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Glucocorticoid effects on memory function over the human life span

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Abstract
Glucocorticoids (GCs), produced by the stress-responsive hypothalamic–pituitary–adrenal axis, are well recognized for their regulatory role in peripheral metabolism. GCs are also known to regulate various brain functions, with well-described effects on human cognition. Increased GC exposure in humans—including exposure to the endogenous GC, cortisol—at levels associated with stress, decreases memory and learning function. These results extend evidence from in vitro studies of synaptic and cell function and evidence from animals indicating the GCs can regulate substrates of memory function. While considerable evidence details these effects in adult humans and animals, relatively less is know about the effect of GCs on cognitive function in children and older adults. Investigators have suggested that children, particularly preschool-aged children, may be vulnerable to adverse consequences of increased GC secretion resulting from stress and neuropsychiatric diseases such as depression. Adverse GC effects on memory substrates and memory function in the adult have also fostered concern that age-related changes, including changes in GC receptors and changes in circulating cortisol levels, could lead to age-related increases in the adverse effect of GCs on brain function. Investigators have reported an association between age-related increases in cortisol levels and age-related memory decline, but this association may or may not be due to a direct effect of cortisol on memory substrates. A number of possible treatment approaches to prevent or remediate adverse GC-induced effects are under development. In general, the use of safe and effective agents for blocking adverse GC effects on brain functions including memory may offer benefits to individuals suffering acute and chronic stressors and could prevent brain changes relevant to stress, aging, and stress-related neuropsychiatric diseases.

Glucocorticoids (GCs) are known to regulate various brain functions, with well-described effects on human cognition. Increased GC exposure in humans, including exposure to the endogenous GC cortisol, at levels associated with stress, decreases memory and learning function (de Quervain, Roozendaal, & McGaugh, 1998; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Newcomer, Selke, Melson, Hershey, Craft, Richards, & Alderson, 1999). These results extend evidence from in vitro studies of synaptic and cell function and evidence from animals, indicating that GCs can regulate substrates of memory function. While considerable evidence details these effects in adult humans and animals, relatively less is know about the effect of GCs on cognitive function in children and older adults.

Adverse GC effects on memory substrates and memory function in the adult has furthered research interest in the effects of GCs on brain development and cognitive development early in life. In general, investigators have focused on determining populations of young children at risk for increased cortisol

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secretion, with limited work on the effects of prenatal GC exposure and postnatal GC effects on early memory development. Particular concern has begun to focus on the cognitive effects during the preschool period when learning and memory functions normally undergo rapid development. GC effects in adults have also fostered concern that age-related increases in GC activity could lead to age-related decreases in cognitive function (Issa, Rowe, Gauthier, & Meaney, 1990). Indirect evidence from aging humans suggests that age-related increases in cortisol levels can be associated with age-related memory declines (Lupien, Lecours, Lussier, Schwartz, Nair, & Meaney, 1994; Seeman, McEwen, Singer, Albert, & Rowe, 1997). In this article, we will review the effects of GC on memory function and on putative substrates of memory in the adult brain, and then address research concerning GC effects in children and during aging.

GC Receptors in the Brain

GCs, produced by the stress-responsive hypothalamic–pituitary–adrenal (HPA) axis, are well recognized for their regulatory role in peripheral metabolism. Stress induces an increased release of corticotropin releasing factor (CRF), which promotes the pituitary release of adrenocorticotropic hormone (ACTH). ACTH, released into the general circulation, causes the adrenal gland to secrete GCs. HPA axis function is controlled in part by negative feedback actions of GCs at the pituitary, hypothalamus, and supra-HPA axis regions that include the amygdala and hippocampus. GC receptors are located throughout the brain, with differential distributions of the two types of GC receptors, Type I (or mineralocorticoid receptors) and Type II (or glucocorticoid) receptors. Type II GC receptors have a high affinity for synthetic glucocorticoid analogues such as dexamethasone and prednisone, and a lower affinity for corticosterone and cortisol. Type I receptors have a high affinity for corticosterone, cortisol, and aldosterone (Reul & de Kloet, 1985; Veldhuis, Van Koppen, Van Ittersum, & de Kloet, 1982). In the rodent, Type II receptors are widely distributed in regions that include brain stem, cerebellum, thalamus, septum, neocortex, and amygdala, with dense representation in hippocampus and hypothalamus (Ahima & Harlan, 1990; Cintra, Zoli, Rosen, Agnati, Okret, Wikstrom, Gustafsson, & Fuxe, 1994; Fuxe, Wikstrom, Okret, Agnati, Harfstrand, Yu, Granholm, Zoli, Vale, Gustafsson, 1985; Jacobson & Sapolsky, 1991; McGimsey, Cidlowski, Stumpf, & Sar, 1991; Morimoto, Morita, Ozawa, Yokoyama, & Kawata, 1996; Reul & de Kloet, 1985; Sousa, Tannery, & Lafer, 1989; Uht, McKelvy, Harrison, & Bohn, 1988; Van Eekelen, Jiang, De Kloet, & Bohn, 1988). Rodent Type I receptors are also widely distributed in most of the same brain regions, with dense distribution in the hippocampus and septum (Ahima, Krozowski, & Harlan, 1991; Agarwal, Mirshahi, Mirshahi, & Rostene, 1993; Arriza, Simerly, Swanson, & Evans, 1988; Chao, Choo, & McEwen, 1989; Van Eekelen et al., 1988). Rodent studies suggest that Type II receptors are activated by peak GC levels, controlling feedback during stress, while Type I receptors regulate basal or trough GC concentrations (de Kloet & Reul, 1987; Jacobson & Sapolsky, 1991; McEwen, de Kloet, & Rostene, 1986).

Receptor binding studies indicate that similar Type I and II GC receptors are also found in primate brain, although these earlier studies did not provide quantitative data concerning regional distribution (Brooke, de Haas–Johnson, Kaplan, & Sapolsky, 1994; Sapolsky & Meaney, 1988; Tsuboi, Kawashima, Tomioka, Nakata, Sakamoto, & Fujita, 1979; Yu, Wrange, Boethius, Gustafsson, & Granholm, 1981). Hippocampal Type II receptor activation has been implicated in mediating the degenerative effects of stress on the hippocampus (Sapolsky, Krey, & McEwen, 1986) and in mediating effects such as GC-induced reductions in glucose transport (Horner, Packan, & Sapolsky, 1990) and GC-induced suppression of neuronal excitability (Joels & de Kloet, 1994). However, the relatively high regional concentration of Type II GC receptors observed in rodent hippocampus, relative to other brain regions, appears to not be present in primate brain. While in situ hybridization histochemistry and immunohistochemistry detect Type II GC receptors in human

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(Lopez, Chalmers, Little, & Watson, 1998; Seckl, Dickson, Yates, & Fink, 1991; Seckl, French, O'Donnell, Meaney, Nair, Yates, & Fink, 1993; Tohgi, Utsugisawa, Yamagata, & Yoshimura, 1995; Wetzel, Bohn, Kazee, & Hamill, 1995) and primate (Johnson, Brady, Gold, & Chrousos, 1996; Sanchez, Young, Plotsky, & Insel, 2000) hippocampus, a recent careful study in rhesus monkeys indicates relatively higher levels of Type II receptor mRNA and protein in neocortex and entorhinal cortex, hypothalamus, and cerebellum, with lower levels in hippocampal formation (Sanchez et al., 2000). In contrast, high levels of Type I receptor mRNA and protein are detected in rhesus hippocampal formation (Sanchez et al., 2000). These results suggest that hippocampal Type II receptors may not be the most important GC target during stress.

