do not impair sensory-motor function, incremental learning can occur during NMDAR blockade; however, impaired memory consolidation is observed. Incremental spatial learning in the face of NMDAR antagonist treatment may result from incomplete receptor blockade which slows rather than blocks learning. Alternatively, NMDAR-independent mechanisms may compensate to permit acquisition of a spatial reference memory following multiple days of distributed training.

The NMDAR is composed of heteromeric subunits involving an essential NR1 subunit and four other possible subunits. Mutant mice have been developed to enable the selective inducible knockout of specific subunits and in some cases the knockout is specific to the hippocampus or hippocampal subregions. Mice with a selective knockout of the NR1 subunit in region CA3 or the dentate gyrus are able to acquire and recall a spatial reference memory during distributed training (McHugh *et al.*, 2007; Nakazawa *et al.*, 2002). However, deficits are observed for repeated acquisition or matching to sample training indicating impaired short-term memory for novel spatial information (Nakazawa *et al.*, 2003). Knockout of CA1 NR1 prior to training severely impairs LTP induction and incremental learning (Shimizu *et al.*, 2000). Furthermore, when CA1-NR1 knockout was initiated at the end of incremental training a memory consolidation deficit was observed. The results are consistent with work examining region specific delivery of NMDAR antagonists (Kesner *et al.*, 2004), pointing to CA3 NMDAR involvement in rapid acquisition and spatial working memory and CA1 NMDAR involvement in spatial information that is maintained for an intermediate period lasting several minutes or longer-term memory consolidation.

The results suggest that a reduction in NMDAR function with age could have differential effects on learning and memory depending on the regions and extent of NMDAR decline. In this regard, studies that knockout the other subunits may be enlightening since, like aging, NMDAR function is reduced, but not eliminated. For example, disruption of NR2A, limited to the hippocampus, impaired short-term spatial working memory and no deficit was observed for incremental learning on the water maze (Bannerman *et al.*, 2008). Indeed, mice with disruption of the NR2A subunit throughout the brain exhibit only a mild impairments in LTP and the acquisition of a spatial reference memory when training is distributed across multiple days (Sakimura *et al.*, 1995). Widespread disruption of NR2B throughout the forebrain resulted in impaired incremental spatial learning and impaired acquisition on the cue discrimination task (von Engelhardt *et al.*, 2008). When disruption of NR2B was limited to the hippocampus, mice exhibited reduced LTP for a pairing protocol and impaired short-term spatial working memory; however, incremental acquisition of a spatial reference memory was identical to that of controls (von Engelhardt *et al.*, 2008). Interestingly, overexpression of NR2B improved the induction of LTP, learning, and memory in aged mice (Cao *et al.*, 2007). Finally, a study employing antisense techniques in rats, found that decreased expression of hippocampal NR2B mimicked aging effects on the incremental learning task. Specifically, the impairment was observed early in training and differences diminished following further training (Clayton *et al.*, 2002). The results suggest that an intermediate-term memory and memory consolidation are sensitive to reduced hippocampal NMDAR function and that incremental learning impairments are only observed following a substantial loss of NMDAR function in region CA1 or a wide spread decline in NMDAR function that impairs sensory-motor function. Together the behavioral data support the idea that the onset of age-related impairment in intermediate-term memory could result from a decrease in hippocampal NMDAR function, leaving incremental learning mechanisms intact.

Is impaired NMDAR-LTP related to memory deficits? Evidence is mounting to indicate a relationship between the appearance of memory deficits, a decline in NMDAR function, and altered synaptic plasticity. Impaired induction of LTP can be observed in middle-age and LTP magnitude is related to cognitive function of middle-aged animals (Brunson *et al.*, 2005; Fouquet *et al.*, 2009; Rex *et al.*, 2005). We recently observed a decrease in NMDAR function, limited to those middle-aged animals that exhibit retention deficits on the water maze following a single training session (Kumar *et al.*, 2011a). For studies that examine aged animals, the LTP magnitude following weak stimulation that would induce NMDAR-LTP (50 pulses at 100 Hz) correlated with retention examined 24 hr after 4 days of training (Deupree *et al.*, 1991) and treatment to enhance NMDAR function improved TBS-induced LTP and performance on the repeated acquisition version of the water maze (Burgdorf *et al.*, 2011). Thus, the weight of evidence supports the idea that the emergence of memory consolidation deficits is associated with a decline in NMDAR function and NMDAR-LTP.

