Social Distancing and Brain Health

Subjects: Clinical Neurology

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Social distancing has been a critical public health measure for the COVID-19 pandemic, yet a long history of research strongly suggests that loneliness and social isolation play a major role in several cognitive health issues. What is the true severity and extent of risks involved and what are potential approaches to balance these competing risks? This review aimed to summarize the neurological context of social isolation and loneliness in population health and the long-term effects of social distancing as it relates to neurocognitive aging, health, and Alzheimer's disease and related dementias. The full scope of the underlying causal mechanisms of social isolation and loneliness in humans remains unclear partly because its study is not amenable to randomized controlled trials; however, there are many detailed experimental and observational studies that may provide a hypothesis-generating theoretical framework to better understand the pathophysiology and underlying neurobiology. To address these challenges and inform future studies, we conducted a topical review of extant literature investigating associations of social isolation and loneliness with relevant biological, cognitive, and psychosocial outcomes, and provide recommendations on how to approach the need to fill key knowledge gaps in this important area of research.

Keywords: social isolation ; cognitive health ; brain health ; loneliness ; brain aging

1. Introduction

Social distancing has been a critical measure to address the COVID-19 pandemic, yet the long-term public health impact of prolonged social distancing is unclear. Although high levels of social isolation and loneliness have been associated with a high risk of morbidity and mortality Holt-Lunstad, Smith [1][2], a growing body of evidence strongly suggests that social isolation and loneliness—notable consequences of social distancing [3]—specifically play a major role in neurocognitive health [4][5][6][7]. Since the outbreak of COVID-19, research has further shown the increased dementia risk that may be due to stress, loneliness, and neuropsychiatric symptoms of prolonged physical distancing [8]. A key barrier to better understand the extent of potential long-term neurocognitive health impacts and to deploy effective strategies that balance competing risks requires clarifying underlying biological mechanisms. Investigating causal pathways that link social isolation and loneliness with neurocognitive aging and neuropathological changes is not readily amenable to be studied using randomized controlled trails. However, there are many detailed experimental models and observational studies that, when brought together, can provide a hypothesis-generating theoretical model for the complex neurobiology and pathophysiology underlying observed associations.

As indicated by the National Institute on Aging, there is a need for more research in the areas of social isolation and loneliness [9]. In response, this topical review was conducted to (1) highlight notable findings from previous studies related to potential biological mechanisms, (2) provide key recommendations to address critical knowledge gaps, and (3) inform future studies for addressing these factors in neurology and population health through targeted interventions. Although social isolation and loneliness may be manifestations of early neuropathological changes [10], the present review focused on summarizing the neurological context of social isolation and loneliness as proposed harmful psychosocial determinants of health and on describing the potential long-term risks of social distancing with respect to general neurocognitive health [11] and aging [12], inclusive of subsequent risk for developing Alzheimer's disease and related disorders (ADRD) [13].

