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The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition

S.J. Lupien [a,*], F. Maheu [b], M. Tu [c], A. Fiocco [a], T.E. Schramek [a]

[a] *Center for Studies on Human Stress, Douglas Hospital Research Center, McGill University, Montreal, Que., Canada*
[b] *Mood and Anxiety Disorders Program, Emotional Development and Affective Neuroscience Branch, National Institute of Mental Health, NIH, Bethesda, MD 20892, USA*
[c] *University of British Columbia, Centre for Community Child Health Research, 480 Oak Street, L408, Vancouver, BC, Canada V6H 3V4*

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Abstract

In this review, we report on studies that have assessed the effects of exogenous and endogenous increases in stress hormones on human cognitive performance. We first describe the history of the studies on the effects of using exogenous stress hormones such as glucocorticoids as anti-inflammatory medications on human cognition and mental health. Here, we summarize the cases that led to the diagnosis of glucocorticoid-induced 'steroid psychosis' in human populations and which demonstrated that these stress hormones could thus cross the blood–brain barrier and access the brain where they could influence cognition and mental health. We then summarize studies that assessed the effects of the exogenous administration of glucocorticoids on cognitive performance supported by the hippocampus, the frontal lobes and amygdala. In the second section of the paper, we summarize the effects of the endogenous release of glucocorticoids induced by exposure to a stressful situation on human cognition and we further dissociate the effects of emotion from those of stress on human learning and memory. Finally, in the last section of the paper, we discuss the potential impact that the environmental context to which we expose participants when assessing their memory could have on their reactivity to stress and subsequent cognitive performance. In order to make our point, we discuss the field of memory and aging and we suggest that some of the 'age-related memory impairments' observed in the literature could be partly due to increased stress reactivity in older adults to the environmental context of testing. We also discuss the inverse negative correlations reported between hippocampal volume and memory for young and older adults and suggest that these inverse correlations could be partly due to the effects of contextual stress in young and older adults, as a function of age-related differences in hippocampal volume.

Keywords: Stress; Glucocorticoids; Catecholamines; Memory; Aging; Hippocampus

1. Introduction

Stress is a popular topic these days. A week seldom passes without hearing or reading about stress and its deleterious effects on health. Given this negative impact of stress on human health, many types of stress management therapies have been put forward to decrease stress and thus, promote health. However, there is a great paradox in the field of stress research, and it relates to the fact that the popular definition of stress is very different from the scientific definition of stress. This has left a multitude of people and experts talking about, and working on, very different aspects of the stress response.

In popular terms, stress is mainly defined as time pressure. We feel stressed when we do not have the time to perform the tasks we want to perform within a given period of time. This time pressure usually triggers a set of physiological reactions that give us the indication that we are stressed. Although this definition is certainly accurate in terms of one component of the stress response, it is

* Corresponding author. Fax: +1 514 888 4064.
E-mail address: sonia.lupien@mcgill.ca (S.J. Lupien).

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important to acknowledge that in scientific terms, stress is not equivalent to time pressure. If this were true, every individual would feel stressed when pressured by time. However, we all know people that seek time pressure in order to perform adequately and others that are extremely stressed by time pressure. This shows that stress is a highly individual experience that does not depend on a particular event such as time pressure, but rather, it depends on specific psychological determinants that trigger a stress response.

2. What is stress?

Prior to becoming part of our day-to-day conversations, the term "stress" was used by engineers to explain forces that can put strain on a structure. For example, one could place strain on a piece of metal in such a way that it would break like glass when it reached its stress level. In 1936, Hans Selye (reproduced in Selye, 1998) borrowed the term of 'stress' from the field of engineering and talked about stress as being a non-specific phenomenon representing the intersection of symptoms produced by a wide variety of noxious agents. For many years, Selye tested various conditions (e.g., fasting, extreme cold, operative injuries, and drug administration) that would produce morphological changes in the body that were representative of a stress response, such as enlargement of the adrenal glands, atrophy of the thymus, and gastric ulceration. Selye's view of the concept of stress was that the determinants of the stress response are non-specific, that is, many unspecific conditions can put strain on the organism and lead to disease, the same way that many unspecific conditions can put strain on a piece of metal and break it like glass.

Not all researchers agreed with Selye's model, particularly with the notion that the determinants of the stress response are non-specific. The reason for this was simple. While Selye spent his entire career working on physical stressors (e.g., heat, cold, and pain), we all know that some of the worst stressors we encounter in life are psychological in nature, and are induced by our interpretation of events. For this reason, a physician named John Mason (1968) spent many years measuring stress hormone levels in humans subjected to various conditions that he thought would be stressful in order to describe the psychological characteristics that would make any condition stressful, to anyone exposed to it. By summarizing the results of studies measuring the circulating levels of stress hormones before and after individuals were exposed to various jobs or situations that were deemed to be stressful (e.g., air-traffic controllers or parachute jumping), Mason (1968) was able to describe three main psychological determinants that would induce a stress response in any individual exposed to them. Using this methodology, he showed that in order for a situation to induce a stress response by the body, it has to be interpreted as being *novel*, and/or *unpredictable*, and/or the individual must have the feeling that he/she *does not have control over the situation*. Although this work led to a general debate between Selye and Mason (Selye, 1975a, 1975b), further studies confirmed that the determinants of the stress response are highly specific, and therefore, potentially predictable and measurable. More recently, a meta-analysis confirmed the importance of these characteristics, and added that the presence of a social evaluative threat to a situation constitutes the fourth characteristic that leads to physiological stress reactivity in humans (Dickerson & Kemeny, 2002) (Table 1).

Table 1
The four grades of steroid psychosis as described by Rome and Braceland in 1952

Grade 1	Mild euphoria Lessened fatigue Improved concentration Elevated mood
Grade 2	Heightened euphoria Flight of ideas Impaired judgment Insomnia Increased appetite Memory impairment
Grade 3	Anxiety Phobia Rumination Hypomania Depression
Grade 4	Psychosis

2.1. The relativity of stress

Stress can be absolute (a *real* threat induced by an earthquake in a town, leading to a significant stress response in every person facing this threat) or it can be relative (an *implied* threat induced by the interpretation of a situation as being novel, and/or unpredictable and/or uncontrollable, for example, a public speaking task; for a complete review of these concepts, see Lupien et al., 2006). The body's response to absolute stressors is adaptive in nature. Being in or witnessing an accident, confronting a dangerous animal, and being submitted to extreme cold or heat are all examples of absolute stressors that will necessarily lead to a stress response in the majority (if not the totality) of individuals when they are first confronted with it. These extreme and particular situations constitute absolute stressors in that, due to their aversive nature, a stress response *has to* be elicited for one's survival and/or well-being. In our western societies, absolute stressors are rare, but are nonetheless those that elicit the greatest physiological response.

Conversely, relative stressors are those events or situations that will elicit a stress response only in a certain proportion of individuals. Moreover, this response may be mild or pronounced (Lupien et al., 2006). For example, having to unexpectedly deliver a videotaped speech may be very stressful for a given individual, and not at all for another. Large inter-individual variations in the

stress-response to psychological challenges have been frequently reported (Hellhammer, Buchtal, Gutberlet, & Kirschbaum, 1997; Kirschbaum & Hellhammer, 1989; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995a, 1995b, Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004a; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004b; Lupien et al., 1997; Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Rohleder, Wolf, & Kirschbaum, 2003; Roy, Steptoe, & Kirschbaum, 1998). It may be argued that absolute stressors are closely linked to physiological systems due to their life- or self-threatening nature. On the contrary, relative stressors, because they are milder or because they necessitate a cognitive interpretation in order to elicit a response, will not necessarily lead to a physiological response, and the presence or absence of a physiological response will depend on the outcome of the cognitive analysis.

The stressor is the event itself, such as the earthquake in the case of the absolute stressor, or the public speech in the case of the relative stressor. The stress response is the body's reaction to the event (Selye, 1975a, 1975b, 1998), and it is this body's response to stress that is the foundation for the studies that determined the impact of stress on cognitive function. The reason for this is that the stress hormones that are secreted in response to an absolute or relative stressor are steroids that can easily cross the blood–brain barrier and access the brain, where they can influence learning and memory by binding to receptors localized in various brain regions known to be involved in learning and memory.

2.2. Stress hormones

As presented in Fig. 1, when a situation is interpreted as being stressful, it triggers the activation of the hypothalamic–pituitary–adrenal (HPA) axis whereby neurons in the hypothalamus, a brain structure often termed the "master gland", releases a hormone called corticotropin-releasing hormone (CRH). The release of CRH triggers the subsequent secretion and release of another hormone called adrenocorticotropin (ACTH) from the pituitary gland, also located in the brain. When ACTH is secreted by the pituitary gland, it travels in the blood and reaches the adrenal glands, which are located above the kidneys, and triggers secretion of the so-called stress hormones.

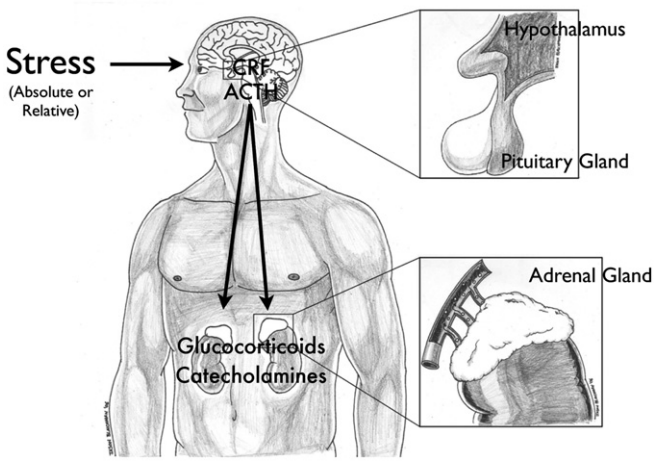

Fig. 1. Schematic representation of the hypothalamic-pituitary–adrenal (HPA) axis. Following the perception of a stressor, the hypothalamus releases CRF, which activates the pituitary and leads to secretion of ACTH. The levels of ACTH are detected by the adrenal cortex which then secretes glucocorticoids and catecholamines (illustration: ©Jason Blaichman).

There are two main classes of stress hormones, the glucocorticoids (called corticosterone in animals, and cortisol in humans), and the catecholamines (adrenaline and noradrenaline). The acute secretion of glucocorticoids and catecholamines in response to a stressor constitutes the primary mediators in the chain of hormonal events triggered in response to stress. When these two hormones are secreted in response to stress, they act on the body to give rise to the fight-or-flight response whereby one would, for instance, experience an increase in heart rate and blood pressure (for a review, see Lupien et al., 2006).

Glucocorticoids have a variety of different effects in target systems throughout the organism, which can be summarized as aiming to increase the availability of energy substrates in different parts of the body, and allow for optimal adaptations to changing demands of the environment. While the activation of the HPA axis can be regarded as a basic adaptive mechanism in response to change, prolonged activation of this system presents a health risk to the organism. The highly catabolic glucocorticoids antagonize insulin and increase blood pressure, thus increasing the risk for developing diabetes, hypertension, and arterial disease. Also, growth and tissue repair are impaired. Furthermore, activation of the HPA axis suppresses immune functions, which in a chronic state can be considered harmful for the organism, since it is associated with increased risk of infection (for a general review, see McEwen, 1998, 2000).

Given their liposoluble characteristics, the glucocorticoids can easily cross the blood–brain barrier and access the brain where they bind to receptors. Three of the most important brain areas containing glucocorticoid receptors are the hippocampus, amygdala, and frontal lobes, which are brain structures known to be involved in learning and memory. Although adrenaline does not readily access the brain, it can still impact the brain through its actions on the sensory vagus outside of the blood–brain barrier, with information transmitted into the brain via the nucleus of the solitary tract. The most important brain area containing adrenergic receptors is the amygdala, which has been shown to play an important role in fear processing, and memory for emotionally relevant information.

Because of their actions on brain structures known to be involved in fear detection and memory for emotionally relevant information, the stress mediators enhance the formation of so-called 'flashbulb memories' of events associated with strong emotions, including fear but also positive emo-

tions. This process involves the amygdala, and the pathway for encoding these memories involves the interaction between neurotransmitters in the amygdala and in related brain areas such as the hippocampus along with circulating stress hormones (McGaugh, 2000; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004; Roozendaal, McReynolds, & McGaugh, 2004; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). The importance of these stress mediators on memory for emotionally relevant information has been recently confirmed by studies in which blockade of either glucocorticoids (Maheu, Joober, Beaulieu, & Lupien, 2004) or noradrenaline (Cahill, Prins, Weber, & McGaugh, 1994) activity impaired the recall of emotionally relevant information. Consequently, secretion of these primary stress mediators is necessary for the adequate encoding of emotionally relevant information. This enhancement of memory for stimuli inducing stressful and/or emotional responses may be essential for species' survival. A recent study published by Zorawski and collaborators goes along with this suggestion. They had subjects participate in a fear conditioning task and assessed the association between fear-induced increase in cortisol, and the consolidation of the memory. Results showed that participants whose fear learning was accompanied by high cortisol levels presented a better consolidation of this memory. Interestingly, this effect was more important in men (Zorawski, Blanding, Kuhn, & LaBar, 2006). Similar gender differences in the pattern of cortisol activation in response to fear have recently been observed using functional brain imaging (Stark et al., 2006).

