Acepted 4th August 2022 doi: 10.2174/1874609815666220304195049.

Loneliness as Risk Factor for Alzheimer´s disease

Marina Avila-Villanueva[1], Jaime Gómez-Ramírez[1], Jesús Avila[2,3*], Miguel A. Fernández-Blázquez[4*]

[1] Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Queen Sofía Foundation Alzheimer Center, Madrid, Spain.
[2] Center of Molecular Biology Severo Ochoa (CSIC-UAM), Campus de Cantoblanco, Madrid, Spain.
[3] Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain.
[4] Department of Experimental Psychology, Cognitive Processes and Speech Therapy, Complutense University of Madrid (UCM), Campus de Somosaguas, Pozuelo de Alarcón, Madrid, Spain.

Abstract: There is considerable empirical evidence that unequivocally points to loneliness as a modifiable risk factor for the development of Alzheimer's disease and other related dementias. With the emergence of the COVID-19 pandemic and the resulting lockdown and social distancing, there has been a renewed interest in studying this topic. The present review examines the links between loneliness and Alzheimer's disease, with particular emphasis on the mechanisms common to both conditions.

Keywords: Dementia, social behavior, Alzheimer disease, cronic stress, amygdala, hippocampus.

1. INTRODUCTION

There is overwhelming empirical evidence about the role of specific unhealthy lifestyle patterns in the development of Alzheimer's disease (AD) and other related dementias. The subjective experience of social isolation, also known as loneliness, may be included among those lifestyle dimensions that are associated with an increased risk of dementia [1, 2]. In fact, the lack of social contacts has been recognized as a very early predictor in the onset of AD [3-7]. In this review, we will focus on the influence of loneliness on the development of Alzheimer´s type dementia.

2. IMPACT OF LONELINESS ON THE ONSET OF ALZHEIMER

Many studies have used cohorts of older adults to analyze the transition through the continuum of AD, from the preclinical phase to the dementia stage. In such cohorts, the majority of participants have social connections not only with other members of the cohort, but also with other individuals [2, 5]. A well-known example is the Vallecas Project [8], in which only 4.3% of the cohort regularly felt lonely. Although some of the most important large multidomain preventive studies such as FINGER, MAPT or PreDIVE have paid little attention to the role of loneliness as a potential risk factor for AD, there are other types of research such as the Lothian Birth Cohort [9] in which social relationships are closely examined.

A recent study analyzed the association of three types of loneliness at mid-life-persistent, transient and incident- with risk of AD dementia two decades later [10]. The results highlighted two important findings. First, persistent loneliness seems to be an independent risk factor for dementia and AD. Second, loneliness is ultimately a modifiable risk factor insofar as recovery from loneliness provides resilience to dementia risk [10]. Regarding transient loneliness, in the last couple of years, we are witnessing the effect of social distancing caused by the COVID-19 pandemic. The health crisis due to SARS-CoV-2 has led to a situation unprecedented in the last century that allows us to study the effects of social isolation on health. Preliminary results in the general population point

out an increase in feelings of loneliness since the outbreak of COVID-19 [11-16], and even that some COVID-19 survivors showed signs of cognitive impairment and dementia [17-20]. Likewise, as a consequence of the pandemic and lockdown, a significant overall decline in patients already diagnosed with Mild Cognitive Impairment (MCI) and dementia has been reported [21]. It has been hypothesized some shared common links between COVID-19 and AD which involve angiotensin-converting enzyme 2 (ACE2) receptors and pro-inflammatory markers such as interleukin-1 (IL-1), IL-6, cytoskeleton-associated protein 4 (CKAP4), galectin-9 (GAL-9 or Gal-9), and APOE4 allele [22]. However, there is a lack of prospective studies on representative samples of older adults and, in fact, more studies should be done to determine the impact of loneliness on dementia.