2. Study Selections

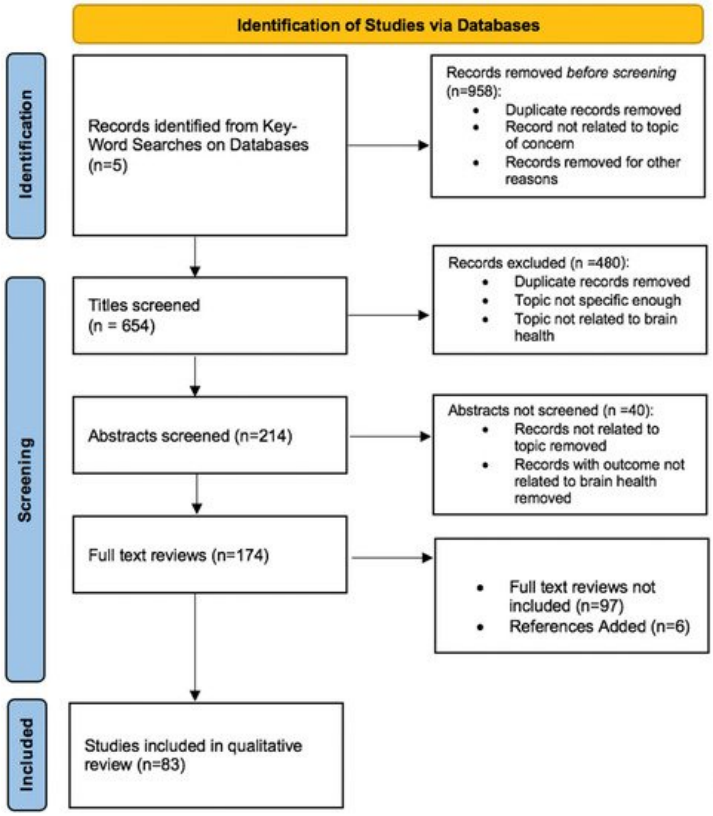

Figure 1. Derivation of literature reviewed: A literature search was conducted through key-word searches on databases that culminated in the inclusion of 83 studies in the qualitative review.

3. Biological Outcomes

3.1. Associations with Inflammation

From the literature included in our qualitative review, social isolation and loneliness have been associated with serum markers of chronic inflammation, such as the neutrophil-to-lymphocyte ratio, the concentration of high-sensitivity C-reactive protein (CRP) [14], and circulating leukocytes [15]. Other circulating inflammatory markers, such as fibrinogen and interleukin-6 (IL-6), have been associated with increased levels of social isolation and loneliness as well [16][17]. In contrast, higher levels of social engagement and living with another individual were associated with lower levels of C-reactive protein and fibrinogen [18].

3.2. Associations with Neuroimaging Measures

Of the studies reviewed, most identified that loneliness or social isolation related with brain MRI measures of brain aging and neuropathology. For example, those who identify with feeling lonely were shown to have smaller hippocampal volumes and a larger volume of cerebral white matter implicated in social cognitive processing and emotional regulation [19]. Regions such as the left posterior superior temporal sulcus, the middle temporal gyrus, and the entorhinal cortex (involved in social perception and associative memory) have also been found to be smaller among participants who had smaller online social networks [20][21]. Furthermore, based on tau PET imaging, it has been found that higher tau pathology in the right entorhinal cortex and clusters in the right fusiform gyrus are associated with greater loneliness [22]. Higher cortical amyloid burden on PET scans has also been shown to be significantly associated with greater loneliness [10]. In addition, lonely individuals have shown stronger functional communication in the default network and higher microstructural integrity in the fornix pathway of the default network in a functional connectivity MRI [23]. Overall, the causal directionality and etiology of these neuroanatomical differences remains unclear.

3.3. Associations with Neuropathology

Of the studies included in this narrative review, Alzheimer's disease pathology, including greater burden of amyloid plaques and neurofibrillary tau tangles, have been associated with greater loneliness even after controlling for other markers such as age, sex, and apolipoprotein E ε4, the genetic risk marker of Alzheimer's disease [10][22][24]. Moreover, the association of high amyloid burden and loneliness has been shown to be stronger in APOE ε4 carriers than in

noncarriers, indicating that individuals with genetic risk for Alzheimer's disease may be at greater risk of loneliness and social isolation [10]. Social network size has also been proven to act as a modifier of association between pathology and cognitive function [25]. For dementia-related neuropathology in the form of greater cerebrovascular disease burden, participants within a smaller social network (and thus greater social isolation) have been shown to be at higher risk of ischemic stroke [26][27].