Type II GC receptors in neocortex, and Type I receptors in hippocampus, may play important roles in mediating the effects of stress on primate brain function. Hippocampal Type I receptors, in contrast to Type II receptors, are expressed at high levels relative to Type I receptors in other brain regions in rodents and primates (Johnson et al., 1996; Sanchez et al., 2000; Seckl et al., 1991). Type I receptors may have important interactions with Type II receptors in regulating feedback as well as other effects (Arriza et al., 1988; de Kloet, Oitzl, & Joels, 1993; Spencer, Kim, Kalman, & Cole, 1998). The activity of the endogenous human GC cortisol at both receptors and important Type I–Type II interactions including Type I–Type II dimer formation (Trapp, Rupprecht, Castren, Reul, & Holsboer, 1994) indicate the potential for complex receptor interactions. Finally, important GC effects on the brain may be mediated by Type II receptors in neocortex. GCs can decrease glutamate reuptake, increasing extracellular glutamate concentrations, in neocortex more than in hippocampus (Lowy, Gault, & Yamamoto, 1993; Moghaddam, 1993; Moghaddam, Bolinao, Stein–Behrens, Lin, & Sapolsky, 1994; Stein–Behrens & Sapolsky, 1994). Discussed below, this may be important for GC-related neurotoxicity but also for reversible, stress-related changes in cognitive function. Glutamate reuptake is energetically linked to glucose uptake into glia, a Type II receptor-regulated effect (Horner et al., 1990), and glial glucose metabolism supports neuronal metabolism and function (Magistretti, Pellerin, Rothman, & Shulman, 1999).

Memory Substrates Relevant to GC Effects on Explicit Memory

A range of evidence supports the role of the hippocampus, as well as regions of neocortex, in declarative or explicit memory, specifically in the acquisition (or encoding), consolidation, and recall of facts and events (Lepage, Ghaffar, Nyberg, & Tulving, 2000; Lepage, Habib, & Tulving, 1998; Squire, 1992; Tulving, Habib, Nyberg, Lepage, & McIntosh, 1999). Interest in a specific role for synaptic plasticity as a memory substrate has focused on the activity-dependent synaptic modification called long-term potentiation (LTP; a sustained increase in synaptic strength induced by certain repeated stimulation of excitatory afferents), extensively studied in hippocampus (Bliss & Collingridge, 1993; Collingridge & Bliss, 1995). Hippocampal LTP has been associated with higher order behavioral memory and learning (Davis, Butcher, & Morris, 1992; Doyere & Laroche, 1992; Morris, Davis, & Butcher, 1990; Moser, Moser, & Andersen, 1994; Sakimura, Kutsuwada, Ito, Manabe, Takayama, Kushiya, Yagi, Aizawa, Inoue, Sugiyama, & Mishina, 1995; Wilson & McNaughton, 1993). LTP and long-term depression (LTD; a sustained decrease in synaptic strength) share important properties with memory and may underlie the brain's ability to store information (Malenka, 1994; Rison & Stanton, 1995; Wilson & Tonegawa, 1997). A line of genetic evidence establishes the role of CA1 *N*-methyl-D-aspartate (NMDA) glutamate receptors in certain types of learning (Huerta, Sun, Wilson, & Tonegawa, 2000; McHugh, Blum, Tsien, Tonegawa, & Wilson, 1996; Rampon, Tang, Goodhouse, Shimizu, Kyin, & Tsien, 2000; Tsien, Huerta, & Tonegawa, 1996). NMDA receptor-dependent synaptic reinforcement also plays a role in memory consolidation (Shimizu, Tang, Rampon, & Tsien, 2000). Finally, important elements of memory function can be regulated

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by transcriptional activation and repression of various genes, and considerable work demonstrates the role that factors such as cAMP responsive element binding (CREB) protein can play in transcriptional regulation (Bartsch, Casadio, Karl, Serodio, & Kandel, 1998; Schulz, Siemer, Krug, & Hollt, 1999; Taubenfeld, Wiig, Bear, & Alberini, 1999).

GC Effects on Brain Physiology

GCs have been recognized for their capacity to regulate neuronal metabolism, physiology, and gene expression in the brain. While particular attention has been devoted to actions in the hippocampus, many GC effects have similarly been observed in other brain regions, including neocortex. GC actions include involution of the dendritic processes of hippocampal neurons (Woolley, Gould, Frankfurt, & McEwen, 1990), regulation of neurotrophin expression (McLay, Freeman, Harlan, Ide, Kastin, & Zadina, 1997), and inhibition of activity-dependent synaptic plasticity (Bennett, Diamond, Fleshner, & Rose, 1991; Diamond, Bennett, Fleshner, & Rose, 1992; Foy, Stanton, Levine, & Thompson, 1987). Increased GC secretion associated with stress can also rapidly reduce the ongoing rate at which new granule cells are added to the dentate gyrus of adult nonhuman primates (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998). GCs acting at Type II receptors can also inhibit glucose transport into neurons and glia from multiple brain regions in vitro, with the relative magnitude of inhibition related to the regional density of Type II GC receptors (Horner et al., 1990). Systemic GC treatment has been reported to inhibit in vivo regional cerebral glucose metabolism in the hippocampus of healthy older humans (de Leon, McRae, Rusinek, Convit, De Santi, Tarshish, Golomb, Volkow, Daisley, Orentreich, & McEwen, 1997).

