Aging Effects on the Limits and Stability of Long-Term Synaptic Potentiation and Depression in Rat Hippocampal Area CA1

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INTRODUCTION

Synaptic plasticity including long-term potentiation (LTP) and long-term depression (LTD) is thought to form the cellular basis of learning and memory (Bliss and Collingridge 1993) and alterations in synaptic plasticity are hypothesized to contribute to age-related memory deficits (Barnes and McNaughton 1985; Foster 1999). The ability to form and use memories is likely to require long-lasting structural and physiological changes in the connections between neurons, especially in the brain areas known to be critical for mnemonic function (Geinisman et al. 1995; Norris et al. 2003; Shapiro and Eichenbaum 1999). If so, then impairment of synaptic plasticity in the hippocampus during aging might account for memory dysfunction observed during senescence (Foster 1999; Rosenzweig and Barnes 2003).

LTP is an extensively studied activity-dependent increase in synaptic strength that satisfies several criteria for a cellular memory mechanism (Morris 2003). Although several studies have shown aging-related decrements in the amount of hippocampal LTP (Deupree et al. 1993; Landfield et al. 1978; Mori et al. 2000), the difference may not reflect a true differences in the maximum level of LTP. Typically deficits take the form of a reduced susceptibility observed for stimulation near the threshold for induction or an accelerated rate of decay (Foster 1999; Geinisman et al. 1995; Rosenzweig and Barnes 2003; Watabe and O’Dell 2003).

A contrasting relaxation of the requirements for depressing synapses (Kumar and Foster 2005; Norris et al. 1996) may contribute to these effects or reflect independent phenomena. Forms of persistent modification of synaptic strength other than LTP are known (Lopez et al. 1990; Stanton 1996) but have received comparatively little attention in the context of aging-related memory dysfunction. Until recently it had been difficult to demonstrate phenomena analogous to LTP for reducing synaptic strength in adult animals except from previously potentiated levels.

LTD is an enduring, activity-dependent decrease in synaptic transmission that can occur in response to low-frequency stimulation (LFS), typically 1 Hz for many minutes (Cummings et al. 1996; Mulkey and Malenka 1992). Although this conditioning stimulation is effective in very young (<35–40 days) (Dudek and Bear 1993; Oliet et al. 1997) and very old (>20 mo) (Foster and Kumar 2007; Hsu et al. 2002; Kumar and Foster 2005; Lee et al. 2005; Norris et al. 1996; Vouima et al. 2000) rats, it is much less effective in rodents of intermediate ages (Fujii et al. 1991; Milner et al. 2004; Norris et al. 1996; O’Dell and Kandel 1994; Wexler and Stanton 1993). One problem is that LFS may be near the threshold for the induction of LTD. Thus like LTP, age-related differences in LTD may reflect an alteration in the susceptibility for LTD induction rather than the maximum magnitude obtainable. Indeed, almost nothing is known concerning age-related changes in asymptotic level of LTD (Foster and Kumar 2007).

Notably, LTD induction can be facilitated in adults by using paired-pulse LFS (pLFS) (Foster and Kumar 2007; Kemp et al. 2000; Thiels et al. 1994; Thinschmidt et al. 2003; Wasling et al. 2002). The current study took advantage of the fact that pLFS reliably induces LTD in adults to examine age-related differences in the asymptotic level of synaptic depression.

Reduction in synaptic strength imposed on synapses after conditioning to induce LTP is known as long-term depotentiation (LTDp) (Barrionuevo et al. 1980; Zhou and Poo 2004). Although LTD and LTDp seem equivalent except for the level of synaptic strength from which they originate, both exhibit...
distinct characteristics. LTdP requires some postnatal maturation of the brain, developing in conjunction with LTP. In contrast to LTD, LTdP can be elicited easily in middle-aged rats using single-pulse LFS (Errington et al. 1995; Kamal et al. 1998; Norris et al. 1996, 1998; Wagner and Alger 1995). There may even be multiple forms of LTdP depending on specific mechanisms mediating LTP (Luthi et al. 2004). LTdP has not been extensively studied in aged animals with LTP deficits (Norris et al. 1996). However, developmental and signal transduction characteristics differentiate distinct mechanisms for reducing synaptic efficacy, (Muller et al. 1995; Wagner and Alger 1996; Zhuo et al. 1999), conditioning protocols that induce LTD are generally effective in inducing LTdP (Burett et al. 1997; Wagner and Alger 1995). De-depression (Dudek and Bear 1993; Zhou and Poo 2004) has received even less attention than depotentiation but reflects the capacity for growth of synaptic transmission even after synaptic plasticity has been substantially reduced.

