Behavioral/Systems/Cognitive

Cognitive Correlates of White Matter Growth and Stress Hormones in Female Squirrel Monkey Adults

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Neurobiological studies of stress and cognitive aging seldom consider white matter despite indications that complex brain processes depend on networks and white matter interconnections. Frontal and temporal lobe white matter volumes increase throughout midlife adulthood in humans, and this aspect of aging is thought to enhance distributed brain functions. Here, we examine spatial learning and memory, neuroendocrine responses to psychological stress, and regional volumes of gray and white matter determined by magnetic resonance imaging in 31 female squirrel monkeys between the ages of 5 and 17 years. This period of lifespan development corresponds to the years 18–60 in humans. Older adults responded to stress with greater increases in plasma levels of adrenocorticotropic hormone and modest reductions in glucocorticoid feedback sensitivity relative to young adults. Learning and memory did not differ with age during the initial cognitive test sessions, but older adults more often failed to inhibit the initial learned response after subsequent spatial reversals. Impaired cognitive response inhibition correlated with the expansion of white matter volume statistically controlling for age, stress hormones, gray matter, and CSF volumes. These results indicate that instead of enhancing cognitive control during midlife adulthood, white matter volume expansion contributes to aspects of cognitive decline. Cellular and molecular research combined with brain imaging is needed to determine the basis of white matter growth in adults, elucidate its functions during lifespan development, and provide potential new targets for therapies aimed at maintaining in humans cognitive vitality with aging.

Key words: brain aging; myelination; cognition; HPA-axis; primates; magnetic resonance (MR) imaging (MRI)

Introduction

Neurobiological studies of stress, cognitive performance, and aging in humans often focus on the hippocampus and adjacent brain regions (Lupien and Lepage, 2001; Miller and O’Callaghan, 2003). The hippocampus is involved in learning and memory (Eichenbaum, 2000), inhibits the hypothalamic-pituitary-adrenal (HPA) hormone stress response (Herman et al., 2003), and various aspects of hippocampal morphology are altered by stress and aging in rats (McEwen, 1999; Sapolsky, 1999; Lupien and Lepage, 2001; Miller and O’Callaghan, 2003). Diminished hippocampal volumes determined in elderly humans by magnetic resonance imaging (MRI) are taken as evidence that stress and aging in rats (McEwen, 1999; Sapolsky, 1999; Lupien and Lepage, 2001; Miller and O’Callaghan, 2003). Diminished hippocampal volumes determined in elderly humans by magnetic resonance imaging (MRI) are taken as evidence that stress during aging contributes significantly to hippocampal atrophy and impairs hippocampal-dependent memory (Lupien et al., 1998).

Far fewer studies have examined the role of white matter growth during midlife adulthood, despite ample evidence that cognitive functions and stress-related brain processes depend on broadly distributed networks and white matter interconnections (Mesulam, 1998; Greenwood, 2000; Kumar and Cook, 2002; Herman et al., 2003). Hippocampal and gray matter volumes decline gradually with aging in adults, whereas frontal and temporal lobe white matter volumes continue to increase in humans throughout the first five decades of life (Courchesne et al., 2000; Bartozzis et al., 2001; Jernigan and Fennema-Notestine, 2004). Adult white matter growth determined in vivo by MRI concurs with the classic postmortem studies of Yakovlev and Lecours (1967).

White matter is composed of axons sheathed in myelin produced by oligodendrocytes. Myelination increases nerve conduction velocities (Baumann and Pham-Dinh, 2001) and facilitates synchronous firing of neurons by reducing the effects of travel distance variability in distributed networks (Salami et al., 2003). Frontal and temporal lobe white matter growth has therefore been viewed as enhancing in humans neuropsychological functions that rely on distributed networks (Greenwood, 2000; Bartozkis et al., 2001; Mulhern et al., 2001; Giedd, 2003). This hypothesis conflicts with evidence from monkeys that myelin production (Peters et al., 2001; Peters and Setares, 2003) and proliferation of oligodendrocytes (Peters, 1996) in adulthood coincide with increased accumulation of myelin decompaction defects that correlate with cognitive decline (Peters and Setares, 2002). Stress hyper-reactivity (Seeman et al., 2001) and diminished glucocorticoid feedback (Wilkinson et al., 2001) are additional aspects of aging that conflict with the view that white matter expansion improves distributed brain functions.

