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社会孤立对阿尔茨海默病影响的研究进展

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摘 要

阿尔茨海默病(Alzheimer disease, AD)是一种不可逆的神经退行性疾病。其病程长，目前没有药物能够有效治疗AD。目前有证据指出，孤独是AD和其他相关失智症发展的可变危险因素，与社会隔绝的人患失智症的风险往往比远离社会孤立的人患失智症风险高。感知到的社会孤立或孤独会促进并加剧大脑中的*β*-淀粉样蛋白斑块(amyloid-protein, A*β*)的沉积和tau蛋白过度磷酸化，而社会孤立和AD的不同阶段大脑区域都会受到影响表现出功能障碍，例如前额叶皮层、杏仁核或海马体。同时，社会孤立和感知孤独感会促进早期AD患者大脑中A*β*的产生和tau蛋白过度磷酸化，来自社会隔离和孤独的压力也会影响A*β*的积累和tau蛋白的过度磷酸化。此外，应激引起的糖皮质激素水平升高会导致A*β*和tau蛋白病变的加剧，从而加速神经纤维缠结的发展。社交孤立也可能通过增加氧化应激加重AD病理。感觉到被孤立和拥有孤独的经历都会对心理和身体健康产生不利影响。随着我国人口老龄化，再加上新型冠状病毒COVID-19的出现以及由此产生的隔离阻碍了社交，疫情隔离使人们减少了社交，会出现社会孤立这一现象，同时也会加剧AD病情发展。有研究指出，晚年远离社会隔离会降低患失智症风险4%，对此早期积极预防社会孤立尤其重要，远离社会孤立，应多出门走动与同伴交流，提高认知储备(Cognitive reserve, CR)水平及多认识新事物是积极预防AD的重要方法。

关键词

阿尔茨海默病，社会孤立，感知孤独，A*β*，认知储备

Research Progress on the Impact of Social Isolation on Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is an irreversible neurodegenerative disease. The course of disease is long, and no drugs can effectively treat AD. Evidence now points to loneliness as a modifiable risk factor for the development of AD and other related dementia. People who are socially isolated tend to have a higher risk of developing dementia than people who are socially isolated. Perceived social isolation or loneliness promotes and intensifies Aβ deposition and tau hyperphosphorylation in the brain. Both social isolation and different stages of AD affect brain regions that show dysfunction, such as the prefrontal cortex, amygdala, or hippocampus. At the same time, social isolation and perceived loneliness promote Aβ production and tau hyperphosphorylation in the brain of early AD patients. Stress from social isolation and loneliness also affects Aβ accumulation and tau hyperphosphorylation. The increase in glucocorticoid levels caused by stress leads to the exacerbation of Aβ and tau protein lesions, thereby accelerating the development of neurofibrillary tangles. Social isolation may also exacerbate AD pathology by increasing oxidative stress. Feeling isolated and having experiences of loneliness can both have adverse effects on mental and physical health. With the aging population in our country, the emergence of COVID-19 and the resulting isolation has hindered social interaction, which makes people reduce social interaction, resulting in social isolation and aggravating the development of Alzheimer's disease. Studies have pointed out that staying away from social isolation in later life can reduce the risk of dementia by 4%. Therefore, it is particularly important to actively prevent social isolation in the early stage. To stay away from social isolation, we should go out and communicate with peers more, improve cognitive reserve (CR) level and learn more about new things are important ways to actively prevent AD.

Keywords

Alzheimer Disease, Social Isolation, Perceived Loneliness, Aβ, Cognitive Reserve

1. 前言

阿尔茨海默病(Alzheimer disease, AD)是最常见的老年性失智类型，约占所有失智症病例的 50%至80%，其表现为大脑中 β-淀粉样蛋白斑块(amyloid-protein, Aβ)的细胞外储存库和神经原纤维缠结(Neurofibrillary Tangles, NFT)的细胞内增生，导致记忆、智力、人格和其他障碍，最终导致创伤性脑损伤死亡[1]。目前我国已步入人口老龄化阶段，而 60 岁及以上人口是最有可能患 AD 的，预计到本世纪中叶，我国 60 岁及以上人口比例将达到 33% [2]。随着人口老龄化和人口增长的增长趋势预测，未来失智症患者的人数会持续上升。据估计，到 2050 年，全球失智症患者数量将从 2019 年的 5740 万例增加到 15,280 万例[3]。阿尔茨海默病是一种不可逆的神经退行性疾病，影响人们日常生活活动和社会功能。AD 病程长，需要长期的医疗和护理，这会给家庭和社会带来沉重的负担，但 AD 药物治疗效果不佳，对此前期干预 AD 尤其重要。而社会孤立对健康有不利的影响[4]，最近的一项系统性综述对 16 项前瞻性纵向研究进行了荟萃分析结果显示，孤独和社会孤立与冠心病(29%)和中风(32%)的风险增加有关[5]。这一发现进一步证实了现有证据，有研究表明孤独和社会孤立是心血管疾病的一项危险因素[6]。社会孤立已被确定