While short-term responses of the brain to novel and potentially threatening situations may be adaptive and result in new learning and acquired behavioral strategies for coping, as may be the case for certain types of fear-related memories, repeated stress can cause both cognitive impairments, and structural changes in the hippocampus, mainly through the actions of glucocorticoids. Consequently, in this paper, we will concentrate our efforts on describing the effects of glucocorticoids on human cognitive function and their potential impact on studies of brain and cognition.

2.3. Important characteristics of glucocorticoids

Under basal conditions, glucocorticoid secretion exhibits a 24-h circadian profile in which glucocorticoid concentrations present a morning maximum in humans (the circadian peak), and slowly declining levels in the late afternoon, evening and nocturnal period (the circadian trough), and an abrupt elevation after the first few hours of sleep (see Fig. 2).

Circulating glucocorticoids bind with high affinity to two receptor subtypes; the mineralocorticoid (hereafter called Type I) and glucocorticoid (hereafter called Type II) receptors. Although both receptor types have been implicated in mediating glucocorticoid feedback effects, there are two major differences between Type I and Type II receptors. First, Type I receptors bind glucocorticoids with an affinity that is about 6–10 times higher than that of Type II receptors. This differential affinity results in a striking difference in occupation of the two receptor types under different conditions and time of day. Thus, during the circadian trough (the PM phase in humans and the AM phase in rats), the endogenous hormone occupies more than 90% of Type I receptors, but only 10% of Type II receptors. However, during stress and/or the circadian peak of glucocorticoid secretion (the AM phase in humans and the PM phase in rats), Type I receptors are saturated, and there is occupation of approximately 67–74% of Type II receptors (see Fig. 2).

The second major difference between these two receptor types is related to their distribution in the brain. The Type I receptor is exclusively present in the limbic system, with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. The Type II receptor, however, is present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex. As we will see in the following sections, the impact of glucocorticoids on cognitive function can be best understood in terms of the differential effects of Type I and Type II receptor activation.

3. Effects of exogenous glucocorticoids on cognition

In an attempt to present the reader with a clear and complete view of the effects of glucocorticoids on human cognition, our background will be historical, as we will present the various models of glucocorticoid-effects on human cognition as a function of new approaches and models that have been described from the nineteenth to the twenty-first century. We use this approach for two main reasons. First, history will teach us that our view of glucocorticoid effects on human cognition remained stable from 1970 to 1999, after which time new data obtained in both animals and humans dramatically modified our views. Second, because the history of the search for glucocorticoid effects on cognitive function took place in many different laboratories across the world, sometimes simultaneously, our historical report of the search for glucocorticoid effects on human cognition will describe one of the best attributes of this field of research, i.e. its rich multidisciplinary nature.

3.1. The era of clinical descriptions

The study of the effects of glucocorticoids on human behavior has always been an emotional one, filled with debate, reconciliations, and the advancement of science. The story starts in 1855, when Thomas Addison described for the first time a "dark skin disease", a pigmentary characteristic that he found to be associated with pathological modifications of the adrenal glands (Addison, 1855). One

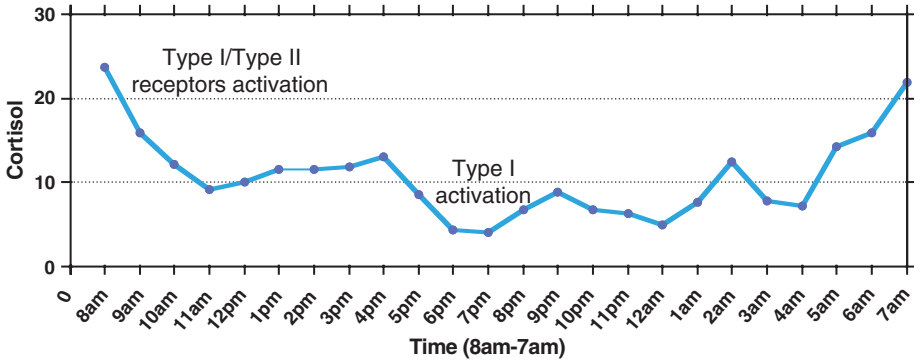

Fig. 2. Example of a circadian rhythm of serum cortisol levels. There is an abrupt elevation a few hours before awakening, and slowly declining levels across the day. At the time of cortisol peak (early AM phase in humans), there is activation of both Type I and Type II glucocorticoid receptors, while at the time of the cortisol trough (PM phase in humans), there is mainly activation of the high affinity, Type I glucocorticoid receptors.

year later, Brown-Séquard (1856) showed the importance of these "small capsules" for an animal's life and confirmed Addison's observations. At about the same time, a debate exploded at the Société de Biologie de Paris, when Dr. Bouillaud publicly accused Brown-Séquard of only doing some "amusing physiology", which is said to have profoundly insulted Dr. Brown-Séquard. In order to clear the name of his colleague, Dr. Armand Trousseau came to the rescue of Brown-Séquard at the Société de Biologie de Paris and defended both his study and the clinical observations of Dr. Addison. He further proposed to name the syndrome described by Addison, "Addison's disease", a disease that later became a textbook clinical description (see Olmsted, 1946). In 1889, after Brown-Séquard had succeeded Claude Bernard as professor of medicine at the Collège de France, he reported another controversial finding to the Société de Biologie de Paris (Brown-Séquard, 1889). In experiments performed on himself, he had shown the rejuvenating effects of testicular extracts from healthy young guinea pigs (Brown-Séquard, 1889). By 1890, an estimated 12,000 physicians were giving testicular extracts to their patients, despite the skepticism and embarrassment expressed by many medical journals (see Olmsted, 1946). This was the birth of "organotherapy" (see Borell, 1976a; Borell, 1976b).

Twelve years later, in 1901, Harvey Cushing, known as the father of neurosurgery, misdiagnosed a patient with headaches, visual troubles and sexual immaturity as having a cerebellar tumor and operated three times in this location (Cushing, 1913). The patient did not survive. A couple of months later, Fröhlich described the case of a young boy with headaches, visual troubles and sexual immaturity in whom he successfully diagnosed a pituitary tumor. The patient did survive (see Fulton, 1946). The disease is now named "Fröhlich syndrome". It is said that Cushing never really accepted this defeat and always remained very alert for pituitary tumors and their manifestations (Fulton, 1946). This vigilance paid off since he described in 1932, at the end of his career, the basophil tumors of the pituitary, leading to hypersecretion of glucocorticoids (Cushing, 1932). The disease is now named "Cushing's disease". However, 19 years earlier, in 1913, Cushing had already described cases of basophil tumors of the pituitary who presented psychic disturbances (Cushing, 1913). In his biography, Dr. Cushing reports that his task had been facilitated by the fact that one of his first patients was in an asylum, due to the psychic disturbances associated with this endocrinological disorder (Fulton, 1946).

3.2. Glucocorticoids and steroid psychosis

In 1949, a century after Addison's observation, occurred what some authors have named the "most cataclysmic event in the history of glucocorticoid endocrinology" (Munck, Guyre, & Holbrook, 1984), that is, the discovery, by Hench, Kendall, Slocumb, and Polley (1949), of the therapeutic effects of glucocorticoids on inflammatory diseases such as rheumatoid arthritis and asthma. Regarded by many scientists and clinicians as the "wonder drugs", glucocorticoids soon became very popular for the treatment of various inflammatory diseases. Besides being employed in hormone replacement therapy in Addison's disease or after adrenalectomy, they have also been used in treating rheumatoid arthritis, ulcerative colitis, asthma, Hodgkins' disease, systemic lupus erythematosus, and various dermatological disorders (Munck et al., 1984). However, no more than 2 years after their introduction as anti-inflammatory drugs, the enthusiasm engendered by glucocorticoids was dampened by the finding that the therapeutic use of glucocorticoids was followed by several side effects, particularly on affect and cognition. The first case was published in 1951 by Borman and Schmallenberg who reported suicide following cortisone treatment (Borman & Schmallenberg, 1951). A year later, three papers were published reporting severe mental disturbances in patients under glucocorticoid therapy (Brody, 1952; Clark, Bauer, & Cobb, 1952; Rome & Braceland, 1952).

The mental side effects of glucocorticoid therapy constituted a full spectrum of psychotic disorders. Most often, a "vitalization effect" was observed, particularly in the aged patient (Kountz, Ackermann, & Kheim, 1953) or in

individuals with reduced vitality due to the underlying illness (von Zerssen, 1976 cited in von Zerssen, 1976). In these cases, the patient displayed an elevation of mood, varying in degree from a feeling of well-being to abnormal degrees of euphoria, psychomotor activation, increased appetite and reduced sleep. However, these changes of mood and behavior were generally observed in the first days or weeks of glucocorticoid therapy (Brody, 1952; Dordick & Gluck, 1955; Rees, 1953), and it was not clear whether these signs were related to glucocorticoid actions or to the relief from severe physical complaints and handicap related to the underlying disease treated with glucocorticoids (Lidz, Carter, Lewis, & Surratt, 1952; Rees, 1953).

In a large proportion of patients, euphoria was not present in the first days or weeks of treatment. Rather, tension, irritability, and sleeplessness were present. Both the euphoric and dysphoric states could gradually increase to a full-blown manic episode in which the patient would present marked euphoria or dysphoria, pronounced self-assertiveness, hyperactivity, logorrhea, and flight of ideas (Cobb, Quarton, & Clark, 1954). These are the mental symptoms that have led some scientists and clinicians to name the side effects of glucocorticoid therapy a "steroid psychosis" (Clark et al., 1952; Rome & Braceland, 1952).

There were other types of aberrant behaviors that could appear with glucocorticoid therapy and these later behaviors closely resembled those observed in Cushing's disease patients (Trethowan & Cobb, 1952). These mood and behavioral changes covered a wide range of symptoms and included feelings of weakness, fatigue and drowsiness, lack of concentration, apathy, anxiety, depression, and sometimes suicide as reported by Borman and Schmallenberg (1951). These behavioral changes were also associated with changes in brain activity as measured by EEG. In one man, glucocorticoid therapy sometimes led to epileptic seizures and even to status epilepticus (Loewenberg, 1954; Stephen & Noad, 1951). Similarly, some EEG abnormalities were also found in patients with Cushing's disease (Glaser, Kornfeld, & Knight, 1955; Plotz, Knowlton, & Ragan, 1952). On the whole, the clinical descriptions of cases of steroid psychosis following glucocorticoid therapy were strikingly similar to the mental disturbances associated with Cushing's disease, leading to the idea that glucocorticoids might be the underlying causes of steroid psychosis.

Despite the adverse mental reactions that were reported to occur in glucocorticoid-treated patients in 1951, it is interesting to note that at about the same time, these compounds were also being tested for their possible psychotropic properties in the treatment of mental disorders (Rees & King, 1952). The rationale for testing the possible positive effects of glucocorticoids on mental disturbances in psychiatric patients was the fact that these compounds could induce euphoric or dysphoric states, and that by doing so, could potentially reverse mental states in depressed and schizophrenic patients respectively. However, the results of these trials were disappointing since neither in neurotic nor in endogenous psychotic disorders was there any striking amelioration of the symptoms. In fact, the reverse was observed in both schizophrenia and depression (Rees & King, 1952).

Today, however, glucocorticoid-induced mood disturbances are recognized and classified in the DSM-IV as substance-induced mood disorders, with an associated specification of depressive, manic or mixed features, throughout history certain authors questioned whether glucocorticoids really could cause psychiatric adverse effects (Mitchell & Collins, 1984). A meta-analysis of randomized controlled trials has provided firm confirmation that they can indeed (Conn & Poynard, 1994). In general, prednisone has been most frequently implicated in causing psychiatric side effects (for a review, see Hall, Popkin, Stickney, & Gardner, 1979), but other less widely used steroids such as methylprednisone (Greeves, 1984; Perry, Tsuang, & Hwang, 1984), dexamethasone (Bick, 1983), and even inhaled beclomethasone (Annett, Stansbury, Kelly, & Strunk, 2005; Kreus, Viljanen, Kujala, & Kreus, 1975) have also been reported to induce mental disturbances. Most patients exhibiting side effects are between 21 and 60 years of age (Ling, Perry, & Tsuang, 1981), but adverse mental changes are also being reported in children (Bender & Milgrom, 1995; de La Riva, 1958; Milgrom & Bender, 1995; Sullivan & Dickerman, 1979), and older individuals (Varney, Alexander, & MacIndoe, 1984). Finally, females appear to be at somewhat greater risk than males, even after controlling for diseases that are more common to women (Lewis & Smith, 1983). Importantly however, a recent study showed that in most patients, the cognitive impairments induced by high doses of exogenous corticosteroids are reversible (Brunner et al., 2006).

3.3. Glucocorticoids, the brain, and vigilance

Armed with a large quantity of clinical and psychiatric data revealing mental disturbances after long-term glucocorticoid treatment in patients, researchers then took over the field of human glucocorticoid research, and started to perform psychopharmacological studies, measuring the effects of acute administrations of glucocorticoids in normal individuals.

In 1970, Kopell and collaborators were the first to study the effects of exogenous administrations of glucocorticoids in human subjects. Averaged event-related potentials (ERPs) were introduced at approximately the same time (1968), and based on the rationale that glucocorticoid-therapy could induce changes in EEG activity (Loewenberg, 1954; Stephen & Noad, 1951), Kopell, Wittner, Lunde, Warrick, and Edwards (1970) measured whether exogenous administrations of glucocorticoids could have a significant impact on brain activity. Averaged ERPs reflect electrical activity produced by the brain in response to sensory stimulation and/or activity associated with the execution of specific cognitive tasks. Using this paradigm, Kopell and collaborators found that after glucocorticoid

treatment, ERP amplitudes to visual stimuli were significantly decreased. They concluded from these results that glucocorticoids may have decreased the participants ability to attend to the stimuli and thus reflected a state of hypovigilance. This suggestion corroborated a clinical observation made by Henkin and collaborators 3 years earlier (Henkin, McGlone, Daly, & Bartter, 1967) in Addison's patients who present very low levels of circulating glucocorticoids. These authors described how sensory acuity is strangely elevated in Addison's patients and that treatment of the hypocorticolism with steroids returns sensory acuity to normal. This led Henkin and collaborators to suggest that glucocorticoids act by inhibiting the central nervous system, possibly leading to a state of hypovigilance.