Here, we examine relationships between age-related differences in learning and memory, neuroendocrine responses to psy-
chological stress, and volumes of gray and white matter determined in vivo by MRI in 31 female squirrel monkeys between 5 and 17 years of age. This period of lifespan development corresponds to the years 18–60 in humans. Age-related brain changes in monkeys during this time are not confounded by Alzheimer’s disease, because this pathology does not occur in monkeys (Walker et al., 1990; Peters et al., 1996). Rodent models are limited because prefrontal connections differ in rats compared with humans and monkeys (Preuss, 1995). Certain features of aging in humans cannot be modeled directly in monkeys, but comparative studies of homologous brain regions in monkeys are essential for understanding the biology of healthy brain aging, stress, and cognition during middle adulthood in humans.

Materials and Methods

Subjects. Female squirrel monkeys (Saimiri sciureus) of Guyanese origin that were born and raised at Stanford University (Stanford, CA) served as subjects for the study. From a colony comprised of 57 healthy adult females with a median age of 10 years (range, 4–17 years of age), matched samples were randomly selected from the young (≤10 years of age) and older (>10 years of age) age classes. As depicted in the bimodal age distribution in Figure 1, 15 monkeys were young adults with a median age of 6 years (range, 5–9). The other 16 monkeys were older adults with a median age of 14 years (range, 10–17). Puberty occurs at 2–3 years of age, and the average maximum lifespan in captivity is ~21 years of age (Brady, 2000).

During assessments of cognitive performance, monkeys were housed and tested individually in wire-mesh cages (60 × 60 × 90 cm) that provided visual, auditory, and olfactory, but not direct physical contact, between familiar animals. At all other times, monkeys were socially housed in cages (1.2 × 1.2 × 1.8 m) that contained three or four familiar females of the same age. All cages were located in climate-controlled rooms with a 12 hr light/dark cycle. Procedures complied with National Institutes of Health policies on the care and use of animals and were approved by the Stanford University animal care committee.

Cognitive tests. The apparatus used for the cognitive tests was a clear Plexiglas box (8 × 8 × 8 cm) with one open side that contained a marshmallow food treat (Lyons et al., 2000a). The box was mounted on a tray and secured to the front of each monkey’s cage. Initially, each monkey was easily trained to retrieve food treats from the clear baited box. Thereafter, each monkey was administered a series of four five-trial sessions each day for 14 consecutive days. Each trial was terminated when the treat was retrieved, with a 20 sec delay between trials in each session and a 30 min delay between each of the four daily five-trial sessions.

For the first two daily five-trial sessions, the box opening was oriented in the same direction (i.e., toward the left on even-numbered days and toward the right on odd-numbered days). Each monkey was required to learn and remember the initial box-opening orientation. On the second two daily five-trial sessions, the box opening was oriented opposite to that presented for the first two sessions. Each monkey was now required to inhibit the previously rewarded reaching response and remember the new orientation. After completion of the four daily sessions, all monkeys were fed unrestricted amounts of commercial monkey chow with fresh fruit and vegetable supplements. The following morning, 1 hr before testing, all uneaten food was removed. Each monkey was tested at the same time of day, between 9:00 A.M. and 12:00 P.M.

Stress tests and hormone measures. Three rounds after the cognitive tests, plasma cortisol and adrenocorticotropic hormone (ACTH) responses evoked by a standardized test were measured in the squirrel monkey nonbreeding season. At this point, circannual rhythms in adrenal and gonadal steroid hormones in squirrel monkeys are at their nadir (Schiml et al., 1999). Cage mates were restrained adjacent to one another for 30 min in separate primate chairs, like those first described by Carmichael and MacLean (1961). Chair restraint provides slight room for movement and ample ventilation and does not induce pain or inflict tissue damage. Blood samples for cortisol and ACTH determinations were collected after the restraint-stress session at 0, 30, and 60 min intervals from monkeys socialized housed in their own home cage.

To test for age-related differences in sensitivity to glucocorticoid negative-feedback regulation of the acute stress response, 7 d after the initial stress test, all monkeys were administered a second stress test preceded by an intramuscular (IM) injection of hydrocortisone sodium succinate (20 mg/kg). This dose of hydrocortisone is known to suppress squirrel monkey plasma levels of ACTH (Lyons et al., 2000b). Hydrocortisone was administered 60 min before the second 30 min restraint-stress test. Sixty minutes before the first stress test, an IM injection of saline was administered to control for injection pretreatment effects. Seven days before and 7 d after the two successive restraint-stress tests, additional blood samples were collected in undisturbed home cage conditions for baseline hormone determinations.