Importantly, GCs can also inhibit glutamate uptake by astrocytes (Virgin, Ha, Packan, Tombaugh, Yang, Horner, & Sapolsky, 1991), increasing extracellular glutamate in neocortex more than in hippocampus (Lowy, Gault, & Yamamoto, 1993; Moghaddam, 1993; Moghaddam et al., 1994; Stein–Behrens et al., 1994). Under severe conditions in which excess glutamate is released and neurons are potentially endangered (i.e., neurotoxicity), GC-induced inhibition of glutamate uptake could prevent the removal of damaging glutamate from the synapse. Glutamate uptake into glia is energetically linked to glucose uptake on a molecule-for-molecule basis, and intracellular glucose stores (i.e., glycogen) are critical to supporting the energy demands of adjacent neurons (Magistretti et al., 1999). GC effects on glucose uptake can increase neuronal vulnerability to a variety of neurotoxic insults, leading to hypotheses concerning severe stress-related decreases in hippocampal integrity. However, under less severe stressful conditions, investigators have remained concerned that increased GC levels can alter the routine functioning of neurons. Cognitive and other neuronal functions require activity-dependent glucose uptake by glia to support neuronal energy needs, so that GC-induced inhibition of glucose uptake is likely to contribute to adverse GC effects on neuronal function (e.g., cognition).

Advances in the understanding of GC regulation of neuronal function include detailed studies of the effect of GCs on voltage- and transmitter-dependent processes in hippocampal neurons (Joels, 1997). GCs exert fast actions probably via membrane receptors (French–Mullen, 1995) that generally inhibit cellular firing, as well as fast actions on synaptic responses via intracellular receptors without the involvement of gene transcription. Delayed GC effects at Type II receptors generally suppress excitatory amino acid neurotransmission (e.g., NMDA receptors), enhance serotonin-induced inhibition, and suppress adrenergic but not cholinergic excitation. In addition, GCs can rapidly increase calcium-dependent after hyperpolarization (Joels & de Kloet, 1994; Landfield, Thibault, Mazzanti, Porter, & Kerr, 1992) by acting at voltage-sensitive calcium channels (Landfield et al., 1992), thus decreasing neuronal excitability. Overall, GC effects on neuronal activity tend to observe an inverted U-shaped curve, with extremely low (e.g., adrenalectomy) and high GC levels suppressing neuronal activity (Joels & de Kloet, 1994). In addition, glucocorticoid receptor-

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dependent transcription and translation in response to acute stress can regulate changes in synaptic plasticity (Xu, Holscher, Anwyl, & Rowan, 1998).

The last decade has also increased our understanding of the hormone–GC receptor complex as a gene transcription factor for a wide variety of genes (Herman, 1993). For example, GCs can regulate serotonin (5-HT) activity in hippocampus and frontal cortex, with Type I GC receptor activation down-regulating hippocampal serotonin 1A (5-HT_{1A}) receptor mRNA and receptor binding (Meijer, Cole, Schmid, Schutz, Joels, & de Kloet, 1997). During chronic high-level stress and in depression, increased CRF mRNA can lead to increases in HPA axis activity (Dieterich, Lehnert, & de Souza, 1997; Herman, Adams, & Prewitt, 1995; Nemeroff, 1988; Nemeroff, Widerlov, Bissette, Walleus, Karlsson, Eklund, Kilts, Loosen, & Vale, 1984). Several weeks (e.g., 8 weeks) of antidepressant treatment can decrease CRF mRNA, transiently increase Type I and II GC receptor mRNA and binding, and correct negative feedback insensitivity and certain cognitive deficits induced by a Type II receptor knockout (Barden, Reul, & Holsboer, 1995; Brady, Whitfield, Fox, Gold, & Herkenham, 1991; Montkowski, Barden, Wotjak, Stec, Ganster, Meaney, Engelmann, Reul, Landgraf, & Holsboer, 1995; Reul, Stec, Soder, & Holsboer, 1993).

The importance of the CRF model of depression could suggest that 5-HT receptors, CRF activity, and long-term GC-induced genomic changes are central to understanding the cognitive effects of GCs. However, some stress-induced memory and learning impairments in the rodent, associated with GC-induced dendritic involution noted above, do not respond to chronic antidepressant treatment. Indeed, tianeptine, a 5-HT reuptake enhancer, and not the antidepressant fluoxetine, a 5-HT reuptake inhibitor, prevents this stress-induced decrease in memory function (McEwen, Conrad, Kuroda, Frankfurt, Magarinos, & McKittrick, 1997). In addition, many GC effects on neuronal activity discussed above do not require chronic elevations of GC exposure, suggesting that a number of important GC effects can occur with subchronic increases in GC exposure. Type II receptor-mediated gene expression is unchanged at 3 and at 30 days of GC treatment using dose levels associated with stress, although higher doses or longer treatment may alter gene expression (Herman & Spencer, 1998). In addition, some GC effects on memory function may not be dependent on protein synthesis (Sandi & Rose, 1994a). Thus, many relevant GC effects on brain function can occur during GC treatment conditions resembling brief (e.g., hours to days) physical and psychological stress, and these effects may not require the changes in gene expression associated with longer term high-dose GC exposure.

GC Effects on Nonprimate Memory

Investigators have reported adverse effects of GC exposure on cognitive functions associated with hippocampal integrity in the rodent (Bardgett, Taylor, Csernansky, Newcomer, & Nock, 1994; Bodnoff, Humphreys, Lehman, Diamond, Rose, & Meaney, 1995; Bohus & De Weid, 1980; Borrell, de Kloet, & Bohus, 1984; Dachir, Kadar, Robinzon, & Levy, 1993; Endo, Nishimura, & Kimura, 1996; Luine, Villegas, Martinez, & McEwen, 1994; Ohl & Fuchs, 1999), including evidence for GC-induced impairments in the retrieval of learned material (de Quervain et al., 1998). Daily corticosterone treatment (10 mg/kg) reduces spontaneous alternation without evidence of hippocampal neuronal loss (Bardgett et al., 1994). In addition, learning deficits occur in mice with a targeted disruption of the gene for the GC type 2 receptor (Oitzl, de Kloet, Joels, Schmid, & Cole, 1997), consistent with the role of this receptor in regulating the excitability of hippocampal neurons (Joels & de Kloet, 1994). Early investigations proposed a role for hippocampal GC receptors in the filtering of irrelevant stimuli (McEwen, 1982). Other investigators using different treatment conditions (e.g., task learning followed by GC treatment) and tasks have reported a facilitating effect of GC treatment (Flood, Vidal, Bennett, Orme, Vasquez, & Jarvik, 1978; Mormede & Dantzer, 1978; Oitzl & de Kloet, 1992; Pugh, Fleshner, &

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Rudy, 1997; Roozendaal & McGaugh, 1996; Roozendaal & McGaugh, 1997a, 1997b; Sandi & Rose, 1994a, 1994b). However, the implications of these findings for explicit memory in humans is complicated by varying species, dose level and timing, and variable task characteristics across different studies. In particular, some studies have demonstrated memory faciliation when GC treatment is given to adrenalectomized animals, modeling GC replacement along with GC exposure. Some studies demonstrating GC-induced memory facilitation have also used conditioned avoidance tasks. These studies elegantly demonstrate that GC Type II receptor activation in basolateral amygdala modulate memory processes in brain regions like the hippocampus (Cahill & McGaugh, 1998; McGaugh, Cahill, & Roozendaal, 1996; Roozendaal & McGaugh, 1996, 1997a, 1997b; Roozendaal, Portillo–Marquez, & McGaugh, 1996). In general, methodological issues concerning the kinds of tasks that can be administered to human versus nonhuman subjects complicate the interpretation of animal studies in terms of human performance.

