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Stress, PTSD, and dementia☆

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Abstract The physiological consequences of acute and chronic stress on a range of organ systems have been well documented after the pioneering work of Hans Selye more than 70 years ago. More recently, an association between exposure to stressful life events and the development of later-life cognitive dysfunction has been proposed. Several plausible neurohormonal pathways and genetic mechanisms exist to support such an association. However, many logistical and methodological barriers must be overcome before a defined causal linkage can be firmly established. Here the authors review recent studies of the long-term cognitive consequences of exposures to cumulative ordinary life stressors as well as extraordinary traumatic events leading to posttraumatic stress disorder. Suggestive effects have been demonstrated for the role of life stress in general, and posttraumatic stress disorder in particular, on a range of negative cognitive outcomes, including worse than normal changes with aging, Alzheimer's disease, and vascular dementia. However, given the magnitude of the issue, well-controlled studies are relatively few in number, and the effects they have revealed are modest in size. Moreover, the effects have typically only been demonstrated on a selective subset of measures and outcomes. Potentially confounding factors abound and complicate causal relationships despite efforts to contain them. More well-controlled, carefully executed longitudinal studies are needed to confirm the apparent association between stress and dementia, clarify causal relationships, develop reliable antemortem markers, and delineate distinct patterns of risk in subsets of individuals.
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1. Introduction

Study of the physiological consequences of acute and chronic stress for a range of organ systems was launched more than 70 years ago in pioneering work on the "general adaptation syndrome" by Hans Selye, who borrowed the term "stress" from physics and applied it to physiology [1]. Since then, an ever-burgeoning body of research has explored the interfaces among the central and autonomic nervous, endocrine, and immune systems. Attempts to link mind and body have established potential pathways of influence–both pathological and therapeutic–for the impact of mental events on bodily tissue, as well as the impact of changes in bodily tissues on the nervous system. More recently a focus on the possible long-term "neurotoxic" effects of stressful life events has been proposed [2].

The potential impact of stress on the development of dementia or other forms of cognitive dysfunction may be considered from the standpoints of the individual, the stressor, and the stress response. People vary widely in their ability to cope with stressful events, a quality referred to as resilience. Factors influencing resilience include cognitive endowment, developmental stage, substance use, mental and physical (e.g., cardiovascular) health, and access to social support as well as a host of putative genetic and physiological markers such as Apoe4 allele types and patterns of cortisol secretion. Stressors may be categorized across several dimensions, including intensity, duration, novelty, and type. Examples of types of stressors include threat of death or bodily injury, personal illness, and loss of a loved one through illness or separation as well as more mundane

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activities such as geographic relocation, night shift work, and commuting. Variation in one's response to a stressor involves appraisal of danger, perceived predictability and controllability, and the potential development of psychopathology.

In 1980, recognition of the common psychopathological effects of extremely traumatic life events such as military combat or sexual assault led to the inclusion of a new diagnosis in the psychiatric nomenclature: posttraumatic stress disorder, or PTSD. Although the appellation for this psychiatric condition contained, and still contains, the word "stress," a body of research during the past two plus decades led by Yehuda and colleagues [3,4] has created doubt as to whether PTSD is a proper stress disorder, in that the pattern of hormonal findings found in PTSD does not appear to conform to the Selye stress model, which emphasizes hyperactivity of the hypothalamic pituitary adrenal (HPA) cortical axis and excessive production of the quintessential glucocorticoid stress hormone cortisol (corticosterone in lower animals). These findings challenge the degree to which the adverse effects of stress and cortisol on the nervous system discussed in much of the subsequent text apply in the case of PTSD.

In the review that follows, we summarize and critically discuss two distinct scenarios for long-term stress-induced cognitive changes based on the relevant human (but not animal) literature. First, we examine the possible role of cumulative, chronic everyday life stressors in cognitive dysfunction associated with aging. We conclude there is reasonable support for the role of stress in negative cognitive outcomes, although not necessarily Alzheimer's disease (AD). We then review the studies to date (only two in number) that have investigated a possible link between PTSD and AD; we conclude that although it is suggested, this link remains unestablished. We then examine the underlying neurophysiological substrate for potential stress-cognition linkages, including hormonal, neuroimaging, neuroimmunological, and neuropathological evidence. We also discuss how molecular events inform the debate. Finally, we call for further study of this important scientific and public health issue.

2. Review of selected epidemiological studies

2.1. Chronic life stress and dementia

Controlling for the numerous potential confounding factors in studies of stress by means of subject selection or statistical manipulation is an onerous task. Cross-sectional studies that characterize and compare subject samples at a single point in time are more feasible, but they do not allow for the serial measurement of changes in cognition over time. Long-term longitudinal studies are limited by the choice of measures adopted at the outset and the problem of subject attrition. Many studies fail to include postmortem brain tissue analysis, which is the gold standard for the diagnosis of dementia, especially AD.