Blood samples were obtained, as described previously (Lyons et al., 1999), between 1:30 and 2:30 P.M. to control for known circadian effects. All samples were transferred to chilled tubes on ice, centrifuged at 4°C, and plasma cortisol and ACTH levels were measured in duplicate using established radioimmunoassays (Lyons et al., 1999, 2000b). The cortisol assay does not distinguish between cortisol and exogenous hydrocortisone and, therefore, plasma levels of ACTH served as our primary index of HPA-axis stress reactivity and feedback regulation. Complete sample subsets from each test condition and age class were included in every hormone assay. Intra- and inter-assay coefficients of variation were 1.4% and 6.4% for cortisol and 5.2% and 5.5% for ACTH, respectively.

Brain image acquisition and analysis. Three months after the restraint-stress tests, brain images were acquired on a General Electric (Milwaukee, WI) Signa 3.0 T system with protocols developed specifically for squirrel monkeys (Lyons et al., 2001). All monkeys were scanned under anesthesia induced by a subcutaneous injection of 20 mg/kg ketamine hydrochloride, 4 mg/kg xylazine hydrochloride, and 0.04 mg/kg atropine sulfate. Body temperatures were maintained within the normal range using a cushioned heat pad. Ear plugs provided protection from noises generated by the scanner.

The first scan was acquired in the sagittal plane with a two-dimensional sequential spoiled gradient pulse sequence. This initial localizer scan was used to standardize head tilt and rotation by assuring that two external markers (vitamin E capsules in the meatus of each ear) were aligned in the coronal and axial planes. The head was repositioned as required, and another sagittal localizer scan was performed. Head pitch was standardized against a mid sagittal image, and the final scan used for volumetric analysis was acquired in the coronal plane with a three-dimensional inversion recovery-prepared fast-spoiled gradient pulse sequence: repetition time = 12 msec; echo time = 3 msec; inversion
were reliabilities expressed as intra-class correlations from fixed effects models onto coronal brain image stacks. Intra-rater drawing anatomical boundaries described previously for adult squirrel rants (Fig. 2). Hippocampal volumes were also determined by hand white, and CSF in four three-dimensional complementary brain quad-taxic sectors. These procedures produced volumetric measures of gray, normalization, and parcellation into proportional Talaraich-like stereo-facts, segmentation into gray, white, and CSF components, positional the removal of all nonbrain tissue, correction of equipment-related arti-tino, CA) (Patwardhan et al., 2001). Briefly, image processing included v5.27 on an Apple Macintosh G4 computer (Apple Computers, Cuper-}

Standardized semiautomated image-processing protocols were per-formed as described for human subjects with the program BrainImage v5.27 on an Apple Macintosh G4 computer (Apple Computers, Cuper-tino, CA) (Patwardhan et al., 2001). Briefly, image processing included the removal of all nonbrain tissue, correction of equipment-related arti-facts, segmentation into gray, white, and CSF components, positional normalization, and parcellation into proportional Talaraich-like stereo-taxic sectors. These procedures produced volumetric measures of gray, white, and CSF in four three-dimensional complementary brain quad-rants (Fig. 2). Hippocampal volumes were also determined by hand drawing anatomical boundaries described previously for adult squirrel monkeys (Lyons et al., 2001) onto coronal brain image stacks. Intra-rater reliabilities expressed as intra-class correlations from fixed effects models were >0.90.

Data analysis. Reach attempt errors summed across days were exam-ined for age and test session effects using ANOVA with repeated mea-sures in the multivariate general linear hypothesis module of Systat (Richmond, CA). Age class was considered as a between-subjects factor, and test session was the repeated measures factor. The Geisser–Greenhouse correction was used to adjust for multiple comparisons across all repeated measures factors. Similar procedures were used to assess age class and hydrocortisone pretreatment effects for poststress measures of cortisol and ACTH and age class differences in regional brain measures. Age effects were also examined using linear least squares regression with age as a continuous variable. Pearson correlations and partial correla-tions were used to assess the relationships between age, cognitive errors, stress hormone levels, and in vivo brain volumes. All statistics were evalu-ated with two-tailed probabilities (p < 0.05).