Although the effects of aging on LTP and LTD are generally described as modifications in induction or maintenance rather than capacity, true changes in capacity cannot be ascertained without knowledge of the total range over which synaptic strength can be modified. Prior to the discovery of synaptic conditioning paradigms for inducing LTD in adult animals, it was not possible to define this dynamic range (the difference between maximal potentiation and depression), and few studies have addressed this property even in very young or old animals where both LTP and LTD could be induced. In the current study, we determined the position of the baseline synaptic strength relative to the minimum and maximum synaptic strengths to which a population of synapses could be modified. This study evaluates whether aging alters the position of baseline synaptic strength relative to the upper and lower limits.

The repeated application of synaptic modification stimuli necessary to measure these dependent variables permitted the analysis of several additional properties of synaptic plasticity that may be affected by senescence. We measured the rates at which LTD and LTP developed with repeated episodes of submaximal conditioning as well as the rates of passive decay from asymptotically depressed and potentiated levels. The present data also address whether properties of synaptic plasticity are themselves altered by repeated modifications (metaplasticity) (Holland and Wagner 1998; Krucker et al. 2002). The results demonstrate that aging had no effect on the synaptic modifications, magnitude of asymptotic LTP, asymptotic LTD, the rate of synaptic plasticity induction, and decay or reversal after posttetanic stimulation.

**Hippocampal slice preparation**

Rats were anesthetized with Halothane (Halocarbon Laboratories, River Edge, NJ) and swiftly decapitated (Guillotine, myNeuroLab.com). The brains were rapidly removed, and the hippocampus was sliced in the transverse plane into 400-µm sections using a tissue chopper (Mickle Laboratory Engineering Company, Surrey, England). The slices were incubated in a holding chamber containing artificial cerebrospinal fluid (ACSF) [which contained (in mM) 125 NaCl, 3.3 KCl, 1.25 KH₂PO₄, 1.0 MgSO₄, 4 CaCl₂, 20 NaHCO₃, and 10 glucose] at 22–24°C for 60 min. The pH was maintained at 7.4 with 95% O₂-5% CO₂. Thirty minutes before recording, one to two slices were transferred to a submersion recording chamber (Warner Instrument, Hamden, CT) and perfused (2 ml/min) with oxygenated ACSF. The recording was performed at 30°C (automatic temperature controller, TC-324B, Warner Instrument).