The age-related decline in NMDAR function does not appear to correlate with impairment of incremental learning and acquisition of a spatial reference memory (Boric *et al.*, 2008). This may not be surprising since the establishment of a spatial reference memory, acquired by incremental learning, is observed for many pharmacological or genetic conditions that decrease hippocampal NMDAR function (Bannerman *et al.*, 2008; Bannerman *et al.*, 2006). In one study, LTP induced by 5 Hz, but not 30 or 70 Hz stimulation correlated with learning across five days of training (Tombaugh *et al.*, 2002). While these researchers found that NMDAR synaptic responses were decreased with age, impaired incremental learning was not related to the NMDAR synaptic responses. The authors suggest that the relationship between LTP for 5 Hz stimulation and incremental learning may be due to a larger sAHP in impaired animals. Importantly, 5 Hz stimulation would result in synaptic activation arriving within a window for the peak of the sAHP from the preceding stimulation induced action potential (Fig 5). In this case, the decrease in NMDAR activation may be enhanced for patterned stimulation that falls within the window of a larger sAHP. The sAHP amplitude is increased in aged animals that exhibit impaired incremental learning (Oh *et al.*, 2010; Tombaugh *et al.*, 2005) and reduction of the sAHP facilitates learning and LTP induction by 5 Hz stimulation in aged animals (Disterhoft *et al.*, 1996; Kumar and Foster, 2004; Norris *et al.*, 1998). Together, the results indicate that the initial memory deficits of senescence are associated with a decline in NMDAR function, including induction of NMDAR-LTP. However, incremental learning deficits observed in advance age are not directly related to the decline in NMDAR function.

5. VDCC-dependent synaptic plasticity and incremental learning

The involvement of L-type Ca^{2+} channels and VDCC-dependent synaptic plasticity in memory is complex and may depend on the brain region examined. It is important to note that L-channel antagonists have effects opposite that of NMDAR antagonists on hippocampal-dependent memory. In young animals, VDCC blockade facilitates retention of inhibitory avoidance and spatial memory, and facilitates the rate of acquisition of the radial arm maze (Batuecas *et al.*, 1998; Kim *et al.*, 2011; Levy *et al.*, 1991; Quartermain *et al.*, 2001; Quartermain *et al.*, 1993; Quevedo *et al.*, 1998). Furthermore, the improved retention following L-channel blockade appears to be specific for the hippocampus (Kim *et al.*, 2011; Quevedo *et al.*, 1998). Similar improvement in retention of hippocampal-dependent memory following L-channel blockade has also been observed for aged animals. In fact, L-channel antagonists ameliorate or prevent age-related memory decline across several species including humans (Ban *et al.*, 1990; Deyo *et al.*, 1989; Ingram *et al.*, 1994; Levere and Walker, 1992; Riekkinen *et al.*, 1997; Rose *et al.*, 2007; Sandin *et al.*, 1990; Solomon *et al.*, 1995; Trompet *et al.*, 2008; Veng *et al.*, 2003; Woodruff-Pak *et al.*, 1997). The results indicate that the beneficial effects of L-channel blockade on memory are specific for

hippocampal-dependent memory, possibly mediated through a reduction in the sAHP (Disterhoft *et al.*, 1996), facilitation of NMDAR-LTP, or inhibition of LTD (Kumar and Foster, 2004; Norris *et al.*, 1998).