Results

Learning and memory was initially assessed with the box opening that was consistently presented toward either the left or right. The marshmallow treat was always retrieved from the one open side of the box, but successful retrievals were often preceded by reach attempt errors toward the incorrect side (Fig. 3A). Significantly fewer errors were observed across the first and second test ses-sions (F(1,30) = 127.10; p < 0.001), and young and older adults did not differ in learning the initial box-opening orientation.

After the first and second test sessions, the box-opening ori-entation was reversed. Third session error rates increased significantly, relative to the first (F(1,30) = 78.92; p < 0.001) and second (F(1,30) = 155.87; p < 0.001) test sessions. Both young and older adults performed as if the box opening had not been reversed. But during the subsequent fourth test session, 30 min after the spatial reversal, older adults continued to make more reach attempt er-rors than young adults (F(1,29) = 7.88; p = 0.009) (Fig. 3B). Age effects were also discerned, with age considered a continuous variable (F(1,29) = 6.42; p = 0.017). Fourth session error rates were nearly identical to second session error rates in young adults (Fig. 3B), whereas fourth session error rates were significantly greater than second session error rates in older adults (F(1,15) = 29.82; p < 0.001). Fourth-minus-second session error rates com-

Figure 2. Brain image processing. A, Gray-scale image (top) from a representative monkey is segmented into CSF, gray, and white matter (top to bottom, respectively) with darker voxels depicting larger proportions of each tissue type. B, Multiplanar views of a gray-scale image show the stereotaxic Talaraich-like grid (dotted lines) used for parcellation of the brain image stack into four three-dimensional quadrants (solid lines).

Figure 3. Age-related differences in cognitive performance. A, Reach attempt error rates did not differ with age before the box-opening orientation was reversed. B, After reversals, error rates increased, and older adults continued to make significantly more errors than young adults during the final test session. Data are presented as mean ± SEM for 15 young and 16 older adults; *p < 0.01.
pressed stress levels of ACTH (Fig. 4B) relative to pretreatment with saline (Fig. 4A). Postrestraint levels of ACTH after hydrocortisone analyzed without baseline variation controlled as a co-variate did not differ significantly with age (Fig. 4B). Nevertheless, the age main effect was statistically significant when baseline was included as a co-variate, regardless of whether age was considered as a continuous ($F_{(1,28)} = 5.35; p = 0.028$) or categorical ($F_{(1,28)} = 7.91; p = 0.009$) variable. Postrestraint levels of ACTH after hydrocortisone were equal to or less than baseline in young adults, but older adults failed to suppress below baseline the initial ACTH stress response (Fig. 4B). This modest difference in ACTH after hydrocortisone cannot be attributed to significant age differences in the overall size of the glucocorticoid feedback signal achieved by administration of hydrocortisone. Plasma levels of glucocorticoid (cortisol and hydrocortisone combined) did not differ with age, whether age was analyzed as a continuous or categorical variable.

Stress reactivity determined from each monkey’s mean plasma level of ACTH after pretreatment with saline correlated with age ($r = 0.37; df = 29; p = 0.041$) and diminished glucocorticoid feedback determined from each monkey’s mean ACTH level after pretreatment with hydrocortisone ($r = 0.67; df = 29; p < 0.001$). The partial correlation between stress reactivity and diminished glucocorticoid feedback sensitivity was also significant after controlling for age-related variation ($r = 0.69; df = 28; p < 0.001$). As summarized in Table 1, stress reactivity ($r = 0.53; df = 29; p = 0.002$) but not diminished glucocorticoid feedback ($r = 0.20; df = 29; p = 0.287$) was likewise associated with impaired cognitive response inhibition determined from each monkey’s fourth-minus-second session errors. The correlation between cognitive performance and stress reactivity was significantly greater than that between cognitive performance and diminished glucocorticoid feedback ($t = 2.66; df = 28; p = 0.013$).

Three months after the neuroendocrine tests, unilateral volumes of gray and white matter in the anterior and posterior brain sectors were measured and analyzed for age-related differences with brain side considered a within-subjects factor. Bonferroni corrections were applied to control for comparisons across multiple brain regions. Each test statistic from the ANOVAs for each correction was applied to control for comparisons across multiple brain regions. Each test statistic from the ANOVAs for each sector was measured and analyzed for age-related variation ($r = 0.69; df = 28; p < 0.001$). As summarized in Table 1, stress reactivity ($r = 0.53; df = 29; p = 0.002$) but not diminished glucocorticoid feedback ($r = 0.20; df = 29; p = 0.287$) was likewise associated with impaired cognitive response inhibition determined from each monkey’s fourth-minus-second session errors. The correlation between cognitive performance and stress reactivity was significantly greater than that between cognitive performance and diminished glucocorticoid feedback ($t = 2.66; df = 28; p = 0.013$).