**Electrophysiological recordings and induction of synaptic plasticity**

At the beginning of each recording, two concentric bipolar stimulating electrodes (FHC, Bowdoinham, ME) were positioned in stratum radiatum of CA1 for stimulation of the Schaffer collateral commissural afferents, one toward CA3 and one toward the subiculum. A glass micropipette containing 4 M NaCl (1–3 M ohms) was positioned in s. radiatum between the stimulating electrodes (~1 mm apart from each) for recording extracellular postsynaptic field potentials. A single diphasic stimulus pulse of 100 µs was alternated between pathways such that each pathway was activated at 0.05 Hz. The preceding configuration allowed for recording two independent pathways. The “test” pathway received LTP- or LTD-inducing stimulation, and the control pathway was used to monitor the stability and overall health of the slice. To evaluate the pathways for independence, we tested for paired-pulse facilitation by delivering a single pulse to the test pathway followed 20 s later by a pair of pulses, one delivered to the control pathway, and one 50 ms later to the test pathway (Velisek et al. 1993). This was repeated four times and the excitatory postsynaptic potential (EPSP) slopes for the test pathway following single-pulse stimulation were compared with the slopes acquired during the paired-pulse delivery. If facilitation exceeded 10%, the electrodes were repositioned, and the evaluation was repeated until the facilitation was <10%. To normalize for input/output variation among slices, we determined the maximal EPSP slopes for each slice and adjusted the stimulus current to produce 25–50% of the maximal slope. For each slice, baseline data were collected for a period of 10 min at 0.05 Hz. Only those slices that demonstrated a full 10 min of stable responding were used for analysis. LTD-inducing stimuli consisted of paired pulses (pLFS) separated by 200 ms delivered at 1 Hz for 15 min (1,800 pulses) (Kemp et al. 2000). High-frequency stimulation (LTP-producing stimuli) was administered using physiologically patterned theta burst stimulation (Larson et al. 1986). Four pulses at 100 Hz were delivered at 200-ms intervals for 1 s; this was repeated four times, and each episode was separated by 10 s. The induction stimulations were repeated multiple times to achieve asymptotic LTP or LTD. For LTD experiments, the test pathway received nine episodes of pLFS conditioning. After each pLFS episode, we recorded EPSPs from the test and control pathways for 10 min. After the last pLFS episode, the EPSP responses were recorded for 60 min to demonstrate the persistence and stability of LTD. For LTD experiments, theta-burst stimulation (TBS) was delivered six times. Both the test and control pathways EPSPs were recorded for 10 min after each TBS episode and for 60 min after the last TBS episode. In experiments testing the ability to reverse LTP (LTdP) and LTD (LTdD), we induced maximal LTP with TBS and then administered two pLFS trains (each followed by a 10-min recording period) or maximal LTD with pLFS and then administered two TBS trains (each followed by a 10-min recording period).
Data acquisition and analysis

Signals were recorded using a Grass P-511 preamplifiers, filtered at 10 kHz, and digitized at 20 kHz by a Digidata 1322A (Axon Instruments, Union City, CA) and a DataWave Technologies (Longmont, CO) interface using the programs Clampex 9.0 (Axon Instruments) and SciWorks (DataWave Technologies) software on Dell computers. EPSP slopes were calculated off-line (Clampfit 9.0, Axon Instruments and Data Wave Technologies) as the ratio of voltage and time differences between time-points 10 and 90% along the rising phase of each individual EPSP. The calculation of TBS and pLFS effects were defined as 100% *ΔL/Δt, where L was the average EPSP slope during the baseline period and L was the average EPSP slope during the last 2 min (for 10-min recording periods) or 10 min (for 60-min recording periods) of recording after patterned conditioning stimulation. To calculate the rate at which LTP and LTD decayed to stable potentiated or depressed levels respectively, we compared the percentages of baseline during the last 2 min of the first 10 min of the final 60 min recording period (to eliminate posttetanic potentiation effects) to the average percentages of baseline during the final 10 min of the last 60 min recording periods and divided by the period of time between the two means (40 min). To calculate the magnitude of the ability to reverse asymptotic LTP (LTdeP) and LTD (LTdeD), new baselines were established that were normalized to 100% from the EPSP slopes recorded during the last 10 min of asymptotic LTP and LTD. Statistical analyses used two-sample one- and two-tailed Student’s t-test as appropriate, assuming equal variances. Induction of synaptic plasticity, LTP and LTD, were determined using paired r-test comparing control pathways (nontetanised) with the pathway receiving pattern stimulation. An ANOVA was used to determine group differences. Repeated measures of ANOVA across each pattern episode were used to analyze the effect of age on synaptic plasticity measures. Where stated, n represents the number of animals used in each set of experiment; twice two slices from the same animal were used for LTP experiments.

RESULTS

Aging effects on asymptotic LTP

The original experimental design used young (1–4 mo), middle-aged (6–12 mo), and aged (22–24 mo) groups. An ANOVA revealed no differences in maximum magnitude of LTP [F(1,5) = 0.70, P > 0.44] between the young (n = 4) and middle-aged (n = 3) or LTD [F(1,7) = 4.69, P > 0.99] between the young (n = 4) and middle-aged (n = 5) groups as they were pooled into a young adult group for comparison with aged animals.