In contrast to facilitation of hippocampal-dependent memory, mounting evidence indicates that blockade of L-channels impairs incremental learning and the consolidation of remote memories in the neocortex. The L-channel antagonist nifedipine, but not the NMDAR antagonist AP5, blocked incremental associative learning on an olfactory discrimination task (Zhang *et al.*, 2010). Comparison of NMDAR and VDCC antagonists on performance of the radial 8-arm maze confirmed that NMDAR blockade impairs rapidly acquired spatial memory. In contrast, animals under VDCC blockade acquired the task to the same extent as controls, but exhibited a deficit in spatial reference memory when retested 7–10 days later (Borroni *et al.*, 2000; Woodside *et al.*, 2004). Furthermore, mice with knockout of L-type VDCCs exhibit intact spatial learning on the water maze; however, retention deficits were observed when examined 30 days after training, indicating disruption of processes for remote memories (McKinney and Murphy, 2006; White *et al.*, 2008), which are thought to be processed in the neocortex (Quinn *et al.*, 2008; Teixeira *et al.*, 2006; Wiltgen *et al.*, 2004). Together with the fact that young rats with hippocampal lesions continue to exhibit incremental acquisition of a spatial reference memory, the results suggest preserved incremental learning in aged rats may involve VDCC-dependent synaptic plasticity in neocortical regions.

Before discussing the relationship between VDCC-plasticity and incremental learning during aging, it is important to point out that there are several parallels between the effects of behavioral stress and aging on memory and synaptic plasticity. As such, the level of stress associated with training and the time between training and examination of synaptic plasticity is important in determining the relationship between synaptic plasticity and memory. An acute stress, including a single day of water maze training, can result in impaired induction of LTP and enhanced induction of LTD lasting hours or days (Kavushansky *et al.*, 2006; Li *et al.*, 2005; Shors *et al.*, 1997; Xu *et al.*, 1997). Stress hormones have a direct effect on NMDAR function (Ooishi *et al.*, 2011) and the sAHP amplitude is influenced by stress hormones, which in turn can influence the induction of synaptic plasticity (Diamond *et al.*, 1992; Joels and de Kloet, 1991; Weiss *et al.*, 2005). Treatments such as environmental enrichment will protect memory, the sAHP, and synaptic plasticity from mild stressors and aging (Kumar and Foster, 2007a; Kumar *et al.*, 2011b; Sierra-Mercado *et al.*, 2008; Yang *et al.*, 2006). Acute stressor effects can be minimized by examining synaptic plasticity several days after a single training session and results indicate no relation between acute stress for a single day of water maze training and altered synaptic plasticity during aging (Foster and Kumar, 2007). In contrast, exposure to stress for several days can impair LTP and enhance LTD for months (Artola *et al.*, 2006; Holderbach *et al.*, 2007; Sterlemann *et al.*, 2010). Furthermore, chronic stress modifies L-channel function and VDCC-synaptic plasticity, (Foster and Kumar, 2007; Liebmman *et al.*, 2008; Mamczarz *et al.*, 1999; Ryan *et al.*, 2010; van Gemert and Joels, 2006). Thus, stress associated with training across multiple days could have enduring effects on synaptic plasticity, particularly in learning impaired animals in which training may be analogous to a being exposed to an uncontrollable swim stress.

A handful of studies have examined the relationship between VDCC-dependent synaptic plasticity and behavior in aged animals. As detailed above, age-related changes in Ca^{2+} regulation include diminished NMDAR function and increased Ca^{2+} from VDCC-ICS. The increase VDCC-ICS component is thought to underlie the increase susceptibility to LTD induction in aged animals (Kumar and Foster, 2007c; Kumar *et al.*, 2007; Norris *et al.*, 1998). The increased susceptibility to LTD is correlated with forgetting examine 24 hrs after a single training session on the spatial version of the water maze (Foster and Kumar, 2007).