GC Effects on Human Memory

Early investigations in humans reported inverse associations between memory function and plasma cortisol concentrations in Cushing disease, with evidence that reducing cortisol levels can improve cognitive function (Mauri, Sinforiani, Bono, Vignati, Berselli, Attanasio, & Nappi, 1993; Starkman & Schteingart, 1981; Starkman et al., 1986; Whelan, Schteingart, Starkman, & Smith, 1980). Inverse correlations between plasma cortisol concentrations and memory function are also reported in disorders such as Alzheimer dementia (Heuser, Litvan, & Juncos, 1988; Jenike & Albert, 1984; Martignoni, Costa, Sinforiani, Liuzzi, Chiodini, Mauri, Bono, & Nappi, 1992; Oxenkrug, Gurevich, Siegel, Dumlao, & Gershon, 1989), depression (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982; Reus, 1984; Roy–Byrne, Weingartner, Bierer, Thompson, & Post, 1986; Rubinow, Post, Savard, & Gold, 1984), and schizophrenia (Newcomer, Craft, Askins, Hershey, Bardgett, Csernansky, Gagliardi, & Vogler, 1998; Newcomer, Faustman, Whiteford, Hoses, & Csernansky, 1991). Case–control study designs indicate decreased memory performance during prednisone treatment of asthmatic children (Bender, Lerner, & Poland, 1991), and decreased verbal declarative memory in prednisone-treated patients versus matched medical controls (Keenan, Jacobson, Soleymani, & Newcomer, 1995). However, the interpretation of these results is limited by nonrandomized treatment assignments, noncausal associations, or disease factors that can decrease performance. In addition, correlations between memory function and cortisol levels in various disease states may be related to acute GC effects or long-term disease-related changes in the brain, which in turn may or may not involve direct GC effects.

Double-blind, randomized, placebo-controlled experiments testing the cognitive effects of GC treatment in healthy humans indicate that pharmacological doses of the synthetic, preferential Type II GC receptor ligands, dexamethasone (DEX) and prednisone, can acutely decrease verbal declarative memory (Newcomer et al., 1994; Wolkowitz, Reus, Weingartner, Thompson, Breier, Doran, Rubinow, & Pickar, 1990). Wolkowitz et al. (1990) tested the effects of DEX and prednisone treatment in healthy adults, reporting GC-induced increases in verbal "commission errors" (recall of distractor vs. target words). Newcomer et al. (1994) tested the cognitive effects of 4 days of DEX treatment and reported time-dependent decreases in both immediate and delayed verbal recall performance, without effects on other cognitive functions. The effects of this subchronic GC exposure on memory function in healthy humans was reversed, achieving levels above baseline and comparable to placebo-treated subjects, after a 1 week washout period. Both studies support the hypothesis that subchronic increases in GC exposure can decrease explicit or declarative memory function in humans.

However, the interpretation of studies using DEX or prednisone as a model of cortisol effects or human stress remains problematic. This is due to uncertainty about whether treat-

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ment-induced impairments result from increased brain GC receptor binding, versus the alternative possibility that treatment-induced suppression of cortisol secretion combined with the relatively slow entry of DEX and prednisone into brain (in contrast to the rapid availability of cortisol; Meijer, de Lange, Breimer, de Boer, Workel, & de Kloet, 1998; Schinkel, Wagenaar, van Deemter, Mol, & Borst, 1995) could result in short-term decreases in brain GC receptor binding (Miller, Spencer, Pulera, Kang, McEwen, & Stein, 1992; Spencer, Young, Choo, & McEwen, 1990). Based on rodent studies noted above, indicating that increased GC exposure can potentially enhance certain types of memory, decreases in GC receptor binding might alternatively be argued to underlie decreased human memory function observed during DEX or prednisone treatment. Further, differences in DEX versus cortisol binding to Type I and Type II receptors (de Kloet & Reul, 1987; McEwen & Wallach, 1973; McEwen, Weiss, & Schwartz, 1969), and differences in role of these receptors in regulating important physiological effects, limits the utility of DEX and similar preferential Type II receptor ligands in modeling the effects of stress in humans.

Most studies of cortisol effects on human memory function have been limited to brief (60 min), single-dose (10–50 mg) treatment (Beckwith, Petros, Scaglione, & Nelson, 1986; Fehm–Wolfsdorf, Reutter, Zenz, Born, & Fehm, 1993; Kirschbaum et al., 1996). These study designs do not model the longer duration of hypercortisolemia relevant to most stress- and disease-related human events, and prevent an assessment of memory performance over the time course expected for genomic GC actions. These studies in healthy humans indicate mixed effects of cortisol treatment on immediate recall (Beckwith et al., 1986; Fehm–Wolfsdorf et al., 1993), and decreases in delayed recall (Kirschbaum et al., 1996). Kirschbaum et al. (1996) reported similar memory effects during exposure to placebo-controlled hydrocortisone and during exposure to stress, using the well-characterized Trier Social Stress Test. de Quervain, Roozendaal, Nitsch, McGaugh, and Hock (2000) reported that brief placebo-controlled cortisone treatment in healthy adults decreased the retrieval component of explicit memory performance, while producing cortisol levels similar to those observed during stress.

Several days of increased cortisol exposure in healthy adults reversibly decreases explicit verbal memory performance, without effects on other cognitive functions (Newcomer et al., 1999). Newcomer et al. (1999) used two different doses of cortisol given for 4 days in a randomized, placebo-controlled design, modeling subchronic elevations of circulating cortisol levels associated with a variety of physical and psychological stressors. In addition, total daily oral cortisol doses and targeted plasma levels for this study were selected to approximate 24-hr cortisol secretion during mild to maximal physiological stress associated with various physical and psychological stressors (Chernow, Alexander, Smallridge, Thompson, Cook, Beardsley, Fink, Lake, & Fletcher, 1987; de Jong, Mallios, Jansen, Scheck, & Lamberts, 1984; Deuss, Dietrich, Kaulen, Frey, Spangenberger, Allolio, Matuszczak, Troidl, & Winkelmann, 1994; Kehlet & Binder, 1973; Kirschbaum, Pirke, & Hellhammer, 1993; Lamberts, Bruining, & de Jong, 1997; Naito, Fukata, Tamai, Seo, Nakai, Mori, & Imura, 1991; Plunkett, Reeves, Ngo, Bellows, Shafer, Roach, Howse, Herskowitz, & Mangano, 1997; Salem, Tainsh, Bromberg, Loriaux, & Chernow, 1994; Vermes, Beishuizen, Hampsink, & Haanen, 1995). The mean cortisol-induced memory decrease on a paragraph recall task that was observed in the higher dose condition, approximating a 1-*SD* reduction from placebo-level performance, is clinically relevant. Similar 1-*SD* changes in performance on the Logical Memory passages (paragraph recall) of the Weschler Memory Scale—Revised would lower an individual's age-normalized classification of paragraph recall performance by one level (e.g., high-average decreased to average, low-average decreased to borderline; Wechsler, 1987). Notably, the results of this study indicate a reversible effect of increased GC exposure on memory performance under these subchronic treatment conditions, consistent with previous results using subchronic DEX treatment (Newcomer et al., 1994). In addition, sub-