3.4. Associations with Neuroplasticity

Social isolation and loneliness have been implicated in neuroplasticity related to post-stroke recovery and vascular health in the literature reviewed. In two mouse models of ischemic stroke, social isolation immediately following cerebral ischemia (for 15 days and 8 and 90 days respectively) was related with greater brain volume loss, higher mortality, delayed motor and sensory recovery, and worsened cognitive function [28][29]. Mice isolated immediately after stroke have shown brain tissue with decreased levels of brain-derived neurotrophic factor (BDNF), a molecule that aids in synaptogenesis and the growth, repair, and maturation of neuronal cells [28][29]. Similarly, group-living animals when socially isolated have been shown to have a decrease in cell proliferation, specifically in the dentate gyrus [30][31]; enriched social environments have been shown to increase cell proliferation and neurogenesis, especially in regions implicated in social interaction, memory, and communication [32][33][34][35][36][37]. A large literature of social animals randomly assigned to normal social living conditions or socially isolated conditions have also indicated the correlation of social isolation to low neurogenesis, BDNF, nerve growth factor (involved in growth and maturation of neurons as well), and low cell proliferation in the amygdala [34][35][38]. Early instances of social isolation in rats have been shown to affect the development of cognitive abilities and the nervous system through the mediation of producing BDNF protein [39]. Adolescent social isolation has correlated with epigenetic modifications, in the form of acetylation, that affect the expression of the BDNF in which isolation-reared rats have shown decreased hippocampal BDNF mRNA levels and protein expression. Thus, social isolation may play a causal role in the production of BDNF through gene regulation pathways, such as epigenetic modifications [39]. Social interaction has also been shown to rescue memory impairment in an Alzheimer's disease mouse model through a hippocampal BDNF-mediated pathway [32]. Even though BDNF levels measured from neural tissue is a more reliable indicator of this brain-enriched pathway, serum BDNF levels in humans have also been shown to partly mediate the association between levels of social support and dementia risk [40].

3.5. Associations with Sleep

From the literature reviewed, in both older adults and adolescents, loneliness and social isolation have been associated with worse sleep quality, typically in the form of sleep fragmentation [41][42][43][44][45][46]. Poor sleep quality has also been linked with a higher risk of cognitive decline and poorer neurocognitive health [47][48]. Although the directionality of these relationships is unclear, one study of older adults suggested that loneliness mediated the association between sleep and psychosocial health [49][50].

4. Cognitive Outcomes

Associations with Cognitive Function

Of the studies reviewed, low levels of social isolation (either from high social activity or large social networks) have been associated with better late-life cognitive functioning [4]. Inversely, social isolation has been associated with worse executive functioning [51][52] and memory loss [53][54]. In rodent models, social isolation decreased the activity of cAMP response element-binding protein (CREB), a transcription factor involved in long-term memory formation [55]. Furthermore, feeling lonely has been associated with an increased risk of all-cause mild cognitive impairment [10][56][57]; social isolation has been associated with global cognitive decline in older adults [58]. Loneliness has also correlated with poorer healthcare and financial decision making in older adults, further implicating executive functioning as a cognitive domain particularly vulnerable to impairment in the setting of loneliness [59]. Although longitudinal studies cannot establish causal directionality, these studies consistently demonstrate an association between loneliness and subsequent cognitive decline [57]. Loneliness has reliably been associated with increased risk of Alzheimer's disease and related dementias [60][61][62][63], in addition to worse behavioral and psychological symptoms of dementia [64]. Moreover, this increase in dementia risk seems to be most relevant for individuals with persistent loneliness compared to individuals with transient loneliness in whom dementia risk remains unchanged [61].

5. Psychosocial Outcomes

5.1. Associations with Depression, Anxiety, and Stress

During the COVID-19 pandemic, isolated older adults reported higher levels of depressive symptoms, specifically worse social well-being and greater loneliness [65]. In studies reviewed, higher levels of loneliness have historically been associated with increased levels of depression and anxiety [66][67]. Though, in addition to psychiatric symptoms, social isolation and loneliness have been linked with related stress-dependent physiological changes [68]. Individuals who tend to be more lonely, including adolescents, are likely to also experience higher levels of social stress [69]. Furthermore, loneliness has been associated with higher levels of stress hormones that are typically elevated in response to psychosocial stressors [70]. In animal studies, chronic stress from social isolation has been shown to affect group-living animals by triggering anxiety-like behavior. At the molecular level, oxytocin expression and oxytocin-Ca^{2+} signaling proteins, which are important for socioemotional and executive functioning, were permanently decreased in the hypothalamus, hippocampus, and prefrontal cortex [68]. Loneliness has been tied to increased hypothalamic pituitary adrenocortical (HPA) activity, mediating corticosteroid production [51][71][72][73], which may also increase risk of depression, anxiety, neurodegeneration, and immune and metabolic disorders [74][75][76]. Similarly, evidence suggests chronic loneliness associates with decreased variance in cortisol levels across the waking day as a biological measure of chronic stress [77].