Moreover, the level of LTD was not correlated with the level of stress measured as the amount of time swimming in the pool. The results suggest that the decline in intermediate-term memory is associated with a shift from NMDAR-dependent to VDCC-ICS-dependent regulation of synaptic plasticity. Other studies have examined VDCC-synaptic plasticity in animals characterized as impaired or unimpaired for incremental acquisition of a spatial reference memory following 8–9 days of distributed training. In one study, researchers induced LTP using 200 Hz stimulation (Schulz et al., 2002), which should favor VDCC-LTP in aged animals (Shankar *et al.*, 1998). No difference in LTP was observed between aged impaired and unimpaired animals; however, a correlation was observed between LTP and behavior for aged unimpaired animals (Schulz et al., 2002). The results suggest a possible relationship between VDCC-LTP and incremental learning in animals that are able to acquire the task. The authors suggest that the lack of correlation for impaired learners may be due to the severity of impairment (Schulz et al., 2002). Thus, aging of systems involved in incremental learning may have precipitated a complete absence of learning in impaired animals. Another series of studies used AP5 to block NMDARs in order to examine VDCC-dependent synaptic plasticity (Boric et al., 2008; Lee et al., 2005). The researchers confirmed an age-related decrease LTP induced by TBS and TBS-induced LTP did not correlate with incremental learning in aged rats. In the presence of AP5, VDCC-dependent synaptic plasticity was enhanced in aged animals that exhibited intact incremental acquisition of a spatial reference memory. The authors suggest that VDCC-dependent synaptic plasticity may compensate for loss of NMDAR-dependent synaptic plasticity in order to preserve acquisition of a spatial reference memory. Together, the results indicate that VDCC-synaptic plasticity is intact in aged animals that can acquire a spatial reference memory. Further investigations using treatments to inhibit or enhance VDCC function may be able to determine whether VDCC-synaptic plasticity contributes to preservation of incremental learning in aged animals or whether increased stress associated with an inability to escape from the water underlies the correlation of VDCC-dependent synaptic plasticity and incremental learning.

As discussed above, in older animals, L-channel blockers improve the rapid acquisition and consolidation of intermediate-term memory that depends on hippocampal NMDARs. However, studies in younger animals indicate that L-channel blockers may impair the storage of remote memories. Thus, there may be a trade off for treatments designed to improve memory during aging through L-channel blockade. While not specifically examined, one study provides evidence for this idea. The study examined the influence of nimodipine treatment on water maze performance over 4 days of training (two trials per day) (Riekkinen et al., 1997). Untreated aged animals (22 months of age) were impaired relative to young (6 months). Nimodipine treatment facilitated acquisition in aged rats, consistent with the idea that L-channel blockade can improve learning and intermediate-term memory. Animals were then re-tested 30 days after drug washout. Young animals exhibited long-term memory observed as carry-over effects of previous training, with improved re-learning on the maze relative to original training. In contrast to young animals, aged animals, treated with nimodipine, which previously exhibited superior spatial learning, did not exhibit a carry-over advantage during retesting. The lack of a carry-over effect for aged animals is in contrast to other studies that indicate previous learning facilitates acquisition on subsequent retesting (Colombo and Gallagher, 2002; Hansalik *et al.*, 2006; van Groen *et al.*, 2002). Rather, the absence of carry-over effects is consistent with work indicating that VDCC-dependent synaptic plasticity is necessary for the storage of long-term or remote memories (Borroni *et al.*, 2000; Lashgari *et al.*, 2006; Seoane *et al.*, 2009; White *et al.*, 2008; Woodside *et al.*, 2004). For example, delivery of Ca²⁺ channel blockers to young rats impaired long-term reference memory in the absence of learning deficits (Borroni et al., 2000; Woodside et al., 2004). Thus, blockade of VDCCs may improve hippocampal and NMDAR-dependent memory in aged animals at the expense of long-term memory. This

idea remains to be tested. If true, then our ideas about treating age-related memory decline with L-channel antagonists may need to be reevaluated.