Wilson and colleagues followed a cohort of more than 800 Catholic nuns, priests, and brothers with a current mean age of 75 in a longitudinal design, with annual assessment of cognitive functioning during an average of almost 5 years. The investigators focused on the stable personality trait of "distress proneness," as measured by the neuroticism subscale of the Neuroticism-Extroversion-Openness (NEO) Five-Factor Inventory. Neurocognitive tests generated scores on several specific domains as well as a global overall measure. Subjects highest on baseline neuroticism (who presumably experience greater stress) had twice the chance of developing AD according to consensus clinical diagnostic criteria. This effect could not be explained by depression or levels of everyday cognitive activity. In addition, episodic memory declined 10 times more in those with high versus low neuroticism. However, this effect was not seen for working memory, semantic memory, processing speed, visuospatial ability, or the global cognitive measure. Moreover, in autopsy, distress proneness was not related to AD neuropathology [5]. This partially positive study highlights the pitfall of equating any form of cognitive decline with AD, and the necessity of having objective confirmation via postmortem pathological data or reliable antemortem surrogate markers. There was no clear explanation for the finding that only one of several domains of cognitive acuity was affected.

Wilson and colleagues further tested approximately 650 healthy subjects with a mean age of 80 who were screened for the trait of neuroticism, again using the NEO Five-Factor Inventory, and also given a battery of cognitive tests and a clinical examination. This cohort was followed for an average of 3 years. Fifty-five subjects received a clinical diagnosis of AD. Those at the 90th percentile on the distress measure had 2.7 times the risk of being diagnosed with AD than those at the 10th percentile. Moreover, increased distress correlated with a more rapid decline. However, at autopsy, distress again was unrelated to markers for AD neuropathology, although it was negatively related to cognitive acuity after controlling for AD pathology. The link between distress and the diagnosis of dementia remained after controlling for depression, levels of social and physical activity, and recency of cognitive symptoms. Echoing their prior work, the authors concluded that psychological distress is associated with cognitive decline, but not specifically with AD [6].

Peavy and colleagues performed a 3-year longitudinal study on 52 individuals, who were either cognitively intact or evidencing signs of mild cognitive impairment (MCI). Subjects with existing dementia were excluded. Stress was measured at 6-month intervals by the Life Events and Difficulties Schedule, a semistructured interview that inquires into stressful life events in 12 categories. A rating of "high stress" was given if there was at least one event in the preceding period rated as high intensity by a professional examiner. Subjects also underwent annual neurological and neuropsychological assessments, including the Mattis Dementia

Rating Scale and new learning measures from the Wechsler Memory Scale. Multiple linear regression analyses were undertaken with individual rates of cognitive change as the predicted variable. Age, education, gender, and mood status did not account for a significant portion of variance. Among those with MCI, high stress levels were associated with accelerated cognitive decline across the Mattis Dementia Rating Scale total and memory subscales, but not other memory instruments. In contrast, high stress among normal subjects was not associated with cognitive decline [7]. This partially positive study undertaken on a small sample underscores the synergistic effects of high stress and existing cognitive impairment and highlights the importance of careful baseline testing, because the inadvertent inclusion of subjects with MCI in ostensibly normal cohorts may introduce a serious confound. It is possible that the 3-year follow-up period may not have been long enough for putative stress effects to have become manifest in the normal subjects. The design did not rule out the possibility that coping with eroding cognitive acuity in the MCI group was causally related to stressful events. For example, evolving cognitive dysfunction could hypothetically have led to financial difficulties significant enough to be rated as a high-stress event in a given subject. To the extent that this alternate direction of causality was operating, the results reported would not support the conclusion that stress exposure causes cognitive decline.

Johansson and colleagues followed 1462 Swedish women in a long-term longitudinal design over 35 years. Stress was measured by a straightforward series of questions administered at three intervals, yielding a total score of 0 (no stress) to 5 (frequent/constant stress). Dementia was diagnosed by clinical examinations, reports of informants, reviews of medical records, and administration of neuropsychological measures at follow-up examinations carried out 7, 13, 25, and 35 years later. During the course of the study, 11% of the sample developed dementia. The association between psychological stress and the incidence of dementia and its various subtypes was analyzed using a Cox regression model adjusted for a number of potential confounding variables including demographic, behavioral, and other known risk factors such as waist-to-hip ratios. There was an increased risk of all-cause dementia associated with reports of frequent/constant stress measured at each of three prior assessments with adjusted hazard ratios (HRs) of approximately 1.6. Subjects who reported frequent/contrast stress in two of three prior assessments had an elevated risk of AD compared with those reporting no periods of stress. Subjects reporting high stress at one, two, and three earlier periods had escalating risks of dementia (HR = 1.1, 1.7, and 2.7, respectively) [8]. This latter finding points to a dose-response curve for the effect of stress exposure. The researchers concluded that there is an association between psychological stress in middle-aged women and the subsequent development of dementia, and AD in particular. The authors rightly pointed out that because brain changes in people who subsequently develop AD have been found many years before symptom onset, it is possible that evolving dementia could increase one's vulnerability to stress, rather than the cumulative experience of stress triggering later onset of dementia. The generalizability of this study is limited by the exclusion of male subjects.