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chronic treatment with both cortisol and DEX indicated GC effects on practice or procedural memory, in addition to decreasing explicit memory performance below baseline levels (Newcomer et al., 1994, 1999). In general, however, treatment with cortisol and DEX produce adverse treatment effects on both immediate and delayed verbal explicit memory performance, without effects on other differentiated elements of cognitive function such as attention or executive function (Newcomer et al., 1994, 1999). These results suggest GC effects on encoding processes or retrieval mechanisms that would be involved in both immediate and delayed recall (de Quervain et al., 1998, 2000). The results of these studies are relevant to the interpretation of memory impairments during periods of sustained stress in humans, where GC elevations are present throughout memory encoding and retrieval processes.

These studies provide additional indications that increased GC levels, rather than changes in other cognitively active compounds such as epinephrine, norepinephrine, ACTH, and CRF, are most likely responsible for memory effects seen in various earlier studies. Memory impairments associated with Cushing disease, certain neuropsychiatric conditions, and stress itself (Cohen et al., 1982; Heuser et al., 1988; Jenike & Albert, 1984; Kirschbaum et al., 1996; Martignoni et al., 1992; Newcomer et al., 1991, 1998; Oxenkrug et al., 1989; Reus, 1984; Roy–Byrne et al., 1986; Rubinow et al., 1984) occur with increased CRF or ACTH levels, while impairments during GC treatment of healthy subjects occur during suppression of CRF and ACTH. GC receptor activation across all these studies suggests that this common factor may underlie the memory disturbance observed across all conditions. The clearest experimental demonstration of this similar memory effect during GC exposure with both stimulated and suppressed ACTH and CRF came from Kirschbaum et al.'s (1996) study, where stress and cortisol treatment both produced similar memory decreases in healthy young adults (Kirschbaum et al., 1996). In addition, the suppression of endogenous ACTH and CRF is known to occur rapidly under these GC treatment conditions, while memory effects in the subchronic studies have a slower onset (Newcomer et al., 1994, 1999). Thus, the time course for GC treatment effects on memory, the similar memory impairment induced by stress and exogenous cortisol, and the cortisol-related memory impairments noted in various clinical populations all argue against a primary role for catecholamines, ACTH, or CRF in the explanation of cortisol-induced memory decreases.

Notably, brief (1-hr) GC treatment producing increases in plasma cortisol to levels associated with mild to moderate physical and psychological stress can also reversibly decrease certain elements of memory performance (Kirschbaum et al., 1996; de Quervain et al., 2000), while these same doses are not associated with memory impairment after 1 day of treatment (Newcomer et al., 1999). However, several (2–4) days of greater GC exposure (e.g., producing cortisol levels associated with major stress) can reliably induce clinically significant, but still reversible, decreases in memory function (Newcomer, Selke, Kelley, Paras, & Craft, 1995; Newcomer et al., 1999). Several days of cortisol treatment modeling mild stress does not have this adverse effect on memory function, leaving open questions about the degree and duration of increase in plasma cortisol required to produce adverse effects on memory. Plasma cortisol concentrations corresponding to various physical and psychological stressors can be used in studies of this kind to understand the effects of different stress levels—for example, 10–30 μg/dl in minor surgical procedures (Chernow et al., 1987; de Jong, Mallios, Jansen, Scheck, & Lamberts, 1984); 25 μg/dl in the Trier Social Stress Test (Kirschbaum et al., 1993); 30–40 μg/dl in more extended surgeries like nonlaparoscopic cholecystectomy or hysterectomy (Chernow et al., 1987); and 40–55 μg/dl in severe sepsis, multiple trauma, or following major abdominal surgery (Chernow et al., 1987; Naito et al., 1991; Vermes et al., 1995). Finally, it is not clear that elements of memory disturbed by brief increases in cortisol, such as retrieval (de Quervain et al., 2000), are the same elements of memory function that are decreased during

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subchronic cortisol elevations, which can more closely resemble a variety of clinically relevant stressful conditions faced by humans. Future studies will need to carefully assess the same measures of memory function across different experimental conditions to clarify these issues.

Memory and Brain Development

Investigators have become concerned that children, particularly preschool-aged children, may be vulnerable to adverse consequences of increased GC secretion resulting from stress. This concern derives in part from the rapid neural development that takes place during this period. Preschool-aged brains are presumed to experience changes in neuronal number, synaptic surface area, rate of synaptogenesis, extent of dendritic arborization, and overall level of neural activity, including changes in medial temporal lobe and hippocampus (Chugani, 1998; Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Nelson, 1994). A preexplicit, or predeclarative, memory exists in infants as young as 2 months, requiring the hippocampal formation (Nelson, 1997; Nelson & Xu, 1995). This early memory system is suggested by increased temporal activity during recognition memory tasks in infants (e.g., preference for novelty; Nelson, 1994). Nelson and colleagues have suggested that adultlike declarative memory emerges around 1 year and long-term storage around 2 years of age, with both functions presumably related to ongoing medial temporal lobe development.

The declarative memory system matures throughout the preschool years (Gathercole, 1998; Luciana & Nelson, 1998). Although preschool children are limited by immature memory strategies, their rapid acquisition of cognitive concepts and vocabulary provides evidence for functional, and in some respects advanced, declarative memory abilities. Early hippocampal damage can result in long-lasting episodic memory impairments (Gadian, Aicardi, Wakins, Porter, Mishkin, & Vargha–Khadem, 2000; Vargha–Khadem, Gadian, Watkins, Connelly, Van Paesschen, & Mishkin, 1997). However, humans and primates with early medial temporal lobe lesions and atrophied hippocampi can also demonstrate spared factual memory, suggesting that early neural reorganization or other changes can potentially spare elements of memory function (Bachevalier & Mishkin, 1984; Gadian et al., 2000; Nelson, 1998; Vargha–Khadem et al., 1997; Webster, Ungerleider, & Bachevalier, 1991). Critical windows for early memory development may give rise to opportunities for compensatory changes in memory systems, while also reflecting periods of vulnerability where adverse events can have potentially long-lasting consequences for learning and memory (Nelson & Carver, 1998).