6. Conclusion

Several advances have been made which refine ideas concerning Ca^{2+} dysregulation in mediating age-related changes in synaptic plasticity and memory (Foster, 1999; Foster and Norris, 1997). NMDAR-dependent and VDCC-dependent mechanisms are likely to interact cooperatively in young animals. Hippocampal NMDAR-dependent mechanisms mediate intermediate-term memory for rapidly acquired information. In turn, intermediate-term memory may contribute to incremental learning and consolidation of spatial reference memories involving VDCC-dependent mechanisms and the neocortex. The decline in NMDAR function and increase in Ca^{2+} from ICS in the hippocampus during aging are thought to underlie the initiation of memory decline. Thus, memory consolidation deficits, increased sAHP, and impaired NMDAR function, including impaired induction of NMDAR-LTP, provide early markers of cognitive decline. The inability to acquire a spatial reference memory through incremental learning manifests later and suggests a decline in other processes or the involvement of other brain regions. It will be important to continue to develop more sophisticated paradigms for early detection of cognitive aging, as well as documenting the mechanisms for changes in synaptic plasticity. Future studies may want to determine if cognitive deficits are progressive. Do memory consolidation impairments in middle-age predict the extent of rapid acquisition or incremental learning deficits?

The translational relevance of animal models will depend on the development of treatments for age-related memory impairments that depend on proper hippocampal function. Several recent reviews have addressed possible mechanisms which increase the vulnerability of the hippocampus to aging and cognitive decline (Burger, 2010; Foster, 2007; Kumar *et al.*, 2009; Lynch, 2009; Magnusson *et al.*, 2010; Oh *et al.*, 2010; Penner *et al.*, 2010; Potier *et al.*, 2010; Schimanski and Barnes, 2010; Schneider *et al.*, 2010; Wang and Michaelis, 2010). Most hypotheses include Ca^{2+} dysregulation and increased oxidative stress as a component of aging. The results from studies examining the effect of redox-active agents on neural physiology indicate that an age-related shift in redox state underlies the pattern of altered Ca^{2+} homeostasis, reducing NMDAR function and increasing Ca^{2+} from ICS, decreasing cell excitability, leading to alter synaptic plasticity processes that are critical for memory. Due to the interaction of NMDARs, RyR-ICS, and redox state in regulating synaptic plasticity (Fig 4), treatments may want to focus on restoring intracellular redox state in order to reverse the age-related shift in Ca^{2+} sources. In this regard, it will be important to identify the source for the shift in redox state. Metabolic changes and increased inflammation during aging provide likely candidates for increased oxidative stress. Recent studies indicate that region CA1 is more susceptible to an age-related increase in inflammation and oxidative stress and exhibits reduced neurotrophic and pro-survival signaling (Jackson and Foster, 2009; Jackson *et al.*, 2010; Zeier *et al.*, 2010). Combined with studies demonstrating that NMDARs in region CA1 are involved in memory consolidation (Daumas *et al.*, 2005; Kesner *et al.*, 2004; Lee and Kesner, 2002), the increased susceptibility to oxidative stress in region CA1 and subsequent decrease in NMDAR function could explain the emergence of memory consolidation deficits in middle-age, as an early sign of age-related cognitive decline.

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Abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CaN	Calcineurin
Ca²⁺	Calcium
CaMKII	Calmodulin kinase II
IP3R	Inositol trisphosphate receptor
ICS	Intracellular calcium stores
F344	Fisher 344
F344BN	Fisher 344 Brown Norway crossed
HFS	High frequency stimulation
LFS	Low frequency stimulation
LTP	Long-term potentiation
LTD	Long-term depression
mGluR	Metabotropic glutamate receptor
NMDAR	N-methyl-D-aspartate receptors
PP-LFS	Paired-pulse low frequency stimulation
K⁺	Potassium
PKA	Protein kinase A
PKC	Protein kinase C
PP1	Protein phosphatase 1
ROS	Reactive oxygen species
RyR	Ryanodine receptor
sAHP	Slow afterhyperpolarization
TBS	Theta burst stimulation
VDCC	Voltage-dependent calcium channel

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Highlights

- The water maze can detect a progressive decline in cognition during aging.
- Dysregulation of Ca^{2+} homeostasis modifies the threshold for synaptic plasticity.
- NMDAR-dependent synaptic plasticity declines with age.
- VDCC and RyR-ICS regulation of synaptic plasticity increases during aging.
- Aging of synaptic plasticity mechanisms contribute to variability in memory deficits.