In 1987, Born and collaborators (1987) performed a study in which they infused glucocorticoids for 2 h, and measured ERPs to auditory stimulation. They confirmed the hypovigilance hypothesis and showed a significant reduction in ERP amplitude after glucocorticoid treatment without changes in behavioral performance. In a second study a year later, however, the same authors found that glucocorticoid treatment had enhanced ERP amplitudes to auditory stimuli (Born, Hitzler, Pietrowsky, Pauschinger, & Fehm, 1988) and improved behavioral performance. Naturally, such a result would suggest that glucocorticoids instead increased vigilance, which contradicted the hypovigilance hypothesis described in their earlier paper (Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987), and others (Kopell et al., 1970).

Although differences in methodology could in part account for these contradictory results (e.g., slight differences in stimulus intensity) one firm conclusion reached by the authors was that glucocorticoids had a significant impact on vigilance (Born et al., 1988). In addition, the differential effects observed on behavioral performance and ERP amplitudes led them to allude to the existence of a more complex relationship between glucocorticoids and cognitive processing that could be akin to the notion proposed by Yerkes and Dodson in 1908 (Yerkes & Dodson, 1908) stating that an inverted-U shape curve describes the relationship between vigilance and cognitive efficiency. Optimal states of vigilance should be related to the optimal state of cognitive efficiency, while significant decrease or increase in vigilance should lead to impaired cognitive efficiency.

3.4. Glucocorticoids, the hippocampus, and declarative memory

At about the same time, and in very different laboratories, researchers were intrigued by the fact that glucocorticoid treatment could lead to psychiatric symptoms. Indeed, for many years, endocrinologists and neuroscientists thought that hormones, which are biological products, secreted by peripheral glands, did not access the brain and acted mainly at the level of the peripheral nervous system. However, in the early 1960s, the discovery of neuropeptides as substances having not only classical endocrine effects, but also affecting brain and behavior, significantly extended our view of hormones and opened the door to new possibilities of hormonal actions on the brain (for a complete historical background, see de Kloet, 2000). The observation that glucocorticoid treatment could lead to steroid psychosis suggested that the excessive concentrations of the steroid may access the brain and exacerbate, perpetuate or modify the presentation of mental symptoms associated with glucocorticoid administration. Such a hypothesis was appropriate since in 1943, Harris had completed a series of landmark anatomical studies that clearly established that the central nervous system regulates the HPA axis (Harris, 1972).

The search for brain receptors able to recognize peripheral hormones began. In 1968, it culminated with Bruce McEwen's seminal *Nature* paper showing that the rodent brain was indeed able to recognize glucocorticoids (McEwen, Weiss, & Schwartz, 1968). The story then took a very important detour when McEwen and collaborators reported that the brain region showing the highest density of receptors for glucocorticoids was the hippocampus, a brain region significantly involved in learning and memory.

At this point in history, one observes a tremendous switch in scientific studies of glucocorticoids from ERP studies to memory-related studies. The rationale was based on the fact that the largest amount of glucocorticoid receptors is found in the hippocampus, a structure now known to be involved in specific types of memory functions in humans. Scoville and Milner (1957) were the first to report that the hippocampus is essential for declarative memory, while it is not essential for non-declarative memory (Squire, 1992). The former underlies the conscious acquisition and recollection of facts and event, while the latter holds information regarding processes and procedures for completing highly practiced tasks such as riding a bike, (Scoville & Milner, 1957). Thus, this somewhat specialized role of the hippocampus served as the basis for specific hypotheses regarding the relation between increased cortisol secretion and impaired cognitive function in humans.

What is very interesting with the history of the search for glucocorticoid effects on human cognition is that from now on, scientists will be interested in showing that glucocorticoids have specific effects on human declarative memory function that cannot be explained by glucocorticoid-induced changes in vigilance or attention. In general, the majority of human studies that have measured the impact of glucocorticoids on cognitive function report impaired declarative memory function after acute administrations of synthetic glucocorticoids (for a complete review, see Lupien & McEwen, 1997).

The first study performed on the acute effects of glucocorticoids on human memory process was a dose–response study that showed that the effects of hydrocortisone on human memory performance depend upon the dose administered (Beckwith, Petros, Scaglione, & Nelson, 1986). Only the highest doses of hydrocortisone (40 mg) enhanced

recall when subjects were presented with lists of words. Hydrocortisone administration in the morning (at the time of cortisol peak) impaired declarative memory function, while it had no effect on cognitive performance when administered at night (Fehm-Wolfsdorf, Reutter, Zenz, Born, & Lorenz-Fehm, 1993). Kirschbaum, Wolf, May, Wippich, and Hellhammer (1996) showed that 60 min after the oral administration of 10 mg of hydrocortisone, declarative memory performance was significantly impaired while non-declarative memory performance remained intact, thus supporting the view that glucocorticoids affect hippocampal-dependent cognitive functions.

More recently, de Quervain, Roozendaal, Nitsch, McGaugh, and Hock (2000) tested the impact of an acute increase in glucocorticoids as a function of the nature of memory processing. High doses of synthetic glucocorticoids were administered either before the acquisition of a list of words, immediately after or just before the retrieval of the list. The results revealed significant impairments in memory when the drug was administered just before retrieval, thus suggesting specific effects of glucocorticoids on the retrieval of previously learned information (see also Domes, Rothfischer, Reichwald, & Hautzinger, 2005).

A specific effect of acute glucocorticoid elevations on retrieval processes in humans has recently been replicated by Wolkowitz et al. (1990). Young and older men were given a medium dose of synthetic glucocorticoids after having learned a list of 10 words. A second word list was learned and recalled after drug administration. Results showed that glucocorticoids impaired recall of the word list learned before treatment in both groups but did not influence recall of the list learned after treatment. These results agree with previous data showing that acute exogenous administrations of glucocorticoids have impairing effects on retrieval processes (de Quervain et al., 2000).

The *in vivo* demonstration of glucocorticoid effects on memory retrieval processes was recently performed by the group of de Quervain et al. (2003) using positron emission tomography (PET). Young subjects were given a medium dose of synthetic glucocorticoids 24 h after learning various declarative memory tasks. Brain activation was measured by PET 1 h after drug administration. Results showed that glucocorticoids induced a large decrease in regional cerebral blood flow in the right posterior medial temporal lobe coupled with impaired cued recall of word pairs learned 24 h earlier. These results were the first to provide an *in vivo* demonstration that acutely elevated glucocorticoid levels can impair declarative memory retrieval processes that are related to measurable changes in medial temporal lobe function. A similar impairment of retrieval function was recently reported by Buss, Wolf, Witt, and Hellhammer (2004). These authors administered a small dose of synthetic glucocorticoids to young adults, and measured retrieval of past events in their life (autobiographical memory). Results showed that when compared to placebo, glucocorticoids significantly impaired retrieval of past personal events.

Besides acute actions, delayed effects of glucocorticoids were reported in several memory studies in human subjects. Impaired memory performance was observed in normal adults following 5 days administration of high doses of prednisone (80 mg p.o. daily), but normal memory performance in another group of subjects following a more acute administration of 1 mg of dexamethasone (Wolkowitz et al., 1990). Similarly, a 4-day administration procedure with 0.5,1, 1, 1 mg/day of dexamethasone in normal controls produced impaired declarative memory performance (acquisition and recall) on the fourth day of treatment only (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994). Similar results were obtained by the same group using hydrocortisone (Newcomer et al., 1999). In both studies, no immediate or delayed effects of dexamethasone were observed on non-declarative memory or on selective attention performance. Similar results were obtained using a 4-day regimen of 160 mg of prednisone. Taken together, these results were in accordance with a hippocampal involvement in glucocorticoid-related cognitive deficits and argued against a nonspecific effect of the steroid on attention and arousal (Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999).

In summary, the majority of studies performed in human populations tend to confirm the rodent literature reporting acute negative effects of glucocorticoids on hippocampal-dependent forms of memory (for a recent meta-analysis, see Het, Ramlow, & Wolf, 2005). Altogether, the rodent and human data strengthened the view that stress hormones have a specific impact on the hippocampus (for a complete critical review of the glucocorticoid-hippocampus link, see Lupien & Lepage, 2001).

3.4.1. Interim: Lessons from history

Let us stop time and go back to Bruce McEwen et al.'s, 1968 discovery of glucocorticoid receptors in the rodent hippocampus (McEwen et al., 1968). It is clear from the literature summarized above that the presence of glucocorticoid receptors in the rodent hippocampus served as the basis for the hypothesis that glucocorticoids should significantly and specifically impair declarative memory function in humans. However, and although the hypothesis was simple, economical, and easy to test, a closer look at history teaches us that the glucocorticoid-hippocampus link might not be the best hypothesis to fully explain glucocorticoid-induced cognitive changes in humans (for a complete review on this topic, see Lupien & Lepage, 2001). Here is what history has to tell us.

In their 1968 paper, McEwen and collaborators described the retention of corticosterone, a naturally occurring glucocorticoid, in the rodent brain (McEwen et al., 1968). The rats were first adrenalectomized (the adrenal glands were removed and the animal was kept alive with physiological doses of corticosterone) in order to deplete the rat's system of any endogenous circulating glucocorticoids, and then corticosterone was injected and the retention of this naturally occurring glucocorticoid was

assessed. Using this method, they showed that corticosterone was highly retained by the hippocampus.

Researchers then sought to determine whether other synthetic glucocorticoids would be retained by the hippocampus. Notable among these was dexamethasone. de Kloet, Wallach, and McEwen (1975) found the compound to be very poorly retained by the rodent hippocampus, irrespective of the route of administration (peripheral *vs.* intracerebroventricular). Later, it was shown that the small amount of dexamethasone that did penetrate the brain was retained in a regional pattern that was distinct from that of corticosterone (McEwen, 1976). In the same study, another steroid (cortisol) that is not a natural glucocorticoid in the rat (although it is in humans) was very poorly retained in the rodent brain, while corticosterone and aldosterone (another naturally occurring glucocorticoid) were highly retained by the rodent hippocampus and surrounding limbic structures.

The different modes of action of dexamethasone and corticosterone on the rodent brain indicated that these two compounds might bind to *different* types of glucocorticoid receptors. This idea was confirmed six years later by the presence of mineralocorticoid (Type I) and glucocorticoid (Type II) receptors in the rodent hippocampus (Veldhuis, van Koppen, van Ittersum, & de Kloet, 1982). The trace amounts of corticosterone that were previously retained so abundantly by the rodent hippocampus were actually bound to Type I and not to Type II receptors (Reul & De Kloet, 1985). In fact, these authors showed that affinity of hippocampal Type II for corticosterone in the rat brain was actually too low for any signal to be detected. At this point in time, history taught us one important fact about Type I and Type II receptors, i.e. that there exists a tremendous difference in the two receptor types in terms of affinity.

We now know that Type I receptors bind glucocorticoids with an affinity that is about 6- to 10 times higher than that of Type II (Reul & De Kloet, 1985). This differential affinity results in a striking difference in occupation of the two receptor types under different conditions and time of day. Specifically, during the circadian trough (the PM phase in humans), the endogenous hormone occupies more than 90% of Type I receptors, but only 10% of Type II receptors. However, during stress and/or the circadian peak of glucocorticoid secretion (the AM phase in humans), Type I receptors are saturated, and there is occupation of approximately 67–74% of Type II receptors (Reul & De Kloet, 1985). This differential affinity of Type I and Type II opened the door to a brand new hypothesis about glucocorticoid effects on cognitive function, i.e. that glucocorticoids could *also* have positive effects on cognitive function.

3.5. Positive effects of glucocorticoids on human cognition

In contrast to human studies in which glucocorticoids were consistently shown to have detrimental effects on declarative memory function (see above), many studies performed in rodents reported that the ratio of Type I/Type II occupation is a major determinant of the direction of glucocorticoid-induced cognitive changes (for a review, see de Kloet, Oitzl, & Joels, 1999). For example, long-term potentiation (LTP), a proposed neurobiological substrate of memory formation, has been shown to be optimal when glucocorticoid levels are mildly elevated, i.e., when the ratio of Type I/Type II occupation is high (see Diamond, Bennett, Fleshner, & Rose, 1992). In contrast, significant decreases in LTP are observed after adrenalectomy, when Type I occupancy is very low (Dubrovsky, Liquornik, Noble, & Gijsbers, 1987; Filipini, Gijsbers, Birmingham, & Dubrovsky, 1991), or after exogenous administration of synthetic glucocorticoids (Bennett, Diamond, Fleshner, & Rose, 1991; Pavlides, Watanabe, & McEwen, 1993), which activate Type II and deplete glucocorticoids, again resulting in low occupancy of Type I.