Johansson and colleagues invited 684 surviving cohort participants to undergo computed tomography scans of the brain. Of these, 344 also had data on psychological distress collected in 1968. A neurologist blind to participants' clinical characteristics rated the computed tomography scans by visual examination as mild, moderate, or severe for white matter lesions (WMLs), regional cortical atrophy, and other ventricular size measurements. Women who reported frequent or constant stress during the 5-year period before any of the examinations in 1968, 1974, or 1980, compared with women who reported no stress, were more likely to have moderate to severe WMLs, multiadjusted odds ratio (OR) = 2.4 as well as moderate to severe temporal lobe atrophy, OR = 2.5. These ORs incorporated adjustments for multiple possible confounders such as those listed in the previous paragraph. Additionally, adjustment for depression did not change the reported associations. The investigators concluded that long-standing psychological stress in midlife increases risks of cerebral atrophy and WMLs in late life. However, they went on to point out that a causal relationship between increased stress and brain changes cannot necessarily be inferred. For example, women with a biological propensity to subsequent brain changes may also have reported more stress [9].

A recent, second follow-up article by the same group reported on the same cohort with the inclusion of the most recent follow-up data. In this analysis, the number of psychosocial stressors in 1968 was positively associated with a slightly increased risk of overall dementia, adjusted HR = 1.2, and AD, adjusted HR = 1.2. No significant association was found between stress levels and vascular dementia (VD). Further analysis demonstrated that not only long-standing distress levels, but also number of psychosocial stressors, independently related to AD [10]. This finding implies that the connection between stress exposure and AD was not fully mediated by the subjects' perceived levels of distress and highlights the importance of capturing objective exposure levels.

Comijs and colleagues studied a sample of 1396 Dutch individuals from the Longitudinal Aging Study Amsterdam cohort at two intervals 3 years apart. Cognitive testing, using the Folstein Mini-Mental State Examination (MMSE), a Dutch version of the Rey Auditory Verbal Learning Test, and the Alphabet Coding Test-15, a speed of processing measure, was performed at both assessments. Stressful life events experienced during the 3-year prior interval were quantified by a structured interview. Cumulative stressful life events were not associated with performance on any of the cognitive measures in the total sample. Subjects with lower initial scores on the MMSE actually improved their

performance on the retention measure in the setting of increased stressful life events. When specific life events were examined, mixed results were obtained, with some life events (e.g., death of a child or grandchild) associated with a decline on the MMSE, but others (e.g., illness of a partner) associated with less decline than in those who did not experience the stressor. There were other counterintuitive findings as well. For example, those subjects who reported serious interpersonal conflict actually had improved learning scores on follow-up [11]. The spotty nature of this study's results highlights the difficulty in making blanket statements about the effect of stress per se on cognition.

Andel and colleagues studied the relationship between work-related stress and dementia risk in a sample of 10,106 Swedish mono- and dizygotic twin subjects culled from a larger twin pool. About half of the subjects were from twin pairs, and half were twins without their co-twin. Job stress was inferred from subjects' past occupational titles using the Karasek-Theorell approach, a previously validated procedure that locates each job on the dimensions of how psychologically demanding it is and how much control the typical employee exerts over his or her work life. The variable of "job strain" is derived from the ratio of job demands to job control. Cognitive difficulties were assessed via telephone screening and in-person interviews using consensus diagnostic criteria. The investigators also measured social support as a moderating variable. The presence of AD was confirmed in 167 subjects, and VD in 46. Mean age at dementia onset was 76.8 years. The remaining 9849 subjects served as controls. There were 60 twin pairs represented among the demented group, 54 of which were discordant for dementia. There were no differences in work-stress measures in affected versus nonaffected twins. Analysis of the entire twin sample showed that contrary to the model, job strain did not predict overall dementia, although the single dimension of job control did show a weak effect, OR = 1.2, which was driven by the association between low job control and VD, OR = 1.4. The combination of high job strain and low social support was also significantly associated with risk of VD, OR = 1.4. This effect held up after accounting for age, education, sex, complexity of work with data and people, manual versus nonmanual work, and known vascular risk factors. This study provides some support for the Karasek-Thorell model of occupational stress and some suggestive data linking job-related stress to the risk of one sub-type of dementia, such as VD. The investigators suggested that greater work stress is associated with VD via a cardiovascular pathway, in which accelerated aging of the cardiovascular system resulting from chronic stress leads to earlier dementia onset [12]. An advantage of the approach of defining stress by reference to job titles is that it eliminates the subjectivity of retrospective self-reports of job stress. Limitations of this study include the absence of objective measures of cognition and autopsy data, and the limited generalizability due to the inclusion of only subjects who were twins.