GC Effects on Brain Development Versus Brain Morphology in Adulthood

While mild early stress can be protective against subsequent adverse stress effects, severe stress can negatively influence hippocampal development (Pham, Soderstrom, Henriksson, & Mohammed, 1997; Tanapat, Galea, & Gould, 1998; Vallee, MacCari, Dellu, Simon, Le Moal, & Mayo, 1999). In rat pups, increased GC secretion during exposure to predator odor can inhibit new granule cell differentiation and growth in dentate gyrus (Tanapat et al., 1998). Prenatal stress in rodents can accelerate later age-related HPA axis dysfunction, while certain forms of postnatal stress can reduce age-related changes in neuroendocrine and cognitive function (Vallee et al., 1999). Increased GC secretion during a critical period for the development of the visual system in the cat can inhibit developmental changes in neurons in ocular dominance columns (Daw, Sato, Fox, Carmichael, & Gingerich, 1991). Investigators have hypothesized that GC-induced inhibition of cerebral glucose transport (de Leon et al., 1997; Horner et al., 1990) may negatively influence neuronal development during the preschool period, based on evidence for peak levels of brain glucose and oxygen use during this period of development (Chugani, 1998). Increased GC exposure during development might impact neuronal development in hippo-

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campus and other brain regions, resulting in decreases in adult memory function.

In adults, the hypothesis that earlier stressful events in adulthood could result in lasting changes in hippocampal morphology has been supported by neuroimaging studies of individuals with post-traumatic stress disorder (PTSD; Bremner, Randall, Scott, Bronen, Seibyl, Southwick, Delaney, McCarthy, Charney, & Innis, 1995) and depression (Sheline, Sanghavi, Mintun, & Gado, 1999). These hypotheses were first suggested by evidence that GCs can increase neuronal vulnerability to a variety of possible neurotoxic insults and that prolonged and severe increases in GC levels can produce pronounced neuronal loss, mainly in hippocampal CA3 pyramidal cells, in rats and monkeys. However, recent postmortem studies of chronically cortisol-treated aged nonhuman primates did not detect decreases in hippocampal neuronal counts (Leverenz, Wilkinson, Wamble, Corbin, Grabber, Raskind, & Peskind, 1999), and studies of hippocampal apoptosis in the brains of depressed, as well as GC-treated, patients have detected only minimal levels of GC-associated apoptotic changes in hippocampus overall, with no changes in CA3 (Lucassen, Muller, Holsboer, Bauer, Holtrop, Wouda, Hoogendijk, de Kloet, & Swaab, 2001).

Childhood Conditions Associated With Increased GC Secretion and Possible Memory Effects

Evidence that early stress, including psychological stress, can result in increased HPA axis activity suggests the potential for early GC effects on memory and learning. In rat pups and infant nonhuman primates, maternal separation or neglect increases CRF and GC secretion, GC receptor density, and HPA axis response to acute stress, and reduces negative feedback sensitivity (Coplan, Andrews, Rosenblum, Owens, Friedman, Gorman, & Nemeroff, 1996; Meaney, Aitken, Bodnoff, Iny, Tatarewicz, & Sapolsky, 1985; Pihoker, Owens, Kuhn, Schanberg, & Nemeroff, 1993; Plotsky, Otto, & Sapolsky, 1986; Viau, Sharma, Plotsky, & Meaney, 1993). Infants with disorganized attachment, young children reared in orphanages, and maltreated preschoolers with insecure attachment and fearful temperament demonstrate elevated salivary cortisol levels and increased stress responses (Carlson & Earls, 1997; Hart, Gunner, & Cicchetti, 1995; Hertsgaard, Gunnar, Erickson, & Nachmias, 1995). Inconsistent evidence suggests that depressed children have increased cortisol secretion (Birmaher, Dahl, Perel, Williamson, Nelson, Stull, Kaufman, Waterman, Rao, Nguyen, Puig–Antich, & Ryan, 1996; Dahl, Ryan, Puig–Antich, Nguyen, al-Shabbout, Meyer, & Perel, 1991; Puig–Antich, Goetz, Hanlon, Davies, Thompson, Chambers, Tabrizi, & Weitzman, 1982). Major depressive disorder is associated with disturbances in memory in both children and adults (Elliott, Sahakian, McKay, Herrod, Robbins, & Paykel, 1996; Ghaziuddin, King, Naylor, Ghaziuddin, Chaudhary, Giordani, Dequardo, Tandon, & Greden, 1996; Ilsley, Moffoot, & O'Carroll, 1995; Tramontana & Hooper, 1989). In adults with depression, increased cortisol secretion is a predictor of poor functional outcome (Rothschild, Samson, Bond, Luciana, Schildkraut, & Schatzberg, 1993). The stress response may also be related to temperamental characteristics or cognitive perception (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992). Increased cortisol secretion has been associated with extreme variations of temperament such as significant fear of novelty, heightened distress in response to limitations, a low threshold for emotional reactivity, and profound anxiousness or inhibition (Granger, Stansbury, & Henker, 1994; Gunnar et al., 1992; Nachmius, Gunnar, Mengelsdorf, Parritz, & Buss, 1998). However, no set of temperamental characteristics is consistently associated with increased cortisol reactivity. In addition, Gunnar, Tout, de Haan, Pierce, and Stansbury (1997) found that cortisol reactivity may not be stable over repeated assessments. While it may be hard to predict who is at greatest risk for early increases in GC secretion, the potential cognitive effects of increased cortisol levels suggest the importance of further studies in this area.

Children with early and severe negative experiences may have increased cortisol exposure and decreased memory function (Carl-

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son & Earls, 1997; Hart et al., 1995; Hertsgaard et al., 1995). Prenatal exposure to dexamethsone is reported to result in no detectable changes in cognitive function in children ages 6 months to 5.5 years, although less specific cognitive measures were utilized, potentially missing specific effects on memory function (Trautman, Meyer–Bahlburg, Postelnek, & New, 1995). Investigators have reported that memory performance in infancy is negatively correlated with basal circulating cortisol (Gunnar & Nelson, 1994). In older asthmatic children, higher dose prednisone treatment was associated with lower memory performance, as compared to lower doses, suggesting a negative effect of increased GCs on memory in childhood (Bender et al., 1991).

In preschool aged children, Heffelfinger et al. (submitted) found that greater increases in salivary cortisol in response to mild psychological stress are associated with lower pre- and poststress declarative memory function. In this study, preschoolers were divided into groups of stress "responders" and "nonresponders" based on previous studies of cognitive function and high-intensity exercise (Deuster, Petrides, Singh, Chrousos, & Poth, 2000; Kirschbaum et al., 1996; Lupien et al., 1997).

