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Can stress increase Alzheimer's disease risk in women?

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of β-amyloid peptides and neurofibrilllary tangles in brain, resulting in neuronal death and loss of cognitive abilities. It has been hypothesized that longstanding psychological stress can result in neural degeneration and AD due to pathological alterations in the hypothalamic–pituitary–adrenal axis. In recent years several epidemiological studies been published on stress as a risk factor for AD. As women are more likely to suffer from stress-related psychiatric disorders, such as post-traumatic stress disorder and clinical burnout syndrome, special effort has been made according to the gender differences in risk of AD. However, few studies have stratified for gender, due to small sample sizes and limited statistic power, and no reliable findings have been found. Additional longitudinal studies are therefore needed for studying gender differences and for determining what mediates the stress and AD association, in both genders.

Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disorder characterized by accumulation of β-amyloid peptides and neurofibrillary tangles in brain, resulting in neuronal death and gradual loss of cognitive abilities. The earliest pathological signs in brain imaging are commonly seen as atrophy in the medial temporal lobe, especially in the hippocampus area. Although it has been an intensive research in the field of AD in recent years, it is still unknown what trig and drives the neuropathological processes in brain. The sporadic nature suggests that, aside from genetic factors, environmental determinants may play a critical role in onset and progression of the disease.

One hypothesize is that longstanding psychological stress can lead to neural degeneration and pathological AD changes. Stress activate the hypothalamic–pituitary–adrenal (HPA) axis axis and thus the levels of a variety of potent hormones, for example, glucocorticoid. According to the 'glucocorticoid cascade hypothesis', high and longstanding levels of cortisol lead to shrink and loss of neurons, especially in some vulnerable areas in the medial temporal lobe because of the high amount of cortisol receptors. Loss of neurons in these areas can lead to inhibitory feedbacks to the HPA axis, which in turn result in even higher cortisol secretion from the adrenal gland with further neuronal loss. Several studies have found associations between severe stress and atrophy in brain, for example, in the hippocampus complex [1]. Cortisol also regulates a variety of important cardiovascular, metabolic, immunological and homeostatic functions in brain, and chronic stress has been associated with hypertension, metabolic syndrome and dysfunctional immune system, which in turn have been related to dementia and AD. Other hypotheses have also been suggested. For example, reduced telomere length has been found in both AD patients [2] and in persons with perceived stress [3], and animal studies have reported that high glucocorticoid levels increase the deposition of β-amyloid peptide and tau protein in the brain [4].

Women are twice as likely as men to suffer from stress-related psychiatric disorders such as post-traumatic stress disorder and clinical burnout syndrome [5,6]. This sex difference might partly be

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biologically determined. Clinical studies have found that sex hormones revealed a considerable degree of the HPA axis response to chronic stress and hippocampal structural plasticity [7], and stress in women has shown greater activity in the brains limbic system [8,9], increased cytokine activity [10] and larger cortisol response [11] compared with men.

In recent years, several epidemiological studies of psychosocial stress as a risk factor for AD have been published. In the 35-year Prospective Population Study of Women in Gothenburg, Sweden, we found that longstanding stress in midlife was associated with AD, temporal lobe atrophy and white matter lesions in late life [12,13], and that higher amount of life stressors was associated with higher incidence of AD [14]. In a sample of more than 4000 older persons in the Utah Population Database, Norton *et al.* found that the traumatic event of parental death during childhood was related to higher incidence of AD in both genders [15]. Wang *et al.* showed that lifelong work-related stress was associated with increased risk of late-life AD, in data from the Kungsholmen project in Sweden [16]. However, although the women in this study had higher job strain than the men, no modification effect of gender was observed. In a 7-year follow-up study of more than 180,000 US war veterans, Yaffe *et al.* found that individuals with clinical post-traumatic stress disorder was twice as likely to develop AD [17]. The study had, however, a great maldistribution of gender with only 4% women, and no gender differences were observed in the risk of AD.

Furthermore, a number of studies have reported associations between stress-prone personality, that is, high neuroticism and development of AD. Personality is defined as characteristics stable over time, which influence an individual's thinking and emotions, and the personality trait neuroticism refers to stress proneness, emotional instability and negative affectivity. The Baltimore Longitudinal Study of Aging assessed personality in a large sample of middle-aged men and women. During the 22 years of follow-up, it was found that high neuroticism was associated with increased risk of developing late-life AD [18]. Wilson *et al.* [19] and Duberstein *et al.* [20] reported associations between high neuroticism and incident AD in elderly men and women and in a clinical sample of AD patients, Archer *et al.* found that retrospective report of high midlife neuroticism predicted earlier onset of AD in females but not in males [21].

To conclude, despite evidence that longstanding stress has damaging effects on brain, little is known about stress as a risk factor for AD. First and foremost longitudinal studies are lacking. It has been suggested that structural AD changes in brain appear already 20–30 years before the disease get clinically manifested, and the pathological levels of β-amyloids have been found to be fully altered 10 years before conversion to AD [22]. So, due to the fact that heightened stress response can be an early signs of AD, it is possible that the associations between stress and AD in short follow-up studies rather might be an early marker for dementia than a causal factor.

With the continuing demographic shift toward greater longevity, the number of people with AD will increase dramatically and the incidence is higher in women than in men. In addition, psychological stress and stress-related disorders have been recognized as a widespread and increasing public health problem, especially among young and middle-aged women. It is therefore also of great interest to learn more about neurobiological consequences of longstanding stress, for example, to investigate the underlying mechanisms of stress and brain damage and to study if psychological stress has different impacts on women and men.

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