为全因发病和死亡的风险因素[7]，其后果可与吸烟、肥胖、缺乏运动锻炼和高血压相当，同时它还与感染抵抗力下降、认知功能下降、失智症有关[8]。本文对社会孤立和阿尔茨海默病之间的关系做一综述。

2. 社会孤立对阿尔茨海默病的影响

早期研究表明，社会环境，特别是社交关系，会影响一个人的行为和心理健康[9]。实际上社会孤立，是包括拥有一个小的社交网络圈、很少与他人一起参加活动，以及感知到的社会孤立，即感到孤独。社会孤立，局限于自己的小圈子，这不仅会增加患失智症的风险，而且还使失智症患者记忆力衰退加剧和症状恶化。据研究结果表明，与社会隔离会使 AD 的病情恶化，同时加重海马体的不对称性[10]。无论是性别、种族、民族、受教育程度或遗传因素风险如何，社会隔离或孤独会增加患失智症风险 40% [11]，尤其是老年人应得到重视，不能被忽视或置之不理。由于老年人生命周期阶段的变化，如退休或与年龄有关的损失例如伴侣或朋友的死亡，加上健康状况下降和行动不便日益严重，越来越多的老年人感到孤独和社会孤立[12]。其他探索孤独对失智症发病影响的研究发现，感知到孤独的老年人患 AD 样失智综合征的可能性是不感到孤独的老年人的两倍多[13]。此外，感知到孤独感是全因失智的重要风险因素，尤其是 AD 的显著危险因素；因此，重视老年人孤独的主观报告有助于预防这种情况，而缺乏与他人的社会互动也与失智症的风险有关[14]。为此，普遍预防孤独和孤立对于实现整体认知健康至关重要。

2.1. 社会孤立会影响认知能力

由于失智症临床前表现出一个漫长的阶段，认知能力下降可以对感知孤独感和社会互动产生高度可变的影响。有一项研究，探究了中年时期个人孤独感的变化与 18 年后失智症和 AD 风险之间的关系，研究结果表明中年时持续的孤独感是失智症和 AD 的独立风险因素[15]。如果人们长期与世隔绝或感知孤独，会提高患 AD 的风险。最近 The Lancet 失智症预防、干预和护理委员会估计，如果消除晚年生活风险因素的社会隔离，失智症患病风险将降低 4% [16]。这种减少比在晚年时对抗身体缺乏活动的 2%患病风险和在中年时对抗高血压的 2%患病风险更多，这突出表明社会孤立是一个值得在预防失智症方面引起更多关注的重要问题。

有研究表明，缺乏社会从属关系像参与数量少且质量低的社会关系或社会孤立与认知功能的快速下降有关，并可能导致在晚年 AD 的发生[17]。此外，从认知发展的角度对社会环境在促进健康中的作用进行的调查表明，增加积极的社会互动可以提高认知能力，并对压力源进行缓冲。例如，受到社会孤立的动物会出现认知障碍，通过增强某些在 Aβ 肽的产生和 tau 蛋白磷酸化中起重要作用的蛋白的活性，从而导致提前发病并加速 AD 的发展不断恶化。在人类社会中，与朋友和亲戚有社交关系的人相比，与社会隔绝的人患 AD 的风险增加，死亡风险增加了 2~4 倍[18]。因此，终身高度的社会依恋代表着动态和复杂的社会系统，影响着健康结果，特别是实现对 AD 的环境保护。

