



**Mental Capital and Wellbeing:
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-E20
Effect of Chronic Stress on Cognitive Function through Life**

Professor Oliver T.Wolf, Ph.D.
Cognitive Psychology, Ruhr University Bochum, Germany

Claudia Buss, Ph.D.
Department of Psychiatry and Human Behavior
University of California, Irvine, US

*This review has been commissioned as part of the UK Government's Foresight Project,
Mental Capital and Wellbeing. The views expressed do not represent the policy of
any Government or organisation.*

Summary

This review describes how chronic stress affects cognitive functioning over the lifespan. The focus is on the causal role of stress hormones, especially glucocorticoids. These neuroendocrine mediators influence the structure and the function of the human brain. A lifespan approach is taken, beginning with fetal life when the brain rapidly develops and is especially vulnerable to insults, and continuing throughout adult life into old age when some of the consequences of stress-associated wear and tear over the life course become most apparent. The review furthermore provides a selective overview of cognitive alterations of psychiatric disorders associated with dysregulations of stress hormone secretion. Our advanced understanding of the effects of stress hormone action in the brain allows more targeted interventions aimed at supporting resilience.

1. Definition of stress

A common definition says that stress occurs when a person perceives a challenge to his or her internal or external balance (homeostasis) (De Kloet et al., 2005; McEwen, 1998). Thus, a discrepancy between what 'should be' and 'what is' leads to stress (Ursin and Eriksen, 2004). A stressor can be physical (e.g. heat, hunger) or psychological (e.g. work overload, neighbourhood violence). In addition, it can be acute or chronic. The subjective evaluation of the stressor and of available coping resources determines its impact on the individual (Lazarus, 1993; Mason, 1968). What is a threat for one person might be an exciting challenge for another. Thus, there is a substantial inter-individual variability in vulnerability to stress. As further outlined below, genetic susceptibilities, in combination with early adversity, render an individual more vulnerable in adulthood (De Kloet et al., 2007).

2. The two stress systems: HPA and SNS

Stress leads to neuroendocrine responses aimed at facilitating adaptation. Here, the hypothalamus pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS) are most important. SNS activity leads to rapid release of (nor)epinephrine from the adrenal medulla, which constitutes the first response wave. Activity of the HPA axis leads to the release of glucocorticoids (GCs; cortisol in humans, corticosterone in most rodents) from the adrenal cortex (De Kloet et al., 2005). This response is slower and constitutes the second response wave (De Kloet et al., 2005; Herbert et al., 2006).

GCs are lipophilic hormones that can enter the brain where they influence regions involved in cognitive functions (e.g. amygdala, hippocampus and prefrontal cortex). These effects are mediated through the two receptors for the hormone: the mineralocorticoid receptor (MR), and the glucocorticoid receptor (GR), which differ in their affinity for GCs and in their localisation. While MR activation leads to enhanced neuronal excitability, GR activation causes a delayed suppression or normalisation of the neuronal network (De Kloet et al., 2005; Herbert et al., 2006). Both receptors lead to an altered expression of responsive genes. For example, in the hippocampus alone MR or GR activation led to altered expression of more than 70 genes (De Kloet et al., 2005). In addition, GCs can exert rapid, non-genomic effects which, in part, are mediated by membrane bound MRs (De Kloet et al., 2007).

The acute HPA stress response helps an organism to cope with a stressor. Rising levels of GCs acutely enhance long-term memory consolidation, but at the same time delayed retrieval as well as working (short-term) memory capacity are reduced (Roosendaal et al., 2006; Wolf, 2006). Chronic stress, in contrast, has mostly a negative impact on the brain (e.g. on the hippocampus and prefrontal regions) and on cognition (De Kloet et al., 1998; Herbert et al., 2006; McEwen, 1998; Belanoff et al., 2001a).

After acute stress, the negative feedback of the HPA axis leads to a return of the GC levels to baseline values within hours (De Kloet et al., 2005; Dickerson and Kemeny, 2004). In situations of chronic stress, though, permanent alterations of the HPA axis can occur. However, elevated cortisol levels do not always result from chronic stress exposure. Alternative scenarios can take place as well. For example, normal mean 24-hour cortisol levels but a disturbed circadian rhythm can be found (McEwen, 1998). Even more striking, reduced cortisol levels occur in several stress-associated somatoform disorders (Fries et al., 2005; McEwen, 1998).

3. Early life stress and cognitive functioning

Development is viewed not as a gradual elaboration of an architectural plan pre-configured in our genes, but rather a dynamic interdependency of genes and environment, characterised by a continuous process of interactions in a place- and time-specific dependent manner (Wadhwa, 2005). This implies that, within genetic constraints, each developing organism plays an active role in its own construction. This developmental plasticity permits a range of phenotypes to develop from a single genotype in response to environmental cues (Gluckman and Hanson, 2004).

Note that developmental responses to environmental stimuli are not always adaptive but can also be disruptive. Overexposure to glucocorticoids in the context of chronic stress during critical periods of brain development is associated with impaired cognitive development potentially resulting from impaired brain maturation. As a consequence, such pathological changes have important implications for future cognitive functioning, since they render the individual more vulnerable to future adversity (De Kloet et al., 2007).

3.1. Prenatal stress effects on cognitive development

Studies in rodents and non-human primates support an association between prenatal stress exposure and impaired postnatal cognitive performance (e.g. Lemaire et al., 2006; Szuran et al., 1994; Vallee et al., 1999) and suggest underlying functional mechanisms to explain this association. For example, in rodents, learning induced neurogenesis in response to a spatial memory task was blocked in prenatally stressed animals, impairing cognitive performance (Lemaire et al., 2000). Furthermore, prenatal stress has the potential to alter synaptic plasticity by impairing long-term potentiation but facilitating long-term depression (Yang et al., 2007; Yaka et al., 2007). In non-human primates, daily acute prenatal stress is associated with 10-12% reductions in hippocampal volume and inhibition of neurogenesis in the dentate gyrus (Coe et al., 2003). Increased intrauterine cortisol exposure in the context of maternal prenatal stress seems to account for a great proportion of these characteristic aberrations (Barbazanges et al., 1996). While prenatal exposure to stress hormones leads to atrophy of the hippocampus, significantly expanded dimensions of the amygdale have been reported in prenatally stressed offspring, due, in part, to the presence of more neurons and glia (Salm et al., 2004).

In humans, too, learning and memory abilities are believed to be affected by the quality of the intrauterine environment in which the fetus develops. These associations already become apparent very early in development, as elevated levels of placental Corticotropin Releasing Hormone (CRH) concentrations during the last trimester of gestation, potentially reflecting high levels of maternal stress (Sandman et al., 1997), are associated with impaired fetal learning (Sandman et al., 1999). A small but growing literature indicates that the consequences of prenatal maternal stress persist into the postpartum period (e.g. Luoma et al., 2004; O'Connor et al., 2002; Van den Bergh et al., 2008). Several recent prospective studies demonstrate that prenatal stress is associated with cognitive development. Prenatal-specific anxiety, for example, is associated with lower mental and motor development scores at eight months of age (Buitelaar et al., 2003).