Figure 1.

Performance differences during aging for distributed or massed training on the water maze. **A)** Schematic illustration of the pool, with an escape platform (grey circle) in the upper right hand quadrant. The line indicates the path length to find the platform, which decreases from the earlier to later training trials. **B)** During a probe trial, the platform is removed and the search pattern is focused on the area (i.e. goal quadrant) in which the platform was located. **C)** Hypothetical performance curves of age-related differences in performance for distributed training, modeled from Aitken and Meaney, 1989; Bizon et al., 2009; Clayton et al., 2002; Diana et al., 1995; Driscoll et al., 2006; Gage et al., 1984; Mabry et al., 1996; Miyagawa et al., 1998; Nyffeler et al., 2010; Rapp et al., 1987; and van Groen et al., 2002. Older animals (filled circles) exhibit an initial impairment compared to middle-aged (grey circles) and young (open circles). However, most aged animals can acquire a spatial reference memory following extended distributed training. The saw-tooth pattern of performance in aged animals may be due to forgetting across days (dashed lines). A subset of aged animals (filled triangles) may exhibit profound learning deficits such that they will not be able to acquire a spatial reference memory with repeated training to the same location across several days. **D)** A probe trial, delivered on alternate days, can be substituted for the

last trial of that day. The average distance from the platform (proximity) is recorded and those animals that exhibit distances greater than young (dashed line) are classified as learning impaired. Most middle-aged animals would not be classified as learning impaired. **E)** Age-related differences in performance for massed training, adapted from Blalock et al., 2003; Foster et al., 1991; Foster and Kumar, 2007; Foster et al., 2003; Mabry et al., 1996; Norris and Foster, 1999. Aged animals exhibit a slower rate of learning when training is massed into a single training session. The acquisition probe trial is delivered near the end of training, followed by three refresher training trials, and a retention probe trial, delivered 24 hrs later. **F)** Measures of the percent time searching the goal quadrant for the initial probe trial (Acquisition) indicate that most animals have acquired a search strategy, focusing their search in the goal quadrant relative to chance (dashed line). The retention probe trial reveals a subgroup of memory impaired aged and middle aged animals (bracket) that exhibit goal search times that are less than that observed for young.

Figure 2.

Performance differences related to aging for repeated acquisition training. **A)** Schematic illustration of the pool, with an escape platform (grey circle) shifted to a new location each day such that the animal must repeatedly learn new escape locations. **B)** Hypothetical performance curves of the age-related decline in the rate of acquisition, modeled from Driscoll et al., 2006; Markowska and Savonenko, 2002; Miyagawa et al., 1998; Nyffeler et al., 2010; van der Staay and de Jonge, 1993; Wyss et al., 2000. The distance for each trial is averaged across days of training. The rate of learning decreases with age (aged: filled circles; middle-aged: grey circles; young: open circles). **C)** For delayed matching-to-sample, a variable delay (minutes to hours) is inserted between the first two trials. The savings (i.e. decrease in path length to find the platform on trial two compared to the first trial) is used as an indication of memory. An age by delay interaction is observed such that similar performance is observed for short delays and age-related memory impairments are seen with increasing delays.

Figure 3.

Synaptic plasticity induced by pattern stimulation. **A)** LTP is an increase in synaptic transmission, induced by HFS or TBS activation of presynaptic fibers to release glutamate, depolarizing the postsynaptic side to release the Mg^{2+} block of the NMDAR, and provoke a brief, large magnitude rise in postsynaptic Ca^{2+} from NMDARs, VDCCs and ICS. In addition, glutamate acting on mGluRs can increase the release of Ca^{2+} from ICS through IP3R activation. The large rise in Ca^{2+} activates kinases (CaMKII, PKC, PKA) to increase the AMPA receptor component of synaptic transmission. **B)** LTD is a decrease in synaptic strength induced by LFS or PP-LFS to produce a modest and prolonged rise in intracellular Ca^{2+} , activating phosphatases (CaN, PP1) to decrease the AMPA receptor component of synaptic transmission.