The cortisol responder group had significantly lower immediate recall in both the pre- and poststress paragraphs. The differences between the groups for delayed recall did not reach significance but maintained moderate effect sizes between groups. Both pre- and poststress recall conditions were strongly correlated with the poststress cortisol levels, suggesting a possible chronic effect of stress on memory in some children. One possible interpretation is that the cortisol responder group had experienced repeated exposure over time to higher cortisol levels, which had already affected the memory and learning systems of these children. Supporting this interpretation, the cortisol responsive group had significantly lower scores on a measure of verbal factual knowledge than the cortisol nonresponsive group, although scores for both responders and nonresponders were still in the average range. These findings suggest that increased cortisol levels may be associated with changes in memory function, and this association may not be restricted to disease states.

GC Effects and Aging

The literature concerning GCs and aging addresses at least three issues of relevance to memory function: (a) GC-induced cell death, (b) age-related changes in Type II GC receptors, and (c) age-related changes in circulating cortisol levels and other aspects of HPA axis function. First, GCs can adversely impact hippocampal neuronal survival, in part via Type II receptor signaling (Reagan & McEwen, 1997). Stress or high-dose GC treatment can increase kainate-induced pyramidal cell death in vivo (Stein–Behrens, Elliott, Miller, Schilling, Newcombe, & Sapolsky, 1992) or cell death induced by glutamate or metabolic challenge in vitro (Elliott, Mattson, Vanderklish, Lynch, Chang, & Sapolsky, 1993; Tombaugh, Yang, Swanson, & Sapolsky, 1992). Hippocampal GC Type II receptors play an important role in negative feedback inhibition of the HPA axis (Jacobson & Sapolsky, 1991), so that receptor down-regulation could lead to GC hypersecretion. Hippocampal GC receptors might be down-regulated by excess GC exposure during chronic stress, high-dose GC treatment, and age-related GC hypersecretion (Herman et al., 1995; Makino, Smith, & Gold, 1995; Sapolsky, Krey, & McEwen, 1984; Sapolsky & McEwen, 1985). Aging has been reported to specifically decrease Type II receptors (Bhatnagar, Cintra, Chadi, Lindberg, Oitzl, de Kloet, Moller, Agnati, & Fuxe, 1997). These and other reports have led to the hypothesis that age-related increases in circulating GC levels could contribute to memory impairment and hippocampal cell loss via Type II receptor effects (Brady et al., 1991; Landfield & Eldridge, 1991; Sapolsky et al., 1986). However, age-related changes in Type II receptors may be complex, with evidence for up-regulation or no change in Type II mRNA under certain conditions (Reagan & McEwen, 1997; Seckl et al., 1993; Wetzel et al., 1995). If aging does decrease Type II receptor density, then one might hypothesize potential decreases in GC-induced effects that

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are mediated by Type II receptors, protecting the brain against the potential adverse effects of any increases in GC secretion that accompany aging.

It remains somewhat controversial whether physiological GC elevations associated with aging, versus high-dose supraphysiological GC treatment, could lead to age-related decreases in human hippocampal neuronal survival. Several important effects that can change neuronal survival appear to require Type II receptor-mediated changes in gene expression, including decreases in Type II receptor expression leading to feedback insensitivity and increased GC levels (Brady et al., 1991; Landfield & Eldridge, 1991; Reagan & McEwen, 1997; Sapolsky et al., 1986). Complex age-related changes in HPA activity in animals include increased ACTH response to CRF as well as feedback insensitivity (Hatzinger, Reul, Landgraf, Holsboer, & Neumann, 1996), with a majority but not all studies indicating decreases in brain Type II GC receptors (Reagan & McEwen, 1997; Reul, Rothuizen, & de Kloet, 1991). While prolonged exposure to high GC levels may produce changes in Type II receptor gene regulation, moderate stress or moderate-dose GC treatment lasting from 3 to as long as 30 days and more closely resembling most physiological stress do not produce such changes (Herman & Spencer, 1998). In addition, unlike the highly studied rodent hippocampus, primate brain may have a relatively low density of hippocampal Type II receptors in comparison to regions such as neocortex (Sanchez et al., 2000). These results suggest that GC receptor changes and increased hippocampal cell death associated with chronic, high-dose GC treatment or severe stress in the rodent may not be readily extrapolated to primates and to milder increases in GC secretion such as human aging. Consistent with this, investigators recently reported that chronic cortisol treatment in aged nonhuman primates did not decrease hippocampal neuronal counts (Leverenz et al., 1999). It remains unclear whether human aging is associated with decreased Type II receptor expression, changes in neuronal survival, and decreases in potential cortisol effects on memory function, or, alternatively, whether healthy older humans have preserved Type II GC receptors and continued vulnerability to GC-induced memory impairments.

In general, studies in healthy humans suggest that basal plasma cortisol levels do not increase with age (Colucci, D'Alessandro, Bellastella, & Montalbetti, 1975; Friedman, Green, & Sharland, 1969; Jensen & Blichert–Toft, 1971; Jensen, Sanders, Frolund, & Hjortrup, 1988; Lakatua, Nicolau, Bogdan, Petrescu, Sackett–Lundeen, Irvine, & Haus, 1984; Linkowski, Mendlewicz, Leclercq, Brasseur, Hubain, Golstein, Copinschi, & Van Cauter, 1985; Pavlov, Harman, Chrousos, Loriaux, & Blackman, 1986; Sharma, Palacios–Bois, Schwartz, Iskandar, Thakur, Quirion, & Nair, 1989; Sherman, Wysham, & Pfohl, 1985; Waltman, Blackman, Chrousos, Riemann, & Harman, 1991; Weitzman, Fukushima, Nogeire, Roffwarg, Gallagher, & Hellman, 1971; West, Brown, Simon, Carter, Kumagai, & Englert, 1961; Zumoff, Fukushima, Weitzman, Kream, & Hellman, 1974). However, human aging has also been associated with complex HPA axis changes characterized by increased responsivity to central stimulation and reduced responsiveness to feedback inhibition at or above the level of the anterior pituitary (e.g., hypothalamus, hippocampus). Investigators have found blunted and delayed suppression of plasma ACTH by cortisol in older healthy subjects (Boscaro, Paoletta, Scarpa, Barzon, Fusaro, Fallo, & Sonino, 1998; Wilkinson, Peskind, & Raskind, 1997), sometimes greater in older women than in men, as well as blunting of ACTH increases following metyrapone challenges (Wilkinson et al., 1997). Increased HPA axis response to a physostigmine challenge and increased cortisol secretion in response to a CRH challenge, representing increased sensitivity to HPA axis stimulation at CNS sites, as well as variably reported insensitivity to DEX feedback, have also been found in older subjects (females more often than males in some reports; Raskind, Peskind, & Wilkinson, 1994). These studies suggest that, as in the rodent, aging may be associated with decreased negative feedback above the level of the anterior pituitary. This is consistent with the decrease in hippocampal Type II receptors reported in rodents and suggests potential age-

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related reductions in Type II receptor-mediated GC effects on memory substrates.

