GUEST EDITORIAL

Sex differences in Alzheimer's disease risk: are we looking at the wrong hormones?

Two-thirds of individuals with Alzheimer's disease (AD) are women, owing largely to the fact that women outlive men (https://www.alz.org/downloads/facts_figures_2012.pdf). Women's increased longevity, however, is not sufficient to explain the fact that women are 1.5 times more likely than men to develop the disease (Gao *et al.*, 1998). After age 80, the incidence of AD is much higher in women than in men, such that the proportion of women with AD is almost twice the proportion of men with the disease (e.g., Zandi *et al.*, 2002; Plassman *et al.*, 2007). Moreover, once diagnosed with AD, women decline more rapidly, both cognitively and functionally, compared to men (Ito *et al.*, 2011; Tschanz *et al.*, 2011).

To explain women's increased risk for AD, and faster progression after onset, sex hormones—estrogens in particular—are often invoked. Numerous studies have established that age-related depletion of sex hormones increases the risk of AD, prompting researchers to hypothesize protective roles of these hormones against AD (see Vest & Pike, 2013, for a review). Further support for the sex-hormone hypothesis came from a series of studies on the relation between fertility and AD. Based on the hypothesis that pregnancy-induced changes in estrogen levels would increase AD risk, this line of work has revealed that women with a greater number of pregnancies have a higher risk of developing AD and/or a younger age of onset (Sobow and Kloszewska, 2004; Colucci *et al.*, 2006). Even more persuasive is that having children increases the likelihood of developing AD in women but not in men (Colucci *et al.*, 2006), and is positively correlated with AD neuropathology in women but not in men (Beeri, 2009). Furthermore, the association between parity and age of AD onset appears confined to women without the APOE4 allele, as it was not observed in women with the APOE4 allele in one study (Corbo *et al.*, 2007), suggesting fertility is an independent risk factor for AD in women. Taken together, these findings provide perhaps the most compelling evidence for the sex hormone hypothesis of sex differences in risk for AD.

The notion that brief periods of altered sex hormone levels lead to the development of AD pathology a half century later, however, is not altogether convincing for several reasons. First, the notion that pregnancy induces *long-term decreases* in basal estrogen has been suggested to explain the delayed temporal association between pregnancy and AD. This explanation does not account for similar associations among parenthood, sex hormone levels, and risk of AD in men. Specifically, just as low estrogen levels increase the risk of AD in women, low testosterone is associated with an increased risk of AD in men. Moreover, men who become fathers evince a steeper decline in testosterone levels over time compared to men who remain childless (Gettler *et al.*, 2011). Thus, if both motherhood and fatherhood are associated with decreased sex hormone levels, then fertility would be expected to increase the risk for AD in both sexes. But it does not. Second, the results of hormone replacement studies suggest strongly that hormone replacement *increases* AD risk, the opposite of what was predicted (e.g., Shumaker *et al.*, 2003). Most importantly, the line of work based on the sex hormone hypothesis has not led to treatments for AD, suggesting a need to consider alternative hypotheses linking female sex and AD risk. Findings from several lines of research implicate *sex differences in the stress response* as a promising candidate.

The stress response

In response to threat, a complex interaction among glands, hormones, and parts of the mid-brain ensues. In humans, stress triggers the release of corticotropin-releasing hormone (CRH) from the para-ventricular nucleus of the hypothalamus. CRH stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH), which in turn causes the adrenal glands to release cortisol. The hypothalamic-pituitary-adrenal (HPA) axis is thus a key component of the stress response system, aberrations of which are associated with various stress-related illnesses.

Prolonged stress-induced release of glucocorticoids leads to alterations in the hippocampus (Sapolsky, 1996; Gould *et al.*, 1998), including

remodeling of dendrites (Gourley *et al.*, 2013), reductions in long-term potentiation (Tadavarty *et al.*, 2009; Kamal *et al.*, 2014) or brain-derived neurotrophic factor (BDNF; Bath *et al.*, 2013), increases in markers of oxidative stress (as reviewed by Rothman and Mattson, 2010), and reduced volume (Lupien *et al.*, 1998). Stress also suppresses neurogenesis in the dentate gyrus (Gould *et al.*, 1997, 1998), an effect that increases with advancing age (Simon *et al.*, 2005). Additionally, stress alters dendritic morphology of prefrontal cortical neurons (Radley *et al.*, 2004; Liston *et al.*, 2006). The functional consequences of these changes include cognitive impairment, particularly in memory (see Lupien *et al.*, 2005, for a review), and also in executive functioning (Plessow *et al.*, 2012).