Figure 4.

The interaction of NMDARs, VDCCs, RyRs, and redox state regulates synaptic plasticity during aging. In young animals, the rise in intracellular Ca^{2+} for induction of synaptic plasticity (LTD/LTP) arises mainly from NMDARs. Activation of NMDARs requires glutamate binding and postsynaptic depolarization (+) due to AMPA glutamate receptor activity and backpropagating action potentials. The action potential will activate VDCCs to increase Ca^{2+} influx along the dendritic membrane. The influx of Ca^{2+} from VDCCs acts on RyRs to release Ca^{2+} from ICS. In turn, the rise in intracellular Ca^{2+} activates K^{+} channels along the membrane, resulting in an efflux of K^{+} , which hyperpolarizes (-) the cell membrane. The K^{+} channels include SK channels near NMDARs and channels involved in the generation of the sAHP. With advanced age, an increase in oxidative stress (ROS) shifts the function of Ca^{2+} sources, decreasing and increasing Ca^{2+} from NMDARs and RyRs, respectively. The increased Ca^{2+} from ICS results in a larger hyperpolarizing response, which further inhibits NMDAR activation, raising the threshold stimulation needed to induce LTP.

Figure 5.

The threshold for LTP is regulated by the sAHP. **A)** Illustration of the sAHP. The resting membrane potential is indicated by the dashed line. Intracellular injection of depolarizing current induced a burst of five action potentials (spike burst), which is followed by the sAHP with a peak ~200 ms from the spike burst and lasting several 100 ms. The sAHP creates a window of hyperpolarization that disrupts the activation of NMDARs. The arrow indicates a reduction in the sAHP induced by pharmacological treatments to decrease Ca^{2+} from VDCC or ICS. **B)** Frequency-response functions for stimulation induced synaptic plasticity. The baseline synaptic response is 100%. Pattern stimulation (900 pulses) of increasing stimulation frequency (1–100) was delivered and the synaptic response was measured at least 30 min after the end of pattern stimulation. The curves indicate the changes in synaptic transmission (LTP > 100 percent of baseline or LTD < 100 percent of baseline). Normally, LTD is observed for LFS between 1–3 Hz and aged animals (solid curve) exhibit increased susceptibility, exhibiting greater LTD relative to younger animals (dashed curve). The threshold for LTP is ~5 Hz in young animals. In contrast, aged animals exhibit a plateau region of no synaptic modification starting at ~5 Hz, such that the threshold stimulation frequency for LTP induction is increased. The age-related shift in synaptic plasticity is due in part to the increase in the sAHP. Pharmacological treatments that decrease the sAHP amplitude in aged animals (Aged (-) AHP, solid curve with open circles) reduce the threshold stimulation required for induction of LTP.

TABLE 1

Method	Cognitive Processes	Advantage	Disadvantage	Age of onset (months)
Distributed Training	Incremental learning, spatial reference memory	Sensitive to incremental learning deficits, may better mimic global deficits of dementia	Lack of sensitivity for early detection of memory deficits, deficits may disappear with extended training, may result in chronic stress	18–24
Massed training	Rapid acquisition and intermediate memory	Sensitive to early detection of acquisition and memory deficits	May induce an acute stress	Acquisition 12–18 Memory 12–14
Repeated acquisition	Rapid, flexible acquisition	Sensitive to early detection of acquisition deficits for rapidly acquired information	May result in a chronic stress with repeated training	18–24
Delayed match-to- sample	Intermediate memory	Sensitive to early detection of memory deficits for rapidly acquired information	May result in a chronic stress with repeated training	Retention duration decreases with age