In a review of these issues, de Kloet et al. (1999) re-interpreted the effects of glucocorticoids on cognitive performance in line with the Type I/Type II ratio hypothesis, suggesting that cognitive function can be enhanced when most of the Type I and only part of the Type II are activated (top of the inverted-U shape function; increased Type I/Type II ratio; see Fig. 3). However, when circulating levels of glucocorticoids are significantly decreased or increased (extremes of the inverted-U shape function; low Type I/Type II ratio), cognitive impairments will result. The authors suggested that the negative view of glucocorticoid actions on human cognitive function could be partly explained by limitations in previous human experimental designs, which did not allow for the differential manipulation of Type I and Type II levels. In order to do this, such studies should measure cognitive function when glucocorticoid receptors occupancy is decreased (rather than increased), thus allowing for functional measures of Type I/Type II occupancy on learning and memory. One way

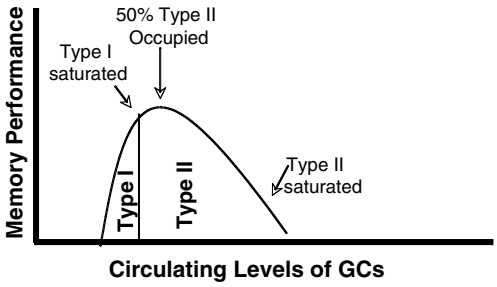

Fig. 3. The Type I/Type II glucocorticoid ratio hypothesis of the association between circulating levels of glucocorticoids, and memory performance (de Kloet et al., 1999). The figure shows occupancy of GC receptors as a function of circulating levels of GCs and resulting modulation of memory. When Type I glucocorticoid receptors are saturated and there is partial occupancy of Type II glucocorticoid receptors, there is maximization of memory, while when both Type I and Type II glucocorticoid receptors are not occupied (left side of the inverted-U shape function) or are saturated (right side of the inverted-U shape function), there is an impairment in memory performance.

to test such a hypothesis is the use of a hormone removal–replacement protocol.

In a hormone removal–replacement protocol, the behavior resulting from the absence of the hormone of interest is first measured, and then baseline hormonal levels are restored to normal values and the same behavior is measured once again. If the hormone of interest has a real impact in the behavior tested, then this behavior should be restored to normal value after hormonal replacement (see Brown, 1998).

In order to test this suggestion, our group performed a hormone removal–replacement study in a population of young normal controls (Lupien et al., 2002). In this protocol, we used a within-subject double-blind experimental protocol in which we first pharmacologically lowered glucocorticoids levels by administrating metyrapone, a potent inhibitor of glucocorticoid synthesis, we then restored baseline circulating glucocorticoid levels by infusing hydrocortisone, a synthetic glucocorticoid. Memory performance of participants under each of these conditions was compared to that measured on a placebo day. The results showed that when compared to placebo, the pharmacological decrease of circulating levels of glucocorticoids induced by metyrapone significantly impaired memory performance. Most importantly, we showed that this impairment was completely reversed after hydrocortisone replacement (see Fig. 4 for a schematic representation of the results). These results showed that glucocorticoids can modulate memory function, and most importantly, they showed that the absence of circulating glucocorticoid levels is as detrimental for human memory function as is a significant increase in glucocorticoids.

We have suggested that this modulation can happen through a differential activation of Type I and Type II receptors. Indeed, during the metyrapone condition, Type I occupancy was low, given the significant decrease of glucocorticoid secretion induced by metyrapone. At this point, impairment in memory was observed. In contrast, during the hydrocortisone replacement condition, glucocorticoid levels were restored to the those typically found in the AM phase, i.e. leading to a saturation of Type I, with partial occupancy of Type II. This differential occupation thus led to an increased Type I/Type II ratio, and a restoration of baseline cognitive performance.

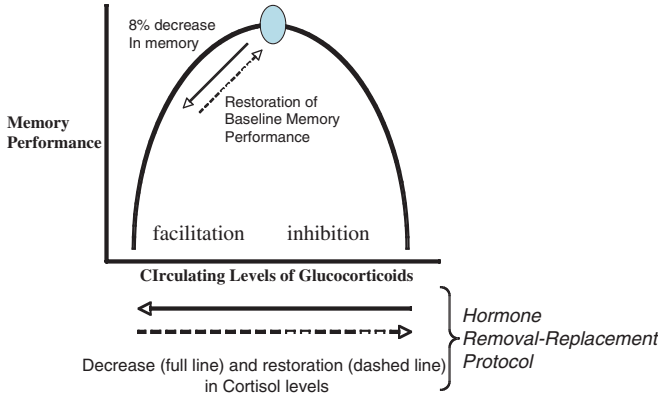

Fig. 4. Schematic representation of the modulation of memory performance by pharmacological inhibition of cortisol secretion (full arrow), and by hydrocortisone replacement (dashed arrow) in young human participants. After corticol decrease, we observed a 8% decrease in declarative memory performance that was restored to placebo level after restoration of circulating levels of cortisol by pharmacological infusion of hydrocortisone (see Lupien et al., 2002).

In a second study (also in Lupien et al., 2002), we took advantage of the circadian variation in circulating levels of glucocorticoids and tested the impact of a bolus injection of glucocorticoids in the late afternoon, at a time of very low glucocorticoid concentrations. In a previous study with young normal controls, we injected a similar dose of glucocorticoids in the morning, at the time of the circadian peak, and reported detrimental effects of glucocorticoids on memory (Lupien, Gillin, & Hauger, 1999). Here, when we injected a similar dose of hydrocortisone in the afternoon, at the time of the circadian trough, we observed that although glucocorticoids did not change memory performance they nonetheless had a positive impact on cognitive efficiency and vigilance by significantly decreasing reaction times on a recognition memory task when compared to the placebo condition.

Data obtained by Oitzl and de Kloet in 1999 led them to propose that each glucocorticoid receptor type contributes to different aspects of cognitive processing. They found that Type I receptor activation is important for behavioral reactivity in response to environmental cues affecting vigilance and attention. Type II activation on the other hand is essential for the consolidation of events/items in memory.

In this view, the delayed memory impairment observed after Metyrapone administration (i.e. due to the lack of Type II activation) in our first experiment is consistent with a Type II receptor-mediated effect on consolidation processes. The significant decreases in reaction times observed in our second experiment are in line with a Type I-mediated effect on behavioral reactivity and vigilance. Taken together these findings offer further support for the notion that the Type I/Type II occupancy ratio is an important factor in determining the direction and magnitude of glucocorticoids effects on cognitive processing and that each receptor type plays a distinct yet complimentary role at different stages of processing.

3.5.1. Interim: Lessons from history

Now, let us stop time again, and go back to Reul and De Kloet's, 1985 work on Type I and Type II receptors. The study of Type I and Type II activity in the brain showed that there exist large differences in terms of affinity for Type I and Type II, a finding that led to the view that glucocorticoids are not only destructive (de Kloet et al., 1999).

However, the search for Type I and Type II receptors in the brain led to another important discovery, i.e. the differential distribution of Type I and Type II receptors in the rodent brain. Following the work by Reul and De Kloet

(1985), it was established that in the rodent brain, the Type I is present exclusively in the limbic system, with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. In contrast, the Type II receptor is present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex (Diorio, Viau, & Meaney, 1993; McEwen, De Kloet, & Rostene, 1986; McEwen et al., 1968; Meaney, Sapolsky, Aitken, & McEwen, 1985). Still, in the rodent brain, the largest concentration of both Type I and Type II receptors was found in the hippocampus, which again led to the glucocorticoid-hippocampus link described before.

However, in 2000, two papers were published which described the distribution of Type I and Type II receptors in the primate brain, more closely related to the human brain in terms of neocortical development. These two recent studies mapping both Type I and Type II receptor distribution in the primate brain strongly suggested that extrapolation from rat brain to primate brain may be misleading when discussing the impact of glucocorticoids on the hippocampus.

The first study reported that, in contrast to its well established distribution in the rat brain, Type II mRNA is only weakly detected in the dentate gyrus and Cornu Ammonis of the macaque hippocampus (Sanchez, Young, Plotsky, & Insel, 2000). In contrast, Type II mRNA is strongly detected in the pituitary, cerebellum, hypothalamic paraventricular nucleus and prefrontal cortices. In a second study, it was reported that Type II receptors were well-expressed in the hippocampus, but were more prominently found in the prefrontal cortex (Patel et al., 2000). Thus, Type I receptors are present in large quantities in the hippocampus and limbic structures in the primate brain, while Type II receptors are present in all these structures and additionally in frontal regions. This latter finding suggested that in humans, glucocorticoids should not only affect the hippocampus, but also the frontal lobes. This has been recently supported.

3.6. Glucocorticoids, the frontal lobe, and working memory

Studies in nonhuman primates (Goldman-Rakic, 1987, 1995), and humans (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Petrides & Milner, 1982) show that lesions of the dorsolateral prefrontal cortex (DLPFC) give rise to impairments in working memory. Working memory is the cognitive mechanism that allows us to keep a small amount of information active for a limited period of time (see Baddeley, 1995). In these working memory tasks, a temporal gap is introduced between a stimulus and a response, which creates the need to maintain the stimulus in temporary memory storage. Data obtained in monkeys showed that cells in the lateral prefrontal cortex become particularly active during delayed response tasks, suggesting that these cells are actively involved in holding on to the information during the delay (Goldman-Rakic, 1990, 1995).

Neuropsychological evidence suggests that humans with DLPFC damage are impaired in working memory (Fuster, 1980; Luria, 1966). These patients are also highly susceptible to cognitive interference and they perform poorly on neuropsychological tests that require response inhibition such as the Wisconsin Card Sorting Test (Shimamura, 1995; Stuss et al., 1982). Moreover, neuroimaging data show a significant relation between working memory processing and the activations observed in the prefrontal cortex (Smith, Jonides, Marshuetz, & Koeppe, 1998; but also see Ungerleider, Courtney, & Haxby, 1998).

Working memory appears to be more sensitive than declarative memory to the effects of acute and short-term administrations of glucocorticoids. Young, Sahakian, Robbins, and Cowen (1999) administered glucocorticoids for 10 days to young normal male volunteers and measured various cognitive functions in a randomized, placebo control, crossover, within-subject design. They showed that this regimen of glucocorticoids led to deficits in cognitive function sensitive to frontal lobe dysfunction (working memory), while it did not impact on cognitive function sensitive to hippocampal damage (declarative memory).

Similar results were obtained by our group using an acute dose–response neuroendocrine protocol (Lupien et al., 1999). In this study, 40 young subjects were infused for 100 min with either glucocorticoids or placebo, and declarative and working memory were tested during the infusion period. Performance on the working memory task decreased significantly whereas performance on the declarative memory task remained the same following an acute elevation of glucocorticoids. Curve fit estimations revealed the existence of a significant quadratic function (U-shape curve) between performance on the working memory task and changes in glucocorticoids levels after hydrocortisone infusion. The results of these two studies suggested that in young individuals, working memory is more sensitive than declarative memory to an acute elevation of glucocorticoids, supporting the suggestion that glucocorticoids have a significant impact on frontal lobe functions in humans.

Similar results were obtained by Hsu, Garside, Massey, and McAllister-Williams (2003). In their study, twenty healthy subjects were treated with a high dose of synthetic glucocorticoids or placebo orally, in a double-blind, two-way crossover study. It was found that glucocorticoids impaired performance on an attentional task (Stroop), while they did not impair performance on a declarative memory task. Other studies, however, report an opposite pattern of findings. Monk and Nelson (2002) for instance showed that working memory task (n-back) performance was unaffected by a moderate dose of exogenous glucocorticoids but that declarative memory performance (intentional face recognition) suffered as a result of the increase in glucocorticoids. These data may in part be explained by the fact that face encoding is not an entirely hippocampus-dependent process and that

it in fact recruits frontal regions (Sergerie, Lepage, & Armony, 2005).

3.7. Glucocorticoids and emotional memory

In humans, the frontal lobes have been shown to be significantly involved in emotional processing (for a review, see Damasio, 1995), and given the impact of glucocorticoids on human frontal lobe function (Lupien et al., 1999; Young et al., 1999), it might be asked whether glucocorticoids also impact on human emotional memory. In a recent study, Buchanan and Lovallo (2001) exposed young participants to pictures varying in emotional arousal after they received a small dose of synthetic glucocorticoids (Buchanan & Lovallo, 2001). During acquisition, subjects were not aware that their memory for the pictures would be tested a week later (incidental memory). Results revealed that glucocorticoid elevations during memory encoding enhanced the delayed recall performance of emotionally arousing pictures while it had no impact on the delayed recall of the neutral pictures.

Similarly, Abercrombie, Kalin, Thurow, Rosenkranz, and Davidson (2003) tested the effects of an exogenous administration of two doses of synthetic glucocorticoids on emotional memory using a dose–response study. Young men were presented with emotionally arousing and neutral stimuli after receiving either a placebo or a low or medium dose of synthetic glucocorticoids. Free recall of the stimuli was assessed 1 h after drug administration and recognition memory of the stimuli was assessed two evenings later. Results showed that glucocorticoid elevations decreased the number of errors committed on the free-recall tasks (increased performance). More importantly, the authors showed that when tested for recognition two evenings later, when cortisol levels were no longer manipulated, recognition performance presented an inverted-U quadratic curve. Glucocorticoid-induced enhancements of recognition memory were only observed in the low-dose condition. In contrast to the data obtained by Buchanan and Lovallo (2001), these results showed beneficial effects of synthetic glucocorticoids on both emotionally arousing and neutral material.