Deng and colleagues studied a sample of 5262 Chinese subjects older than age 55, drawn from a larger pool screened for neurological, medical, psychiatric, and sensory impairments, for 5 years. At baseline, adverse life events were captured by a truncated life events scale that focused on eight common negative experiences. Cognitive function was assessed with the MMSE; low scorers were further studied with additional neuropsychological tests. All subjects below the threshold at baseline were excluded; additional analyses were also undertaken to rule out the possibility of occult cognitive dysfunction at baseline, and potential confounding risk factors for vascular disorders and depression. Annual follow-up visits were carried out with repeat MMSE and activities of daily living assessments. Results revealed that experiencing the death of a spouse or a financial crisis increased the risk of cognitive impairment. These effects were still seen after controlling for a set of known potentially confounding variables, with an HR of approximately 1.5. However, no effects were seen for other significant stressors such as death of an offspring, onset of a serious illness or accident, or involvement in a lawsuit [13]. This partially positive study extends research in this area to a large Asian sample. A strength of the study was the systematic exclusion of conditions that could cause abnormal cognitive performance at baseline.

Leng and colleagues measured childhood stressors, cumulative lifetime stressors, and recent stressors as well as coping and social support, in a cohort of 5129 British subjects aged 49–90 who were participating in a prospective epidemiological study monitoring cancer risk. Primary measures were derived from subject responses on the Health and Life Experiences Questionnaire. These included total adverse events experienced during the prior 5 years; number of events involving loss; difficult childhood circumstances; indices of impact, adaptation, and social support; and self-perceived stress coded into five levels. Cognitive function was assessed during a follow-up session by a modified, 11-item short form of the MMSE. Performance was dichotomously classified into high and low levels. On average, 10 years had elapsed between the stress reporting and the assessment of cognitive acuity. After adjusting for sex and age, MMSE scores were found to be related to the number of loss events reported. Subjects with higher levels of self-reported stress were more likely to have low MMSE scores, with an increasing OR of 1.1 for each unit of increased perceived stress. However, this effect was limited to the highest level of perceived stress and was stronger in subjects with lower educational attainment. In contrast, actual measures of stressful exposure per se were unrelated to MMSE scores, as were subjects' own estimates of the adequacy of their adaptation/coping with experienced events [14]. This partially positive study underscores the role of the subjective perception of stress, and it illustrates a dose-response effect and the role of the moderating variable of education level, which may be a proxy for "ego-strength" or coping skills/resilience.

In summary, although multiple studies have found positive results linking increased life stress to negative cognitive outcomes, there are many caveats to the claim that adverse life events cause cognitive decline. Typically the effect sizes, although statistically significant, were small, with modest or even trivial increases in relative risk. Moreover, these effects were often seen only in selected subsamples of subjects and/or only on selective cognitive measures. The contradictory findings, with some studies supporting the relationship between stress and AD and others not, some studies supporting the relationship between stress and VD but not AD, and some studies supporting the relationship between stress and cognitive decline but not AD or VD, preclude in our view any disease-specific claims at this time. The frequent absence of neuropathological analysis of tissue data further underscores the need for caution. Continued study of this area, however, is supported by the strongly suggestive findings in the existing literature. Incorporating approaches that use the latest consensus criteria and capture multiple aspects of life stress, including for example exposure parameters, individual reactivity, and the role of "stress buffers," will improve this effort. As reliable biomarkers of specific dementing syndromes become better established, greater clarity will no doubt emerge from long-term studies of the cumulative risk of psychological stress.

2.2. PTSD and dementia

Qureshi and colleagues analyzed a database of veterans age 65 years or older who were seen at least twice at U.S. Department of Veterans Affairs (VA) health care facilities between October 1997 and September 1999, and who either had been diagnosed with PTSD or had received a Purple Heart (PH). PH status was used as a proxy for combat-related trauma. These patients were compared with age- and sex-matched, non-PTSD, non-PH VA patients. Outpatient encounters between October 1997 and September 30, 2008, were searched for diagnoses of PTSD, dementia, and other physical comorbidities with known associations with dementia. The incidence of a dementia diagnosis was 6.2% in all groups: 6.8% in the PTSD+/PH+ group, 9.5% in the PTSD+/PH−, 5.6% in the PTSD−/PH+, and 4% in the PTSD−/PH− group. The incidence of a dementia diagnosis was two times higher in the PTSD+/PH− group compared with both PTSD− groups combined, adjusting for confounding factors. The authors concluded that veterans with PTSD have a higher incidence of dementia than veterans without PTSD. However, they were careful to point out that the observed association between PTSD and the subsequent development of dementia does not necessarily imply a causal relationship, in that it could also be due to common risk factors underlying both PTSD and dementia [15]. One such common risk factor could be lower intelligence [16]. A limitation was that dementia was not separated into its different subtypes, leaving a possible association between PTSD and any specific pathophysiological mechanism(s) potentially leading to the development of dementia unclear. The higher incidence of illnesses such as hypertension and diabetes in those with PTSD could predispose them to developing VD. It is more difficult to postulate a pathophysiological pathway between PTSD and neurodegenerative diseases such as AD or Pick's disease.