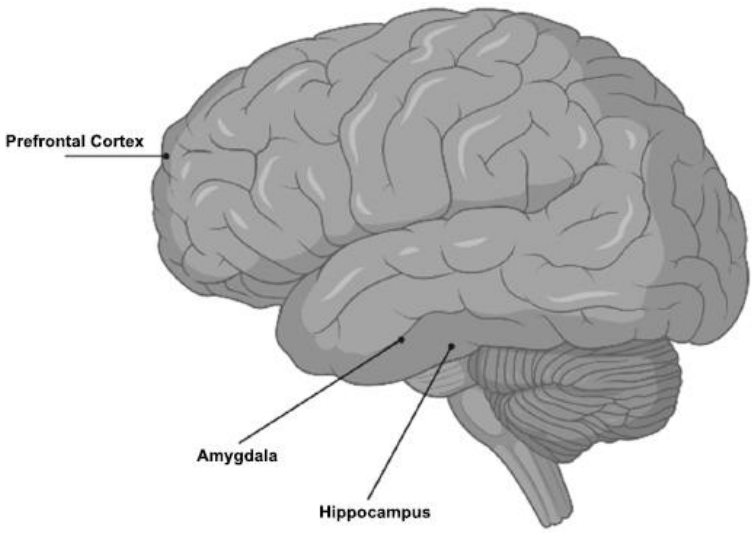

Fig. (1). This figure shows the prefrontal cortex, amygdala and hippocampus, brain regions that are damaged in various stages of social isolation and in Alzheimer's disease.

3. LONELINESS AND ALZHEIMER DISEASE: COMMON MECHANISTIC PATHWAYS

Some common features have been found in nondemented lonely individuals and future AD patients at early stages prior to clinical diagnosis of dementia [23, 24]. Fig. (1) shows some common brain areas that are affected in both lonely people and in the preclinical stages of AD. The figure illustrates those brain regions such as prefrontal cortex, amygdala or hippocampus that have shown dysfunction at various stages in social isolation [23] and in AD [25]. From a mechanistic perspective, loneliness has been related to chronic stress or depression due to changes in the hypothalamic-pituitary-adrenal (HPA) axis, which can also occur in early preclinical stages of AD [4, 26, 27]. Activation of the HPA axis in loneliness could lead to an increase in corticosterone levels in the prefrontal cortex [23]. In addition, loneliness has been reported to lead to decreased hippocampal neurogenesis along with reduced brain-derived neurotrophic factor (BNDF) or nerve growth factor (NGF) [23].

Such decreased hippocampal neurogenesis in adults has also been reported in AD patients [28]. Furthermore, the presence of AD hallmarks such as amyloid plaques [23] or tau pathology [24] has been reported in non-demented older adults

with loneliness.

4. LONELINESS, ALZHEIMER'S DISEASE AND OTHER CONDITIONS

There are different types and degrees of loneliness that research should take into account. Many people may experience stressful life events, such as living alone, widowhood, financial distress, lack of social support, environmental catastrophes, and medical illness, which are all likely to increase the feeling of loneliness [10]. Perhaps the stereotype of loneliness is embodied by an older adult who has sensory deficits such as hearing loss and this may result in a decrease in social interactions, isolation, and loneliness, followed by the development of dementia [7, 29]. However, loneliness is not a characteristic restricted to the elderly, but it can be found in young adults who have maladaptive personality traits, for example, low self-esteem, depressed mood or social maladjustment; in those cases, loneliness may have fatal consequences as suicide [30]. In older adults, there are cases of a strong need for individualism, as was the case of the American tycoon Howard Hughes. Loneliness can also arise as a result of a poor socio-economic situation, which could result in a homeless status. In this case, a neurological disorder, schizophrenia (SZ), which Kraepelin described a long time ago as a “dementia precox”, could be at the root of the problem. SZ has some differences with AD and other types of dementia. There are different biomarkers for each disorder. In

the case of SZ, changes in the dopamine/cholinergic axis are the main feature. In turn, AD is mainly characterized by the presence of two aberrant structures: senile plaques composed of amyloid peptide and neurofibrillary tangles made up of tau protein [31]. Also, imaging analysis could differentiate brain damages that take place in each neurological disorder [32]. Indeed, it has been proposed that SZ could be related to frontotemporal dementia (FTD) rather than AD [33]. However, SZ patients are almost four times more likely to develop AD than the general population [34], suggesting that the presence of SZ could be a risk for developing AD. In addition, SZ and AD shared some white matter abnormalities [34].