4. Stress, emotion, and cognition

Now that we have described the exogenous effects of glucocorticoids on cognition, it is important to turn our attention to the fact that endogenously released glucocorticoids in the face of stress can also impact cognitive performance. Indeed, most of the previous literature covered used exogenous administrations of synthetic glucocorticoids in order to delineate the effects of glucocorticoids on human cognitive function. Yet, and as presented in Fig. 1, glucocorticoids are natural substances that are secreted in the face of a challenge. Interestingly, glucocorticoids that are secreted endogenously in the face of a challenge still have the ability to cross the blood–brain barrier and impact cognitive performance through binding to Type I and Type II glucocorticoid receptors in the brain. However, before describing the effects of stress and related stress hormones on cognitive performance, it is important to dissociate the effects of emotions from those of stress on human cognition.

4.1. Stress versus emotion

Emotionally arousing and stressful experiences are often cited as the cause of many psychological and physical problems. Many of us have experienced emotionally arousing and stressful experiences at one point or another in life, and noted that these experiences can have important effects on our memory. One can have forgotten an important meeting or anniversary due to work overload, or else, one can have a vivid recollection of a car accident or any other emotionally arousing experience. Because of their impact on our lives, we have a tendency to pay more attention to the negative effects of stress on our memory, and to forget that under certain conditions, emotionally arousing and stressful experiences can also have a positive impact on memory function.

Emotion and stress share many characteristics. A stressful experience will often cause a particular emotion (e.g., surprise, fear, joy, etc.), and particular emotions can create stressful situations (e.g., blushing due to extreme timidity can cause a stressful situation for an individual). Moreover, an emotion possesses many of the properties of a stressor. First, it often has an identifiable source. Second, it is usually brief and leads to an intense and conscious experience of short duration. Finally, an emotion creates bodily reactions (e.g., increase in heart rate, perspiration, etc.) that are similar to those induced by a stressor, and both states act by increasing arousal. Because of these similarities between emotion and stress, most of the literature on emotion, stress and memory intermixes the effects of emotion and those of stress upon memory function. However, emotion and stress are two different entities. Although a stressful experience will almost always trigger a specific emotion, a particular emotion does not always elicit a stress reaction (for a complete review on the difference between a stress and an emotion, see Lupien & Brière, 2000).

As far as laboratory settings are concerned, emotion and stress differ in the way they are induced and thus, in the way they influence memory in humans. Hence, emotions are usually induced by the presentation of emotional words, films or pictures, while stress is usually induced by putting the individual in a social situation known to create stress (e.g., a public speaking task). Because of this important difference between the experimental paradigms used to measure the effects of emotion and stress on memory, different questions have been asked. Induction of emotion has been used to measure memory *for* emotionally arousing events, while induction of stress has been used to measure the specific effects of stress *on* subsequent memory function.

4.1.1. Mechanisms underlying memory for emotionally arousing events

It is well known that what we encode and remember from an event depends primarily on the attention that is devoted to this event and its components. If you do not pay attention to what you are reading right now, there is less chance for you to remember it at a later time than if you give all your attention to your reading. This is because the more attention given to an event, the higher the probability that this event will be elaborated (relating the information from this event to other situations and related concepts in memory) at the time of encoding.

The level of attention devoted to an event at the time of encoding will greatly depend on the emotional salience of this event. Most of us remember what we were doing and with whom we were at the time we learned about the World Trade Center attacks, but the majority of us may have difficulty remembering what we were doing and with whom we were 13 days before or after the attacks. This "flashbulb memory" phenomenon may be explained by the fact that the emotions (e.g., surprise, anger, fear etc.) that were triggered by the announcement of the World Trade Center attacks directed the totality of our attention to the event, leading to a deeper elaboration and thus, to an optimization of our memory for this event.

Studies with trauma victims have reported how vividly the traumatic event is recalled, in the absence of any memory for information surrounding the traumatic event. A closely analogous situation appears in the field of law enforcement and describes the "weapon focus" phenomenon. Witnesses to violent crimes demonstrate a weapon focus effect in which the weapon captures most of the victim's attention, resulting in a reduced ability to recall other details of the scene and to recognize the assailant at a later time (see Christianson, 1992). This phenomenon has been explained by Easterbrook's (1959; see Christianson 1992) cue utilization theory which suggests that emotionally arousing events narrow subjects' attention and lead them to attend only to the center of an event, and to exclude more peripheral information. In general, laboratory experiments have confirmed this hypothesis (Christianson, 1992). Recently, Cahill, Gorski, Belcher, and Huynh (2004) pushed this analysis further and reported gender-related influences in the recall of central *vs.* peripheral information from an emotional story (Cahill et al., 2004). Men and women with high male-related traits on the Bem Sex-Role Inventory show better memory for central aspects of an emotional story, relative to peripheral details. On the other hand, women and men with high female-related traits on the Bem Sex-Role Inventory have a better memory for peripheral details of an emotional story, as opposed to central information (Cahill et al., 2004; Cahill, Gorski, & Le, 2003).

Studies have examined the relation between emotion, retention intervals and memory. What these studies have shown so far is that emotionally arousing events delay forgetting. In a highly cited study, Kleinsmith and Kaplan (1963) asked participants to learn neutral and emotionally laden (e.g., "rape", "mutilation") word pairs. Both short-term (2 min) and long-term (1 week later) declarative memory for the words pairs was assessed. The results showed that emotional word pairs were better recalled after a long retention delay (Kleinsmith & Kaplan, 1963; Kleinsmith, Kaplan, & Tarte, 1963). These results have been replicated many times and the majority of studies have shown enhanced memory for emotionally arousing material, provided that memory is tested at longer retention intervals.

There are extensive data showing that the observed retrograde enhancement of long-term memory for emotionally arousing events is related to the hormones released during these experiences. Emotionally arousing events give rise to the secretion of the peripheral catecholamines adrenaline and noradrenaline by the adrenal medulla, central noradrenaline secretion by the locus coeruleus and to glucocorticoids secretion by the adrenal glands. Glucocorticoids readily access the brain and can thus act directly to impact emotional memory processing (Roozendaal, 2002; Roozendaal, Brunson, Holloway, McGaugh, & Baram, 2002). The peripheral catecholamines on the other hand, enhance memory by reaching the vagus nerve, the nucleus of the solitary tract and the locus ceruleus. Central noradrenaline is then secreted by the locus ceruleus, activating noradrenergic neurons throughout the brain (Roozendaal, 2002). Importantly, central noradrenaline is also triggered as soon as an emotionally arousing event occurs, independently of peripheral catecholamines (McGaugh & Roozendaal, 2002; Roesler, Roozendaal, & McGaugh, 2002; Roozendaal, 2002). Specifically though, hormonal effects on emotional memory processing are achieved via the interactions between adrenergic hormones and glucocorticoids and their respective receptors in the amygdala (Roozendaal, 2002). This then results in a modulation of hippocampal activity and ultimately, enhanced long-term memory for emotional material (Roozendaal, 2002; Roozendaal et al., 2002; Roozendaal, Quirarte, & McGaugh, 2002).

Animal and human studies have confirmed the role of these hormones in the memory-modulating effects of emotionally arousing events. In rodents, post-learning stimulation of the noradrenergic system enhances, whereas post-learning blockade inhibits, long-term declarative memory of an inhibitory avoidance task (McGaugh, 2000). Likewise, post-training injections of moderate doses of synthetic glucocorticoids enhance, and pre-training glucocorticoid synthesis inhibition impairs, long-term expression of inhibitory avoidance in animals (Roozendaal, 2002; Sandi, 1998). In humans, pre-learning blockade of central β-adrenergic receptors or pre-learning glucocorticoid synthesis inhibition impairs long-term declarative memory for emotionally arousing material (Cahill et al., 1994; Maheu et al., 2004), whereas pre-learning or post-learning stimulation of the noradrenergic or glucocorticoid systems enhances it (Abercrombie et al., 2003; Buchanan & Lovallo, 2001; Cahill & Alkire, 2003). Although psycholog-

ical and biological explanations of the arousal hypothesis were used to explain the positive effects of emotion on memory function, research performed to this day shows that arousal is significant as an intervening variable only when the source of the arousal (in this case, the emotionally arousing event) is directly related to the information to be remembered (Gore, Krebs, & Parent, 2006; Kuhlmann & Wolf, 2006). However, when the source of emotion is not directly related to the information to be remembered, other psychological and biological mechanisms come into play and have a stronger impact on memory function than arousal itself. Consistent with this suggestion, Rimmele, Domes, Mathiak, and Hautzinger (2003) reported that cortisol administration increased memory for details of neutral pictures, while it impaired memory for details of emotional pictures (Rimmele et al., 2003), showing the intricate relationship existing between stress, emotion, and memory.

4.2. Effects of stress on human memory

Remembering with great accuracy a particular emotionally arousing event is very different from performing various tasks involving memory in a day-to-day situation when one is faced with stress. We may remember with great accuracy the events in our lives surrounding the World Trade Center attacks, but we may also have forgotten an important appointment due to work stress.

Interestingly, rodent studies have shown that, when a laboratory stressor (e.g., tailshocks, water immersion or restraint stress) is administered at various time-points before or after learning, as well as before recall, stress-induced elevations in glucocorticoid levels modulate declarative memory according to an inverted U-shaped function, a finding that is equivalent to the observed effects of exogenous glucocorticoids on human cognition. Optimal declarative memory for material unrelated to the stressor (e.g., inhibitory avoidance protocols or spatial water-maze tasks) occur at moderate levels of stress and stress-induced increases in circulating glucocorticoid levels, whereas lower (i.e., boredom or drowsiness) or higher stress levels and stress-induced increases in circulating glucocorticoid levels are less effective or may even impair declarative memory performance on these tasks (Roozendaal, 2002; Sauro, Jorgensen, & Pedlow, 2003).

In humans, when a laboratory stressor (e.g., a public speaking task or a public mental arithmetic task) is administered before learning or retrieval, high glucocorticoid levels following these stressors are associated with memory impairments for material unrelated to the stressor such as neutral words lists (see Jelici, Geraerts, Merckelbach, & Guerrieri, 2004; Lupien, Buss, Schramek, Maheu, & Pruessner, 2005; Lupien, Fiocco, Wan, Maheu, Lord, Schramek, et al., 2005; Sauro et al., 2003; Takahashi et al., 2004; cf. Domes, Heinrichs, Reichwald, & Hautzinger, 2002; Wolf, Schommer, Hellhammer, Reischies, & Kirschbaum, 2002). Recently, studies measuring the influence of stress on memory for emotional material unrelated to the stressor reported more heterogeneous findings. Thus, when a laboratory stressor was presented before learning or retrieval of emotional and neutral information unrelated to the stressor, high glucocorticoid levels following stress were associated with memory impairments for emotional information (whether positive or negative), while they had no influence on memory for neutral material (Abercrombie, Speck, & Monticelli, 2006; Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004; Kuhlmann, Piel, & Wolf, 2005; Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005; but see Elzinga, Bakker, & Bremner, 2005). However, two other studies showed that stress administered before (Jelici et al., 2004) or after (Cahill et al., 2003) learning enhanced memory for emotional material, while it had no impact (Cahill et al., 2003), impaired (Buchanan, Tranel, & Adolphs, 2006) or increased (Andreano & Cahill, 2006) subsequent memory for neutral information (Jelici et al., 2004).

Altogether, these results show that stress-related elevations in glucocorticoids can have different effects on subsequent memory for material unrelated to the stressor. The effects of emotionally arousing and/or stressful events on declarative memory vary according to the *nature* of the to-be-remembered material, with elevated levels of glucocorticoids enhancing memory for the emotionally arousing event itself but leading, more often than not, to poor memory for material unrelated to the source of stress/emotional arousal.

The *time of day* (morning *vs.* afternoon) and *levels of circulating glucocorticoids* at the time of testing could also be important factors influencing the effects of stress-related elevations in glucocorticoids on subsequent memory for material unrelated to the stressor. Glucocorticoid receptors differ in terms of their affinity for circulating levels of glucocorticoids. As we have discussed previously, Type I receptors have a 6- to 10-times higher affinity for glucocorticoids than Type II receptors. A wealth of evidence now demonstrates that activation of Type I receptor is mandatory for successful acquisition of environmental cues necessary to encode information, whereas activation of Type II receptors is necessary for long-term memory consolidation of this information (Oitzl & de Kloet, 1992). Endogenous levels of glucocorticoids and thus, activation of Type I and Type II receptors will vary across the day, with higher endogenous levels of glucocorticoids in the AM phase compared to the PM phase. Consequently, the addition of a stressful event in the AM or PM phase, which by itself will trigger a significant increase in endogenous levels of glucocorticoids, should have a differential impact on activation of Type I and Type II receptor as a function of time of day, and consequently, on memory performance. As indicated earlier, in the AM phase, most of the Type I receptors and about half of the Type II receptors are activated, while in the PM phase, most of the Type I receptors and about a tenth of the Type II receptors are activated. If one applies a stressor in the AM phase, the endogenous increase in glucocorticoid levels that will be induced by the stressor will

act by saturating Type II receptors, while the same stressor applied in the PM phase will act by activating about half of the Type II receptors. Since stress-induced elevations in glucocorticoid levels have been shown to modulate declarative memory for material unrelated to the stressor according to an inverted U-shaped function, the differential activation of Type I and Type II receptors at different times of the day thus implies that a stressor applied in the morning should impair memory function (right hand-side of the inverted U-shaped curve), while the same stressor applied in the PM phase should increase or have no impact on memory (left-hand-side or top of the inverted U-shaped curve; see Lupien, Fiocco et al., 2005).