2.2. 社交网络圈及健康状况对老年人群的影响

人到老年时，健康状态在逐渐减弱，如抵抗力下降、生理机能下降等。然而健康状况较差的人往往会感到更孤独。当人们上了年纪变老时，一般来说，他们的活动量会减少，并且活动空间也更有限，因此他们可能会比年轻人感到更孤独。此外，如果老年人与伴侣住在一起并且有更多孩子，他们往往会感到不那么孤独。此外，研究表明，较高的收入、与儿童、子女的接触以及非专业活动可以对社会满意度产生积极影响[19]。同时受教育水平低和收入水平低的人更容易感到孤独。有研究发现，对社交网络的满意度与老年人群的孤独感和孤独感之间存在关联[20]。通过贝叶斯信念网络(Bayesian belief network, BBN)建模模型表明，对自己的社交网络非常不满意的人有很高的几率感到非常孤独，相反，对自己的社交网

络非常满意的人一般不会感到孤独[21]。也有研究发现，与年轻人相比，老年人的社交互动更少，社交网络更小[20]。感觉被孤立和孤独的经历会对心理和身体健康产生不利影响，而科学研究表明，这与出现严重健康问题的高风险有关。在有精神健康问题、听力和视力障碍、慢性健康问题的个体以及自闭症患者等神经分歧群体中，观察到高度孤独和社会隔离。

2.3. COVID-19 大流行会影响 AD

社会隔离对失智症风险的影响在 2020~2022 年尤为重要，许多人因 COVID-19 大流行而被迫封锁隔离。AD 不仅会导致标志性的认知障碍，还会导致精神运动功能障碍[22]。因此，它是全世界老年人残疾和依赖的主要原因之一。由于其认知和功能缺陷，AD 患者在危机期间，特别是在 COVID-19 大流行期间容易受到伤害，并且封闭似乎会影响基线认知功能低的 AD 患者的神经精神症状[23]。对于那些受影响的人及其护理人员和家人来说，这可能是难以承受的，直接和间接的医疗成本压力非常大[24]。在目前的情况下，患有 AD 的人由于其复杂的认知和精神运动功能障碍而特别脆弱。记忆问题增加了他们理解正在发生的事情的困难[24] [25]。由于新冠病毒的发病率和死亡率以及大流行对他们所依赖的卫生系统和支持网络的间接影响，这种大流行进一步加剧了他们的脆弱性[26]。一些研究报告了封闭及其对 AD 有关的认知的影响和行为症状的改变与加重。已经检测到认知症状的恶化，特别是记忆和定向能力的恶化，改变的出现，如烦躁—攻击、冷漠和抑郁，这些是最实际的表现[23]。此外，了解到老年人因年龄、共病和身体虚弱而更容易感染 COVID-19，可能会增加这一年龄组的不确定性和对 COVID-19 大流行的恐惧[27]。强制隔离和屏蔽措施也减少了运动锻炼的机会，缺乏身体运动会进一步增加失智症的风险[26]。

3. 社会孤立作为 AD 的一项危险因素

3.1. AD 病理学特征

AD 病理学的特征是细胞外 Aβ 的积累和细胞内 NFT 的过度磷酸化 tau 蛋白的积累以及伴有炎症、神经变性和突触丢失[28]。越来越多的证据表明，AD 的病理生理学涉及由胶质细胞如小胶质细胞和星形胶质细胞介导的免疫机制[29]。活性星形胶质细胞和小胶质细胞的增加以及广泛的胶质细胞增生被认为是 AD 的神经病理学特征[28]。尽管病理性蛋白质积累会触发大脑内的先天免疫反应，但神经炎症也可以驱动病理。事实上，许多迟发性 AD 的风险基因主要在神经胶质细胞中表达，这表明炎症在 AD 中起着至关重要的作用[30]。

社会孤立和 AD 的不同阶段大脑区域都会受到影响表现出功能障碍，例如前额叶皮层、杏仁核或海马体。从机制的角度来看，由于下丘脑－垂体－肾上腺(Hypothalamic-Pituitary-Adrenal, HPA)轴的变化，社会孤立与慢性压力或抑郁有关，这也可能发生在 AD 的早期临床前阶段[31]。在孤独中启动 HPA 轴可能导致前额叶皮质中皮质酮水平的增加[32]。此外，有研究指出，孤独会导致海马神经发生减少以及脑源性神经营养因子(brain derived neurotrophic factor, BDNF)或神经生长因子(nerve growth factor, NGF)减少[32]。也有研究指出，在 AD 患者中这种成人海马神经发生减少[33]。此外，据研究，在孤独的非失智老年人中存在 AD 标志物，如 Aβ 斑块[32]或 tau 蛋白病变病理[34]。

