Brief Communication

Memory deficits are associated with impaired ability to modulate neuronal excitability in middle-aged mice

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Normal aging disrupts hippocampal neuroplasticity and learning and memory. Aging deficits were exposed in a subset (30%) of middle-aged mice that performed below criterion on a hippocampal-dependent contextual fear conditioning task. Basal neuronal excitability was comparable in middle-aged and young mice, but learning-related modulation of the post-burst afterhyperpolarization (AHP)—a general mechanism engaged during learning—was impaired in CA1 neurons from middle-aged weak learners. Thus, modulation of neuronal excitability is critical for retention of context fear in middle-aged mice. Disruption of AHP plasticity may contribute to contextual fear deficits in middle-aged mice—a model of age-associated cognitive decline (AACD).

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Plasticity of intrinsic neuronal excitability increases the overall storage capacity of neurons and therefore likely plays a critical role in learning and memory (Zhang and Linden 2003). Increased neuronal excitability via reductions of the post-burst afterhyperpolarization (AHP) is hypothesized as a general mechanism underlying learning and memory tasks (Disterhoft et al. 1986; Disterhoft and Oh 2006). The AHP serves to limit subsequent firing in response to excitation (Madison and Nicoll 1984; Lancaster and Adams 1986; Storm 1990; Sah and Bekkers 1996). Generally speaking, the size of the AHP is inversely related to neuronal excitability, and the measurement of the AHP is routinely used as an index of neuronal excitability.

Our laboratory and others have shown that AHP reductions are observed in hippocampal neurons from animals that learn hippocampal-dependent tasks including trace eyeblink conditioning in rabbit and rat (de Jonge et al. 1990; Moyer Jr et al. 1996, 2000; Kuo 2004) and spatial water maze in rat and mouse (Oh et al. 2003; Tombaugh et al. 2005; Ohno et al. 2006b). Learning-related reductions in the AHP have also been observed in cortical neurons following odor discrimination (Saar et al. 1998) and extinction learning (Santini et al. 2008). In vitro, activity-dependent plasticity of the AHP is induced using physiologically relevant stimuli (Kaczorowski et al. 2007). Because the AHP serves to limit subsequent firing, learning-related reductions in the AHP are poised to facilitate mechanisms crucial for information storage, such as long-term potentiation (LTP), synaptic integration (Sah and Bekkers 1996), metaplasticity (Le Ray et al. 2004), and spike-timing dependent plasticity (STDP) (Le Ray et al. 2004).

Hippocampal neurons from naïve aged rodents and rabbits show a decrement in basal excitability evidenced by a robust enhancement of the AHP (Landfield and Pitler 1984; Moyer Jr et al. 1992, 2000; Oh et al. 1999; Kumar and Foster 2002, 2004; Power et al. 2002; Hemond and Jaffe 2005; Murphy et al. 2006b; Gant and Thibault 2008). Enhancement of the AHP in hippocampal neurons in aged animals correlates with impaired performance on learning paradigms that depend on a functional hippocampus, such as trace eyeblink and spatial water maze (Moyer Jr et al. 2000; Tombaugh et al. 2005; Murphy et al. 2006a). Pharmaceuticals aimed at reducing the AHP and increasing basal excitability (Moyer Jr et al. 1992; Moyer Jr and Disterhoft 1994) have been successful at restoring performance of aged rats on trace eyeblink conditioning (Deyo et al. 1989; Straube et al. 1990; Kowalska and Disterhoft 1994). Interestingly, AHPs from neurons recorded from aged learners are indistinguishable from young learners; both are reduced compared to that of aged weak-learners (Moyer Jr et al. 2000; Tombaugh et al. 2005). These data suggest that mechanisms that permit learning-related modulation of the AHP are also critical determinants of learning abilities in an aged population. To date, age-related impairments in hippocampal-dependent tasks and biophysical alterations in hippocampal neurons have largely focused on studies that compare animals at extreme ends of the aging spectrum.