As maternal stress during pregnancy is a risk factor for premature birth (Wadhwa, 2005), it is of interest to review the association between poor birth outcomes and cognitive performance. Very low birth weight children perform poorer in academic achievement tests (Finnstrom et al., 2003). In another prospective study, low birth weight was found to be related to lower scores on tests measuring language, spatial, fine motor, tactile, and attention abilities (Breslau et al., 1996). In line with these results, intelligence test scores at age 17 years were shown to increase with increasing birth weight (Seidman et al., 1992). Furthermore, intrauterine growth restriction (IUGR) has been found to be associated with a greater risk of neurodevelopmental impairment (McCarton et al., 1996) and impaired spatial navigation (Leitner et al., 2005).

3.2. Postnatal stress effects on cognitive development

In animal models, early maternal separation is associated with cognitive impairment (e.g. Huot et al., 2002b), whereas the offspring of mothers exhibiting higher quality of maternal care show superior cognitive performance (e.g. Fenoglio et al., 2005). Animal studies suggest that postnatal adversity contributes to the risk for cognitive impairments through direct effects on the development of neural structures such as the hippocampus. The offspring of mothers showing high levels of pup licking and grooming and arched-back nursing have increased expression of NMDA receptor subunit and brain-derived neurotrophic factor (BDNF) mRNA, increased cholinergic innervation of the hippocampus, and enhanced spatial learning and memory (Liu et al., 2000). In contrast, maternal separation results in elevated levels of glucocorticoids which down-regulate the expression of neurotrophic factors and impair hippocampal development (Huot et al., 2002a; Roceri et al., 2002).

In humans, adverse experience in the postnatal period is associated with cognitive impairment. Individuals with a history of childhood sexual abuse, for example, present with neuropsychological deficiencies (Bremner et al., 2004; Navalta et al., 2006), as well as smaller hippocampal volumes (Vythilingam et al., 2002). Also, other adverse childhood circumstances such as, for example, those resulting from low socioeconomic status, are related to impaired cognitive and academic attainment (Bradley and Corwyn, 2002; Richards and Wadsworth, 2004).

3.3. Modulation of prenatal stress effects

Rodent studies provide evidence of postnatal compensation for prenatal adversity. For example, the positive effects of postnatal handling are consistently greater in prenatally-stressed than control animals (Smythe et al., 1996). Furthermore, postnatal handling or increased maternal care can actually reverse the effects of prenatal stress or glucocorticoid administration on spatial memory performance, HPA stress response and hippocampal GR expression (Brabham et al., 2000). And intriguingly, postnatal handling has recently been shown to prevent the prenatal stress-induced deficits in hippocampal neurogenesis (Lemaire et al., 2006).

Importantly, individuals who are more vulnerable by virtue of stress exposure in fetal life may actually be more susceptible to the effects of postnatal conditions. In support of this hypothesis, it was recently shown in humans that low quality of parental care was only associated with smaller hippocampal volumes in young adults born small for gestational age, but not in those born appropriately for their gestational age (Buss et al., 2007). As a further example (Landry et al., 1997), certain parenting styles promote faster rates of cognitive-language and social development – an effect that is extremely pronounced in children with very low birth weight.

3.4. Long-term consequences of early-life stress

Several studies support the notion of early stress exposure being associated with accelerated neurodegenerative processes and early onset of memory decline in the course of ageing (Meaney et al., 1991; Vallee et al., 1999; Brunson et al., 2005). Permanent neurodevelopmental impairment in association with early stress exposure may be a factor explaining such cognitive disadvantage at an older age. Early programmed changes in stress susceptibility might account for such deficits. There is evidence for pre- and postnatal stress exposure being associated with chronically increased reactivity of the HPA axis, potentially resulting from reduced expression of central glucocorticoid receptors (Meaney, 2001; Welberg and Seckl, 2001). Animal models show increased corticosterone concentrations and lower GR density in the hippocampus in the offspring of prenatally stressed mothers (Henry et al., 1994; Barbazanges et al., 1996). Also, postnatal maternal separation and lower quality of maternal care have been associated with reduced GR gene expression in the hippocampus (Meaney and Aitken, 1985; Meaney et al., 1985) which, in turn, is associated with reduced feedback sensitivity of the HPA axis. Recently, a mechanism has been discovered in rodents that explains how environmental stimuli can impact on gene expression. Permanent alterations of GR gene expression result from methylation/demethylation of specific GR promoters, which is associated with variations in maternal care (Weaver et al., 2004). More specifically, DNA methylation of the GR promoter I₇ prevents gene expression, resulting in reduced density of the GR protein in the hippocampus.

Whether the *human* GR gene is also subject to early-life programming remains to be determined, but elevated cortisol concentrations have, for example, been reported in association with reduced birth weight (Phillips et al., 1998) in humans. Moreover, associations between changes in GR gene expression and specific pathologies have also been shown in humans. For example, in patients with the metabolic syndrome which is associated with impaired intrauterine growth, muscle GR mRNA levels correlate with blood pressure and insulin resistance (Reynolds et al., 2002; Whorwood et al., 2002).

As we continue to describe the consequences of chronic stress exposure throughout life on cognitive functioning, it will become apparent that individuals with increased stress susceptibility (reflecting genetic susceptibilities and/or early adversity) are especially vulnerable to stress-induced cognitive impairments in adulthood and ageing.

4. Chronic stress during adulthood: effects on cognition

Animal research provides insights into the structural alterations caused by chronic stress (McEwen, 2002). One main finding is that the integrity of the hippocampus is impaired while, in parallel, the amygdala (the 'fear centre' of the brain) becomes hyperactive. In the hippocampus chronic stress leads to a retraction of dendrites-dendritic atrophy (Herbert et al., 2006; McEwen, 2003), and similar effects occur in the medial PFC (Radley and Morrison, 2005). This atrophy is reversible after stress termination, pinpointing to substantial neuroplasticity (McEwen, 2003; Radley et al., 2005). In addition, stress leads to reduced neurogenesis in the dentate gyrus and the mPFC (Czeh et al., 2007; Joels et al., 2004; Gould et al., 2000; Herbert et al., 2006; McEwen, 2003). Even though the function of these newborn neurons is disputed, impairment of memory and learning resulting from reduced neurogenesis is likely (Gould et al., 2000; Leuner et al., 2006). At the behavioural level, impaired performance in hippocampal-dependent spatial memory tasks (Bodnoff et al., 1995; Conrad et al., 1996; Herbert et al., 2006) and impaired PFC-dependent set shifting capabilities (Liston et al., 2006) can be observed.

In contrast to the hippocampus and the PFC, the amygdala becomes hypertrophic in conditions of chronic stress (McEwen, 2003; Radley and Morrison, 2005; Sapolsky, 2003). Increases in dendritic arborisation (Vyas et al., 2002) and spine density (Mittra et al., 2005) take place. Moreover activity of the CRF system in the

amygdala, which is involved in anxiety (Landgraf, 2005; Mitchell, 1998), is enhanced (Schulkin et al., 1998). Chronically stressed animals show enhanced fear conditioning (Conrad et al., 1999).