突触缺失是 AD 患者认知能力下降的最强病理相关因素[35]。在 AD 小鼠模型中，社会隔离被观察到会降低 AMPA 受体的表面表达[36]。在另一种 AD 模型中，增加塌陷反应调节蛋白 5 (Collapsin response mediator protein 5, CRMP5)的表达会减少社交互动，可能是通过改变 GluA2 的表面表达并触发 AMPA 受体的内吞作用[37]。在 AD 小鼠模型中，抑制 AMPA 受体内吞可防止长期增强衰减和减少记忆丧失，这表明 AMPA 受体在病理性记忆丧失中发挥作用[38]，以及社会孤立导致 AD 认知症状的机制。社交孤立还会降低海马部位突触可塑性的突触蛋白的水平[39]。被社会孤立的雌性啮齿类动物也发现在情境恐惧记

忆方面有缺陷，这是一项依赖于海马体的任务，这表明社会孤立可能改变突触可塑性的机制，潜在地增加了 AD 中突触缺失的脆弱性。

研究发现，慢性社会隔离可能通过启动小胶质细胞增加啮齿动物的氧化应激[40]。氧化应激标志物往往在 AD 疾病过程中的早期发现，因此氧化应激被认为是 AD 发病机制的重要因素，特别是通过增加淀粉样蛋白-β和 tau 蛋白的病理[41]。活性氧的增加还与线粒体功能障碍、DNA 损伤和突触损伤等相关[42]。在社交孤立的 APP/PS1 小鼠中，慢性抗氧化治疗逆转了加速的淀粉样蛋白-β病理[17]，这表明社交孤立可能通过增加氧化应激加重 AD 病理。

3.2. Aβ沉积和 tau 蛋白过度磷酸化的机制

无论任何形式的互动，无论是人类还是动物，互动中的中断都会对正在经历孤独和焦虑的患者产生负面影响疾病[43]。令人惊讶的是，感知到的社会孤立或孤独会促进并加剧大脑中的 Aβ沉积和 tau 蛋白过度磷酸化。一项研究报告称，在感到孤独的老年患者的大脑中观察到 Aβ积累，无论他们是否被诊断为失智症[44]。此外，一些研究报告称，与标准住房相比，与社会隔离的淀粉样前体蛋白(amyloid precursor protein, APP)/早老蛋白-1(Presenilin-1, PS1)转基因小鼠的 Aβ42 和 Aβ40 的水平显著升高，这是由于γ-分泌酶活性的增加和脑啡肽酶表现的降低[17] [45]。

类似地，一些使用大鼠模型的研究报告称，社会隔离增加了糖原合成酶激酶-3β (Glycogen synthase kinase-3β, GSK-3β)和 tau 蛋白过度磷酸化的水平，但降低了 ser9 磷酸化的 GSK-3β的水平[46]。这一证据表明，社会孤立和感知孤独感可促进早期 AD 患者大脑中 Aβ的产生和 tau 蛋白过度磷酸化。此外，来自社会隔离和孤独的压力也会影响 Aβ的积累和 tau 蛋白的过度磷酸化。应激引起的糖皮质激素水平升高会导致 Aβ和 tau 蛋白病变的加剧[47]。特别是，AD 和轻度认知障碍患者的血浆和脑脊液常规检验(Cerebrospinal Fluid, CSF)皮质醇水平明显高于认知正常患者，还表现出 HPA 轴的失调[48] [49]。3xTg 小鼠应激诱导的糖皮质激素水平升高，通过增加生长树突 tau 蛋白的积累和通过增加 APP 和β-分泌酶水平提高神经元内 Aβ水平，从而加速神经纤维缠结的发展[47]。

3.3. 社会孤立使啮齿动物的 AD 恶化

在啮齿类动物中模拟社会隔离的所有方面和复杂性是不可能的，特别是感知到的社会隔离和孤独感。然而，在 AD 小鼠模型中，通过让小鼠远离笼子、同伴来唤起社会孤立，为补充人类发现提供了有用的信息。APP/PS1 和 Tg2576 小鼠的社交隔离导致斑块形成增加和记忆恶化[17] [45]和诱导的 Sprague-Dawley 大鼠空间记忆缺陷、tau 过度磷酸化和突触蛋白表达降低[46] [50]。与非社交孤立的 APP/PS1 小鼠相比，AD 的其他病理特征也有所恶化，包括海马萎缩加剧、突触丢失和神经胶质炎症改变[18]。最近的一项研究发现，即使给社交孤立的 5xFAD 小鼠提供滚轮或丰富的环境，AD 病理也会增加，这表明孤立压力的影响超过了缺乏锻炼或认知刺激造成的任何影响[51]。