Significant main effects of age class ($F_{(1,28)} = 23.32; p < 0.001$) and time course ($F_{(2,56)} = 14.01; p < 0.001$) were evident in postrestraint levels of ACTH when monkeys were pretreated with saline. Postrestraint levels of ACTH were greater than baseline but declined over time, and older adults at all time points responded with greater postrestraint levels of ACTH relative to young adults. These same age effects were likewise discerned without controlling for baseline as a covariate (Fig. 4A), and regardless of whether age was considered a continuous or categorical variable.

As expected, hydrocortisone pretreatment robustly sup-

Table 1. Correlations between age, cognitive errors, neuroendocrine measures, and anterior bilateral white matter volumes in 31 adult female squirrel monkeys

<table>
<thead>
<tr>
<th>Cognitive errors</th>
<th>Stress response</th>
<th>Impaired glucocorticoid feedback</th>
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</thead>
<tbody>
<tr>
<td>0.59**</td>
<td>0.53**</td>
<td>0.67**</td>
</tr>
<tr>
<td>0.67</td>
<td>0.20</td>
<td>0.67**</td>
</tr>
<tr>
<td>0.43*</td>
<td>0.46*</td>
<td>0.28</td>
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<td>0.15</td>
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*p < 0.05; **p < 0.01.

Figure 4. Age-related differences in stress reactivity and glucocorticoid feedback. A, Poststress levels of ACTH were greater in old than young adults after pretreatment with saline. B, After hydrocortisone, poststress levels of ACTH were equal to or less than baseline levels in young adults, but older adults failed to suppress below baseline the initial ACTH stress response. Data are presented as mean ± SEM for 15 young and 16 older adults; *p < 0.01.
did not correlate significantly with stress reactivity nor with diminished glucocorticoid feedback, regardless of whether white matter measures were analyzed as separate unilateral volumes or combined as a bilateral measure (Table 1).

**Discussion**

Neither cortisol nor ACTH levels at baseline differed with age during midlife adulthood, but older adult monkeys responded to stress with larger increases in HPA hormones relative to young adults. Stress reactivity was mediated in part by modest reductions in glucocorticoid feedback sensitivity determined by administration of exogenous hydrocortisone. Stress reactivity also correlated with age-related differences in cognitive control. Cognitive performance did not differ with age during the first or second test sessions, but older adults more often failed to inhibit the initial learned response after subsequent spatial reversals. Impaired cognitive response inhibition correlated with the expansion of white matter volume in anterior but not posterior brain regions statistically controlling for age effects, neuroendocrine responses to psychological stress, CSF, and gray matter volumes. These results indicate that instead of enhancing cognitive control during midlife adulthood, white matter volume expansion contributes to aspects of cognitive decline.

Neurobiological studies of stress and cognitive decline during aging tend to focus on the hippocampus (Lupien and Lepage, 2001; Miller and O’Callaghan, 2003). Our findings reflect a different aspect of cognition, because prefrontal lesions (Diamond et al., 1989; Jentsch et al., 1997; Wallis et al., 2001) and not hippocampal ablations (Diamond et al., 1989) impair response inhibition on tests like those administered here to healthy nonlesioned squirrel monkeys. Moreover, we failed to find age-related differences in monkey hippocampal volumes determined *in vivo* by MRI. Hippocampal atrophy gradually emerges during the mid-fifties in healthy humans (Raz et al., 2004) and may occur earlier in men compared with healthy middle-age women (Pruessner et al., 2001). All but 5 of the 31 monkeys in our study were younger than the equivalent of 55 years in human development, and all of the monkeys were females. The absence of hippocampal atrophy in monkeys therefore agrees with human studies and cannot be generalized to adult males or elderly female squirrel monkeys.