Yaffe and colleagues analyzed the VA National Patient Care Database in a retrospective cohort design. Participants were an impressive 181,093 veterans 55 years of age or older who were without a dementia diagnosis from fiscal years 1997 through 2000. Of these, 53,155 had and 127,938 did not have a PTSD diagnosis. Almost all patients (96.5%) were men, with a mean baseline age of 69 years. During the follow-up period between October 2000 and December 2007, 31,107 (17.2%) veterans were found to have newly diagnosed dementia according to International Classification of Diseases, Ninth Revision, Clinical Modification codes. Patients were classified with dementia if they received one of the following diagnoses: senile dementias (n = 3450), VD (n = 2698), AD (n = 3882), frontotemporal dementia (n = 139), Lewy body dementia (n = 356), and dementia not otherwise specified (n = 10,291). The patients with preexisting PTSD had a 7-year cumulative incident dementia rate of 10.6%, whereas those without PTSD had a rate of 6.6%. Patients with PTSD were more than twice as likely to develop incident dementia compared with those without PTSD, HR = 2.3. After adjustments for multiple factors, including medical and neuropsychiatric comorbidities, patients with PTSD were still more likely to develop dementia, HR = 1.8. Results were similar after excluding patients with a history of head injury, substance abuse, or clinical depression. Interestingly, PTSD was associated with all types of dementia, the strongest association being with frontotemporal dementia, and the weakest with VD. (Information was not provided regarding the statistical significance of the differences of relative risks among dementia subtypes). The authors concluded that, within the population studied, those diagnosed with PTSD had close to two-fold higher risk of developing dementia compared with those without a diagnosis of PTSD [17]. Data from the previous study illustrate an important point that is common to all the studies of stress or PTSD and dementia reviewed in this chapter, namely that statistical estimates alone (e.g., HRs or ORs) fall short of conveying the full picture. In the previous study, approximately 90% of the PTSD patients did not go on to develop dementia, and approximately 7% of the non-PTSD patients did develop dementia. These percentages illustrate that, although PTSD may be associated with a greater risk, it is neither a necessary nor a sufficient condition for developing dementia—far from it.

3. Substance abuse

Both exposure to chronic life stressors [18,19], and PTSD [20] are known to be associated with an elevated risk of substance abuse. This is often thought to involve a given

individual's misguided attempt at self-medication, although genetic data also support a common vulnerability to PTSD and substance dependence. Either way, chronic use of substances including alcohol [21], marijuana [22], opioids [23], cocaine [24], and methamphetamine [25] has been linked to the development of cognitive impairment. This pathway establishes a potential indirect mechanism for the effects of stress, and PTSD, on cognitive integrity that needs to be accounted for in etiological models positing a causal relationship between stress and PTSD, and risk of dementia.

4. Biology of stress, PTSD, and dementia

4.1. Neuroimaging

A longitudinal study of normal aging found a relationship between chronic stress and decreased hippocampal and orbitofrontal gray matter volume [26]. Structural neuroimaging studies have revealed a lower volume of the hippocampus in persons with PTSD [27,28]. More recent studies using high-resolution magnetic resonance imaging (MRI) have identified the CA3 and dentate gyrus subfields of the hippocampus as showing the greatest group differences [29]. Whether the hippocampal volume is a result of PTSD, a risk factor for PTSD, or both, remains unresolved (see the following section). Other areas that have been found to have a lower volume in PTSD versus non-PTSD subjects, albeit less consistently and to a lesser extent than hippocampus, are amygdala and anterior cingulate cortex [28]. In a recent study, 42 people who happened to have undergone MRI before an earthquake were rescanned after it had occurred. Lower gray matter volumes in the right ventral anterior cingulate cortex before the earthquake were associated with more PTSD symptoms after the earthquake, and greater decreases in before to after earthquake left orbitofrontal cortex volume were associated with more PTSD symptoms[30].