Finally, very few studies have measured the influence of the central noradrenergic system, activated following stress, on subsequent memory for material unrelated to the stressor. Animal studies report that stress-induced elevations in noradrenaline levels (following footshocks) modulate declarative memory according to an inverted U-shaped function, with optimal levels enhancing, and lower or higher levels of noradrenaline, impairing memory for information unrelated to the source of stress (e.g., passive aversive conditioning; Gold & McGaugh, 1975; Gold, van Buskirk, & McGaugh, 1975). In humans, one recent study showed that blockade of peripheral and central noradrenergic β-receptors before the administration of a stressor did not impair memory for material unrelated to the source of stress (Maheu et al., 2005). These results suggest that the β-adrenergic system is not implicated in the effects of stress on subsequent declarative memory function, contrasting with the well-established role of this system during the memorization of events that are emotionally arousing in nature. Further studies in humans will be needed to determine the exact role played by the central noradrenergic system in the effects of stress on subsequent memory for information unrelated to the stressor.

5. Stress, memory, and the testing environment

In previous sections, we have summarized the studies showing that both exogenous and endogenous increases in stress hormones can impact on cognitive function. We have also shown that the memory-enhancing effects of emotions are mainly sustained by the catecholaminergic system, while the memory-impairing effects of stress on neutral memory are sustained by the glucocorticoid system. Now, can these studies showing impairing effects of stress on neutral memory have any implications for the field of brain and cognition? We would like to end this large review of the literature on the effects of stress and stress hormones on cognition by arguing that this field of research is of great importance for research on brain and cognition, and particularly for neuropsychology. The reason for this lies in the potential effects that the environmental context in which we test our study participants may have on their stress response, and what this stress response could induce in terms of neuropsychological performance. In order to make our point, we chose to discuss potential stress effects of the testing environment in young versus older adults and the impact that testing-induced stress could have on the obtained results.

5.1. When we test, do we stress?

In the early 1990s, when most models of human memory function were developed, they were based on the computer-model of information processing (Schacter, 1992; Squire, 1992). These models were tested in both animals and humans, most of the time without taking into consideration the physiological and/or neural mechanisms *underlying* memory function. However, in the last decade, new data emerged showing that memory performance in animals can be acutely modulated by manipulations of the testing environment itself. More often than not, the paradigms used to study learning and memory in animals are aversive in nature, involving either shock, water immersion, restraint, or challenge to the homeostasis of the organism through food restriction or deprivation. All these parameters have been shown to activate, during the training procedure, the physiological stress response (Cordero, Kruyt, Merino, & Sandi, 2002; Sandi, Loscertales, & Guaza, 1997; Sandi & Rose, 1997).

Given that circulating levels of glucocorticoids change in response to various stressors, it has been postulated that changes in circulating levels of glucocorticoids, *induced* by the nature of the learning procedure used in animal protocols, might be one of the most important factors influencing the strength of the memory trace obtained in these studies (Cordero et al., 2002; de Kloet et al., 1999; Sandi & Rose, 1997). This hypothesis has been confirmed by studies showing that training conditions that result in long-term memory formation are the same training conditions that induce a release of glucocorticoids.

For example, it has been shown that in the Morris Water maze, in which a rat is immersed in water and has to find a platform using spatial cues in the room, the water temperature is a potent modulator of the rate of acquisition of the task. Rats that are trained at 19 °C learn faster and display better long-term retention than those trained at 25 °C (Sandi et al., 1997). Glucocorticoid levels are significantly higher in rats in the 19 °C group relative to those in the 25 °C group (cold water is a stressor). The role of glucocorticoids in the strength of memory consolidation has further been confirmed using pharmacological protocols. So, when one combines a stimulus that leads to an endogenous release of glucocorticoids (e.g. water temperature) with a pharmacological dose of glucocorticoids, this leads to a modulation of the consolidation process. In the Morris water maze, rats that are trained at 25 °C (low endogenous release of glucocorticoids), and given synthetic glucocorticoids show good long-term retention, while rats trained at 19 °C (high endogenous release of glucocorticoids), and given synthetic glucocorticoids (same dose) show impaired long-term retention (Sandi & Rose, 1997).

These results again reveal the presence of a biphasic modulation of memory formation by glucocorticoids, whereby an increase of glucocorticoids up to an optimum level should lead to enhanced consolidation, while glucocorticoid levels above this optimum level should lead to a decrease in the consolidation process. These results confirmed the presence of an inverted-U shaped function relating the circulating levels of glucocorticoids *induced by the experimental context* and the memory performance obtained on the task.

Now, let us be frank. Although most rodent studies use aversive tasks to assess learning and memory, most human studies assess learning and memory with tools that are not thought to be stressful by nature, such as word lists and story recall. Consequently, many would say that the protocols used in humans are non-aversive and non-stressful by nature.

However, this may not be the case, as the testing environment itself may lead to a different stress response in young and aged humans. In 1968, Mason published a seminal literature review in which he described the most important psychological determinants of a stress response, i.e. those psychological determinants that would lead to the secretion of glucocorticoids in most of the subjects, whatever their age, origin or background. The most important variables found were novelty, unpredictability, and lack of control over the situation to which individuals are exposed (Mason, 1968).

Since then, a large number of human studies have documented the provocative nature of the anticipation of a novel, unpredictable or uncontrollable situation on glucocorticoid levels. For example, admission to a hospital has been noted to be very provocative of glucocorticoids (Mason, 1968), and other studies have shown that individuals *anticipating* exhausting exercise show significant rise in glucocorticoids that are comparable to that seen during the actual practice of the physical task (Mason, 1968).

From these studies, it is apparent that individuals show a significant activation of the hypothalamic–pituitary–adrenal (HPA) axis when they are exposed to important changes in their environment. With regard to the aging population, various studies have shown that they are significantly more reactive to the testing environment when compared to young individuals (Kudielka et al., 2004a, 2004b; Wolf et al., 2001).

Fig. 5 shows the glucocorticoid levels of 18 young and 18 older participants who came to our laboratory in 1995 (S.J.L.'s first stress study) for a study on stress reactivity. The results showed that when compared to young participants, the glucocorticoid levels of older participants were significantly elevated *at the time of arrival at the laboratory*, 60 min before exposure to stress (participants were not aware that they would be exposed to a stressor, but were rather told that their verbal capacity would be tested). In contrast, 45 min after exposure to the stressor, older adults presented the same glucocorticoid levels as young adults. Clearly, coming to a laboratory for a particular test induced a larger increase in glucocorticoids in older adults compared to young adults.

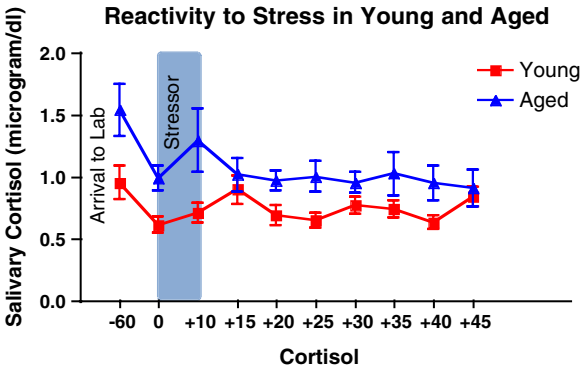

Fig. 5. Salivary cortisol levels in a group of young and aged humans upon their arrival to the laboratory and before and after exposure to a psychosocial stress (personal data from Lupien, S.J.). The Figure shows that older adults presented an increase in cortisol levels upon arrival to the laboratory, 1 h before *actual* exposure to the laboratory stress.

These results were never published due to this spurious result, and great care is now taken in our studies to acclimatize the older participant to the testing environment before exposing them to any test (memory or stress). This is achieved by inviting them to a group session with other older participants. This procedure increases the sense of affiliation, which has been shown to be a potent moderating variable on stress reactivity (Hellhammer et al., 1997; Kirschbaum & Hellhammer, 1989; Kirschbaum et al., 1995a). During this session, we introduce our laboratory (members, space facility, etc.), and explain the study. Participants are then invited for a second session for testing, and during this session, they are once again acclimatized to the laboratory environment for 60 min by interacting with the lab members that they now know, and discuss various topics of interest to them. Memory is assessed after this period of acclimatization. Our subsequent studies on stress and memory in aged humans were successful at showing equivalent glucocorticoid levels *before* exposure to stress.

In 1997, we published a study assessing the effects of a psychosocial laboratory stressor on memory performance in acclimatized older adults (Lupien et al., 1997). The results revealed similar glucocorticoid levels before exposure to stress, and also showed that older participants who presented an early increase in glucocorticoid levels in *anticipation* of the stressor had poor memory performance *before* and *after* being confronted with the stressor, while older participants not showing any change in glucocorticoid levels in anticipation of the stressor did not present changes in memory performance before or after the stressor. These results showed that increases of glucocorticoids in response to environmental changes are potent predictors of memory performance in older adults.

Now, a close look at the studies that reported impaired memory performance in older adults when compared to young show that the majority of studies tested memory

in undergraduate students directly at their university department. Consequently, when tested for memory, these university students were in a familiar (they did not have to find their way to the department), predictable (they had been there before) and controlled (they were familiar with the setting of university life) environment, and were presented with a task that was unchallenging for them, such as learning a list of words (Chantome et al., 1999), or learning a short story (Foster et al., 1999). These are tasks that are intrinsically related to the life of university students who have to perform similar tasks on a daily basis (Hasher, Zacks, & Rahhal, 1999; Radvansky, Zacks, & Hasher, 1996).

Many studies have now revealed that these memory tests, which emphasize the memory component of the task, put older adults at a disadvantage relative to younger adults (Hasher et al., 1999; Radvansky et al., 1996; Rahhal, Colcombe, & Hasher, 2001; Rahhal, May, & Hasher, 2002). These studies revealed that if instructions on the *same* memory test are modified in order to de-emphasize the memory component of the test, the age differences previously observed on the memory test are absent (Hasher et al., 1999; Rahhal et al., 2001). Other studies showed that age-related differences in memory performance on tests of short narratives can be abolished when the information to be remembered convey information about the character (a good or a bad person), more than about perceptual details (a man or a woman) (Fung & Carstensen, 2003; Radvansky et al., 1996; Rahhal et al., 2002). So when the testing environment allows for more control from the older adults, age differences in memory performance are abolished.

Also, and although time of testing in the various studies that have assessed memory performance in young and older adults is not seldom provided, there is some evidence that many studies tend to be scheduled in the afternoon hours (May, Hasher, & Stolzfus, 1993). Numerous studies have revealed that older adults perform better on various cognitive tasks when tested in the morning (between 8 and 11am), while young adults perform better when tested in the afternoon hours (between 1 and 5 pm) (Hasher et al., 1999; Li, Hasher, Jonas, Rahhal, & May, 1998; May & Hasher, 1998; May et al., 1993; Winocur & Hasher, 2004; Winocur & Hasher, 1999). Given that optimal levels of glucocorticoids are reached *at the time of awakening* and not at a particular time (e.g. 8 am) of the day, and since young adults tend to wake up later than older adults, this "synchrony effect" reported in the literature could partly be explained by the circadian variations of glucocorticoids that occur as a function of awakening time in young and older participants.

In contrast to young participants, in most of the studies measuring memory in older adults, the older individual had to travel (by car, taxi or by bus) to the location (in most cases, a hospital or a university setting) where the study was performed, and once there, was asked to perform tasks of word lists, paragraph recall, etc. In summary, the necessity for these older participants to find their way to the university or hospital, enter an unfamiliar building, and meet with new people who would test their "*maybe declining*" memory (see Lupien & Wan, 2004) with tasks that did not provide any meaning for them constituted the perfect cocktail of novelty, unpredictability and uncontrollability that defines a stressful situation. Given the well-known effects of stress-induced endogenous increase in glucocorticoids on learning and memory, it might be possible that due to the larger stress response induced by the testing environment in older adults, a certain proportion of the 'age-related memory impairments' reported in this population is spurious, and induced by the testing environment (and the stress response that goes with it) to which we expose them when we test their memory performance.

The data and points presented above could just as well be related to memory performance and have little impact on our general models of brain and cognition in human populations. Yet, we believe that a closer look at various models of brain and cognition in terms of the potential impact of stress are necessary in order to understand some of the discrepancies reported in the field of brain and cognition. Here, we would like to discuss the association between memory and hippocampal volume in young and older populations.

5.2. The association between memory and hippocampal volume: A potential impact of stress?

One day, I was giving a presentation to a group of 5-year-old children about the basis of memory function in humans. I told them that in our brains, we have a small structure that looks like a sea horse (which is why we call it the 'hippocampus'), which varies in size from 2 to 5 cc. I continued my story by telling them that we know that the hippocampus helps us to memorize things and that the bigger it is, the better is our memory. A little girl sitting in the front row then looked at me very seriously and asked me the following very interesting question: "*Are you sure?*"

The response of many of us to this blunt question would likely be "no", mainly because the macroscopic size of the hippocampus as revealed by magnetic resonance imaging (MRI) studies is still a very crude neurobiological measure, and also because this little girl's question elicits in most of us memories of the failures of phrenology a century ago. However, when carefully reading the literature on memory and hippocampal volumes (HVs) in human populations, one can easily grasp the implicit assumption that such a relation exists, and this assumption finds its origins in two very different fields.