As mentioned above, loneliness could be related to the presence of chronic stress or depression, two features that could favor the occurrence of dementia [23]. Indeed, forced persistent loneliness, as being isolated in prison without social contact, could lead to stress, depression and (pseudo) dementia, as was the case of Rudolf Hess. Before the onset of dementia, a cognitive decline may occur in lonely people [35]. Thus, it can be suggested that loneliness could act as an early risk factor for dementia, facilitating the induction of other risk factors like stress and depression, followed by subjective cognitive decline (SCD), MCI and dementia [36, 37]. Just as loneliness could be a modifiable risk factor for dementia at an early stage, it can be reverted [38] or reduced through interventions related to the information and

communications technology and internet's use [39]. If it can be treated, then its analysis should be done in cohorts.

CONCLUSION

In this review, we have commented on the possible role of loneliness as a risk factor for the development of AD. As a suggestion for future studies, we propose higher number of lonely people to carry out an analysis of the transition through the AD continuum, from preclinical phase to dementia stage. Moreover, it would be of great interest to examine whether early intervention on loneliness can modify the course of Alzheimer's disease in the long term.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The study is supported by the Ministerio de Ciencia e Innovación (PGC2018-096177-B-100).

MA is awarded a "Margarita Salas postdoctoral grant" from the Universidad Complutense de Madrid, funded by the Ministry of Universities with funds from the European Union Next Generation of the European Union.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

[1] Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive

decline and dementia: A population-based perspective. Alzheimers Dement 2015; 11(6): 718-26.http://dx.doi.org/10.1016/j.jalz.2015.05.016 PMID: 26045020
[2] Flicker L. Modifiable lifestyle risk factors for Alzheimer's disease. J Alzheimer's Dis 2010; 20(3): 803-11.http://dx.doi.org/10.3233/JAD-2010-091624 PMID: 20182016
[3] Balouch S, Rifaat E, Chen HL, Tabet N. Social networks and loneliness in people with Alzheimer's dementia. Int J Geriatr Psychiatry 2019; 34(5): 666-73.http://dx.doi.org/10.1002/gps.5065 PMID: 30706526
[4] Ávila-Villanueva M, Gómez-Ramírez J, Ávila J, Fernández-Blázquez MA. Alzheimer's disease and empathic abilities: The proposed role of the cingulate cortex. J Alzheimers Dis Rep 2021; 5(1): 345-52.http://dx.doi.org/10.3233/ADR-200282 PMID: 34189406
[5] MacRae H. Self and other: The importance of social interaction and social relationships in shaping the experience of early-stage Alzheimer's disease. J Aging Stud 2011; 25(4): 445-56. http://dx.doi.org/10.1016/j.jaging.2011.06.001
[6] Donovan NJ, Okereke OI, Vannini P, et al. Association of higher cortical amyloid burden with loneliness in cognitively normal older adults. JAMA Psychiatry 2016; 73(12): 1230-7. http://dx.doi.org/10.1001/jamapsychiatry.2016.2657 PMID: 27806159
[7] Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007; 64(2): 234-40. http://dx.doi.org/10.1001/archpsyc.64.2.234 PMID: 17283291
[8] Olazarán J, Valentí M, Frades B, et al. The Vallecas Project: A cohort to identify early markers and mechanisms of Alzheimer's disease. Front Aging Neurosci 2015; 7: 181. http://dx.doi.org/10.3389/fnagi.2015.00181 PMID: 26483681
[9] Deary IJ, Gow AJ, Taylor MD, et al. The Lothian Birth Cohort 1936: A study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC Geriatr 2007; 7(1): 28. http://dx.doi.org/10.1186/1471-2318-728 PMID: 18053258
[10] Akhter-Khan SC, Tao Q, Ang TFA, et al. Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. Alzheimers Dement 2021; 17(10): 1619-27.http://dx.doi.org/10.1002/alz.12327 PMID: 33760348
[11] Dahlberg L. Loneliness during the COVID-19 pandemic. Aging Ment Health 2021; 25(7): 1161-4. http://dx.doi.org/10.1080/13607863.2021.1875195 PMID: 33491474
[12] Ausín B, González-Sanguino C, Castellanos MÁ, Muñoz M. Gender-related differences in the psychological impact of confinement as a consequence of COVID-19 in Spain. J Gend Stud 2021; 30(1): 29-38. http://dx.doi.org/101080/0958923620201799768
[13] Bu F, Steptoe A, Fancourt D. Who is lonely in lockdown? Crosscohort analyses of predictors of loneliness before and during the COVID-19 pandemic. Public Health 2020; 186: 31-4. http://dx.doi.org/10.1016/j.puhe.2020.06.036 PMID: 32768621
[14] Elran-Barak R, Mozeikov M. One month into the reinforcement of social distancing due to the covid-19 outbreak: Subjective health, health behaviors, and loneliness among people with chronic medical conditions. Int J Environ Res Public Health 2020; 17(15): 1-16. http://dx.doi.org/10.3390/ijerph17155403 PMID: 32727103
[15] Kotwal AA, Holt-Lunstad J, Newmark RL, et al. Social isolation

