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Stress-Induced Corticosterone Secretion Covaries with Working Memory in Aging

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Abstract

A substantial literature details the relationship between age-related changes to the hypothalamic-pituitary-adrenal (HPA) axis and deterioration of mnemonic functions that depend on the hippocampus. The relationship between adrenocortical status and other forms of memory that depend on the prefrontal cortex (PFC) is less well-understood in the context of advanced age. Here we characterized performance of young adult and aged F344 rats on a PFC-dependent working memory task and subsequently measured corticosterone levels over the diurnal cycle and during exposure to an acute stressor. Our analyses revealed that aged rats with better working memory mounted a greater corticosterone response during acute stress exposure than either young adults or age-matched rats with impaired working memory. We also observed that age-related elevation of basal corticosterone levels is not associated with working memory performance. Jointly, these data reveal that the HPA-mediated response to acute stress is positively associated with working memory in aging.

1. Introduction

Secretion of glucocorticoids mediated by the hypothalamic-pituitary-adrenal (HPA) axis is an essential physiological process that balances cellular energy requirements over the circadian cycle and also in response to stressful experiences (de Kloet et al., 2005; Herman

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et al., 2003; Keller-Wood and Dallman, 1984). Lower expression of glucocorticoid receptors (GR) in the aging hippocampus associates with dysregulated release of glucocorticoids and impaired spatial memory (Bizon et al., 2001; Issa et al., 1990; Montaron et al., 2006; Yau et al., 1995). GRs in the prefrontal cortex (PFC) also regulate HPA axis activity (Diorio et al., 1993; Radley et al., 2006a), but few studies have investigated the relationship between modulation of glucocorticoid secretion and age-related decline of PFC-dependent memory. Specifically, working memory, which involves the temporary maintenance of information used to guide current and future action, critically depends on PFC (Funahashi et al., 1993; McQuail et al., 2016; Sloan et al., 2006) and deteriorates with age across species (Bachevalier et al., 1991; Beas et al., 2013; Hernandez et al., 2017; Lamar and Resnick, 2004; Oscar-Berman and Bonner, 1985; Rapp and Amaral, 1989). In this study, we examined differences in circadian- and stress-associated glucocorticoid secretion between young and aged rats in relation to performance on a PFC-dependent working memory task.

2. Materials and Methods

2.1 Subjects

Male, Fischer 344 (F344) rats were acquired at ages of 4 mo (young adults, $n=11$) or 20 mo (aged, $n=16$) from the Aging Rodent Colony maintained by Charles River Laboratories for the National Institute on Aging. All rats were housed in an AAALAC-accredited vivarium in the McKnight Brain Institute Building at the University of Florida in accordance with the rules and regulations of the University of Florida Institutional Animal Care and Use Committee and NIH guidelines. The facility was maintained at a consistent 25°C with a 12 h light/dark cycle (lights on at 0600 h) with free access to food and water except as noted below.

2.2. Delayed Response Testing

All rats were restricted to 85% of *ad libitum* fed weight and shaped to perform a delayed response test of working memory (Fig 1A). This task requires intact function of medial PFC (mPFC; McQuail et al., 2016; Sloan et al., 2006), the rodent homolog of the primate dorsolateral PFC. Behavioral testing was conducted in operant testing chambers (Coulbourn Instruments, Whitehall, PA, USA) using shaping procedures identical to those described previously (Beas et al., 2013; McQuail et al., 2016). In the testing phase of the task, each trial was comprised of 3 phases. In the “sample” phase, a single response lever (left or right, randomly counterbalanced within pairs of trials) was extended into the chamber. A lever press resulted in retraction of the lever and initiated a delay of 0, 2, 4, 8, 12, 18, or 24 s (presented in a randomized order in each block of 7 trials). During this “delay” phase, rats were required to nose-poke into the central food trough. The “choice” phase was initiated by the first such nose-poke emitted after the delay period expired. In the “choice” phase, both left and right levers were extended, and a press on the same lever presented during the sample phase (a correct response) resulted in retraction of both levers and delivery of a single food pellet. A response on the opposite lever (an incorrect response) resulted in the retraction of both levers and initiation of 5 s “timeout” during which the house light was extinguished. Rats were tested in one 40-minute session per day until achieving stable

performance over 5 consecutive days. Stability was defined as <10% variation in performance at 18 and 24 s delays while completing no fewer than 70 trials per day.