The first one concerns the study of the effects of hippocampal resection on memory function (Milner, 1972; Scoville & Milner, 1957). In humans, studies of temporal lobe epilepsy patients whose epileptogenic focus was surgically excised have shown relations between the extent of resection and the degree of memory impairment (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997; Rempel-Clower, Zola,

Squire, & Amaral, 1996; Stefanacci, Buffalo, Schmolck, & Squire, 2000; Zola-Morgan, Squire, & Amaral, 1986). Similarly, studies in monkeys showed that monkeys with circumscribed hippocampal lesions were moderately impaired, whereas monkeys with lesions that included the hippocampal region as well as adjacent cortex were severely impaired (Zola-Morgan, Squire, & Ramus, 1994). The second field of research that contributed to the notion that bigger HVs are associated with better memory performance concerns studies of brain morphology in older individuals suffering from Alzheimer's disease (AD). In this population, studies revealed the presence of a significant positive association between HV and memory performance (Bondi & Kaszniak, 1991; Kohler et al., 1998). Further post-mortem studies confirmed that a significant pathological process was under way in the hippocampus of these populations (Braak & Braak, 1991; Mann, 1991; McKhann et al., 1984), which lent unequivocal support to the notion that hippocampal atrophy is related to memory impairments.

The results obtained in AD patients were then extended to older human populations, who were also known to show memory impairments when compared to younger populations (see above). In 1994, Golomb and collaborators (Golomb et al., 1994) published the first study showing a positive correlation between HV and memory performance in a group of healthy older adults, thus leading the way toward the hypothesis that in terms of HV, "bigger is better" (van Petten, 2004), even in normal populations. Over the years, this result has been confirmed on many occasions (Convit et al., 1995; Convit et al., 1995; Convit, Wolf, Tarshish, & de Leon, 2003; de Leon et al., 1995; de Leon et al., 2001; de Leon et al., 1993; Golomb et al., 1994; Golomb et al., 1994; Hackert et al., 2002; Lupien et al., 1998; Reiman et al., 1998; Rusinek et al., 2003; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995), although an absence of a significant correlation between HV and memory in older humans has also been frequently reported (Cahn et al., 1998; de Toledo-Morrell et al., 2000; Laakso, Hallikainen, Hanninen, Partanen, & Soininen, 2000; MacLullich et al., 2002; Marquis et al., 2002; Petersen, Jack, Xu, Waring, & O'Brien, 2000; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Rodrigue & Raz, 2004; Tisserand, Visser, van Boxtel, & Jolles, 2000; van Petten, 2004; Visser et al., 1999).

Based on the hypothesis that there exists a positive correlation between HV and memory, Foster et al. (1999) then measured HV and memory performance in a group of 18 young university students. Results revealed the presence of a significant *negative* correlation between HV and memory performance in these young subjects. The same year, Chantome et al. (1999) reported a similar *negative* correlation between HV and memory performance in a group of 72 young adults. More recently, van Petten (2004) published a meta-analysis on the correlations between HV and memory across the lifespan. The results showed that a negative relationship between HV and memory ("smaller is better") was significant for studies with children, adolescents, and young adults. For studies with older adults, the meta-analysis revealed that the correlation between HV and memory performance grew more positive as the age of the sample increased. Consequently, the significance of small *versus* large HV for memory performance seems to be different in young and aged populations. How could this be?

These results have been interpreted as suggesting that there may be at least two *different* mechanisms operating in determining the direction of the correlation between HV and memory performance in young and older populations. In healthy young people, the factor explaining the observed negative correlation between HV and memory would be the degree of neural pruning that has taken place during childhood and adolescence. It is known that during development, more neurons, axons, synapses and receptors are generated than are subsequently retained in the brain during adulthood ("pruning", Cowan, Fawcett, O'Leary, & Stanfield, 1984). It has thus been suggested that an "*inadequately pruned hippocampus may mediate memory less efficiently than a well pruned hippocampus*" (Foster et al., 1999), which would explain why there is a negative correlation between HV and memory performance in young subjects. The meta-analysis by van Petten (2004) also revealed that between the ages of 4 and 18, the volume of the hippocampus shows little absolute change while whole brain volume increases until the age of 15. Thus, throughout development the hippocampus takes up a declining percentage of the brain. One would therefore expect memory performance to improve as hippocampal volume decreases when taken as a proportion of whole brain volume; hence the observed negative correlation (van Petten, 2004). In older individuals, the factor explaining the observed positive correlation between HV and memory would be the degree of hippocampal atrophy that has taken place as a result of aging. Indeed, many studies have reported significant negative correlations between age and HV (Goldstein et al., 2001; Good et al., 2001a, 2001b; Grachev, Swarnkar, Szeverenyi, Ramachandran, & Apkarian, 2001; Gur et al., 1991; Jernigan et al., 2001; Sullivan et al., 1995), suggesting that with aging, there is a gradual loss of hippocampal tissue. The first effect of this age-related decline in HV would be greater variability in the HV of older adults, when compared to young people. The second effect of this age-related decline in HV would be the presence of poor memory abilities in older adults with hippocampal atrophy. The net consequence of these two effects would be the presence of a positive correlation between HV and memory performance in older adults (Foster et al., 1999; van Petten, 2004).

However, there are two major problems with this interpretation. The first one relates to the notion that a significant age-related decline in HV has to be present in older subjects in order to induce sufficient variability and observe a positive correlation between HV and memory performance. The problem with this postulate is that it implies

that the dispersion around the mean (i.e., the standard deviation) of HV in young subjects should be smaller than the dispersion observed in older individuals. However, this is not the case. In fact, already in 1995, it was reported that a wide range of "normal" HV was present in studies of normal young individuals (Jack, Theodore, Cook, & McCarthy, 1995). At the time, these authors attributed this variability to inter-institutional differences in hippocampal boundary criteria and in the software employed for assessing HV. However, in 1993, the International Consortium for Brain Mapping (ICBM) was formed with a grant from the NIMH. This consortium is composed of four core research sites (UCLA, MNI, U. Texas, Heine U. Germany), and it allows for a distribution of labor into parallel, complementary tasks and creates a "real world" environment among participants such that differences in equipment, software, and protocols are minimized, thus leading to a statistical atlas of the normal adult brain using the same methodology. In order to assess the degree of variability in HV in young and older adults, we have gathered data on the HV of 177 individuals ranging from 18 to 86 years of age from the ICBM database. In this population, we replicated the negative correlation between age and HV usually obtained in the scientific literature (Lupien et al., In press). In order to assess the degree of variability in HV as a function of age, we split participants into 5 age groups of 40 ± 2 individuals (18–24, 25–40, 41–59, 60–75, and 76–85 years), and assessed the percentage of difference in HV in the lowest and highest quartile of each age group.

In accordance with the results of previous studies on age and HV, the ANOVA comparing HV across age groups revealed a significant main effect of Group [$F(4, 175) = 20.79$, $p < .0001$], with a stepwise decline in HV across groups. Although we replicated previous age differences in HV, we were most interested in assessing whether young individuals would present a smaller inter-individual variability (a significantly smaller standard deviation) in HV when compared to older individuals.

Here, five important results emerge from our analysis. The first thing that emerges from our data is that even if we observed significant age differences in HV, there is the presence of a very large inter-individual variability of HV in *each* group, as shown by the large SD of the mean HV for each age group.

The second interesting observation that emerges is that within the same age-range, the percentage of difference between the lowest quartile of HV and the mean HV of the age group is substantive, ranging from 12% in the 18–24 and 41–59 age groups, to an average of 21% in the other age groups.

Third, we found that these differences in quartiles can be attributed to age, *only* in the oldest group of individuals (76–85 years). Age ranges below 76–85 years do not present differences in the age of the lowest and highest quartiles, although HV differences are substantial.

Four, these data show that the *smallest HV* in young adults (lowest quartile in the 18–24 group being 3.82) is equivalent to the highest HV in older adults (highest quartile in the 76–85 group being 3.86), showing modest but significant overlap between the distributions of HV in these two age groups (see Fig. 6).

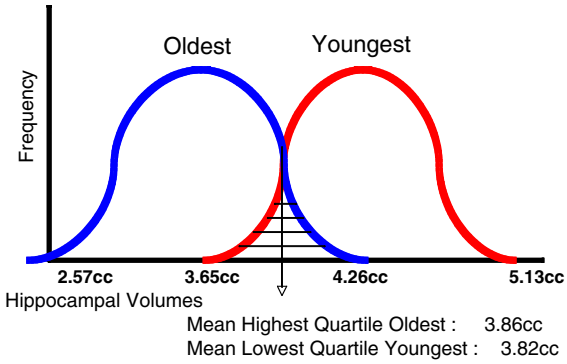

Fig. 6. Schematic representation of the distribution of HV in the age groups in the Lupien et al., study (in press). The values displayed on *X*-axis represent the minimum and maximum HV observed in each age group in a total population of 177 individuals.

Finally, there is a systematic difference of about 1 cubic centrimeter (cc) between the HV of the lowest and highest quartiles in *each* age group, and there is a similar difference of about 1 cc in the mean HV of young adults (18–24) and older adults (76–85 years). In summary, these results show that even if older individuals present smaller HV when compared to young individuals, the inter-individual variability in HV within the same age group is equal to, or larger than, the inter-individual variability across age groups.

The observation of a large inter-individual variability in HV in young healthy participants has important implications for the notion of hippocampal 'atrophy' in older adults. Indeed, our results showing that about 25% of 18- to 24-year-old individuals present HV as small as those observed in the average older adults aged 60–75 years raise the issue of the significance of the negative association usually obtained between age and HV (Goldstein et al., 2001; Good et al., 2001a, 2001b; Grachev et al., 2001; Gur et al., 1991; Jernigan et al., 2001; Sullivan et al., 1995). These correlations have been interpreted as showing that during aging, there is a gradual atrophy of the hippocampus. However, given the fact that 25% of young adults present very small HV that fall in the range of individuals aged 60–75 years, it might still be possible that the HV measured at any given age reflects a volume that was pre-determined based on early experiences.

Indeed, the significant inter-individual variability in HV that we observed in young adults could arise from both genetic and experiential factors. From a study of monozygotic and dizygotic elderly twins, Sullivan, Pfefferbaum, Swan, and Carmelli (2001) estimated that some 40% of the variance in late-life HV can be attributed to genetics, while the other 60% reflect experiential factors. Such experiential factors could operate to increase or decrease HV across the life span. Animal studies have shown that environmental enrichment (Kempermann, Jessberger, Steiner,

& Kronenberg, 2004; Kempermann, Kuhn, & Gage, 1997; Kempermann, Kuhn, & Gage, 1998; Mlynarik, Johansson, & Jezova, 2004) and nutritional factors (Will, Galani, Kelche, & Rosenzweig, 2004) are potent inducers of changes in neurogenesis and/or dendritic arborization in the hippocampus, documented to lead to changes in HV (Clayton & Krebs, 1994; Suzuki & Clayton, 2000). Also, glucocorticoids have been shown to be one of the most potent factors acting on the volume of the hippocampus (Gould, Beylin, Tanapat, Reeves, & Shors, 1999; Gould, Tanapat, Hastings, & Shors, 1999; Kozorovitskiy & Gould, 2004; Mirescu, Peters, & Gould, 2004). Studies showed that gestational stress decreases hippocampal neurogenesis in adult rats (Lemaire, Koehl, Le Moal, & Abrous, 2000) and juvenile monkeys (Coe et al., 2003), and these deficits are long-lasting since they are observed over the entire lifespan of the animals (Lemaire et al., 2000). Also, post-natal handling has been shown to prevent the prenatal stress-induced deficits in hippocampal neurogenesis (Lemaire, Lamarque, Le Moal, Piazza, & Abrous, 2006).

The similar distribution of volumes across age groups does not mean that normal aging could not have effects on HV. Here, a longitudinal study of *both* young and older participants would help resolve this issue. Such a study would be very important because any age effect observed in a cross-sectional study can be obscured by a cohort effect. Indeed, if experience has an impact on HV as suggested by the studies reported above, then different life experiences as a function of date of birth could have a significant effect on HV in humans. An individual born in 1915, during World War I, who lived through two major wars, could present smaller HV due to exposure to these stressful experiences, compared to an individual born in 1980, at a time of relatively peaceful events. Tested in 2001, the first individual would be significantly older than the second, yet it does not mean that the 'age difference' observed in HV is mainly due to chronological age (for a review on this issue, see Lupien & Wan, 2004). It could also be related to different life experiences, as a function of date of birth. Fig. 7 presents the HV of the ICBM participants as a function of the generation in which they fall given their birth date. One can see from this figure that there may be other ways to look at HV as a function of age. One way to disentangle the effects of life experience (cohort effect) versus age (age effect) on HV would be to assess differences in HV as a function of different experiences (e.g., socioeconomic status) in individuals of the same cohort or age. Any difference in HV would then represent the effect of experience, rather than age.

The second major problem with the interpretation that a *different mechanism* (pruning *vs.* atrophy) can explain the inverse correlations between memory and HV in young and older adults, is that such an interpretation would imply the intriguing notion that there is something like an "expiration date" on a small HV. Why would a small HV in an individual be good for memory when this person is 25 years old and suddenly turn bad when the individual is 65? If the pruning hypothesis is taken as a plausible explanation for the negative correlation between HV and memory obtained in young people, then it would *not* apply to young individuals with small HV, since this small HV would imply that adequate pruning has been achieved. Clearly, no one would suggest a pathological process leading to a small HV in a young individual. Indeed, only in older individuals would this interpretation seem plausible.