Thus, the balance between brain regions involved in cognition is altered by chronic stress. While 'analytic' cognitive functions mediated by the hippocampus and PFC are impaired, 'affective' fear-related amygdala functioning is enhanced.

In humans, exposure to chronic stress (e.g. shift workers, airplane personnel, soldiers) is associated with cognitive deficits in several domains such as working memory and declarative memory (Cho et al., 2000; Cho, 2001; Morgan et al., 2006). These observed cognitive deficits can in part be explained by GC overexposure in the presence of chronic stress, which is supported by studies administering GCs for days to weeks, resulting in cognitive impairments (Newcomer et al., 1999; Schmidt et al., 1999; Young et al., 1999). Further evidence comes from studies with patients receiving GC therapy (Keenan et al., 1996; Roozendaal and de Quervain, 2005; Wolkowitz et al., 1997; Wolkowitz et al., 2004). Whether the negative effects on memory reflect acute or chronic effects is sometimes hard to disentangle (Keenan et al., 1996; Roozendaal and de Quervain, 2005; Wolkowitz et al., 1997; Wolkowitz et al., 2004). Data from patients with Cushing's disease point in the same direction. Cognitive impairments (Whelan et al., 1980) and hippocampal volume reductions (Starkman et al., 1992) have been reported. Hippocampal atrophy might be reversible once successful treatment has occurred (Bourdeau et al., 2002; Starkman et al., 1999). This would be in line with the remaining plasticity of this structure observed in animal studies.

4.1. Stress-associated psychiatric disorders

Depression

Chronic stress or negative life events are major risk factors for several psychiatric disorders (Caspi et al., 2003; Wurtman, 2005; Heim and Nemeroff, 1999). The three hit model proposes that genetic susceptibility (e.g. two short alleles of the serotonin transporter gene) combined with adverse early- (pre- or postnatal) life influences shape the stress response in adulthood and create a vulnerable phenotype (De Kloet et al., 2007). In line with these concepts is the evidence that a substantial portion of patients with major depression show HPA hyperactivity (Holsboer, 2000; Nemeroff, 1996), which might be characteristic for subgroups like melancholic (Gold and Chrousos, 2002) or psychotic depression (Belanoff et al., 2001b). Interestingly, a few studies have reported that the cortisol elevations are associated with cognitive deficits in these patients (Belanoff et al., 2001b; Rubinow et al., 1984), but the results are inconsistent. Hippocampal atrophy has been reported reliably in depressed patients (Campbell et al., 2004; Videbech and Ravnkilde, 2004), but associations with stress hormone levels have been found only infrequently (Axelson et al., 1993; O'Brien et al., 2004; Vythilingam et al., 2004).

In the future, better characterisation and understanding of subtypes of this disorder, as well as more longitudinal studies combining neuroimaging with neuro-endocrinology, should lead to a clearer empirical situation (Gold and Chrousos, 2002).

Post traumatic stress disorder (PTSD)

PTSD is characterised by re-experiencing, avoidance and hyperarousal (American Psychiatric Association, 1994). In contrast to patients with major depression, patients with this disorder show often reduced basal cortisol levels. This probably reflects an enhanced negative feedback of the HPA axis (Yehuda, 2002). Whether these alterations occur in response to the trauma or are a risk factor for developing the disorder is not well understood (Delahanty et al., 2000). Also, hippocampal atrophy has been reported in PTSD (Karl et al., 2006). Again, rather than a consequence of this disorder, smaller hippocampal volumes may be a risk factor for PTSD, potentially resulting from genetic vulnerability (Gilbertson et al., 2002), and/ or from early adverse exposure (see above).

Recent small studies have reported that cortisol treatment might help to prevent (Schelling et al., 2004) or treat PTSD (Aerni et al., 2004). Cortisol-induced impairment in emotional memory retrieval (Wolf, 2006) in combination with an enhanced and more elaborate reconsolidation could reduce symptoms of PTSD. This illustrates that too much, as well as too little, endogenous cortisol can be associated with distinct cognitive disturbances (Aerni et al., 2004; Schelling et al., 2004; Wolf, 2006).

4.2. *Intervention strategies*

In animals, stress-induced dendritic atrophy as well as reduced neurogenesis can be prevented with antidepressants and anticonvulsants (Conrad et al., 1996; Czeh et al., 2001; Magarinos et al., 1996; Magarinos et al., 1999). Also, treatment with a glucocorticoid receptor antagonist is effective in preventing such stress-induced changes in neurophysiology (Mayer et al., 2006). Similarly, memory impairments can be prevented with these drugs (Conrad et al., 1996; Czeh et al., 2001; Magarinos et al., 1996).

In humans, chronic stress without associated psychopathology could be ameliorated by psychological stress intervention strategies. Possible examples are stress inoculation training (Gaab et al., 2003; Meichenbaum, 1985), or mindfulness-based stress reduction training (Carlson et al., 2007). In addition, social support is an effective stress buffering factor (Heinrichs et al., 2003; Kuper et al., 2002).

Pharmacological treatment with a beta blocker can prevent the effects of acute GC elevations on memory retrieval (de Quervain et al., 2007). It remains to be shown whether similar approaches are effective in conditions of chronic stress. In addition, GR antagonists and/or CRF antagonists might be candidate drugs (see below). Moreover, drugs that influence local GC metabolism in the brain could also be effective (Seckl et al., 2002; Seckl and Walker, 2004).

Depression is often associated with HPA hyperactivity (Herbert et al., 2006; Ising et al., 2005). Successful antidepressant treatment leads to a normalised HPA axis (Herbert et al., 2006; Ising et al., 2005). One study observed that treatment with a selective serotonin reuptake inhibitor (SSRI) improved memory performance and reduced cortisol levels (Vythilingam et al., 2004). More direct interventions targeting the HPA axis have been tested in laboratory animals, and clinical trials are on the way. In this context, CRF antagonists as well as GR antagonists appear promising (Berton and Nestler, 2006).

In sum, then, in chronically stressed animals, as well as in human patients suffering from stress-related psychiatric disorders, reinstating appropriate HPA signalling appears to be a promising treatment approach (De Kloet et al., 2007).

5. Chronic stress or rising cortisol levels during ageing: effects on cognition

In older laboratory rodents, an increase in basal corticosterone levels as well as a less efficient negative feedback of the HPA axis can be detected. Studies have reported that enhanced HPA activity is associated with poorer memory in those animals (Issa et al., 1990; Yau et al., 2001).