In an effort to better understand physiological changes that underlie the onset of early cognitive decline, the development of rodent models of "normal" age-associated cognitive decline (AACD), as well as mild cognitive impairment (MCI), is critical (Pepeu 2004). Therefore, we set out to characterize the development of age-related deficits indicative of hippocampal dysfunction in middle-aged C57Bl6/SJL mice and to examine the biophysical changes in hippocampal neurons that accompany such deficits.

Recently, age-related deficits in contextual fear memory following trace fear conditioning were reported in a subset of middle-aged rats (Moyer Jr and Brown 2006). Because the dorsal hippocampus is critical for trace and contextual fear conditioning in mice and rats (McEchron et al. 1998; Chowdhury et al. 2005; Misane et al. 2005), trace fear conditioning is an ideal paradigm for exploring cellular mechanisms that underlie early-age-related cognitive decline.

Here we investigate the effects of "early" aging on trace fear conditioning by comparing performance outcomes of young (2 mo, $n = 7$; and 4 mo, $n = 8$) and middle-aged (8 mo, $n = 22$) male C57/SJL F1 hybrid mice. Mice were trained and tested singly, and the experimenter was blind to the training and retention status of the mice. All animal procedures were approved by the Northwestern University Animal Care and Use Committee. Preliminary data were reported previously (Kaczorowski 2006).

To assess hippocampal function with aging, young and middle-aged mice were trained on a trace fear conditioning task followed by retention tests of the auditory conditioned stimulus

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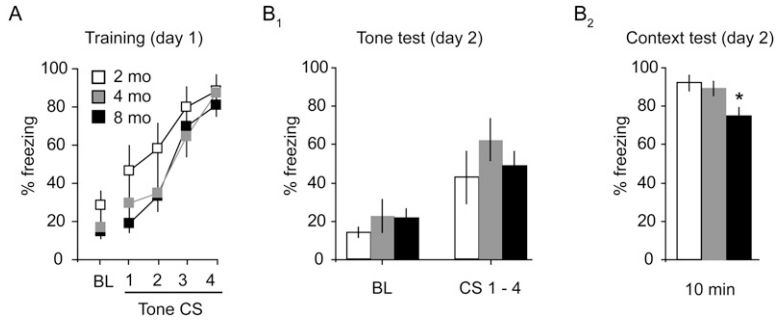

Figure 1. Onset of early aging deficits in 8-mo-old middle-aged mice. (*A*) Baseline (BL) freezing and auditory CS freezing during trace fear conditioning was similar between young (2 mo and 4 mo) and middle-aged (8 mo) mice. (*B1*) Mean baseline freezing and retention of the auditory CS memory (tones 1–4) were comparable in young (2 mo and 4 mo) and middle-aged (8 mo) mice. (*B2*) Middle-aged mice showed a significant decrease in freezing compared to young (2 mo and 4 mo) mice when exposed to the original context chamber where they had been trained 1 d earlier; (*) $P < 0.05$.

(CS) and contextual CS memory. The basic protocol for trace fear conditioning has been described previously (Ohno et al. 2006a). Mice were trained in a Plexiglas conditioning chamber with a stainless-steel floor grid used for shock delivery. After the baseline period (150 sec), mice received four pairings of the CS (tone; 15 sec, 3 kHz, 75 dB) and US (shock; 1 sec, 0.7 mA). The CS and unconditioned stimulus (US) were separated by a 30-sec empty trace interval. The intertrial interval was set at 210 ± 10 sec. The training chamber was wiped with 95% ethyl alcohol, illuminated with a 10-W bulb in an otherwise dark room, and provided with 65-dB white noise to make it distinct. During training on trace fear conditioning, no effect of age was observed on measures of baseline freezing ($F_{(2,34)} = 2.0$, $P = 0.15$), the expression of freezing during tone ($F_{(2,34)} = 0.6$, $P = 0.6$), or post-shock freezing ($F_{(2,34)} = 0.2$, $P = 0.8$), suggesting that middle-aged and young mice do not differ in measures of anxiolysis or expression of behavioral freezing (measured index of fear) (Fig. 1A).