and loneliness among Sanfrancisco bay area older adults during the COVID-19 shelter-in-place orders. J Am Geriatr Soc 2021; 69(1): 20-9.http://dx.doi.org/10.1111/jgs.16865 PMID: 32965024
[16] van Tilburg TG, Steinmetz S, Stolte E, van der Roest H, de Vries DH. Loneliness and mental health during the COVID-19 pandemic: A study among dutch older adults. J Gerontol B Psychol Sci Soc Sci 2021; 76(7): e249-55.http://dx.doi.org/10.1093/geronb/gbaa111 PMID: 32756931
[17] Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021; 8(2): 130-40.http://dx.doi.org/10.1016/S2215-0366(20)30462-4 PMID: 33181098
[18] Sutin AR, Stephan Y, Luchetti M, Terracciano A. Loneliness and risk of dementia. J Gerontol B Psychol Sci Soc Sci 2020; 75(7): 1414-22.http://dx.doi.org/10.1093/geronb/gby112 PMID: 30365023
[19] Hampel H, Lista S, Khachaturian ZS. Development of biomarkers to chart all Alzheimer's disease stages: The royal road to cutting the therapeutic Gordian Knot. Alzheimers Dement 2012; 8(4): 312-36.http://dx.doi.org/10.1016/j.jalz.2012.05.2116 PMID: 22748938
[20] Mahalakshmi AM, Ray B, Tuladhar S, et al. Does COVID-19 contribute to development of neurological disease? Immun Inflamm Dis 2021; 9(1): 48-58.http://dx.doi.org/10.1002/iid3.387 PMID: 33332737
[21] Tsapanou A, Papatriantafyllou JD, Yiannopoulou K, et al. The impact of COVID-19 pandemic on people with mild cognitive impairment/ dementia and on their caregivers. Int J Geriatr Psychiatry 2021; 36(4): 583-7.http://dx.doi.org/10.1002/gps.5457 PMID: 33166418
[22] Rahman MA, Islam K, Rahman S, Alamin M. Neurobiochemical cross-talk between COVID-19 and Alzheimer's Disease. Mol Neurobiol 2021; 58(3): 1017-23.http://dx.doi.org/10.1007/s12035-020-02177-w PMID: 33078369
[23] Cacioppo S, Capitanio JP, Cacioppo JT. Toward a neurology of loneliness. Psychol Bull 2014; 140(6): 1464-504.http://dx.doi.org/10.1037/a0037618 PMID: 25222636
[24] d'Oleire Uquillas F, Jacobs HIL, Biddle KD, et al. Regional tau pathology and loneliness in cognitively normal older adults. Transl Psychiatry 2018; 8(1): 282.http://dx.doi.org/10.1038/s41398-018-0345-x PMID: 30563962
[25] Braak H, Braak E. Neuropathological stageing of Alzheimerrelated changes. Acta Neuropathol 1991; 82(4): 239-59.http://dx.doi.org/10.1007/BF00308809 PMID: 1759558
[26] Avila J, Perry G. A multilevel view of the development of Alzheimer's disease. Neuroscience 2021; 457: 283-93.
[27] Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. Annu Rev Psychol 2015; 66(1): 733-67.http://dx.doi.org/10.1146/annurev-psych-010814-015240 PMID:25148851
[28] Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 2019; 25(4): 554-60.http://dx.doi.org/10.1038/s41591-019-0375-9 PMID:30911133
[29] Brewster KK, Golub JS, Rutherford BR. Neural circuits and behavioral pathways linking hearing loss to affective dysregulation in older adults. Nat Aging 2021; 1(5): 422-9.http://dx.doi.org/10.1038/s43587-021-00065-z
[30] Tiwari SC. Loneliness: A disease? Indian J Psychiatry 2013; 55(4):