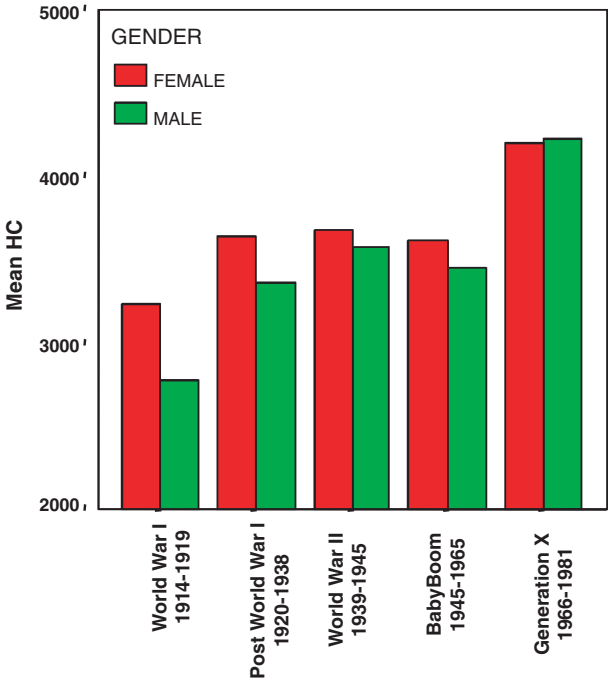

Fig. 7. Mean hippocampus (HC) of 177 individuals from 18 to 86 years of age from the International Consortium for Brain Mapping project. The hippocampal volume of participants is presented as a function of the generation in which they fall given their birth date.

5.2.1. Hypothesis 1: Optimal hippocampal volume threshold for memory processing

One way to interpret these results would be to suggest that there exists an optimal hippocampal volume threshold for memory processing in humans. In our study, the oldest adults with the largest HV presented a mean HV of 3.86 cc. This volume is similar to the one observed in the youngest adults with the smallest HV (3.82 cc). Given the overlap between the distribution of HV in young and older adults, it might be possible that a hippocampal volume threshold exists with regard to memory processing, thus ensuring optimal memory performance at a certain HV (e.g., 3.8 cc). Given that older populations present an age-related decline in HV, this optimal HV would represent the largest HV in the older adults, while it would represent the smallest HV in younger populations, explaining the positive correlation between HV and memory observed in older adults, and the negative correlation between HV and memory observed in younger adults (see Fig. 8).

One way to test this hypothesis would be to assess HV in a large sample of young and older adults and test for the

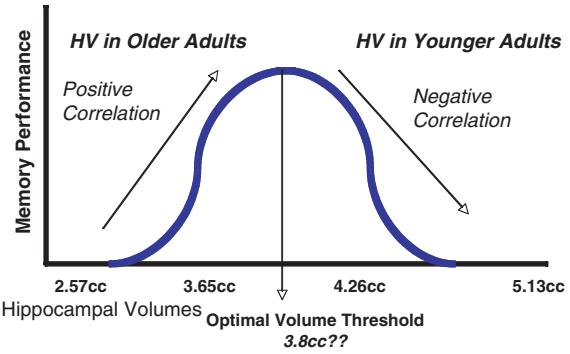

Fig. 8. Schematic representation of the optimal volume threshold hypothesis. See text for a description of this hypothesis.

presence of a *quadratic* function between HV and memory performance across the entire age range of participants.

5.2.2. Hippocampal volume and memory: An epiphenomenon?

If the optimal volume threshold hypothesis is not valid, then the data and arguments presented above would thus tend to suggest that the reverse correlations between HV and memory performance observed in young and older humans are spurious results. However, there is a second important factor that could explain these reverse correlations without the necessity of using two different mechanisms (i.e., pruning *vs.* atrophy). This factor has its origin in the differential stress reactivity of young and older humans to the testing environment to which they are exposed when their memory is assessed, and in the impact of this stress reactivity on memory performance. As we have seen earlier, there are many factors that are related to stress responsivity in humans and that are more frequent when we test older adults compared to young adults. It might thus be possible that the inverse correlations observed between HV and memory in young and older adults is not due to an optimal threshold for memory in HV (as suggested above in hypothesis # 1), but rather to variation in memory performance as a function of the environment in which we test young and older adults. Here, older adults would be at a disadvantage because they are more reactive to the environment in which we test their memory and they have a smaller HV. We based this suggestion on new studies showing that the price to pay for stress seems to be greater in individuals with small hippocampal volumes, when compared to individuals with large hippocampal volumes.

5.2.3. Stress, memory, and hippocampal volume—the debate

The same year that Golomb et al. (1994) published the positive correlation between HV and memory in older adults, we published the results of a longitudinal study (Lupien et al., 1994) showing that one of the correlates of memory impairments in older humans is chronic secretion of elevated levels of glucocorticoids over years. A few years later, we reported that older participants with chronic exposure to high levels glucocorticoids over years had a 14% smaller HV when compared to older participants with normal glucocorticoid levels over years (Lupien et al., 1998). These results were in line with the "glucocorticoid cascade hypothesis" proposed by Sapolsky, Krey, and McEwen (1986), which stated that chronic secretion of high levels of glucocorticoids can have neurotoxic effects on the hippocampus, with disturbances in dendrite branching, neurogenesis and glucose metabolism, eventually resulting in atrophy of the structure (Sapolsky et al., 1986).

Following the publication of this hypothesis, various studies were performed in humans which revealed significant "atrophy" of the hippocampus in various psychiatric disorders that present both memory impairments and high reactivity to stress, such as depression (Krishnan et al., 1991; Sheline, 1996; Sheline, Gado, & Kraemer, 2003; Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Vythilingam et al., 2004), post-traumatic stress disorder (PTSD) (Bremner, 2003; Bremner, 2002; Vythilingam et al., 2002), and schizophrenia (Heckers, 2001; Nelson, Saykin, Flashman, & Riordan, 1998). Here, recent meta-analyses have calculated HV reduction in the range of 4% in schizophrenia (Nelson et al., 1998), 7% in PTSD (Smith, 2005), and 9% in depression (Videbech & Ravnkilde, 2004), when comparing the HV of patients to that of healthy normal controls. These percentages of HV differences between patients and control groups were in line with experiments performed in rodents that reported that chronic exposure to stress leads to hippocampal atrophy (Magarinos & McEwen, 1995; Magarinos, Orchinik, & McEwen, 1998; Magarinos, Verdugo, & McEwen, 1997; McEwen et al., 1997; McEwen & Magarinos, 1997; McEwen, Magarinos, & Reagan, 2002; McKittrick et al., 2000). However, in these animal post-mortem studies, HVs were never measured *before* and *after* exposure to chronic stress, given the invasive nature of the assessment of hippocampal morphology in this species. The use of repeated *in vivo* MRI assessments *before* and *after* exposure to chronic stress in tree shrews (Ohl, Michaelis, Vollmann-Honsdorf, Kirschbaum, & Fuchs, 2000) and monkeys (Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001) failed to show changes in HV after stress in these species.

Consequently, researchers started to look at the other side of the correlation between HV and mental health, and to raise the possibility that *inherited* variations in HV may lead to variations in the vulnerability of humans to the effects of stress on cognition and mental health. Results in humans in line with this suggestion have been obtained. Remember that a significant number of studies revealed the presence of a hippocampal "atrophy" (in the range of 7%) in patients suffering from PTSD when compared to individuals exposed to the same trauma, but who did not develop PTSD. In 2002, Gilbertson and collaborators (2002) published a study in which they confirmed the presence of smaller HV in war-veterans suffering from PTSD (Gilbertson et al., 2002). However, in the same study, they showed

that these men's *monozygotic twin brother who never went to war also* had small HV when compared to the monozygotic twin brother of the war-veterans who did not develop PTSD. Given the large similarities of HV reported to occur in human monozygotic twins (Sullivan et al., 2001), these results strongly suggested that the men who went to war and developed PTSD entered the war zone with a smaller HV *to begin with* relative to the men who went to war and did not develop PTSD. Consequently, the HV may actually be a pre-existing condition that increases vulnerability to PTSD upon exposure to a traumatic experience, rather than the consequence of the trauma.

Support for the notion of inherited variations in HV comes from studies that have revealed smaller HV in *first-episode untreated* depressed patients (Frodl et al., 2002), and *first episode untreated* schizophrenics (Narr et al., 2004), a finding that goes against a neurotoxic effect of depression and/or schizophrenia on HV. In summary, these results suggest that individuals with small HV may be more reactive to environmental stress than individuals with large hippocampal volumes. At first glance this notion would also seem to fall short in explaining the negative correlation observed in young populations.

5.2.4. Hypothesis 2: Sensitive volume threshold for adequate memory processing under stress

Given that older adults present smaller hippocampal volumes when compared to young, it may be suggested that the positive correlation reported between hippocampal volumes and memory in older adults is due to the acute stress response induced by the testing environment in these participants. Taken in its purest form, this hypothesis implies that the real association between hippocampal volumes and memory is negative in both young and old. However, since we have no indications that this might be the case, we have to adopt the null hypothesis and postulate that under baseline, non stressful conditions, there is no correlation between hippocampal volumes and memory performance in young or older adults. This postulate is represented by the blue line in Fig. 9 below. We also postulate the presence of a sensitive volume threshold for adequate memory processing under stress. This sensitive volume threshold is represented by the red line in the Fig. 9.

Given that older adults present smaller hippocampal volumes than younger adults, their hippocampal volume has a greater probability of falling within the sensitive volume threshold range. If this is the case, any exposure to a stressful event would have a significant detrimental impact on memory performance in older adults. Given that memory testing may be more stressful in older populations, this factor could explain the presence of a positive correlation between hippocampal volumes and memory performance in older adults. In contrast, young adults present larger HV than older adults, and consequently, they fall in the range of lower sensitivity to stress and consequently, less impairment of memory function under stress. Moreover, most of the time, young adults are tested in non-stressful

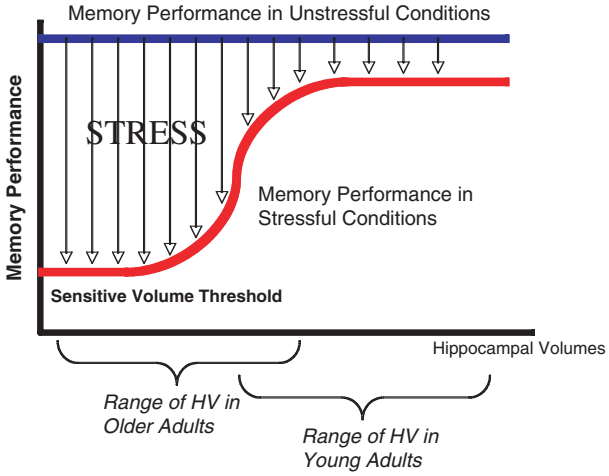

Fig. 9. Schematic representation of the sensitive volume threshold hypothesis. The arrows represent changes in memory processing during stress as a function of hippocampal volume and age of the participant.

conditions, which give them an additional advantage over older adults. The main problem with this model is that it does not explain the negative correlations obtained between HV and memory performance in young adults. Here, the model suggests the absence of any correlation between HV and memory in young adults. The absence of a correlation between HV and memory performance could have been obtained in a large set of studies, but given the fact that most of the negative findings are seldom published, we may not be aware of these data in the development of a scientific model of the association between stress, HV, and memory performance in humans. It is clear, however, that these associations need further investigation.

6. Conclusions

In this paper, we have reviewed the literature on the effects of stress and stress hormones on human cognitive function with a special emphasis on glucocorticoids given their capacity to cross the blood–brain barrier and access the brain where they can influence learning and memory through binding to specific receptors.

We have first provided a historical background of the effects of glucocorticoids on cognitive function with a particular emphasis on steroid psychosis. Our goal here was to inform the clinical neuropsychologist and other researchers interested in cognitive function that some of the neuropsychological impairments observed in certain patients could be related to exogenous exposure to high levels of glucocorticoids, due to certain medical conditions and/or steroid medications.

In the second part of the paper, we have summarized the literature showing the effects of exogenous administration of glucocorticoids on cognitive function sustained by the hippocampus and frontal lobes, the two brain regions containing the largest concentrations of glucocorticoid receptors. We have shown here that the effects of stress

hormones on human cognition are best understood in line with the inverted-U shape function between glucocorticoids and cognitive performance. This inverted-U shape function between circulating levels of glucocorticoids and memory performance is explained by the presence of two glucocorticoid receptor types that differ greatly in terms of their affinity for glucocorticoids.

In the third part of the paper, we have summarized the studies that have assessed the effects of an endogenous increase of glucocorticoids as induced by exposure to a stressful situation, on cognitive performance. Here, it was shown that an endogenous increase of glucocorticoids as induced by exposure to environmental and/or psychosocial stress is as efficient at inducing cognitive impairments, as is an exogenous increase of glucocorticoids.

Finally, in the last section of the paper, we have argued that the environmental context in which we test our participants might induce a stress response in sensitive individuals, which could then impact on their cognitive performance. In order to delineate this point, we have used the model of studies on human aging in which the majority of studies reported impaired cognitive function in older adults when compared to young. We have argued that some of these effects might be due to the stress that is generated by the testing conditions that we use to study young and older adults. We went one step further in our analysis by suggesting that the inverse correlations observed between HV and memory performance in older and young adults could also be due to a differential reactivity of young and older adults to the testing environment.

Clearly, the field of psychoneuroendocrinology, which studies the effects of hormones on human brain and behavior, contributed significantly at showing the impact of stress on human cognitive function. It is our hope that by combining our expertise with that of the field of cognitive neuropsychology, we will be able to delineate with high accuracy the processes of cognitive function in humans that are not tainted by stress effects. We also hope that the combination of our fields will help in the understanding of the effects that stress can have on learning and memory in humans of all ages.

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