2.3 Blood Collection and Corticosterone Measurement

After behavioral testing was complete, rats were returned to free feeding for a minimum of 2 weeks before blood collection. To evaluate circadian variation in corticosterone (CORT) levels, blood was obtained via tail bleed between 0700-0800 h (lights on at 0600 h) and between 1900-2000 (lights off at 1800 h; similar to time course used in Sapolsky et al., 1983). One week later, rats were subjected to a 60 minute period of restraint stress. Beginning between 0900 and 0930 h, rats were placed into Plexiglas restrainers and blood collected at 0, 15, 30 and 60 minutes following the onset of restraint and also at 120 minutes, or 60 minutes after being released and returned to home-cage (similar to time course used in Segar et al., 2009). Plasma CORT was assayed in duplicate using the ImmunChem™ Double Antibody Corticosterone ¹²⁵I RIA Kit for rats and mice (MP Biomedicals, Orangeburg, NY, USA) as previously described (Daubert et al., 2014).

2.4 Statistical Analyses

The chief index of delayed response performance was choice accuracy, or the percentage of correct responses after each delay. Choice accuracy was analyzed using a two-way, mixed factors analysis of variance (ANOVA) testing age as a between-subject factor and delay as a repeated, within-subjects factor. Aged rats were classified into cognitive subgroups on the basis of whether choice accuracy of each rat at 18 and 24 s delays fell within (aged-unimpaired; AU) or below (aged-impaired; AI) the range of young adults. CORT concentration ([CORT]; ng/ml) was determined by fitting activity counts of unknown samples to a standard curve comprised of known [CORT] after accounting for non-specific binding (determined in the absence of primary anti-corticosterone). To account for non-normal distribution of circadian [CORT], non-parametric Mann-Whitney U or Kruskal-Wallis tests were used to compare [CORT] between ages or cognitive subgroups. To analyze [CORT] during/following restraint, age or cognitive subgroup was tested as a between-subject factor and time point as a repeated, within-subjects factor followed by Bonferroni post hoc comparisons at specific time points. Bivariate correlations were used to test the relationship between [CORT] and working memory in aged rats. All data are reported as the mean ± standard error (SEM) and $p < 0.05$ was considered significant in all comparisons.

3. Results

Choice accuracy of aged rats was significantly impaired compared to young adults in a delay-dependent manner (effect of age: $F(1,25)=27.735$, $p < .001$; age × delay interaction: $F(6, 150)=3.350$, $p = .010$; Fig 1B). Using the average of performance at the longest delays (18 and 24 s) as an index of individual differences in accuracy, $n=8$ aged rats performed within the range of young (aged-unimpaired; AU), while $n=8$ rats performed below the range of young (aged-impaired; AI; Fig 1C).

Although [CORT] was not significantly different between age groups one hour into the dark phase (1900 h; $U=82$, $p = .790$), [CORT] one hour after the start of the light phase (0700h)

was significantly higher in aged compared to young ($U=148$, $p=.002$). When the latter data were tested according to cognitive subgroups, a significant effect ($\chi^2(2)=8.782$, $p=.012$) was due to the fact that both AU ($p=.046$) and AI ($p=.031$) differed from young but not each other ($p=1.0$; Fig 2A).

One hour of restraint stress induced a significant elevation of [CORT] (main effect of time point: $F(4,100)=111.897$, $p<.001$) that was not significantly different between age groups (main effect of age: $F(1,25)=.597$, $p=.447$; age $\times$ time point interaction: $F(4, 100)= 1.510$, $p=.205$). In contrast, comparisons between cognitive subgroups revealed significant differences in [CORT] (main effect of subgroup: $F(2,24)=6.815$, $p=.005$; subgroup $\times$; time point interaction: $F(8,96)=1.810$, $p=.084$; Fig 2B). Post hoc comparisons determined that [CORT] was greater in AU compared to young ($p=.037$) and AI ($p=.005$) but young and AI did not differ from each other ($p=.807$). Bivariate correlations between maximal [CORT] observed after 60 minutes of restraint and working memory choice accuracy in aged rats revealed that higher [CORT] was significantly associated with better working memory performance ($r=.540$, $p=.031$; Fig 2C).