320-2.http://dx.doi.org/10.4103/0019-5545.120536 PMID: 24459300
[31] White KE, Cummings JL. Schizophrenia and Alzheimer's disease: Clinical and pathophysiologic analogies. Compr Psychiatry 1996; 37(3): 188-95.http://dx.doi.org/10.1016/S0010-440X(96)90035-8 PMID:8732586
[32] Zhang T, Davatzikos C. Optimally-discriminative voxel-based morphometry significantly increases the ability to detect group differences in schizophrenia, mild cognitive impairment, and Alzheimer's disease. Neuroimage 2013; 79: 94-110.http://dx.doi.org/10.1016/j.neuroimage.2013.04.063 PMID:23631985
[33] de Vries PJ, Honer WG, Kemp PM, McKenna PJ. Dementia as a complication of schizophrenia. J Neurol Neurosurg Psychiatry 2001; 70(5): 588-96.http://dx.doi.org/10.1136/jnnp.70.5.588 PMID: 11309451
[34] Kochunov P, Zavaliangos-Petropulu A, Jahanshad N, et al. A white matter connection of schizophrenia and Alzheimer's disease.Schizophr Bull 2021; 47(1): 197-206.http://dx.doi.org/10.1093/schbul/sbaa078 PMID: 32681179
[35] Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: Relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. PsychosomMed 2013; 75(2): 161-70. http://dx.doi.org/10.1097/PSY.0b013e31827f09cd PMID:23362501
[36] Ávila-Villanueva M, Fernández-Blázquez MA. Subjective cognitive decline as a preclinical marker for Alzheimer's disease: The challenge of stability over time. Front Aging Neurosci 2017; 9:377. http://dx.doi.org/10.3389/fnagi.2017.00377 PMID: 29201004
[37] Fernández-Blázquez MA, Ávila-Villanueva M, Maestú F, Medina M. Specific features of subjective cognitive decline predict faster conversion to mild cognitive impairment. J Alzheimers Dis 2016; 52(1): 271-81.http://dx.doi.org/10.3233/JAD-150956 PMID: 27060949
[38] Veronese N, Galvano D, D'Antiga F, et al. Interventions for reducing loneliness: An umbrella review of intervention studies. Health Soc Care Commun 2021; 29(5): e89-96. http://dx.doi.org/10.1111/hsc.13248 PMID: 33278311
[39] Campbell AJ, Cumming SR, Hughes I. Internet use by the socially fearful: Addiction or therapy? Cyberpsychol Behav 2006; 9(1): 69-81.http://dx.doi.org/10.1089/cpb.2006.9.69 PMID: 16497120