Stress and AD

In rodents, stress provokes misprocessing of the amyloid precursor protein, leading to increased levels of Aβ40 and Aβ42 in the hippocampi (Martisova *et al.*, 2013), increases tau phosphorylation in the hippocampus and prefrontal cortex (Yang *et al.*, 2014), and accelerates cognitive impairment (Cuadrado-Tejedor *et al.*, 2012). Interestingly, these effects are observed in only "stress-sensitive" (rather than "stress-resistant") animals (Briones *et al.*, 2012), suggesting that the apparent AD-inducing effects of stress are not inevitable, but *require a particular vulnerability* to the effects of stress.

In patients with AD, both plasma and cerebrospinal fluid contain increased cortisol, the level of which is positively correlated with the degree of cognitive impairment (see, e.g., Dong and Csernansky, 2009), but unrelated to symptoms of depression (Hoogendijk *et al.*, 2006). Longitudinal studies have found that experiencing major stressful life events is associated with younger age of onset in familial AD (Mejia *et al.*, 2003). Furthermore, death of a spouse more than doubles the risk of AD in those who never remarry, a risk that is further increased in individuals who carry at least one APOE4 allele (Håkansson, 2009).

Sex differences in the stress response

Cortisol

Both preclinical and human studies show sex differences in the cortisol response to stress. In rodents, stress induces a greater cortisol response in males compared to females (Beck and Luine, 2002; Luine, 2002; Bowman *et al.*, 2003). Findings in humans are less consistent, as they are more dependent on factors such as type of stressor, age of subjects, and the timing of hormone measures (see Kudielka and Kirschbaum, 2005, for a review).

In studies examining the effects of stress on cognition, the degree of cortisol response to stress, rather than the mere experience of it, better predicts the cognitive effects of stress (Wolf *et al.*, 2001; Takahashi *et al.*, 2004). Whereas findings in young adults do not consistently favor men or women, advancing age appears to place women at a disadvantage. In a meta-analysis of 45 studies, Otte and colleagues (2005) found that the effect of age on the cortisol response to a pharmacological or psychological stressor was almost three times higher in women than in men. Importantly, the effect sizes of studies that controlled for sex hormone variations in women (e.g., standardizing menstrual cycles, excluding women on oral contraceptives or hormone replacement therapy) did not differ from those that did not, suggesting that sex hormones do not alter the effect of aging on the stress response in women. In line with this finding, studies examining the effect of stress on cognition in older men and women find that an acute psychosocial stressor causes memory impairment *in women only* (Wolf *et al.*, 1998; Almela *et al.*, 2011).

BDNF

In addition to cortisol, the association between stress and BDNF is another mechanism by which women may be more vulnerable than men to AD. In mice, stress reduces hippocampal BDNF in females but not in males (Yamaura *et al.*, 2013). In rats exposed to stress, females show greater stress hormone (corticosterone) response, less cell proliferation in the dentate gyrus, and lower levels of hippocampal BDNF than males (Malheiros *et al.*, 2014). In non-human primates, stress alters plasma BDNF in females but not males (Cirulli *et al.*, 2009).