In AD, neuroimaging has been used to track the progression of the disease from its presymptomatic to its full-blown stage in specific and nonspecific ways. Ventricular enlargement, the most prominent radiological feature in AD, is a nonspecific finding. In cognitively intact older adults, lower baseline volumes of the CA1, and subiculum regions of the hippocampus [31] as well as larger lateral ventricles measured by MRI, predict cognitive decline to the point of MCI. Lower volumes of CA1, subiculum, and (hypothesized spread of atrophy to) the CA2-3 subfields of the hippocampus among amnestic MCI individuals predict a future diagnosis of AD [32]. Additionally, lower volume of the right caudate nucleus predicts conversion from MCI to AD [33]. Medial temporal regions including the entorhinal cortex and amygdala are also decreased in volume in MCI patients who later develop AD. Similarly, atrophy of the temporal and frontal lobes, the temporoparietal cortices, anterior and posterior cingulate gyrus, and precuneus are associated with a 3-year progression from MCI to AD [34]. Among AD patients, hippocampal atrophy occurs first, followed by atrophy of the cingulum bundle and the uncinate fasciculus [35]. Temporal, parietal, and frontal lobe atrophy worsen with the progression of the disease [36]. Importantly, no such progression has ever been reported in the now-voluminous PTSD literature.

4.2. Endocrine responses

In the face of adversity or threat, the body's stress system is activated to provide the organism the necessary resources for a fight or flight response. Two main stress axes are engaged in response to a stressor. First, activation of the sympathetic-adrenal-medullary axis results in the rapid secretion of epinephrine. Second, activation of the HPA axis, through a chain of hormones, results in the secretion of glucocorticoids (GCs), mainly corticosterone in lower animals and cortisol in humans. GCs are liposoluble and cross the blood–brain barrier to bind to mineralocorticoid (type I) and glucocorticoid (type II) receptors. Type I receptors are mainly distributed in the limbic system, whereas type II receptors are present in subcortical and cortical structures, including the prefrontal cortex. HPA axis activity is regulated by negative feedback loops, which are in part driven by the binding of GCs to type II receptors located at the levels of the hypothalamus and pituitary. Three brain structures have been identified as important regulators of the HPA axis: the amygdala, which has an excitatory influence, and the hippocampus and prefrontal cortex, which exert inhibitory influences on the HPA axis. Because these brain structures have a high density of GC receptors, the functions that they subserve are likely to be influenced by stress. When the stress response goes unterminated, negative consequences may arise, such as receptor desensitization and tissue damage. This long-term cost of stress has been referred to as "allostatic load [37]." Higher allostatic load has been linked to lower cognitive functioning in older adults [38].

The impact of stress on cognition has been studied across various paradigms and populations. Older adults show wide variability in hippocampal volume and function, cortisol secretion, and cognitive performance. Many research endeavors have been undertaken to understand the relationships among these variables, from normal to pathological aging. Rodent studies have found that aged rats with memory impairments have higher HPA axis activity than rats with normal memory performance [39]. In aged rats, HPA axis activity is negatively associated with both spatial memory performance and hippocampal neurogenesis. Injecting adult rats with cortisol for long periods leads to similar memory impairments [40]. Lowering cortisol levels has been found to promote neurogenesis and prevent the spatial memory impairments usually observed with aging in rodents [41]. Humans who showed increasing 24-hour cortisol for 3 to 6 years progressing to the point of high levels were found to have more memory impairments and smaller hippocampal volumes [42].

Animal studies have led to the glucocorticoid cascade hypothesis [43], which is sometimes also known as the neurotoxicity hypothesis. This theory suggests that chronically elevated levels of cortisol impair HPA axis regulation, and this dysregulated stress system leads to lower hippocampal volume and memory deficits. Chronically elevated levels of GCs have been shown to lead to lower dendritic branching in the hippocampus, CA3 regional atrophy, and degeneration of pyramidal neurons [43,44]. Moreover, studies have suggested that chronic exposure to high GC levels after brain insults, such as trauma or ischemia, further promote neuronal loss [45]. AD has also been linked to higher cortisol levels [46] and, as noted previously, lower hippocampal volume. To our knowledge, no study has yet elucidated whether the hypercortisolemic profile causes the hippocampal volume diminution, or whether having a smaller hippocampal volume confers vulnerability to higher secretion of cortisol.