5.2. Mediating and Modifying Factors

Eleven studies investigated sociodemographic factors as potential mediators in the association between loneliness and neurocognitive health. These factors include age, gender, socioeconomic status, and race/ethnicity. Loneliness has closely related with the mental health of both adolescents [78] and older adults [79], though older adults are uniquely susceptible to observed relationships between loneliness and increased risks of physical inactivity, cognitive impairment, fatigue, and impaired activities of daily living [80].

Because loneliness is more prevalent among women [81], gender has been a proposed modifier of the relationship between loneliness and neurocognitive health. Older women are also more likely to be socially isolated based on census data demonstrating that, compared to men, women live alone more frequently [28]. In addition to higher risk for exposure to social isolation and loneliness in women, animal models suggest long-standing sex-dependent effects on abnormal gene expression in the brain related to neurological dysfunction [68][82][83].

While gender and age likely play a modifying role in health and disease mechanisms that relate with loneliness and social isolation, to the best of our knowledge fewer studies (1 of 174 studies reviewed) have been published that were specifically designed from inception to analyze how race/ethnicity play a role in the complex associations of loneliness and social isolation with neurocognitive health. After adjusting for differences in income, employment status, depressive symptoms, and social network size, compared to White older adults, lonely Black older adults had higher risk of dementia and cognitive impairment [84].

6. Future Directions

6.1. Intervention Studies

More intervention studies are needed to identify pragmatic, cost-effective strategies that decrease or prevent social isolation and loneliness and can attenuate their associated risks. For the present review, two intervention studies were identified. Examples of existing evidence-based interventions include community initiatives and social prescribing, or establishing a link between health services and social interventions to improve well-being [85]. Other interventions identified in a metanalysis targeted the improvement of social skills, enhancing social support, increasing occasions for social contact, and addressing maladaptive social cognition [85][86]. Successful interventions that reduce levels of loneliness are centered around promoting a sense of belonging and social connectedness [85], which tend to use methods tailored to address the precise barriers that underly an individual's or a group's social isolation or loneliness. For instance, some individuals lack social connectedness due to government orders to socially distance and stay home, and other individuals experience loneliness or social isolation due to a lack of mobility, untreated mood disorder that limits frequency and quality of social interactions, or a lack of skills in interpersonal effectiveness to meet their desire for greater social contact and support. Similarly, some older adults may lack the access or knowledge to use technologies that facilitate virtual or in-person opportunities for interaction. For older adults, interventions have revolved around physical exercise [87], social activities [88], or a mix of these [89]. Importantly, despite examples of significant findings with notable magnitude of effects, there are a limited number of community-based intervention studies compared to the more common primary care

and home-based interventions [86]. New research may benefit from recruiting and training members of the community to create and perpetuate intergenerational companionships aimed at reducing the burden of loneliness and social isolation in older adults. Other possible interventions may explore brief yet effective pragmatic strategies to promote social support or rapid screening methods to assess loneliness and social isolation.

6.2. Recommendations to Address Knowledge Gaps

First, given existing gaps in understanding how social isolation and loneliness both modify and mediate pathways of experience-induced neuroplasticity and physiological responses to environmental and psychical stressors, studies to clarify specific mechanisms and pathways concerning inflammatory, neuroendocrine, and vascular dysfunction pathways can help to remediate the implications of broken or small social networks. Characterizing the intricacies of the effects of social isolation and loneliness on these biological pathways—through experimental and observational studies—will inform strategies that are better targeted to reverse such effects through medical or psychosocial interventions, or both.

Second, additional studies are needed that not only characterize the pathways of impact in the human brain, but also identify how these socioeconomic-based factors may compound these pathways. Future longitudinal studies designed to clarify the role that race and ethnicity plays in the effect of social isolation and loneliness on brain health are required to develop successful public health interventions.

Third, policy initiatives to support this research and that promote and enhance supportive social connections should be prioritized. This may include supporting and further highlighting the need for psychosocial intervention studies or efforts to increase technology and internet access for older adults. After the pandemic subsides, the long-term impact of increased levels of loneliness and social isolation will remain to be seen, but building on prior work to address the important knowledge gaps recommended above creates a valuable opportunity to radically improve public health and well-being in the decades to come. As a result, it is critical that all members of the community, from healthcare workers to politicians to scientists, come together to address the potential consequences of social isolation and loneliness.

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