Increases in basal cortisol levels occur during ageing (Lupien et al., 2005; Van Cauter et al., 1996). In addition, pharmacological or behavioural challenge studies observe an increased HPA response (Otte et al., 2005). Moreover, negative feedback of older subjects is less efficient (Heuser et al., 1994; Wilkinson et al., 1997; Wolf et al., 2002). These alterations might reflect age-associated diseases, stress exposure over the lifespan, genetic vulnerabilities, the long-term consequences of exposure to early-life adversity or a combination of the above (Lupien et al., 2005; McEwen, 2002). In older adults, correlations between elevated or rising cortisol levels and cognitive impairments have been reported (Kalmijn et al., 1998; Karlamangla et al., 2005;

Lupien et al., 1994; MacLulich et al., 2005). The association between rising cortisol levels and atrophy of the hippocampus is not sufficiently understood, and the current empirical situation is heterogeneous (Lupien et al., 1998; Wolf et al., 2002; MacLulich et al., 2005). Similar associations with other GC-sensitive brain regions (e.g. PFC) have received even less attention so far (MacLulich et al., 2006; Wolf et al., 2002).

Evidence for HPA hyperactivity has been observed in patients with Alzheimer's dementia (de Leon et al., 1988; O'Brien et al., 1996). This could just reflect the damage to HPA feedback centres in the brain, but it might also be causally involved in disease progression (Csernansky et al., 2005). Recent work in animals has documented that HPA hyperactivity can influence amyloid metabolism as well as tau phosphorylation (Green et al., 2006; Kang et al., 2007; Rissman et al., 2007). In human patients, treatment with prednisone resulted in an exaggerated memory loss (Aisen et al., 2000). Moreover, a genetic susceptibility to AD could be linked to the gene encoding 11 β -HSD, which influences local GC metabolism (de Quervain et al., 2004). In addition, at the self-report level, evidence exists that enhanced stress susceptibility is associated with a greater dementia risk (Wilson et al., 2005; Wilson et al., 2003).

Another condition associated with HPA hyperactivity is the metabolic syndrome or Type 2 diabetes. There are close links between the stress system and the glucoregulatory system. Several authors have suggested that chronic stress facilitates the occurrence of the metabolic syndrome by influencing visceral fat deposition, impairing insulin sensitivity or by changing eating habits towards unhealthier (comfort) food (Dallman et al., 2003; Rosmond, 2003). Alternatively, the negative impact of glucose intolerance on the brain might lead to HPA hyperactivity and, in turn, elevated cortisol levels (Convit, 2005; Convit et al., 2003).

5.1. *Intervention strategies (during ageing)*

In rodents, behavioural (e.g. neonatal handling) and pharmacological (adrenalectomy with low dose corticosterone replacement) intervention strategies, leading to stable HPA activity throughout life, prevent age-associated cognitive decline (Landfield et al., 1981; Meaney et al., 1988). Similarly, a pharmacological reduction of active GC concentrations in the hippocampus (11 β HSD synthesis inhibition) is efficient in preventing memory impairments in ageing mice (Seckl et al., 2002; Yau et al., 2001).

In humans, a pilot study showed that the 11 β -HSD inhibitor carbenoxolone improved some aspects of memory in older men and in older patients with Type 2 diabetes (Sandeep et al., 2004). Future studies are needed to better investigate possible side-effects of long-term treatment with this drug (Chrousos, 2004). Against the metabolic syndrome, lifestyle modifications are often successful if started early enough (Matthaei et al., 2000). In addition, pharmacological approaches are available (Cohen and Horton, 2007; Matthaei et al., 2000). They should be able to prevent or reduce memory impairment and hippocampal atrophy associated with diabetes and the metabolic syndrome (Convit, 2005; Convit et al., 2003).

6. Looking forward

This review illustrates that chronic stress has a negative impact on cognition throughout life. A lifespan approach in research on stress and cognition emphasises the long-lasting effects of exposure to early-life adversity. Genetic risk factors, in combination with early-life adversity, render an individual more susceptible to stress and stress-associated diseases in later life.

Thus, by reducing early adversity one is able to support the development of a more resilient phenotype which will be less susceptible to stress-associated cognitive disturbances in later life.

Importantly, a previously unappreciated amount of neuroplasticity remains in adulthood, allowing an optimistic view of the potential to successfully treat stress-associated neurophysiological changes in the future. These interventions should aim at reinstating appropriate HPA signalling and thus will rely upon a thorough diagnostic neuroendocrine work-up of the phenotype.

Taken together, substantial progress has been made in understanding the impact of chronic stress on the brain. These advances allow us to characterise better those people at risk for stress-related disorders and associated cognitive impairments.

They furthermore open up the possibility of tailored treatment approaches. These will have to consist of psychological and/or pharmacological interventions.

References

- Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A. et al. 2004. Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am J Psychiatry*, 161:1488-1490.
- Aisen, P.S., Davis, K.L., Berg, J.D., Schafer, K., Campbell, K., Thomas, R.G. et al. 2000. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. *Neurology*, 54:588-593.
- American Psychiatric Association. 1994. *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Association.
- Axelson, D.A., Doraiswamy, P.M., McDonald, W.M., Boyko, O.B., Tupler, L.A., Patterson, L.J. et al. 1993. Hypercortisolemia and hippocampal changes in depression. *Psychiatry Res*, 47:163-173.
- Barbazanges, A., Piazza, P.V., Le Moal, M. and Maccari, S. 1996. Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *J. Neurosci*, 16:3943-3949.
- Belanoff, J.K., Gross, K., Yager, A., and Schatzberg, A.F. 2001a. Corticosteroids and cognition. *J Psychiatr Res*, 35:127-145.
- Belanoff, J.K., Kalehzan, M., Sund, B., Fleming Ficek, S.K., and Schatzberg, A.F. 2001b. Cortisol activity and cognitive changes in psychotic major depression. *Am J Psychiatry*, 158:1612-1616.
- Berton, O. and Nestler, E.J. 2006. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.*, 7:137-151.
- Bodnoff, S.R., Humphreys, A.G., Lehman, J.C., Diamond, D.M., Rose, G.M. et al. 1995. Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *Journal of Neuroscience*, 15:61-69.
- Bourdeau, I., Bard, C., Noel, B., Leclerc, I., Cordeau, M.P., Belair, M. et al. 2002. Loss of Brain Volume in Endogenous Cushing's Syndrome and Its Reversibility after Correction of Hypercortisolism. *J Clin Endocrinol Metab*, 87:1949-1954.
- Brabham, T., Phelka, A., Zimmer, C., Nash, A., Lopez, J.F. and Vazquez, D.M. 2000. Effects of prenatal dexamethasone on spatial learning and response to stress is influenced by maternal factors. *Am J Physiol Regul Integr Comp Physiol*, 279:R1899-R1909.