4.3. Oxidative stress

Beyond HPA axis stress, the notion of oxidative stress has also been studied in an attempt to elucidate the mechanisms of progression from normal to pathological aging. Mitochondria produce reactive oxygen species, which can exert deleterious effects on body tissues. Oxidative stress occurs when the activity of antioxidants is insufficient to counteract these pro-oxidants [47]. Studies on a range of animal species from rodents to nonhuman and human primates report an association between severe life stress and oxidative stress markers. It has been suggested that heightened life stressors can increase oxidative stress, which could in turn compromise the integrity of the HPA axis [47]. High oxidative stress has been linked to cognitive impairments and AD. Oxidative stress has been found to be associated with decreased neurogenesis in the dentate gyrus, increased blood–brain barrier permeability, neuroinflammation (see the following section), neuronal death, and an overall higher likelihood of brain tissue damage [47,48]. Neuroinflammation may in turn further promote oxidative stress, potentially creating a vicious cycle. Studies have shown that amyloid-beta (Aβ), a neuropathological hallmark of AD, can be generated by the interaction of oxidative stress and neuroinflammation. Both oxidative stress and neuroinflammation have been associated with lower telomerase activity, which in turn promotes telomere shortening [49]. Telomere shortening is a normative process that takes place with aging, but excessive shortening has been associated with cognitive impairments, increased risk of mortality, and multiple pathologies including AD. Moreover, oxidative stress increases the activity of excitatory neurotransmitters, notably glutamate. Sustained high levels of oxidative stress for prolonged periods can lead to dysregulated signaling processes that could result in neuronal loss, a process called excitotoxicity [50]. This process has been reported in multiple neurodegenerative diseases, including AD. Finally, it remains important to keep in mind that chronic stress can increase caloric intake, insulin resistance, and the risk of obesity, with consequent deleterious effects on mental disorders [51] as well as lead to metabolic syndrome, which has been linked with elevated levels of inflammation and AD [52]. Although a role for oxidative stress has been suggested from animal models of PTSD [47,53], markers of increased oxidative stress have not reliably been linked to the actual disorder in humans[54].

4.4. Neuroinflammation and cytokines

Neuroinflammation is a process that is initiated to counteract an insult to the brain. It is characterized by the activation of microglia and astrocytes, which are associated with the release of inflammatory mediators, notably cytokines. Cytokines mediate communication between the immune and neuroendocrine systems. There are two distinct classes of cytokines: pro-inflammatory and anti-inflammatory. Stress increases the production of pro-inflammatory cytokines in the periphery and in the central nervous system. Chronically stressed individuals often have compromised immune function and show high serum levels of pro-inflammatory cytokines. Elevated pro-inflammatory cytokines have also been reported in PTSD [55,56].

The role of chronic stress in inducing neuroinflammation may be mediated through the release of GCs. In the brain, GCs exert stimulate leukocyte migration. Neuroinflammation, in turn, contributes to the disruption of the normal process of proliferation, migration, and differentiation of neural stem cells, leading to decreased neurogenesis with impaired new learning and memory. Findings of activated microglial cells around amyloid plaques support a role of neuroinflammation in the pathophysiology of AD [57]. In epidemiological studies, treatment with nonsteroidal anti-inflammatory drugs has been found to decrease AD risk [58]. Nonsteroidal drugs have been explored as a potential treatment to delay AD onset [58,59].

Increasing age has been associated with a change in the immune response, with upregulation of proinflammatory and downregulation of anti-inflammatory mediators. There is a negative correlation between the degree of inflammation and the age at onset of AD (i.e., the greater the degree of inflammation, the earlier the onset). Individuals with greater degrees of inflammation have been found to lose more points on the MMSE during a 3-year period [60].

4.5. Neuropathology

In considering stress-induced effects on neural tissue, it is important to emphasize that not every alteration implies a degenerative process. As with other organs of the body, the brain is capable of changing morphologically in response to the environment. These changes occur at molecular, cellular, synaptic, tissue, and possibly even gross anatomical levels, not only in neurons but also in neuroglia. Brain changes in response to stress are numerous and vary according to the brain region affected [61]. The most studied region

has been the hippocampus. A concomitant of the glucocorticoid cascade hypothesis is that chronically elevated levels of cortisol can lead to dendritic atrophy in that structure [62]. Such changes have been reported in rodents and monkeys exposed to chronic stressful situations as well as to exogenous corticoids. Importantly, up to a point at least, hippocampal dendritic atrophy is reversible with the cessation of stress. Also importantly, other brain areas, notably amygdala, may respond to stress in the opposite direction (i.e., with increased dendritic proliferation and hypertrophy) [63,64]. All these responses may be adaptive. Under stressful environmental conditions (e.g., the constant presence of danger), it may be advantageous to have a hyperfunctioning amygdala, given this organ's central role in recognizing threat and coordinating the fear response. In contrast, in the presence of danger, functions subserved by the hippocampus (e.g., learning about the environment under safe conditions and allowing behavioral flexibility) may be disadvantageous.

The observation of regional neuronal variations in response to stress, with atrophy in some areas but hypertrophy in others, precludes a simplistic assertion that stress damages the brain. Rather, stress appears to sculpt the brain according to the exigencies of the environment. If the stress is prolonged, neuronal death might occur, although recent research has challenged the constancy of this effect [61]. In contrast to the mixed picture in stress, a review of volumetric MRI studies showed comparable amygdala and hippocampal volume loss in AD [65]. This suggests a qualitative difference in the neuropathological processes underlying stress and AD, with the former more appropriately classified as plastic and the latter as degenerative.