4. Discussion

The PFC is essential for working memory (Funahashi et al., 1993; McQuail et al., 2016; Sloan et al., 2006) and contributes to regulation of the HPA axis (Diorio et al., 1993; Radley et al., 2006a). Prior work shows that aging increases individual differences in corticosterone secretion stimulated during acute stress in F344 rats (Segar et al., 2009). The current data expand upon this finding, revealing that, within this enhanced variation, the neuroendocrine stress response among aged rats is positively associated with working memory ability. Although evidence expressly linking hormonal responses to acute stress and working memory in aging humans is limited, our present finding complements data showing that a greater cortisol response elicited by a psycho-social stressor associates with better working memory in older humans (Almela et al., 2014; Pulopulos et al., 2015). Significantly, this relationship is distinct from circadian modulation of cortisol that is also affected in aging (Evans et al., 2012, 2011; Geerlings et al., 2015). Consistent with prior work (Sapolsky, 1992; Sapolsky et al., 1983), basal corticosterone level is greater in aged rats. This difference was most evident during the inactive (i.e., light) phase of the day, and likely reflects diminished capacity to down-regulate corticosterone during rest. Alternatively, this difference could reflect a temporal shift in the circadian variation of corticosterone secretion, although others, sampling at more frequent intervals, have not observed such a shift in aged male, F344 rats (Morano et al., 1994; Sonntag et al., 1987). Regardless, changes in circadian modulation of corticosterone were not reliably associated with working memory. Together these data suggest multi-faceted changes in regulation of glucocorticoids with age. While elevations in basal corticosterone occur as a consequence of chronological age, it is specifically the ability to effectively mount a robust corticosterone response during a stressor that is strongly linked to working memory function.

Notably, these findings differ somewhat from a recent study in which elevated diurnal corticosterone in aged Sprague-Dawley rats was associated with impaired performance on a spatial delayed alternation working memory task (Anderson et al., 2014). It is not clear the

degree to which methodological differences influence the specific conclusions of the aforementioned study and the present work. While HPA axis responses differ between F344 and Sprague-Dawley rats (Dhabhar et al., 1993, 1995, 1997; Uchida et al., 2008), corticosterone release stimulated by acute stress was not evaluated in Anderson et al (2014). It may also be consequential that the delayed spatial alternation task used by Anderson et al (2014) and other studies of age-related decline of working memory (Kang et al., 2013; Mizoguchi et al., 2009) is partially dependent on hippocampus (Aggleton et al., 1986). Consequently, hippocampal contributions to spatial working memory complicate the ability to fully ascribe deficits to PFC-dependent processes given that a plethora of previous work relates elevated corticosterone in aged rats to impaired performance on hippocampal-dependent memory tasks (Bizon et al., 2001; Issa et al., 1990; Montaron et al., 2006; Yau et al., 1995). The operant delayed response task used in the present study was specifically chosen because performance depends on the rodent mPFC but not hippocampus (Sloan et al., 2006). Collectively, the findings of this and other studies indicate that simply attenuating excessive glucocorticoid levels in older adults is unlikely to serve as an effective intervention to mitigate deleterious effects on cognition. Rather, effective interventions will likely involve restoration of precise HPA axis function that reinstates the appropriate dynamic regulation of glucocorticoids in synchrony with circadian cues and in response to stressors.