Age-related differences in hippocampal-dependent memory were not evident during the prereversal tests, but older mid-age adult female squirrel monkeys more often failed to inhibit the initial learned response after spatial reversals designed to assess prefrontal-dependent cognitive functions. Similar studies of adult rhesus monkeys indicate that spatial but not object reversal learning is an especially sensitive marker of prefrontal cognitive decline (Bartus et al., 1979; Lai et al., 1995). Human abilities that likewise rely on prefrontal-dependent cognitive control, spatial orientation, inhibition, and reasoning also show approximately linear declines throughout adult midlife development (Baltes et al., 1999; McArdle et al., 2002; De Luca et al., 2003). In humans and monkeys, stress hormones impair prefrontal-dependent cognitive control (Young et al., 1999; Lyons et al., 2000a), and monkey cognitive response inhibition impairments after spatial reversals correlate with increased stress reactivity as determined by HPA hormones.

Although squirrel monkey HPA-axis physiology differs from humans because of mutations in the glucocorticoid receptor and related chaperones that result in glucocorticoid resistance (Chrousos et al., 1982; Patel et al., 2000a; Scammell et al., 2001), the high cortisol set-point in monkeys counteracts end-organ

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**Table 2. Asymmetries in gray and white matter volumes in 31 adult female squirrel monkeys**

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
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<tbody>
<tr>
<td>Anterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray</td>
<td>2939 ± 60</td>
<td>2973 ± 62</td>
</tr>
<tr>
<td>White</td>
<td>1481 ± 48</td>
<td>1574 ± 48*</td>
</tr>
<tr>
<td>Posterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray</td>
<td>3371 ± 101</td>
<td>3412 ± 105</td>
</tr>
<tr>
<td>White</td>
<td>1843 ± 64</td>
<td>1940 ± 65*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM mm$^3$ for anterior and posterior sectors on the left and right sides of the brain (*p* < 0.05).
resistance (Cassorla et al., 1982; Moore et al., 1993), and squirrel monkeys demonstrate otherwise normal regulation of the HPA hormone stress response. Corticotropin-releasing factor stimulates secretion of pituitary ACTH (Lyons et al., 2000b), which stimulates secretion of cortisol from the squirrel monkey adrenal cortex (Lyons et al., 1995). Exogenous or endogenous stress levels stimulate secretion of pituitary ACTH (Lyons et al., 2000b), which

hormone stress response. Corticotropic-releasing factor stimu-
lates secretion of pituitary ACTH (Lyons et al., 2000b), which

lates secretion of cortisol from the squirrel monkey adrenal
cortex (Lyons et al., 1995). Exogenous or endogenous stress levels

of cortisol, in turn, suppress the secretion of squirrel monkey
ACTH (Lyons et al., 1999, 2000a,b).

Relative to young adult female squirrel monkeys, older
middle-age adult females exhibit greater stress hormone re-
sponses and modest reductions in sensitivity to glucocorticoid
feedback. These findings agree with evidence that increased stress
reactivity is mediated in part by diminished glucocorticoid feed-
back sensitivity with aging in adult rhesus monkeys, baboons, and
healthy humans (Sapolsky and Altmann, 1991; Gust et al., 2000;Wilkinson et al., 2001). Diminished sensitivity to glucocorti-
coid feedback during aging results from decreased glucocorti-
coid receptor densities (Sapolsky, 1999) and age-related impair-
ments in glucocorticoid receptor signaling (Murphy et al., 2002)
in the adult rodent hippocampus. Glucocorticoid receptors are
expressed throughout the hippocampus and neocortex in squir-
rel monkeys (Patel et al., 2000b) and rhesus macaques (Sanchez et
al., 2000), but little is known about age-related changes in glu-
cocorticoid receptors in primates.

Glucocorticoid receptors also reside in myelin-producing oli-
godendrocytes (Vielkind et al., 1990), and glucocorticoid recep-
tor signaling stimulates myelination of axons in vitro (Chan et al.,
1998; Afshari et al., 2002). However, white matter volumes in
squirrel monkeys are not correlated with glucocorticoid levels at
baseline or after an acute restraint stress. White matter volumes
in anterior but not posterior brain regions on the left and right
sides are significantly larger in older middle-age adult monkeys
compared with young adults. This white matter volume expa-
sion does not result in an overall change in brain size, because a
small proportion of brain is comprised of anterior white matter.
Gray matter volumes gradually decline, but the decrease is three-
fold less than the increase discerned in anterior white matter.
Therefore, it seems unlikely that white matter growth during
midlife adulthood is caused by a shift in gray-white T1 contrast
with age. In human brain imaging, T1 is stable throughout adult
midlife development compared with the changes observed in
childhood, adolescence, and late adulthood (Cho et al., 1997;
Steen and Schroeder, 2003). Moreover, postmortem studies of
humans and monkeys suggest that in midlife adulthood, subtle
cell shrinkage and modest pruning of synaptic connectivity
in gray matter is accompanied by continued myelination of axon
connections in anterior brain regions (Yakovlev and Lecours,
1967; Huttenlocher and Dabholkar, 1997; Peters and Sethares,
2002; Uylings and de Brabander, 2002; Duan et al., 2003; Peters
and Sethares, 2003).