GC Effects on Memory During Aging

Comparing aged rodents with cognitive impairment to those without impairment and to young control animals, the cognitively impaired older animals demonstrate significantly increased plasma corticosterone levels, as well as hippocampal pyramidal neuron loss, as compared to older unimpaired and younger animals (Issa et al., 1990). Long-term exposure to increased corticosterone levels has also been reported to decrease spatial learning in middle-aged, but not young, rats, in the absence of any hippocampal neuron loss (Bodnoff et al., 1995). Complex interactions between aging and GC effects on memory and learning have been described in rats (Hebda–Bauer, Morano, & Therrien, 1999). Noted above, associations between circulating cortisol levels and human memory function have been reported in various disease conditions. While healthy humans generally do not have age-related increases in basal plasma cortisol levels, increases in basal cortisol levels can be found in aged humans with dementia (Davis, Davis, Greenwald, Mohs, Mathe, Johns, & Horvath, 1986; de Leon, McRae, Tsai, George, Marcus, Freedman, Wolf, & McEwen, 1988; Dodt, Dittmann, Hruby, Spath–Schwalbe, Born, Schuttler, & Fehm, 1991). These studies in humans suggest a relationship between GC secretion and cognitive impairment that is analogous to results by Issa et al. (1990) in rodents. In addition, complex age-related increases in HPA axis function may produce individual variations in cortisol levels in healthy older adults that could potentially be related to memory function. Healthy elderly subjects have lower declarative memory performance following acute psychological stress (public speaking), and larger increases in salivary cortisol following stress were associated with lower declarative memory scores (Lupien, Gaudreau, Tchiteya, Maheu, Sharma, Nair, Hauger, McEwen, & Meaney, 1997).

Important studies have detected poorer cognitive, in particular memory, function in individuals with rising, versus falling, cortisol levels over 1.9 to 5-year follow-up periods (Kalmijn, Launer, Stolk, de Jong, Pols, Hofman, Breteler, & Lamberts, 1998; Lupien et al., 1994; Seeman et al., 1997). A recent report suggested that such memory impairments may be associated with decreased hippocampal volumes (Lupien, de Leon, de Santi, Convit, Tarshish, Nair, Thakur, McEwen, Hauger, & Meaney, 1998), again analogous to results by Issa et al. (1990) in rodents. Notably, one of these reports (Seeman et al., 1997), using subjects from the MacArthur Study of Successful Aging, demonstrated the association between rising cortisol levels and declining memory function only in female subjects, again highlighting possible gender differences. This study also noted improvements in memory over time in female subjects with declining cortisol levels. Decreases in memory impairment with decreasing cortisol levels are not consistently reported, leaving open the possibility that decreased memory function in the human studies could be related to hippocampal neuronal loss. Alternatively, decreases in hippocampal volumes, reported by Lupien et al. (1998), could represent reversible changes in neuronal counts given recent evidence for stress-regulated neurogenesis (Gould et al., 1998).

Notably, older nondemented healthy adults may be less sensitive, rather than more sensitive, than younger adults to GC-induced memory decreases (Newcomer et al., 1995), consistent with evidence for an age-related reduction in GC receptor density. In addition, existing studies of cortisol effects in younger adults, reviewed above, suggest that robust rather than trivial increases in cortisol levels are required to decrease memory function. Additional studies will be required to confirm that the reported association between small increases in cortisol levels and memory function in older humans is in fact due to a causal effect of cortisol on memory. The apparent association may be related to other factors (e.g., age-related decreases in hippocampal integrity may reduce memory function and increase cortisol levels via decreased negative feedback), rather than to a direct effect of GCs on a memory substrate such as neuronal excitability.

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Future Directions: Clinical Significance, Treatment and Prevention

While previous studies demonstrate that increased cortisol exposure at levels associated with major stress can significantly decrease memory performance (Newcomer et al., 1999), it is not known precisely what level of cortisol secretion (e.g., levels associated with mild or moderate stress) begins to produce adverse effects on human memory functions. GC effects in children and the elderly may present special cases, potentially associated with altered vulnerability to adverse GC effects. Several factors contribute to the significance of research in this area. First is the observation that mild to moderate stress is exceedingly common in the human population. Second, scientific and public interest in the effects of stress on health and memory has increased, particularly over the last decade (Adler, 1999; Bartlett & Coles, 1998a, 1998b; Knight, 1999; Levi, 1990; Schwartz, Friedman, Tucker, Tomlinson–Keasey, Wingard, & Criqui, 1995; Stronks, van de Mheen, Looman, & Mackenbach, 1998; Villiger, 1999). Third, there is a growing recognition of the public health implications of GC effects on memory (Bremner & Narayan, 1998). Cortisol effects on memory and learning can be clinically significant, based on effect sizes observed in studies reviewed above, with a potential impact on performance in many stressful situations where optimal performance would be required to achieve personal, public, or economic goals. Long-range scientific, education, industry, and public health goals concerning the development of treatments to block adverse GC effects are dependent on identifying adverse levels of cortisol exposure for various age groups.

A number of possible treatment approaches to prevent or remediate adverse GC-induced effects have recently been under development. Some of these may be more relevant to the prevention of potential age-related GC-induced memory impairments than others. Investigators have reported that the antidepressant amitriptyline can increase spatial memory function in young but not older rodents (Yau, Olsson, Morris, Meaney, & Seckl, 1995), and 5-HT reuptake enhancement, but not reuptake inhibition, can prevent another model of stress-induced memory impairment (McEwen et al., 1997). A more direct approach to blocking the adverse effect of GCs is through the ongoing development of a number of Type I and Type II GC receptor antagonists, although the success of Type II receptor antagonists (e.g., mifepristone) is currently limited by unwanted side-effects (Sutanto & de Kloet, 1995). A very promising approach to the prevention of adverse GC effects targets voltage-activated calcium influx, which has been associated with decreases in neuronal activity and neuronal endangerment. Investigators have recently reported that the L-type calcium channel blocker nimodipine fully blocked GC-induced morphological changes in hippocampal pyramidal cells (Dachir, Kadar, Robinzon, & Levy, 1997), suggesting a promising strategy to prevent GC-induced changes implicated in hippocampal aging. In general, the use of safe and effective agents for blocking adverse GC effects on hippocampal functions including memory may offer benefits to individuals suffering acute and subchronic stressors and could prevent changes in hippocampal function relevant to stress, aging, and neuropsychiatric diseases. In addition, results from this field suggest the importance of early identification and intervention with preschool children at risk for chronic stress and stress-related disease states.

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