Chronic stress or long-term corticosterone treatment provokes remodeling of dendritic spines on PFC neurons, with “thin” spines comprising an especially susceptible subpopulation (Anderson et al., 2016; Goldwater et al., 2009; Gourley et al., 2013; Radley et al., 2006b, 2008, 2013). In aging individuals, loss of thin spines on PFC neurons associates with severity of cognitive impairment (Anderson et al., 2014; Dumitriu et al., 2010; Hao et al., 2007). The significance of thin spine loss may relate to their enriched content of ionotropic glutamate receptors of the NMDA-subtype (NMDARs; Kasai et al., 2003; Noguchi et al., 2005), which are essential for persistent firing activity of PFC neurons during cognitive task performance and accurate maintenance of memoranda in working memory stores (McQuail et al., 2016; Wang et al., 2013). Although we cannot infer causality in the present study, NMDARs are well-positioned to modulate the relationship between working memory and HPA axis via interactions with GRs in PFC neurons. On the one hand, regressive structural modifications could defend aging PFC neurons from NMDAR-mediated excitotoxicity that is exacerbated by increased glucocorticoid exposure resulting from diminished negative feedback on to HPA axis (Armanini et al., 1990; Li et al., 2018). On the other hand, mild, acute stress potentiates working memory and NMDAR synaptic currents through a GR-dependent mechanism (Yuen et al., 2009). Consequently, lower expression of NMDARs (McQuail et al., 2016; Piggott et al., 1992) and GRs (Bizon et al., 2001; Perlman et al., 2007) in the aging PFC could reflect homeostatic adjustments that protect neural viability at the expense of cognitive function. The current data highlight the need for mechanistic studies that investigate interactions between GRs and NMDARs in the aging PFC, with the goal to differentiate between processes that support cognition versus those that endanger neuron survival.

In conclusion, the current findings show that an augmented glucocorticoid response to stress is associated with maintained working memory function in aged rats. This relationship coincides with, but is distinct from, age-related increases in basal corticosterone. Notably,

the increased corticosterone response to stress in aged rats with intact working memory exceeded that of young rats, indicating a distinct phenotype that does not simply reflect maintenance of physiological responses typical of young. Instead, this response may reflect an effective compensation for dysregulated neuroendocrine function in aging that protects appropriate signaling through mechanisms such as NMDARs that are critical for working memory. Future studies are needed to identify the mechanisms that drive these effects.

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Highlights

- Aging impairs mPFC-dependent working memory in inbred, male F344 rats
- Basal corticosterone is not associated with working memory in aging
- Acute stress-induced corticosterone is associated with working memory in aging

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Fig 1. Age-related decline of working memory.

A: Schematic of a trial in the operant delayed response task used to assess working memory in rats. **B:** Delayed response choice accuracy of aged rats (n=16; black circles) is reduced relative to young (n=11; white circles), particularly at longer delays (age $\times$ delay interaction: $p < .05$). Data are mean % correct choices (y-axis) $\pm$ SEM plotted as a function of delay (in s; x-axis). **C:** Choice accuracy (averaged across 18 and 24 s delays) of individual young and aged rats. Within the aged population, some performed within the range of young (n=8; aged-unimpaired, AU) whereas the remaining aged rats performed below the range of young (n=8; aged-impaired, AI). Solid lines indicate group mean performance and dashed line indicates the lowest level of young performance.

Fig 2. Relationship between age-related changes to HPA axis function and working memory.

A: Plasma corticosterone concentration [CORT] was greater in aged-unimpaired (AU; $n=8$; gray bar) or aged-impaired (AI; $n=8$; black bar) compared to young adult (Y; $n=11$; white bar) at 0700 h ($*p<.05$ versus Y), but AU and AI were not significantly different from each other. Further, there was no difference between cognitive groups at 1900 h. Data are mean [CORT] (ng/ml; y-axis) $\pm$ SEM plotted as a function of time of day (h; x-axis). **B:** Secretion of CORT during and after 60 minutes of restraint stress was significantly different between cognitive groups ($**p<.01$). **Inset:** Post hoc comparisons determined that elevation of [CORT] was greater in the AU (gray circles) subgroup relative to both AI (black circles) and Y (white circles); AI and Y were not significantly different from each other. Data are mean [CORT] (ng/ml; y-axis) $\pm$ SEM plotted as a function of time following onset of restraint (min; x-axis); the shaded portion indicates the period of restraint. **C:** [CORT] at the conclusion of 60 min restraint stress (ng/ml; y-axis) is positively associated with choice accuracy (average % correct at 18 and 24 s delays; x-axis) in aged rats ($n=16$; black circles); solid line denotes line of best fit. **Inset:** Pearson's r and p .