- Bradley, R.H. and Corwyn, R.F. 2002. Socioeconomic status and child development. *Annu.Rev.Psychol*, 53:371-399.
- Bremner, J.D., Vermetten, E., Afzal, N. and Vythilingam, M. 2004. Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. *J Nerv Ment Dis*, 192:643-649.
- Breslau, N., Chilcoat, H., DelDotto, J., Andreski, P. and Brown, G. 1996. Low birth weight and neurocognitive status at six years of age. *Biol.Psychiatry*, 40:389-397.
- Brunson, K.L., Kramar, E., Lin, B., Chen, Y., Colgin, L.L., Yanagihara, T.K. et al. 2005. Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci*, 25:9328-9338.
- Buitelaar, J.K., Huizink, A.C., Mulder, E.J., de Medina, P.G. and Visser, G.H. 2003. Prenatal stress and cognitive development and temperament in infants. *Neurobiol Aging*, 24:Suppl 1, S53-S60.
- Buss, C., Lord, C., Wadiwalla, M., Hellhammer, D.H., Lupien, S.J., Meaney, M.J. et al. 2007. Maternal care modulates the relationship between prenatal risk and hippocampal volume in women but not in men. *J Neurosci*, 27:2592-2595.
- Campbell, S., Marriott, M., Nahmias, C. and MacQueen, G.M. 2004. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry*, 161:598-607.
- Carlson, L.E., Speca, M., Patel, K.D. and Faris, P. 2007. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain Behav Immun*, 21:1038-49.
- Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H. et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, 301:386-389.
- Cho, K., Ennaceur, A., Cole, J.C. and Suh, C.K. 2000. Chronic jet lag produces cognitive deficits. *J Neurosci*, 20:RC66.
- Cho, K. 2001. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nat Neurosci*, 4:567-568.
- Chrousos, G.P. 2004. Is 11beta-hydroxysteroid dehydrogenase type 1 a good therapeutic target for blockade of glucocorticoid actions? *Proc.Natl.Acad.Sci.U.S.A.*, 101:6329-6330.
- Coe, C.L., Kramer, M., Czeh, B., Gould, E., Reeves, A.J., Kirschbaum, C. et al. 2003. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biol Psychiatry*, 54:1025-1034.
- Cohen, A. and Horton, E.S. 2007. Progress in the treatment of type 2 diabetes: new pharmacologic approaches to improve glycemic control. *Curr.Med.Res.Opin.*, 23:905-917.
- Conrad, C.D., Galea, L.A., Kuroda, Y. and McEwen, B.S. 1996. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. *Behavioral Neuroscience*, 110:1321-1334.
- Conrad, C.D., LeDoux, J. E., Magarinos, A.M. and McEwen, B.S. 1999. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. *Behavioral Neuroscience*, 113:902-913.

Convit, A., Wolf, O.T., Tarshish, C. and de Leon, M.J. 2003. Reduced glucose tolerance is associated with poor memory and hippocampal atrophy among normal elderly. *Proc. Natl. Acad. Sci. U.S.A.*, 100:2019-2022.

Convit, A. 2005. Links between cognitive impairment in insulin resistance: An explanatory model. *Neurobiol Aging*, 26:Suppl. 1:31-35.

Csernansky, J.G., Wang, L., Swank, J., Miller, J.P., Gado, M., McKeel, D. et al. 2005. Preclinical detection of Alzheimer's disease: hippocampal shape and volume predict dementia onset in the elderly. *Neuroimage*, 25:783-792.

Czeh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., van Kampen, M. et al. 2001. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci U S A*, 98:12796-12801.

Czeh, B., Muller-Keuker, J.I., Rygula, R., Abumaria, N., Hiemke, C., Domenici, E. et al. 2007. Chronic Social Stress Inhibits Cell Proliferation in the Adult Medial Prefrontal Cortex: Hemispheric Asymmetry and Reversal by Fluoxetine Treatment. *Neuropsychopharmacology*, 32:1490-503.

Dallman, M.F., Pecoraro, N., Akana, S.F., la Fleur, S.E., Gomez, F., Houshyar, H. et al. 2003. Chronic stress and obesity: a new view of "comfort food". *Proc. Natl. Acad. Sci. U.S.A.*, 100:11696-11701.

De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S. and Joels, M. 1998. Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews*, 19:269-301.

De Kloet, E.R., Joels, M. and Holsboer, F. 2005. Stress and the brain: from adaptation to disease. *Nat. Rev. Neurosci.*, 6:463-475.

De Kloet, E.R., Derijk, R.H. and Meijer, O.C. 2007. Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nat. Clin. Pract. Endocrinol. Metab*, 3:168-179.

de Leon, M.J., McRae, T., Tsai, J.R., George, A.E., Marcus, D.L., Freedman, M. et al. 1988. Abnormal cortisol response in Alzheimer's disease linked to hippocampal atrophy. *Lancet*, 2:391-392.

de Quervain, D.J., Poirier, R., Wollmer, M.A., Grimaldi, L.M., Tzolaki, M., Streffer, J.R. et al. 2004. Glucocorticoid-related genetic susceptibility for Alzheimer's disease. *Hum Mol Genet*, 13:47-52.

de Quervain, D.J., Aerni, A. and Roozendaal, B. 2007. Preventive Effect of β -Adrenoceptor Blockade on Glucocorticoid-Induced Memory Retrieval Deficits. *Am. J. Psychiatry*, 164:967-969.

Delahanty, D.L., Raimonde, A.J. and Spoonster, E. 2000. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biol Psychiatry*, 48:940-947.

Dickerson, S.S. and Kemeny, M.E. 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull*, 130:355-391.

Fenoglio, K.A., Brunson, K.L., Avishai-Eliner, S., Stone, B.A., Kapadia, B.J. and Baram, T.Z. 2005. Enduring, handling-evoked enhancement of hippocampal memory function and glucocorticoid receptor expression involves activation of the corticotropin-releasing factor type 1 receptor. *Endocrinology*, 146:4090-4096.

- Finnstrom, O., Gaddlin, P.O., Leijon, I., Samuelsson, S. and Wadsby, M. 2003. Very-low-birth-weight children at school age: academic achievement, behavior and self-esteem and relation to risk factors. *J. Matern. Fetal Neonatal Med.*, 14:75-84.
- Fries, E., Hesse, J., Hellhammer, J. and Hellhammer, D.H. 2005. A new view on hypocortisolism. *Psychoneuroendocrinology*, 30:1010-1016.
- Gaab, J., Blattler, N., Menzi, T., Pabst, B., Stoyer, S. and Ehlert, U. 2003. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. *Psychoneuroendocrinology*, 28:767-779.
- Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P. et al. 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat. Neurosci.*, 5:1242-1247.
- Gluckman, P.D. and Hanson, M.A. 2004. Living with the past: evolution, development, and patterns of disease. *Science*, 305:1733-1736.
- Gold, P.W. and Chrousos, G.P. 2002. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry*, 7:254-275.
- Gould, E., Tanapat, P., Rydel, T. and Hastings, N. 2000. Regulation of hippocampal neurogenesis in adulthood. *Biol Psychiatry*, 48:715-720.
- Green, K.N., Billings, L.M., Roozendaal, B., McGaugh, J.L. and LaFerla, F.M. 2006. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J. Neurosci.*, 26:9047-9056.
- Heim, C. and Nemeroff, C.B. 1999. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, 46:1509-1522.
- Heinrichs, M., Baumgartner, T., Kirschbaum, C. and Ehlert, U. 2003. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol. Psychiatry*, 54:1389-1398.
- Henry, C., Kabbaj, M., Simon, H., Le Moal, M. and Maccari, S. 1994. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *J Neuroendocrinol*, 6:341-345.
- Herbert, J., Goodyer, I.M., Grossman, A.B., Hastings, M.H., De Kloet, E.R., Lightman, S.L. et al. 2006. Do corticosteroids damage the brain? *J. Neuroendocrinol.*, 18:393-411.
- Heuser, I.J., Gotthardt, U., Schweiger, U., Schmider, J., Lammers, C.H. et al. 1994. Age-associated changes of pituitary-adrenocortical hormone regulation in humans: importance of gender. *Neurobiology of Aging*, 15:227-231.
- Holsboer, F. 2000. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, 23:477-501.
- Huot, R.L., Plotsky, P.M., Lenox, R.H. and McNamara, R.K. 2002a. Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats. *Brain Res.*, 950:52-63.
- Huot, R.L., Plotsky, P.M., Lenox, R.H. and McNamara, R.K. 2002b. Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats. *Brain Res.*, 950:52-63.