4. 社会孤立的预防与干预方法

认知储备(Cognitive reserve, CR)是一种假设性结构，可减轻与年龄相关的衰退和病理损伤的影响[52]。认知储备可以降低失智症的风险。CR 可能是一种机制，通过这种机制，即使在存在神经病理学的情况下，个体也可以免受临床上显著的认知能力下降[53] [54]。它指的是大脑对萎缩和病变进行缓冲的结构和动态能力。特定大脑区域的组织或功能丧失可能会通过其他更努力工作的神经元来补偿，以尽可能保持相同的功能水平。这种补偿可能发生在“局部”层面，从某种意义上说，相邻的神经元弥补了区域性损伤失去的神经活动。被一些学者称为“大脑储备”，这种容量储备也被称为认知储备的被动或静态

模型[52]。这一概念基于社会行为代理的概念，例如教育，智力参与职业和各种其他活动，有助于建立更具弹性的神经元网络，保护认知功能，即使 AD 生物标志物指向进展中的神经病理学[55]。体育活动可以通过增强海马神经发生、突触可塑性、神经营养因子水平和心血管健康来促进认知[56]。体育活动还与海马体、前额叶皮层和基底神经节更大的体积、更大的白质完整性和增强的大脑功能连通性有关[56]。在老龄化社会中，促进老年人的智力活动尤为重要，因为较少参与智力活动是认知能力下降的主要危险因素[16]。参与智力活动已被发现可以增强突触传递和神经可塑性，并增加认知储备[57]。有观察性研究报告表明，在未来生活中经常参与智力活动可以降低发生失智的风险，并维持或改善认知功能[58]。CR 有望调节神经病理学与认知表现之间的关系；在认知缺陷或临床损伤变得明显之前，CR 较高的个体能够比 CR 水平较低的个体忍受更高水平的神经病理学[54] [59]。也就是说，具有高 CR 的个体对 AD 相关神经病理学表现出更强的恢复力[60]。

根据一些估计，只要将失智症的发病时间推迟 5 年，失智症的患病率就会下降 50% [61]。因此，提高 CR 水平的干预措施可能会随着年龄的增长而延长寿命和生活质量。由于大多数 CR 指标反映的是可改变的体验，其可以在整个生命周期中得到增强，终身参与认知、社交和体育活动有利于提高 CR 水平，同时远离社会孤立，降低失智症的患病风险。社会关系会随着时间的推移而改变。例如在丧偶、迁徙或功能能力下降后，孤独感和社会孤立可能会增加[62]。相反，例如在孙辈出生等之类的变化可增加以后在生活中与儿童接触的机会，研究表明，人们在年老时继续结交认识新的朋友及新事物或重新点燃已经减弱的联系可减少社会孤立[63]。

有研究发现，提供满足感和感知到互惠感的社会互动可以作为 15 年以上失智症的保护因素[64]。此外，一项 12 年的队列研究证实，有一个知己可以确保个人免于失智症状[65]。由于 COVID-19 的出现，产生的隔离阻碍了人们的社交。有研究表明，可以通过使用视频通话来扩大参与者的社交圈或增加与现有熟人的联系频率以减少社交孤立[66]。因此，扩大社交圈或增加与现有熟人接触的频率可能会解决社会孤立问题，从而有可能在保持身体距离的时期解决社会孤立问题。

5. 结论与展望

基于目前形势情况来看，我国人口老龄化加剧，加上人到老年时生命周期阶段的变化，健康状态在逐渐下降，同时周围相处环境的变化，社会孤立即感知孤独会对 AD 病情影响，甚至加重或恶化病情。减少社会孤立在 AD 早期尤其重要。在某种程度上，较高的 CR 可以预防疾病相关临床症状的发生或预防与年龄相关的认知衰退的发生，这为老年时期保持认知功能提供了一个重要的机制。总的来说，改善经济、社会和教育机会的举措可能会对随着年龄增长的认知和大脑健康产生深远的影响。例如，社区为老年人提供学习机会，如开设学习班、开展互动活动等，以及促进与社会联系，如增加绿地面积、公共运动设施等，有利于促进认知健康，同时也预防社会孤立现象。同时老年人的社交及心理问题应得到重视，有助于减少患 AD 的风险。此外，研究对社会孤立的早期干预是否能在长期内改变阿尔茨海默病的进程将是非常有益的。

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