Multiple episodes of TBS were used to generate asymptotic LTP in slices from both young adult (1–12 mo) and aged (22–24 mo) animals. The TBS induced a significant increase in the synaptic responses measured 10 min after each TBS episode in young and aged animals (Table 1). There were no significant age effects on the magnitude of asymptotic LTD during any of the recording periods (Fig. 1). Furthermore, repeated-measures ANOVA across the six TBS episodes indicated a significant increase in the synaptic responses [F(5,80) = 22.47, P < 0.0001] in absence of an age effect, indicating no age difference in the rate of LTD induction. In addition, asymptotic LTD 60 min after the last episode of pLFS was decreased from baseline in aged (38.59 ± 4.35%, n = 6, P < 0.0001) and young adult (32.29 ± 7.88%, n = 9, P < 0.0001) rats, and an ANOVA revealed no significant difference between groups [F(1,13) = 1.59, P > 0.23]. Finally, the LTD decay rates were not different [F(1,13) = 1.59, P > 0.23] in aged (11.89 ± 2.47%/h) and young adult (7.39 ± 2.39%/h) rats. These recordings were acquired over a period of nearly 5 h, and in both age groups, the control pathways remained remarkably stable. EPSP slopes during the last 10 min of the final 60 min recording were not significantly different from each other and initial 10 min baseline, indicating that slice health was stable over the 2-h recording period (Fig. 1B).

TABLE 1. LTP induced by multiple episodes of TBS in young-adult and aged rats

<table>
<thead>
<tr>
<th>TBS Episode</th>
<th>Young-Adult</th>
<th>Aged</th>
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<tbody>
<tr>
<td>1st</td>
<td>180.45 ± 13.41*</td>
<td>169.34 ± 7.64*</td>
</tr>
<tr>
<td>2nd</td>
<td>198.46 ± 14.73*</td>
<td>182.34 ± 9.54*</td>
</tr>
<tr>
<td>3rd</td>
<td>204.39 ± 12.79*</td>
<td>190.63 ± 10.64*</td>
</tr>
<tr>
<td>4th</td>
<td>203.46 ± 12.87*</td>
<td>196.66 ± 11.11*</td>
</tr>
<tr>
<td>5th</td>
<td>208.04 ± 16.48*</td>
<td>196.62 ± 11.26*</td>
</tr>
<tr>
<td>6th</td>
<td>214.80 ± 20.20*</td>
<td>197.34 ± 11.18*</td>
</tr>
</tbody>
</table>

Means ± SE percent of baseline excitatory post synaptic potential (EPSP) slopes for the last 2 min of each 10-min recording period after each theta-burst stimulation (TBS) episode. LTP, long-term potentiation. *: significant potentiation of synaptic responses compared to baseline.

Aging effects on asymptotic LTD

Multiple episodes (9) of pLFS were used to generate asymptotic LTD in slices from both young adult and aged animals. The pLFS induced a significant decrease in the synaptic responses measured 10 min after each pLFS episode in young and aged animals (Table 2). There were no significant age effects on the magnitude of asymptotic LTD during any of the recording periods (Fig. 2). Furthermore, repeated-measures ANOVA across the nine pLFS episodes indicated a significant decrease in the synaptic responses [F(8,104) = 95.92, P < 0.0001] in absence of an age effect, indicating no age difference in the rate of LTD induction. In addition, asymptotic LTD 60 min after the last episode of pLFS was decreased from baseline in aged (25.52 ± 9.06%/h) and young adult (44.82 ± 11.88%/h) rats. Control pathways in both age groups showed transient heterosynaptic short-term posttetanic depression (see Fig. 1A) after each TBS episode, and slices from young adults were impacted more than the aged rats; however, the responses returned to the baseline such that the EPSP slopes during the last 10 min of recording were not significantly different from each other and initial 10 min baseline, indicating that slice health was stable over the 2-h recording period (Fig. 1B).