Retention of the auditory CS:US memory was tested 24 h later in a novel context that differed in its location, size, scent, lighting, background noise, and flooring (bedding) compared to the training chamber. Data from three mice (one young, two middle-aged) were excluded because of video malfunction. Following a 150-sec baseline, mice received four presentations of the tone CS in the absence of footshock. Neither baseline freezing ($F_{(2,31)} = 2.6$, $P = 0.1$) nor conditional freezing in response to the tone CS ($F_{(2,31)} = 1.6$, $P = 0.2$) differed between young and middle-aged mice (Fig. 1B1). Thus, retention of the auditory CS following trace fear conditioning was intact in middle-aged compared to young mice. Although deficits in retention of auditory trace fear have been reported in aged mice and rats (Blank et al. 2003; McEchron et al. 2004; Villarreal et al. 2004), the results herein agree with report of intact trace fear memory in middle-aged rats (Moyer Jr and Brown 2006).

One hour after this testing, retention of the contextual fear memory was assessed by placing mice in the original context (in the absence of the tone and footshock) and measuring freezing for 10 min. A subtle but significant difference in freezing was observed as a function of age ($F_{(2,31)} = 4.3$, $P = 0.02$; Fig. 1B2). A student's post-hoc *t*-test revealed that mean freezing (collapsed across 10 min) of middle-aged mice was reduced compared to 2-mo ($P < 0.05$) and 4-mo ($P < 0.05$) young mice. Contextual fear memory deficits have been similarly reported in aged mice (Fukushima et al. 2008). Studies that failed to observe contextual fear deficits in aged (>18 mo) mice may result from a floor effect because young mice showed weak conditioning to the context (~30% freezing) (Feiro and Gould 2005; Gould and Feiro 2005) or employment of delay (Corcoran et al. 2002; Feiro and Gould 2005; Gould and Feiro 2005) compared to trace procedures (Moyer Jr and Brown 2006). Although differences in experimental parameters are plausible, heterogeneity in the performance of aged mice may make