- Ising, M., Kunzel, H.E., Binder, E.B., Nickel, T., Modell, S. and Holsboer, F. 2005. The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog.Neuropsychopharmacol.Biol.Psychiatry*, 29:1085-1093.
- Issa, A. M., Rowe, W., Gauthier, S. and Meaney, M.J. 1990. Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *J Neurosci*, 10:3247-3254.
- Joels, M., Karst, H., Alfarez, D., Heine, V.M., Qin, Y., van, R.E. et al. 2004. Effects of chronic stress on structure and cell function in rat hippocampus and hypothalamus. *Stress*, 7:221-231.
- Kalmijn, S., Launer, L.J., Stolk, R.P., de Jong, F.H., Pols, H.A., Hofman, A. et al. 1998. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *Journal of Clinical Endocrinology & Metabolism*, 83:3487-3492.
- Kang, J.E., Cirrito, J.R., Dong, H., Csernansky, J.G. and Holtzman, D.M. 2007. Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. *Proc.Natl.Acad.Sci.U.S.A.*, 104:10673-10678.
- Karl, A., Schaefer, M., Malta, L.S., Dorfel, D., Rohleder, N. and Werner, A. 2006. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci.Biobehav.Rev.*, 30:1004-1031.
- Karlamangla, A.S., Singer, B.H., Chodosh, J., McEwen, B.S. and Seeman, T.E. 2005. Urinary cortisol excretion as a predictor of incident cognitive impairment. *Neurobiol.Aging*, 26:Suppl 1:80-84.
- Keenan, P.A., Jacobson, M.W., Soleymani, R.M., Mayes, M.D., Stress, M.E. and Yaldao, D.T. 1996. The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology*, 47:1396-1402.
- Kuper, H., Marmot, M. and Hemingway, H. 2002. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Semin.Vasc.Med.*, 2:267-314.
- Landfield, P.W., Baskin, R.K. and Pitler, T.A. 1981. Brain aging correlates: retardation by hormonal-pharmacological treatments. *Science*, 214:581-584.
- Landgraf, R. 2005. Neuropeptides in anxiety modulation. *Handb.Exp.Pharmacol.*, 335-369.
- Landry, S.H., Smith, K. E., Miller-Loncar, C.L. and Swank, P.R. 1997. Predicting cognitive-language and social growth curves from early maternal behaviors in children at varying degrees of biological risk. *Dev.Psychol.*, 33:1040-1053.
- Lazarus, R.S. 1993. Coping theory and research: past, present, and future. *Psychosom.Med.*, 55:234-247.
- Leitner, Y., Heldman, D., Harel, S. and Pick, C.G. 2005. Deficits in spatial orientation of children with intrauterine growth retardation. *Brain Res.Bull.*, 67:13-18.
- Lemaire, V., Koehl, M., Le Moal, M. and Abrous, D.N. 2000. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc.Natl.Acad.Sci.U.S.A.*, 97:11032-11037.
- Lemaire, V., Lamarque, S., Le Moal, M., Piazza, P.V. and Abrous, D.N. 2006. Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. *Biol.Psychiatry*, 59:786-792.
- Leuner, B., Gould, E. and Shors, T.J. 2006. *Is there a link between adult neurogenesis and learning?* Hippocampus.

- Liston, C., Miller, M.M., Goldwater, D.S., Radley, J.J., Rocher, A.B., Hof, P.R. et al. 2006. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J.Neurosci.*, 26:7870-7874.
- Liu, D., Diorio, J., Day, J.C., Francis, D.D. and Meaney, M.J. 2000. Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience*, 3:799-806.
- Luoma, I., Kaukonen, P., Mantymaa, M., Puura, K., Tamminen, T. and Salmelin, R. 2004. A longitudinal study of maternal depressive symptoms, negative expectations and perceptions of child problems. *Child Psychiatry Hum.Dev.*, 35:37-53.
- Lupien, S., Lecours, A.R., Lussier, I., Schwartz, G., Nair, N.P. and Meaney, M.J. 1994. Basal cortisol levels and cognitive deficits in human aging. *Journal of Neuroscience*, 14:2893-2903.
- Lupien, S.J., de Leon, M., De Santi, S., Convit, A., Tarshish, C., Nair, N.P. et al. 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, 1:69-73.
- Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T. et al. 2005. Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology*, 30:225-242.
- MacLulich, A.M., Deary, I.J., Starr, J. M., Ferguson, K.J., Wardlaw, J.M. and Seckl, J.R. 2005. Plasma cortisol levels, brain volumes and cognition in healthy elderly men. *Psychoneuroendocrinology*, 30:505-515.
- MacLulich, A.M., Ferguson, K.J., Wardlaw, J.M., Starr, J.M., Deary, I.J. and Seckl, J.R. 2006. Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamic-pituitary-adrenal axis regulation in healthy elderly men. *J.Clin.Endocrinol.Metab*, 91:1591-1594.
- Magarinos, A.M., McEwen, B.S., Flugge, G. and Fuchs, E. 1996. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *Journal of Neuroscience*, 16:3534-3540.
- Magarinos, A.M., Deslandes, A. and McEwen, B.S. 1999. Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *European Journal of Pharmacology*, 371:113-122.
- Mason, J.W. 1968. A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom.Med.*, 30, 576-607.
- Matthaei, S., Stumvoll, M., Kellerer, M. and Haring, H.U. 2000. Pathophysiology and pharmacological treatment of insulin resistance. *Endocr Rev*, 21:585-618.
- Mayer, J.L., Klumpers, L., Maslam, S., De Kloet, E.R., Joels, M. and Lucassen, P.J. 2006. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalises the corticosterone-induced reduction of adult hippocampal neurogenesis. *J.Neuroendocrinol.*, 18:629-631.
- McCarton, C.M., Wallace, I.F., Divon, M. and Vaughan, H.G.Jr. 1996. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. *Pediatrics*, 98:1167-1178.
- McEwen, B.S. 1998. Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338:171-179.