Aging effects on the active reversal of LTP (LTdeP)

To evaluate potential aging differences on the ability to reverse asymptotic LTP (LTdeP), we administered strong...
LTD-inducing stimulation, pLFS, 60 min after induction of the asymptotic LTP in young adult (n = 14) and aged (n = 11) rats (Fig. 3A). LTdeP was measured as the last 2 min of the 10-min recording period after each pLFS episode. One group Student’s t-test indicated that the synaptic response was decreased following the first pLFS episode in young adult \[t(13) = 10.17, P < 0.00001; 66.07 \pm 3.33\% \text{ of baseline}] and aged \[t(10) = 15.19, P < 0.00001; 68.59 \pm 2.07\% \text{ of baseline}] rats. An additional modest decrease in the synaptic responses was observed after the second pLFS episode in young adult \[t(13) = 10.92, P < 0.00001; 51.85 \pm 4.41\% \text{ of baseline}] and aged \[t(10) = 20.73, P < 0.00001; 57.11 \pm 2.07\% \text{ of baseline}] rats (Fig. 3B). Moreover, ANVOAs revealed no age-related 

### Table 2. LTD induced by multiple episodes of pLFS in young-adult and aged rats

<table>
<thead>
<tr>
<th>pLFS Episode</th>
<th>Young-Adult</th>
<th>Aged</th>
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<tbody>
<tr>
<td>1st</td>
<td>89.81 ± 3.26*</td>
<td>87.52 ± 8.26*</td>
</tr>
<tr>
<td>2nd</td>
<td>76.34 ± 3.93*</td>
<td>72.17 ± 10.97*</td>
</tr>
<tr>
<td>3rd</td>
<td>64.60 ± 5.23*</td>
<td>60.59 ± 9.92*</td>
</tr>
<tr>
<td>4th</td>
<td>54.47 ± 6.45*</td>
<td>56.54 ± 9.31*</td>
</tr>
<tr>
<td>5th</td>
<td>37.25 ± 6.58*</td>
<td>42.56 ± 7.80*</td>
</tr>
<tr>
<td>6th</td>
<td>33.78 ± 7.33*</td>
<td>38.21 ± 6.68*</td>
</tr>
<tr>
<td>7th</td>
<td>28.44 ± 5.99*</td>
<td>32.15 ± 5.21*</td>
</tr>
<tr>
<td>8th</td>
<td>25.91 ± 6.54*</td>
<td>26.67 ± 4.82*</td>
</tr>
<tr>
<td>9th</td>
<td>27.35 ± 6.96*</td>
<td>30.67 ± 2.75*</td>
</tr>
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</table>

Means ± SE percent of baseline EPSP slopes for the last 2 min of each 10-min recording period after each paired low frequency stimulation (pLFS) episode. LTD, long-term depression. * significant depression of synaptic responses compared to baseline.
difference in the magnitude of early depotentiation, measured during 10-min recording between the two groups following the first \(F(1,23) = 0.36, P = 0.55\) or the second \(F(1,23) = 0.98, P = 0.33\) pLFS episode.

Aging effects on the active reversal of LTD (LTdeD)

To evaluate potential aging differences on the ability to reverse asymptotic LTD (LTdeD), we administered intense LTP-inducing stimulation, TBS, 60 min after induction of the asymptotic LTD in young adult (\(n = 6\)) and aged (\(n = 6\)) rats (Fig. 4A). LTdeD was measured as the last 2 min of the 10-min recording period after each TBS episode. An increase in the synaptic responses was observed after the first TBS episode in young adult (229.88 ± 57.13% of baseline) and aged (182.63 ± 40.68% of baseline) rats; however, one group Student’s t-test indicated that the synaptic response only approached significance in young adult \((t(5) = 2.27, P = 0.07)\) and in aged \((t(5) = 2.03, P < 0.09)\) rats. After the second TBS episode, an increase in the synaptic responses was observed, and one group Student’s t-test indicated synaptic responses were increased significantly in young adult \((t(5) = 2.77, P < 0.04; 300.44 ± 72.36\% \text{ of baseline})\) and aged \((t(5) = 2.91, P < 0.03; 205.79 ± 36.33\% \text{ of baseline})\) rats (Fig. 4B). Moreover, two-way ANVOAs revealed no age-related difference in the magnitude of incremental induction or early maintenance of de-depression measured during the 10th minute after the first \([F(1,23) = 2.84, P = 0.1056]\) or the second \([F(1,23) = 0.25, P = 0.6248]\) TBS episode, or equivalent time points in asym-