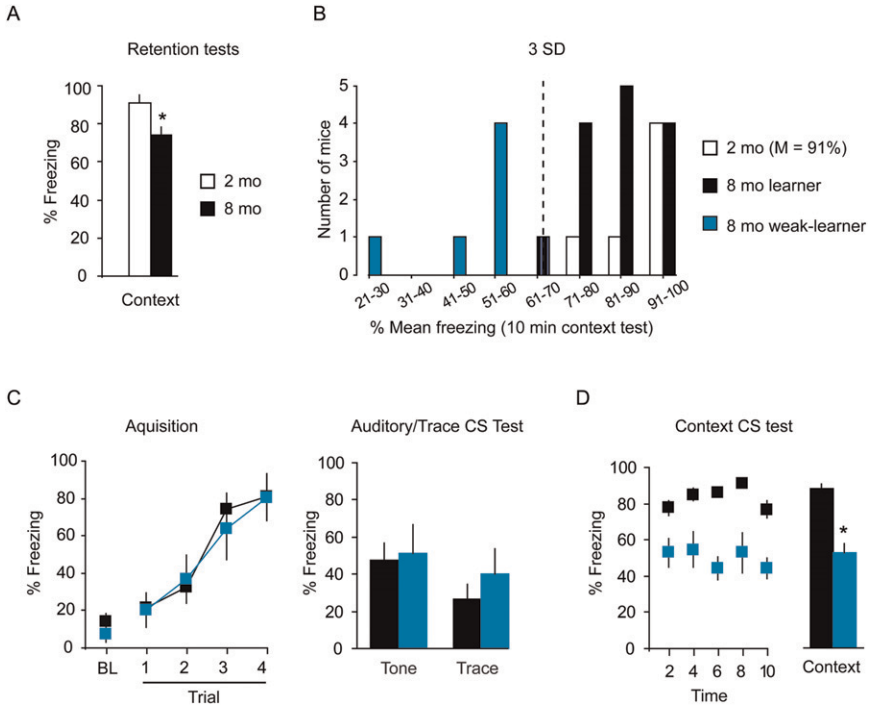

Figure 2. Selective deficits on retention of contextual fear in middle-aged weak-learner mice. (*A*,*B*) Summary plot and histogram show young mice (100%, $n = 6$) at 2 mo of age showed robust recall of contextual fear memory (range 75%–99%) with mean and standard deviation (SD) of 91% ± 10%, whereas retention of middle-aged mice ($n = 21$) varied to a much greater extent (range 21%–95%; M, SD = 74% ± 19%). Distribution of middle-aged mice relative to their mean percent freezing shows two distinct populations. Middle-aged mice with freezing levels less than 3 SD from the mean freezing in young wild-type (WT) mice (61%, dashed line) were characterized as having weak contextual fear memory (weak learners) and those with freezing levels ≥62% as having strong contextual fear memory (learners). (*C*) Baseline (BL) freezing, expression of post-shock freezing and freezing during retention tests for auditory CS and trace CS memories, were comparable in both weak-learners and learners. (*D*) Selective deficits in retention of contextual fear memories were observed in middle-aged weak learners as compared to middle-aged learners; (*) $P < 0.05$.

detection of age-related impairments difficult owing to increased variability.

Previous studies in the rat report heterogeneity in spatial water maze and contextual fear conditioning in middle-aged and/or aged rats compared to young animals (Fischer et al. 1992; Wyss et al. 2000; Moyer Jr and Brown 2006). Therefore, we determined if middle-aged impairments of context fear (Fig. 2A) were driven by a subset of impaired mice. The degree of age-related impairment in each middle-aged mouse was determined by comparison to a reference group of young mice tested concurrently (shown in Fig. 1). The behavioral criterion for retention of contextual fear in middle-aged mice was set at 61%, which was 3 standard deviations (SD) below the mean freezing in young mice (mean and SD, 91% ± 10%; Fig. 1). A bimodal distribution of freezing of middle-aged mice was observed (Fig. 2B), where 70% of middle-aged mice performed above criterion and were labeled learners (n = 14), and 30% of middle-aged mice performed below criterion and were labeled as weak learners (n = 6). Comparison on measures of baseline freezing ($F_{(1,18)}$ = 1.8, P = 0.2) and expression of post-shock freezing ($F_{(1,18)}$ = 2.1, P = 0.2) revealed no differences between the groups during auditory trace fear training (Fig. 2C). Similarly, no differences in baseline freezing ($F_{(1,18)}$ = 0.03, P = 0.9) or acquisition/recall of conditioned auditory trace fear (tone, $F_{(1,18)}$ = 0.08, P = 0.8; trace, $F_{(1,18)}$ = 2.4, P = 0.1) were observed 24 h later during retention tests. Thus, deficits ascribed to middle-aged weak learners were limited to contextual processing/retention, where middle-aged weak learners responded to the contextual CS with significantly lower levels of freezing compared to middle-aged learners ($F_{(1,18)}$ = 47, P = 0.001; Fig. 2D). To summarize, we found that onset of cognitive decline in the C56Bl6/SJL mice was first apparent in a subset of middle-aged mice. Middle-aged weak learners showed a mild but specific deficit in hippocampal-dependent contextual learning/memory (spatial learning) but not hippocampal-dependent auditory trace learning/memory (temporal learning), assessed following trace fear conditioning.

Given that contextual fear deficits occurred in a subset of middle-age mice, we were able to directly assess age-related alterations in excitability and AHP plasticity in CA1 neurons as they relate to learning abilities (learners vs. weak learners). Within 1 h of cessation of behavioral tests, middle-aged learners and weak learners were decapitated under deep halothane anesthesia and their brains quickly removed and placed into ice-cold artificial cerebral spinal fluid (aCSF): 125 mM NaCl, 25 mM glucose, 25 mM $NaHCO_3$, 2.5 mM KCl, 1.25 mM NaH_2PO_4, 2 mM $CaCl_2$, 1 $MgCl_2$ (pH 7.5, bubbled with 95%O_2/5%CO_2). Naïve mice were removed from their home cage and underwent identical decapitation procedures. Slices (300 μm) of the dorsal hippocampus and adjacent cortex were made using a Leica vibratome. The slices were first incubated for 30 min at 34°C in bubbled aCSF, and held at room temperature in bubbled aCSF for 1–4 h before use. Recording electrodes prepared from thin-walled capillary glass were filled with potassium methylsulfate-based internal solution and had a resistance of 5–6 MΩ.

