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Does Vestibular Dysfunction Contribute to the Increased Prevalence of Alzheimer's Disease in Females?

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ABSTRACT

Alzheimer's disease (AD) is twice as likely to occur in females as males, and it is also linked to vestibular impairment, especially if spatial symptoms predominate. Given large-scale epidemiological data showing a two-fold greater prevalence in females for most vestibular disorders, the greater prevalence of AD in females could be linked to their greater prevalence of clinical vestibular dysfunction, although there are also sex differences in vestibularly mediated cognitive abilities in normals. Preliminary evidence suggests that the percentage of vestibular impairment in AD patients with predominant loss of topographical and other spatial abilities is similar in males and females. This and other evidence suggest that the overall greater prevalence of AD in females may be more due to their greater susceptibility to vestibular disorders rather than to normal differences in vestibular-mediated cognitive abilities associated with AD.

Keywords
Alzheimer's, Vestibular, Sex, Prevalence.

One of the consistent findings concerning Alzheimer's Disease (AD), is the nearly two-fold greater prevalence in females [1,2]. The pronounced female bias in AD which strikingly differs from other dementias that mostly show male biases [1], has been attributed to a variety of causes, including sex differences in longevity, inflammation, genetics, beta-amyloid production, sex hormones, and sociocultural factors [1].

None of these putative explanations seems by itself entirely satisfactory in accounting for the greater AD risk among females overall. For example, the female bias still exists in most studies when age-adjusted risk is considered [2], and the longevity as well as possibly the inflammation and sociocultural explanations should also apply to the other dementias, which show the opposite sex bias in most cases. Estrogen has been proposed as a protective agent against AD, but that would hardly account for the reduced male prevalence; furthermore, hormone (estrogen)-replacement therapy has produced equivocal results in preventing or delaying AD [2]. Finally, the most well-studied genetic difference between the sexes involves the ApoE4 gene variant [1,2], which affects beta-amyloid clearance even though beta-amyloid may not even be causal to AD [3].

One alternative explanation for the greater prevalence of AD among women is the role of sex differences in both normal and abnormal vestibular function. Based on a wide range of evidence, it has been proposed that vestibular loss contributes to the development of AD [4,5]. Vestibular inputs help drive a topographical/navigational system comprising the hippocampus and posterior cingulate and parietal-temporal cortices, all of which are involved in the signaling of the head in relation to extrapersonal space. One of the important functions of this system is to orient to, navigate in, and retain memories of, topographical space [4]. Vestibular loss causes deficits in navigation, path integration, and other topographical functions along with degeneration of key structures in the topographical neural network such as the hippocampus [4,5,7]. Loss of topographical functions such as way-finding and memory are among the earliest and most specific signs of impending AD [6], while the hippocampus, posterior cingulate, and parietal-temporal cortices are the first neural regions to degenerate in AD [4]. Vestibular and topographical functions are positively correlated in the normal population [8], and a dominant subtype of AD that presents with topographic spatial symptoms is almost always accompanied by vestibular impairment [5,9].

A recent review [10], relying heavily on data from a large-scale epidemiological study from Germany involving 70 million cases [11], highlighted the greater prevalence of vestibular disorders and dysfunction in females. Specific vestibular disorders with a female bias include benign paroxysmal positional nystagmus, Meniere's disease, and vestibular neuritis, with females showing a general 2:1 prevalence over males across disorders [11]. The basis for the sex disparity is not clear, but reporting bias is unlikely [10] and, because the greater female prevalence in clinical vestibular disorders is present before and after menopause (15 to 74 years) [11], it is also unlikely to be caused by hormonal factors per se [10]. There are also sex differences in vestibularly mediated postural control [10] and topographical memory [12-14] in normals, with males superior in both functions. Disparities in normal vestibular functions begin in childhood and persist throughout the lifetime [13], possibly interacting with sexual hormones and the menstrual cycle [10,14]. The superior male topographical performance is consistent with the greater gray-matter volume of the hippocampus in males [15], although this anatomical difference is mostly found in those below age 50.

Despite the overall link between vestibular dysfunction and AD, it remains to be shown what percentage of the sex difference in AD can be attributed to vestibular influences. No published data exist on this subject, although a recent study that showed an overall female predominance of AD and mild cognitive impairment (MCI) [9] also revealed an equivalent percentage (76%) of vestibular impairment in males and females with AD/MCI (E. Wei, written communication, 9 Dec 19). This would suggest that the effects of clinical vestibular dysfunction on AD may be similar for males and females but that the latter are twice as likely to suffer from both.

Although the above unpublished finding is preliminary due to the limited overall sample size (50 participants), it implies that the vestibular influence on the greater female prevalence in AD may be more clinically related than an extension of normal sex differences in vestibular function. This interpretation would be consistent with the smaller differences between males and females in the normal population in hippocampal volume beyond age 50. One problem with the clinical vestibular explanation is that the sex differences in vestibular disorders are minimal after age 74, when the prevalence of AD begins to ramp up [16]. However, neural predictors of AD can predate the actual behavioral signs by 10-15 years [17], so sex differences at an earlier age could still prove causally linked to the later appearance of AD signs.

Obviously, there is a need for further research to determine the exact nature of the linkage between sex and vestibular function in AD. Such research could provide additional clues as to the vestibular role in AD in general and the potential benefits of vestibular-based therapies.

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