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**FIG. 3.** The ability to reverse LTP [long-term de-depotentiation (LTdeP)] is equivalent in slices from young adult (○, \(n = 14\)) and aged (●, \(n = 11\)) rats. A: illustration shows the mean percentage change in the synaptic responses after pLFS episodes (dark solid line) and plotted relative to a normalized baseline (dashed line) calculated using EPSP slopes recorded 60 min after the 6th TBS episode. B: bar diagram representing mean percentage change in the EPSP slopes of synaptic responses during the last 2 min of a 10-min recording following the 1st and 2nd pLFS episode for aged (●) and young adult (○) rats. * significant difference from baseline (dashed line).

**FIG. 4.** The ability to reverse LTD [long-term de-depotentiation (LTdeD)] is equivalent in slices from young adult (○, \(n = 6\)) and aged (●, \(n = 6\)) rats. A: illustration shows the mean percentage change in the slope of synaptic responses after TBS episodes (↓) and plotted relative to normalized baseline (dashed line) calculated using EPSP slopes recorded 60 min after the 9th pLFS episode. B: bar diagram representing mean percentage change in the slopes of synaptic responses during the last 2 min of a 10-min recording after the 1st and 2nd TBS episode for aged (●) and young adult (○) rats. * significant difference from baseline (dashed line).
tically depressed slices that received no further conditioning for 60 min. A significant $[F(1,23) = 16.55, P = 0.0005]$ main effect was found for conditioning, and TBS resulted in greater changes in EPSP slope in slices from both young and old rats compared with unconditioned slices examined at equivalent time points (Fig. 4C). Despite obvious trends toward an age effect and age-conditioning interaction $[F(1,23) = 4.18, P = 0.0525]$, the high attrition rate inherent in these prolonged recording sessions precluded us from increasing the statistical power with more cases.

**DISCUSSION**

Under the conditions used in the current study, aging had no effect on the rate of development, rate of decay, or asymptotic magnitude of LTP, LTD, LTdeP, or LTdeD. The absence of an age effect in the asymptotic magnitude of synaptic modifications indicates that overall dynamic range of synaptic plasticity does not change significantly over this age range. Furthermore, the results suggest that the mechanisms for expression of synaptic plasticity for this population of synapses are not altered with age. The current study, using Brown Norway rats, confirms previous work, which indicates that the maximum magnitude of LTP (Barnes et al. 1996; Norris et al. 1996; Shankar et al. 1998; Tombaugh et al. 2002) and LTD (Foster and Kumar 2007) is not altered with advanced age in Fischer 344 rats. In addition, the results extend these findings to indicate no age effect on reversal of synaptic plasticity, using intense reversal stimulation paradigms (TBS, pLFS).

The Brown Norway rat has demonstrated advantages for studying effects of aging but has rarely been used to study neurobiological and behavioral consequences. The median survival age for this strain has been estimated at 28–30 mo (Mos and Hollander 1987); thus our 22- to 24-mo aged animals may represent a late-middle-age time point in their life span. However, by this age, this strain exhibits age-related reductions in plasma testosterone accompanied by loss of vasopressin neurones in amygdala and locus coeruleus (Van Zwieten et al. 1997), and dendritic regression in some neocortical pyramidal neuron dendrites (Grill and Riddle 2002). Moreover, at about middle age, Brown Norway and Fischer 344 hybrid rats begin to display impairments in hippocampal-dependent place learning (Goudsmidt et al. 1990; Wu et al. 2004). Thus although we were not able to obtain behavioral data for the rats in the current study, deficits in hippocampal function are likely to emerge for this older age group. In this regard, the absence of an age-related difference in the range of synaptic plasticity examined using intense induction stimulation indicates that the maximal limits of synaptic plasticity do not underlie well-characterized behavioral differences.