Whole-cell current-clamp recordings were performed on CA1 hippocampal pyramidal neurons of middle-aged learners (n = 36, 14 mice) and weak-learners (n = 15, 6 mice), as well as middle-aged naïve mice (n = 35 cells, 18 mice). Neuronal excitability was compared by measuring the post-burst AHP generated by 25 action potentials at 50 Hz (Fig. 3A), a stimulus shown to reliably evoke an AHP of sizable—but not maximal—amplitude from hippocampal neurons of mice (Ohno et al. 2006b). A significant difference in the peak amplitude of the AHP from learners, weak learners, and naïve mice was observed ($F_{(2,83)}$ = 5, P < 0.01). Because the peak AHP and sAHP amplitudes did not differ between neurons from weak-learners and naïve mice (Table 1; peak AHP, $F_{(1,48)}$ = 0.3, P = 0.6; sAHP, $F_{(1,48)}$ = 0.6, P = 0.5), these data were pooled for subsequent comparisons with neurons from learners. Both the peak AHP ($F_{(1,84)}$ = 10, P < 0.01) and sAHP ($F_{(1,84)}$ = 4.6, P < 0.05) were significantly reduced in neurons from learners compared to weak learners and naïve mice (Fig. 3B). No differences in membrane resistance ($F_{(2,83)}$ = 1.6, P = 0.2) or action potential properties, elicited using a brief (2 msec) near threshold current step (pA), were observed (Table 1).

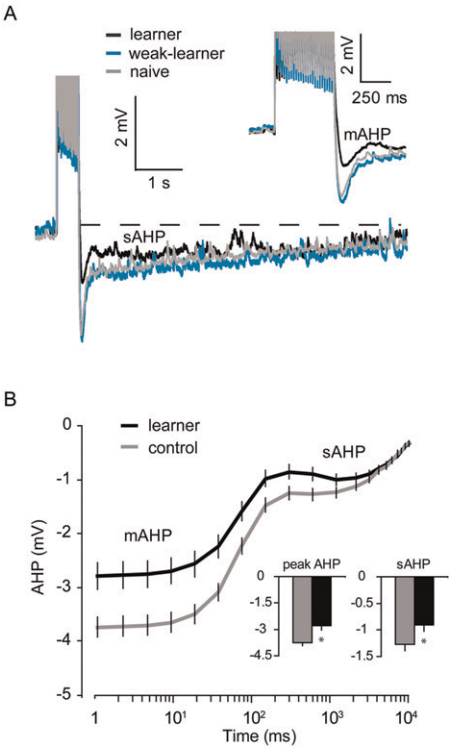

Figure 3. Learning-related AHP plasticity is impaired in middle-aged weak-learner mice. (*A*) Representative traces showing the sAHP is reduced in neurons from (black) middle-aged learners compared to (blue) weak-learner mice and (gray) naïve mice. (*Inset*) The medium AHP (mAHP) of neurons from (black) learner mice was decreased compared to (blue) weak-learner mice and (gray) naïve mice. (*B*) No differences in the AHP from naïve and weak learners were observed; therefore, their data were pooled, and mean AHP was plotted by time on a log scale. (*Inset*) The mean amplitude of the peak AHP (1 msec) and sAHP (600 msec) was significantly reduced in neurons from learners compared to AHPs from weak learners and naïve labeled control; (*)P < 0.05.