- McEwen, B.S. 2002. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. *Neurobiol Aging*, 23:921-939.
- McEwen, B.S. 2003. Mood disorders and allostatic load. *Biol Psychiatry*, 54, 200-207.
- Meaney, M.J. and Aitken, D.H. 1985. The effects of early postnatal handling on hippocampal glucocorticoid receptor concentrations: temporal parameters. *Brain Res*, 354:301-304.
- Meaney, M.J., Aitken, D.H., Bodnoff, S.R., Iny, L.J., Tatarewicz, J.E. and Sapolsky, R.M. 1985. Early postnatal handling alters glucocorticoid receptor concentrations in selected brain regions. *Behav Neurosci*, 99:765-770.
- Meaney, M.J., Aitken, D.H., van Berkel, C., Bhatnagar, S. and Sapolsky, R.M. 1988. Effect of neonatal handling on age-related impairments associated with the hippocampus. *Science*, 239:766-768.
- Meaney, M.J., Aitken, D.H., Bhatnagar, S. and Sapolsky, R.M. 1991. Postnatal handling attenuates certain neuroendocrine, anatomical, and cognitive dysfunctions associated with aging in female rats. *Neurobiol.Aging*, 12:31-38.
- Meaney, M.J. 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci*, 24:1161-1192.
- Meichenbaum, D. 1985. *Stress inoculation training*. New York: Pergamon Press.
- Mitchell, A.J. 1998. The role of corticotropin releasing factor in depressive illness: a critical review. *Neurosci. Biobehav.Rev.*, 22:635-651.
- Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A. and Chattarji, S. 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proc.Natl.Acad.Sci.U.S.A.*, 102:9371-9376.
- Morgan, C.A.III, Doran, A., Steffian, G., Hazlett, G. and Southwick, S.M. 2006. Stress-induced deficits in working memory and visuo-constructive abilities in Special Operations soldiers. *Biol.Psychiatry*, 60:722-729.
- Navalta, C.P., Polcari, A., Webster, D.M., Boghossian, A. and Teicher, M.H. 2006. Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *J.Neuropsychiatry Clin.Neurosci.*, 18:45-53.
- Nemeroff, C.B. 1996. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry*, 1:336-342.
- Newcomer, J.W., Selke, G., Melson, A.K., Hershey, T., Craft, S., Richards, K. et al. 1999. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry*, 56:527-533.
- O'Brien, J.T., Ames, D., Schweitzer, I., Mastwyk, M. and Colman, P. 1996. Enhanced adrenal sensitivity to adrenocorticotrophic hormone (ACTH) is evidence of HPA axis hyperactivity in Alzheimer's disease. *Psychological Medicine*, 26:7-14.
- O'Brien, J.T., Lloyd, A., McKeith, I., Gholkar, A. and Ferrier, N. 2004. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry*, 161:2081-2090.

- O'Connor, T.G., Heron, J., Golding, J., Beveridge, M. and Glover, V. 2002. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br.J.Psychiatry*, 180:502-508.
- Otte, C., Hart, S., Neylan, T.C., Marmar, C.R., Yaffe, K. and Mohr, D.C. 2005. A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology*, 30:80-91.
- Phillips, D.I., Barker, D.J., Fall, C.H., Seckl, J.R., Whorwood, C.B., Wood, P.J., Walker, B.R. 1998. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? *J Clin Endocrinol Metab*, 83:757-760.
- Radley, J.J. and Morrison, J.H. 2005. Repeated stress and structural plasticity in the brain. *Ageing Res.Rev.*, 4:271-287.
- Radley, J.J., Rocher, A.B., Janssen, W.G., Hof, P.R., McEwen, B.S. and Morrison, J.H. 2005. Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Exp.Neurol.*, 196:199-203.
- Reynolds, R.M., Chapman, K.E., Seckl, J.R., Walker, B.R., McKeigue, P.M., Lithell, H.O. 2002. Skeletal muscle glucocorticoid receptor density and insulin resistance. *JAMA*, 287:2505-2506.
- Richards, M. and Wadsworth, M.E. 2004. Long term effects of early adversity on cognitive function. *Arch.Dis Child*, 89:922-927.
- Rissman, R.A., Lee, K. F., Vale, W. and Sawchenko, P.E. 2007. Corticotropin-releasing factor receptors differentially regulate stress-induced tau phosphorylation. *J.Neurosci.*, 27:6552-6562.
- Roceri, M., Hendriks, W., Racagni, G., Ellenbroek, B.A. and Riva, M.A. 2002. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. *Mol.Psychiatry*, 7:609-616.
- Roosendaal, B. and de Quervain, D.J. 2005. Glucocorticoid therapy and memory function: lessons learned from basic research. *Neurology*, 64:184-185.
- Roosendaal, B., Okuda, S., de Quervain, D.J. and McGaugh, J.L. 2006. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience*, 138:901-910.
- Rosmond, R. 2003. Stress induced disturbances of the HPA axis: a pathway to Type 2 diabetes? *Med Sci Monit*, 9:RA35-RA39.
- Rubinow, D.R., Post, R.M., Savard, R. and Gold, P.W. 1984. Cortisol hypersecretion and cognitive impairment in depression. *Archives of General Psychiatry*, 41:279-283.
- Salm, A.K., Pavelko, M., Krouse, E.M., Webster, W., Kraszpulski, M. and Birkle, D.L. 2004. Lateral amygdaloid nucleus expansion in adult rats is associated with exposure to prenatal stress. *Brain Res.Dev.Brain Res.*, 148:159-167.
- Sandeep, T.C., Yau, J.L., MacLulich, A.M., Noble, J., Deary, I.J., Walker, B.R. et al. 2004. 11 β -Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc.Natl. Acad.Sci.U.S.A.*, 101:6734-6739.