Previous studies that have reported changes in the induction of LTP during aging have employed weaker induction paradigms and longer intervals between induction episodes (Barnes and McNaughton 1985). Under our experimental conditions, several intense conditioning stimulation episodes were delivered under conditions of an elevated Ca²⁺/Mg²⁺ ratio in the recording media to ensure the induction of asymptotic synaptic modifications. The results demonstrate that the basic cellular machinery involved in changing synaptic strength is not altered in s. radiatum. However, our results cannot rule out the possibility that age alters the threshold activity required to increase or decrease synaptic strength in this animal model. Indeed, a number of studies have demonstrated a primary deficit in the induction mechanisms, such that susceptibility to induction of LTP, reversal of LTP, and LTD is decreased and increased, respectively (Barnes et al. 1996, 2000; Foster and Kumar 2007; Hsu et al. 2002; Kumar and Foster 2004; Murphy et al. 2004; Norris et al. 1996; Rosenzweig et al. 1997; Tombaugh et al. 2002). In addition, age-related changes in the decay of LTP have been observed when synaptic responses are examined over several hours or days (Bach et al. 1999; Barnes 1979). As such, age-related changes in the threshold for induction of synaptic plasticity or the decay/reversibility over extended durations may mediate memory decline during senescence (Barnes and McNaughton 1985; Deupree et al. 1993; Foster 1999; Foster and Kumar 2007; Foster and Norris 1997; Landfield et al. 1978; Lee et al. 2005; Murphy et al. 2004; Norris et al. 1996). Regardless, the current results suggest that age-related memory dysfunction cannot be explained by alterations in the intrinsic capacity of these synapses to express synaptic plasticity.

Repeated conditioning confirmed that LTP and LTD were saturable, reaching asymptotic levels within six (LTP) and nine (LTD) conditioning episodes. Upper limits to synaptic strength have been appreciated since the earliest studies of LTP (Bliss and Lomo 1973), and studies of single-pulse LFS LTD found lower limits of ~50% of baseline in juvenile rats after three conditioning episodes (Dudek and Bear 1993). An examination of the lower limits attainable after pLFS conditioning found that synaptic strength could be reduced to ~60% of baseline with repeated episodes using 50-ms interpulse interval (IPI) paired pulses (Kemp et al. 2000). A single subsequent application of 200-ms IPI conditioning reduced synaptic strength to ~40% of baseline, similar to the average levels attained in current study, but it cannot be determined that this was asymptotic as further conditioning was apparently not attempted.

LTP and LTD were also reversible with the same patterned synaptic activity used to induce their respective counterparts. Equivalent LTdeP and LTdeD after prolonged conditioning suggests that aging did not introduce any effects on metaplasticity. The limits of synaptic strength we observed position the baseline approximately halfway between maximum and minimum. This is similar to what was reported for juvenile rats (Dudek and Bear 1993) and implies that in this population, the strengths of individual synapses are distributed equally above and below the center of the dynamic range. Along with obvious implications for synaptic network function, and assuming that this reflects the in vivo situation, this demonstrates that the procedures used in making the in vitro slice preparation do not substantially bias the baseline away from the midpoint.

In summary, results of the current study show, using strong synaptic plasticity induction stimuli, no age differences in the magnitude of asymptotic LTP, asymptotic LTD, reversal of synaptic modifications, the rate of synaptic plasticity induction, or decay rates. Thus impairment of the basic synaptic mechanisms responsible for expression of these forms of plasticity is not likely to account for decline in memory function within this age range. Future studies should focus on other synaptic processes such as induction mechanism, synaptic connectivity, and baseline synaptic strength rather than asymptotic magnitude of synaptic modification to determine whether or how age-related alterations interact with these synaptic plasticity.
mechanisms to produce adverse effects and contribute to memory impairment.

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