The results presented here are important in two respects. First, we demonstrate that the successful acquisition and recall of trace fear conditioning results in a significant reduction in the AHP in CA1 hippocampal neurons from the mouse. Our data are similar to previous reports showing learning-related reductions of the AHP in hippocampal neurons following training on hippocampal-dependent tasks (Disterhoft and Oh 2007) and thus strengthen the case for neuronal excitability change as a general mechanism underlying hippocampal-dependent learning. Second, we demonstrate that the onset of age-related cognitive decline in the C56Bl6/SJL mouse (termed "weak learners") first manifests as a specific deficit in spatial associative learning in a subset of middle-age mice. These data, combined with a previous report from middle-aged rats (Moyer Jr and Brown 2006), suggest that initiation of age-related hippocampal dysfunction results in specific spatial—as opposed to temporal—deficits in associative learning and memory during middle age. By combining trace fear conditioning with whole-cell patch-clamp recordings in middle-aged mice, we

Table 1. AHP and basic membrane properties of neurons from naïve, weak learners, and learners

(*n* = Cells)	mAHP peak (mV)	sAHP 600 msec (mV)	AP threshold (mV)	Threshold current (pA)	AP amplitude (mV)	AP HW (msec)	fADP amplitude (mV)
Learner (36)	−2.78 ± 0.24[a,b,c]	−0.9 ± 0.12[b,c]	−54 ± 0.6	377 ± 26	115 ± 1.0	1.0 ± 0.01	8 ± 0.4
Weak L (15)	−3.88 ± 0.44	−1.4 ± 0.26	−53 ± 0.1	341 ± 28	113 ± 2.0	1.0 ± 0.02	8 ± 0.7
Naïve (35)	−3.68 ± 0.19	−1.2 ± 0.13	−55 ± 0.6	361 ± 18	116 ± 1.0	1.1 ± 0.02	8 ± 0.4
Pooled (50)	−3.74 ± 0.19	−1.3 ± 0.12	−54 ± 0.5	355 ± 15	115 ± 0.9	1.1 ± 0.01	8 ± 0.3

[a] $P < 0.05$ compared to Weak L.
[b] $P < 0.05$ compared to Naïve.
[c] $P < 0.05$ compared to Pooled.

revealed that "early" age-related impairments in spatial associative learning—like those in the aged hippocampus (Tombaugh et al. 2005)—result in part from an impairment of AHP plasticity of hippocampal neurons. Because AHP reductions are poised to facilitate mechanisms crucial for information storage, it is interesting that trace fear conditioning facilitates the long-term potentiation (LTP) of field excitatory postsynaptic potentials in the CA1 region of the rat hippocampus (Song et al. 2008).

Generally speaking, both LTP and activation of AHP currents (I_{AHP} and sI_{AHP}) are sensitive to changes in intracellular Ca^{2+} (Storm 1990; Sah 1996; Malenka and Nicoll 1999). Thus, dysregulation of Ca^{2+} homeostasis in the hippocampus of middle-aged rats via enhancement of Ca^{2+}-induced Ca^{2+} release (CICR) is an important finding (Gant et al. 2006). Age-related enhancement of Ca^{2+}-dependent AHPs has been shown to raise the threshold for induction of LTP (Kumar and Foster 2004). These data support our hypothesis that impairments in contextual fear reported herein, as well as deficits in spatial water maze reported in middle-aged rats (Frick et al. 1995; Markowska 1999; Kadish et al. 2009), result from dysfunction of AHP plasticity.

Studies in middle-aged mice have important implications for the treatment of "normal" age-associated cognitive decline (AACD), as well as mild cognitive impairment (MCI) (Pepeu 2004). Further studies aim to examine alterations in cholinergic function in our middle-aged mouse model, as the cholinergic agonist carbachol suppressed the AHP in neurons from naïve middle-aged mice (Supplemental Fig. 1). Activation of cholinergic receptors shape neuronal excitability and synaptic throughput (Tai et al. 2006) through multiple Ca^{2+}-dependent processes (Gahwiler and Brown 1987; Tai et al. 2006). Restoration of cholinergic function has been shown to rescue deficits on hippocampal-dependent tasks in aged rodent and mouse models of Alzheimer's disease (AD) (Disterhoft and Oh 2006), as well as in human AD patients (Cummings et al. 1998; Morris et al. 1998; Pettigrew et al. 1998), and therefore is a potential target aimed at the rescue of early age-related cognitive decline.

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