- Sandman, C.A., Wadhwa, P.D., Chicz-DeMet, A., Dunkel-Schetter, C. and Porto, M. 1997. Maternal stress, HPA activity, and fetal/infant outcome. *Ann.N.Y.Acad.Sci.*, 814:266-275.
- Sandman, C.A., Wadhwa, P.D., Chicz-DeMet, A., Porto, M. and Garite, T.J. 1999. Maternal corticotropin-releasing hormone and habituation in the human fetus. *Dev.Psychobiol.*, 34:163-173.
- Sapolsky, R.M. 2003. Stress and plasticity in the limbic system. *Neurochem Res*, 28:1735-1742.
- Schelling, G., Roozendaal, B. and de Quervain, D.J. 2004. Can posttraumatic stress disorder be prevented with glucocorticoids? *Ann.N.Y.Acad.Sci.*, 1032:158-166.
- Schmidt, L.A., Fox, N.A., Goldberg, M.C., Smith, C.C. and Schulkin, J. 1999. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. *Psychoneuroendocrinology*, 24:461-483.
- Schulkin, J., Gold, P.W. and McEwen, B.S. 1998. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology*, 23:219-243.
- Seckl, J.R., Yau, J. and Holmes, M. 2002. 11Beta-hydroxysteroid dehydrogenases: a novel control of glucocorticoid action in the brain. *Endocr.Res.*, 28:701-707.
- Seckl, J.R. and Walker, B.R. 2004. 11beta-hydroxysteroid dehydrogenase type 1 as a modulator of glucocorticoid action: from metabolism to memory. *Trends Endocrinol Metab*, 15:418-424.
- Seidman, D.S., Laor, A., Gale, R., Stevenson, D.K., Mashiach, S. and Danon, Y.L. 1992. Birth weight and intellectual performance in late adolescence. *Obstet.Gynecol.*, 79:543-546.
- Smythe, J.W., McCormick, C.M. and Meaney, M.J. 1996. Median eminence corticotrophin-releasing hormone content following prenatal stress and neonatal handling. *Brain Res.Bull.*, 40:195-199.
- Starkman, M.N., Gebarski, S.S., Berent, S. and Schteingart, D.E. 1992. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biological Psychiatry*, 32:756-765.
- Starkman, M.N., Giordani, B., Gebarski, S.S., Berent, S., Schork, M.A. et al. 1999. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biological Psychiatry*, 46:1595-1602.
- Szuran, T., Zimmermann, E. and Welzl, H. 1994. Water maze performance and hippocampal weight of prenatally stressed rats. *Behav Brain Res*, 65:153-155.
- Ursin, H. and Eriksen, H.R. 2004. The cognitive activation theory of stress. *Psychoneuroendocrinology*, 29:567-592.
- Vallee, M., Maccari, S., Dellu, F., Simon, H., Le Moal, M. and Mayo, W. 1999. Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. *Eur.J.Neurosci.*, 11:2906-2916.
- Van Cauter, E., Leproult, R. and Kupfer, D.J. 1996. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *Journal of Clinical Endocrinology & Metabolism*, 81:2468-2473.

- Van den Bergh, B.R., Van Calster, B., Smits, T., Van Huffel, S. and Lagae, L. 2008. Antenatal Maternal Anxiety is Related to HPA-Axis Dysregulation and Self-Reported Depressive Symptoms in Adolescence: A Prospective Study on the Fetal Origins of Depressed Mood. *Neuropsychopharmacology*, 33:2301.
- Videbech, P. and Ravnkilde, B. 2004. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am.J.Psychiatry*, 161:1957-1966.
- Vyas, A., Mitra, R., Shankaranarayana Rao, B.S. and Chattarji, S. 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci*, 22:6810-6818.
- Vythilingam, M., Heim, C., Newport, J., Miller, A.H., Anderson, E., Bronen, R. et al. 2002. Childhood Trauma Associated With Smaller Hippocampal Volume in Women With Major Depression. *Am J Psychiatry*, 159:2072-2080.
- Vythilingam, M., Vermetten, E., Anderson, G.M., Luckenbaugh, D., Anderson, E.R., Snow, J. et al. 2004. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol Psychiatry*, 56:101-112.
- Wadhwa, P.D. 2005. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. *Psychoneuroendocrinology*, 30:724-743.
- Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J. 2004. Epigenetic programming by maternal behavior. *Nat Neurosci*, 7:847-854.
- Welberg, L.A. and Seckl, J.R. 2001. Prenatal stress, glucocorticoids and the programming of the brain. *J.Neuroendocrinol.*, 13:113-128.
- Whelan, T.B., Schteingart, D.E., Starkman, M.N. and Smith, A. 1980. Neuropsychological deficits in Cushing's syndrome. *Journal of Nervous & Mental Disease*, 168:753-757.
- Whorwood, C.B., Donovan, S.J., Flanagan, D., Phillips, D.I., Byrne, C.D. 2002. Increased glucocorticoid receptor expression in human skeletal muscle cells may contribute to the pathogenesis of the metabolic syndrome. *Diabetes*, 51:1066-1075.
- Wilkinson, C.W., Peskind, E.R. and Raskind, M.A. 1997. Decreased hypothalamic-pituitary-adrenal axis sensitivity to cortisol feedback inhibition in human aging. *Neuroendocrinology*, 65:79-90.
- Wilson, R.S., Evans, D.A., Bienias, J.L., Mendes De Leon, C.F., Schneider, J.A. and Bennett, D.A. 2003. Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology*, 61:1479-1485.
- Wilson, R.S., Bennett, D.A., Mendes De Leon, C.F., Bienias, J.L., Morris, M.C. and Evans, D.A. 2005. Distress proneness and cognitive decline in a population of older persons. *Psychoneuroendocrinology*, 30:11-17.
- Wolf, O.T. 2006. Effects of stress hormones on the structure and function of the human brain. *Expert Review of Endocrinology & Metabolism*, 1:623-632.
- Wolf, O.T., Convit, A., de Leon, M.J., Caraos, C. and Quadri, S.F. 2002. Basal hypothalamo-pituitary-adrenal axis activity and corticotropin feedback in young and older men: Relationship to magnetic resonance imaging derived hippocampus and cingulate gyrus volumes. *Neuroendocrinology*, 75:241-249.

Wolkowitz, O.M., Reus, V.I., Canick, J., Levin, B. and Lupien, S. 1997. Glucocorticoid medication, memory and steroid psychosis in medical illness. *Annals of the New York Academy of Sciences*, 823:81-96.

Wolkowitz, O.M., Lupien, S.J., Bigler, E., Levin, R.B. and Canick, J. 2004. The "steroid dementia syndrome": an unrecognized complication of glucocorticoid treatment. *Ann.N.Y.Acad.Sci.*, 1032:191-194.

Wurtman, R.J. 2005. Genes, stress, and depression. *Metabolism*, 54:16-19.

Yaka, R., Salomon, S., Matzner, H. and Weinstock, M. 2007. Effect of varied gestational stress on acquisition of spatial memory, hippocampal LTP and synaptic proteins in juvenile male rats. *Behav.Brain Res.*, 179:126-132.

Yang, J., Hou, C., Ma, N., Liu, J., Zhang, Y., Zhou, J. et al. 2007. Enriched environment treatment restores impaired hippocampal synaptic plasticity and cognitive deficits induced by prenatal chronic stress. *Neurobiol. Learn.Mem.*, 87:257-263.

Yau, J.L., Noble, J., Kenyon, C.J., Hibberd, C., Kotelevtsev, Y., Mullins, J.J. et al. 2001. Lack of tissue glucocorticoid reactivation in 11beta -hydroxysteroid dehydrogenase type 1 knockout mice ameliorates age-related learning impairments. *Proc.Natl.Acad.Sci.U.S.A.*, 98:4716-4721.

Yehuda, R. 2002. Post-traumatic stress disorder. *N.Engl.J.Med.*, 346:108-114.

Young, A.H., Sahakian, B.J., Robbins, T.W. and Cowen, P.J. 1999. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology*, 145:260-266.

All the reports and papers produced by the
Foresight Mental Capital and Wellbeing Project may be downloaded from the Foresight website
(www.foresight.gov.uk).

Requests for hard copies may also be made through this website.

First published September 2008.

The Government Office for Science.

© Crown copyright