Myelination increases nerve conduction velocities (Baumann
and Pham-Dinh, 2001) and facilitates synchronous firing of neu-
rons by reducing the effects of travel distance variability in dis-
tributed brain circuits (Waxman, 1997; Lang and Rosenbluth,
2003; Salami et al., 2003). Frontal and temporal lobe white matter
growth has therefore been viewed as enhancing neuropyscholog-
ical functions that rely on distributed networks in humans
(Greenwood, 2000; Bartzokis et al., 2001; Mulhern et al., 2001;
Giedd, 2003). However, instead of enhancing cognitive control
during midlife adulthood in monkeys, our results indicate that
white matter volume expansion in anterior brain regions corre-
sponds with impaired cognitive control of a simple learned re-
sponse. These results are in keeping with postmortem studies that
show how continued myelination coincides with increased ac-
mulation of myelin decompaction defects that correlate in rhesus
monkeys with aspects of cognitive decline (Peters et al., 2001;
Peters and Sethares, 2002, 2003). Increased stress reactivity and
diminished regulation of the HPA axis are additional aspects of
aging that conflict with the view that white matter volume expan-
sion improves distributed brain functions. However, white mat-
ter volumes in monkeys are not correlated with measures of stress
reactivity or glucocorticoid feedback.

The extent to which data from monkeys can be generalized to
aspects of aging in humans is limited in several respects. Frontal
and temporal lobe white matter volumes in humans increase
throughout childhood, adolescence, and early and midlife adult-
hood and then decline after 50 years of age (Giedd et al., 1999;
Courchesne et al., 2000; Bartzokis et al., 2001; Jernigan and
Fennema-Notestine, 2004). Many more measures from monkeys
are needed to precisely define lifespan trajectories of white matter
growth and subsequent decline for comparative studies with hu-
mans. White matter hyperintensities discerned by MRI on T2-
weighted images (Gunning-Dixon and Raz, 2000) are a promi-
nent aspect of human brain aging that has not been examined in
monkeys. Of particular interest is a recent report that the devel-
opment of perseverative behavior in midlife adulthood correlates
with increased white matter hyperintensities in the human fron-
tal lobe (Gunning-Dixon and Raz, 2003). Gender comparisons
also warrant attention in light of sex differences in white matter
trajectories (Bartzokis, 2004) and human hemispheric asymme-
tries (Allen et al., 2003). In monkeys, larger right than left vol-
umes of white but not gray matter resemble asymmetries in hu-
mans (Allen et al., 2003; Raz et al., 2004), with gender differences
generally more prominent in white than gray matter tissue (Allen
et al., 2003; Szeszko et al., 2003). Aging likewise appears to in-
crease HPA-axis stress reactivity and diminish glucocorticoid
feedback sensitivity to a greater extent in women than in men
(Seeman et al., 2001).

Apart from these issues, our study highlights an additional
major concern. Instead of revealing favorable forms of myelina-
tion in midlife adulthood, white matter volume expansion deter-
mined by neuroimaging may actually reflect increased accumu-
lation of myelin decompaction defects that correlate with
cognitive decline. The hypothesis that white matter growth rep-
resents myelin decompaction agrees with diffusion tensor MRI
evidence that interstitial or intracellular fluid accumulates lin-
early with age in adult human frontal lobe white matter tissue
determined by microstructural changes in water proton diffusiv-
ity (Abe et al., 2002; Moseley, 2002; Pfefferbaum and Sullivan,
2003). Cellular and molecular research combined with in vivo
brain imaging is needed to determine the basis of white matter
growth in adults, elucidate its functions during lifespan develop-
ment, and provide potential new targets for therapies aimed at
maintaining in humans cognitive vitality with aging.

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