The neuropathology of AD is characterized by extracellular Aβ plaques and intracellular neurofibrillary tangles. Aβ is produced from the amyloid precursor protein (APP). Tau protein is the essential ingredient of neurofibrillary tangles. In AD, tau protein becomes hyperphosphorylated, which impairs its function. Astrocytes and microglia cluster around neurons and plaques and are activated, interacting with proinflammatory molecules and disrupting the balance between proinflammatory and anti-inflammatory molecules [58].

Evidence in animals does suggest that stress may accelerate or aggravate neuropathological processes relevant to AD. One approach is to study animals that have been genetically modified so as to enhance pathophysiological features associated with AD and then to examine the effect of stress and stress hormones on them. Transgenic mice that overexpress a mutation in APP show decreased capacity for cell proliferation in the dentate gyrus. Isolation stress has been found to accelerate the underlying process of Aβ plaque deposition in these mice [66]. In another transgenic mouse model of AD, long-term stress was associated with increased numbers and densities of vascular and extracellular deposits, especially in the hippocampus, containing Aβ and carboxyl-terminal fragments of APP [67]. Exogenous administration of stress levels of glucocorticoid to transgenic mice has also been found to increase Aβ formation by increasing steady-state levels of APP and β-APP cleaving enzyme and to augment Tau protein accumulation [68]. In nontransgenic Wistar rats, both stress and glucocorticoids have been found to provoke misprocessing of APP in the rat hippocampus and prefrontal cortex [69]. In healthy, middle-aged Wistar rats, chronic stress and glucocorticoids have been found to induce abnormal hyperphosphorylation of Tau protein in the hippocampus and prefrontal cortex, with contemporaneous impairments of hippocampal- and prefrontal cortical–dependent behaviors [70]. For a recent, detailed review of the neuropathology of stress, see [61].

Paradoxically, the leap from PTSD to AD may be wider than the leap from stress to AD. Consistent with the glucocorticoid cascade hypothesis, in AD, as in depression, cortisol levels tend to be high [71] and resistant to negative feedback [72]. However, an extensive body of research has found this not the case in PTSD; if anything, the pattern appears to be the opposite. [4] Given that what evidence there is that stress is involved in AD's pathogenesis relies heavily on a mediating role of excessive glucocorticoids, it is difficult to apply such a model to a condition (PTSD) in which glucocorticoids have not been found to be excessive. At this point, non–glucocorticoid-mediated mechanisms by which PTSD could influence AD have not been well delineated.

Diminution of hippocampal volume is a well-replicated finding in PTSD. Initially, this discovery was heralded as seminal evidence that stress can damage a brain structure in humans. This interpretation, however, received a setback in an identical twin study that supported the conclusion that hippocampal diminution in PTSD was a constitutional abnormality that was shared by PTSD combat veterans' combat-unexposed twins [73]. Results of a meta-analysis has since revealed that a history of exposure to traumatic events, even in the absence of PTSD, is associated with diminished hippocampal volume (albeit to a lesser extent than in PTSD), suggesting a causal role for trauma exposure in hippocampal diminution [74]. However, even the very risk of exposure to trauma has genetic determinants. Evidence that psychopharmacological treatment can increase hippocampal volume in PTSD [75] suggests but does not prove an acquired, reversible origin of the diminution. Even if a portion of the volumetric decrease found in PTSD in hippocampus, and possibly other brain structures, is eventually shown to be acquired rather than constitutional, it is unclear what relevance this would have for AD and other dementias, given that PTSD and dementia are very different psychiatric and biological entities. The question might be illuminated by the postmortem examination of brain tissue in PTSD in a search for AD-like changes, but few such studies have been reported [76,77]. Until that time, any neuropathological link between PTSD and AD remains speculative.

5. Conclusions

Epidemiological studies of chronic stress and PTSD have fairly convincingly shown that both are associated with a greater statistical risk for various forms of dementia. However, effect sizes have generally been modest. It is clear that neither chronic stress nor PTSD is either necessary or sufficient to result in dementia. Rather, these conditions appear to play an ancillary role among numerous factors that are involved in the pathogenesis of dementia, including AD, about which much remains to be discovered. Causal links between stress and PTSD and dementia, although suggested, have not been established. Controlling for all the potential confounding factors is an onerous task on which progress has been made, but more remains to be done. At the biological level, several plausible routes from stress to dementia have been delineated in preclinical studies, which have typically relied on animals genetically modified so as to be at greater risk. This may have an analogy, or even homology, in humans (i.e., stress may only increase the risk of dementia in otherwise predisposed persons). Translation of findings from these animal studies to human dementing conditions has yet to be accomplished. AD has a distinctive neuropathological profile that neither stress nor PTSD alone has been found to produce. Although no specific anti-stress or anti-PTSD interventions have been shown to be useful, given the importance of the problem, further research is called for. Meanwhile, public health interventions aimed at reducing chronic stress and PTSD are likely to have a salutary, if limited, effect on the risk of dementia (by whatever mechanism), as well as on numerous other medical conditions.

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