In humans, a cross-continent meta-analysis found that the Met66 polymorphism of the BDNF gene, shown to reduce the transport of BDNF, conferred an increased risk of AD in women but not in men (Fukumoto *et al.*, 2010). While the role of estrogen in BDNF expression was postulated to underlie this finding, it is notable that BDNF is correlated with cortisol (Begluiomini *et al.*, 2008). In a study of young adults, women with the Met66 (compared to the Val/Val) BDNF polymorphism had an increased cortisol response to a social stressor, whereas the same polymorphism was associated with a *decreased* cortisol response in men (Shalev *et al.*, 2009). Taken together, these findings underscore the potential importance of
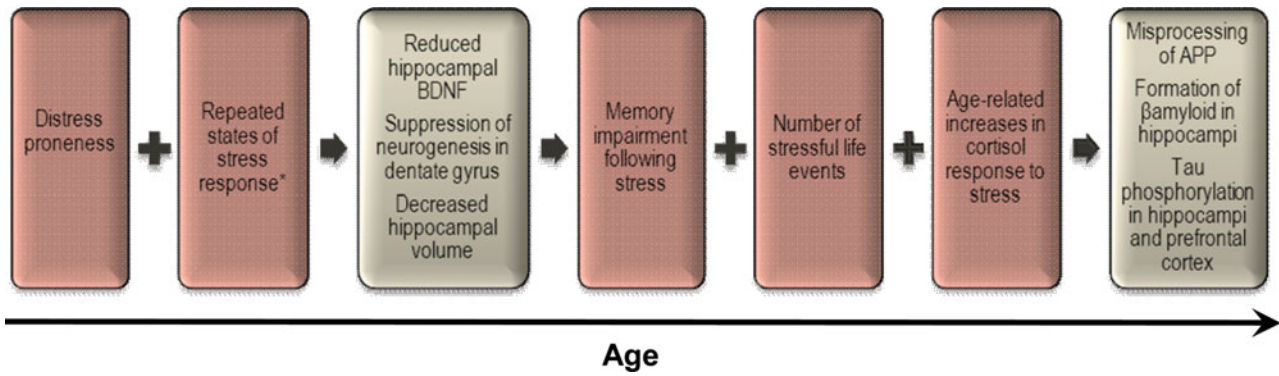
Figure 1. Influence of stress on the development of AD. Factors for which women show greater vulnerability than men are shaded in red. *Increased vulnerability in women considers that pregnancy is a stressful event.

stress hormones in explaining women's increased risk of AD.

Sex differences in stress vulnerability

In a 35-year longitudinal study of women, Johansson and colleagues (2010) found that reports of "frequent/chronic" stress during mid-life increased the risk of AD at follow-up. Similarly, a recent meta-analysis of five prospective studies (Terraccino *et al.*, 2014) found that individuals in the top quartile of distress proneness (high scores on neuroticism) had a three-fold risk of AD. Sex differences in neuroticism are consistently found across the world, with women scoring higher than men (Lynn and Martin, 1997). The magnitude of the sex difference, slightly greater than one-half of a standard deviation, is almost identical in young and older adults (Costa *et al.*, 2001; Chapman *et al.*, 2007). These findings correspond to those from animal studies, and suggest that "stress-sensitive" individuals are at increased risk for AD, and also that women are more vulnerable than men to this particular risk.

Sex differences in major stressful life events

Given the links between stress and risk of AD, it is notable that one of life's most stressful events—death of a spouse—is much more common in women than in men. Not only do women marry men who average two years their senior (Copen *et al.*, 2012), they also live longer than men (81 vs. 76 years; Population Reference Bureau 2013 World Population Data Sheet). For these reasons, the sex difference in the proportion of individuals experiencing widowhood increases with age. From ages 75–84, fewer than 20% of men, but over half of women (54%) have lost a spouse to death. After age 85, 35% of men and 72% of women have been

widowed (U.S. Census Bureau, 2006). If stress can induce the development of AD pathology or hasten its clinical manifestation in both sexes, then women would be at greater risk for AD simply by virtue of being much more likely than men to experience death of a spouse, even if there were no sex differences in the stress response. In this sense, the higher incidence of AD in women after age 80 could, indeed, be explained by the fact that they outlive men.

Pregnancy and stress hormones

Considering the studies reviewed above, it is intriguing to consider whether findings from the fertility studies might lend themselves to re-interpretation in the context of stress, rather than sex, hormones. During pregnancy, the adrenal glands become hypertrophic, and basal cortisol levels rise. By the third trimester, cortisol increases to two to three times higher than in the non-gestational period (Dörr *et al.*, 1989), similar to the levels seen in Cushing's syndrome (Magiakou *et al.*, 1997). At the same time, women's cortisol response to acute stress is attenuated (Kammerer *et al.*, 2002). That repeated states of pregnancy-induced alterations in the stress response might lead to enduring perturbations of the HPA axis in a manner that increases the risk for AD is a tempting hypothesis. Indeed, multiparity reveals alterations in both diurnal cortisol and cortisol response to stress that are not evident in primiparous mothers (Tu *et al.*, 2006a; 2006b).

Conclusion

Efforts to elucidate the mechanisms underlying sex differences in risk of AD have been dominated by research on sex hormones. While this work has done much to increase our knowledge of hormonal risk factors for AD, it has not led to effective treatments.

As depicted in the Figure, the preponderance of the evidence reviewed herein convincingly argues that stress hormones should be afforded their rightful place in the lineup of suspects underlying women's increased vulnerability to AD.

Conflict of interest

None

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