Chronic loneliness: neurocognitive mechanisms and interventions

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Main text

Loneliness has been associated with detrimental effects on mental and physical health and is increasingly recognized as a critical public health issue which may be further exacerbated by societal challenges such as increasing urbanization, an aging society as well as the COVID-19 pandemic. A recent clinical study published in Psychotherapy and Psychosomatics has demonstrated that an internet-based cognitive behavioral therapy can significantly reduce loneliness and such a preventive intervention may be co-opted to target suicidality in the elderly [1, 2]. As such, it is now an opportune time to review current conceptualization of chronic loneliness, its detrimental consequences and potential neurocognitive mechanisms as well as initial treatment strategies.

Loneliness is not a clinical diagnosis, but a psychological state with detrimental effects on physiological and mental health if it is experienced chronically. Prevalence estimates vary depending on the assessment criteria, but representative samples surveyed before the onset of the COVID-19 pandemic showed that 22% of inhabitants in the United States and 23% in Britain always or often feel lonely [3]. Loneliness can occur at any life stage, but elevated levels have been observed during late adolescence and in elderly people [4]. Various lines of research also indicate that the extended lockdowns and necessary social isolation during the COVID-19 pandemic have increased not only feelings of loneliness but also depression and suicidal ideation [5-7]. However, of note, loneliness is a subjective feeling which is distinct from objective social isolation [8, 9]. It is possible to have a large and diverse social network and feel lonely, and vice versa, to live a life with only a few meaningful social connections and experience no loneliness at all. Therefore, loneliness can be best described as a discrepancy between desired and actual social connectedness [10]. In humans as a social species loneliness may have evolved as an adaptive function and evolutionary coping strategy to promote behavioral changes, which increase the chance of survival [11]. Loneliness can be seen as a social equivalent to hunger, such that the feeling of loneliness triggers the need to form new social relationships, in the same way as hunger triggers the need to eat [12-14]. If

loneliness is an evolutionary signal to form social bonds, the question of why some people stay lonely over extended periods of time arises. Current models of loneliness postulate that lonely individuals exhibit negative social biases which paradoxically lead to even more withdrawal from social connections [15]. Clearly, the effects of acute loneliness are distinct from the impact of chronic loneliness [16, 17]. For instance, a recent study found that chronic loneliness was associated with a greater preferred interpersonal distance, whereas acute loneliness was related to smaller preferred distances [18], possibly reflecting the evolutionary desire to form social bonds. Although acute social exclusion elicits activations in neural pathways overlapping with those mediating physical pain and may lead to severe distress [19, 20], chronic loneliness exerts more harmful effects, such as strongly increased mortality in comparison to acute social isolation [21]. Given that the COVID-19 pandemic and the necessary measures of social distancing may facilitate the transition from acute to chronic loneliness [22], interventions in vulnerable populations may help prevent detrimental health consequences of loneliness.

Detrimental Health Consequences of Loneliness

Accumulating evidence from different lines of research convergently indicates the detrimental impact of chronic loneliness and perceived social isolation on both, somatic and mental health. A number of studies have established associations between chronic loneliness and increased morbidity and mortality mirroring the negative impact of well-established risk factors such as obesity or smoking. Thus, loneliness and social disconnection are increasingly recognized as a major public health concern [23-26]. Increasing evidence suggests associations between chronic loneliness and an impaired integrity of the immune system, including reduced numbers of natural killer cells [27, 28] and diminished immune responses to acute stressors [29] in lonely individuals. Chronic loneliness has also been linked to heightened blood pressure [30, 31] and an increased risk for coronary heart diseases and stroke [32]. In addition, feelings of social isolation are a risk factor for obesity [33-35] and impaired sleep quality [36, 37]. Sleep deprivation in turn can trigger feelings of loneliness, starting a self-reinforcing cycle of social

withdrawal [38]. Importantly, the detrimental effects of loneliness are not restricted to somatic disorders, but extend to mental health. Perceived social isolation has been identified as a significant predictor for cognitive decline in dementia and Alzheimer disease [39, 40] and is associated with higher levels of depressive symptoms [41, 42], anxiety [43, 44], and psychosocial stress [45]. Furthermore, patients with substance abuse [46-48], borderline personality disorder [49, 50], and schizoid personality disorder [51] report more loneliness and social disconnection than healthy controls. In addition, loneliness is a potential risk factor for post-traumatic stress disorder [52, 53] and enhances intrusive thoughts after trauma exposure [54, 55]. Overall, loneliness and social isolation are critical risk factors for several somatic and mental disorders and thus should be considered in therapeutic protocols. The development of neurobiologically informed interventions for loneliness critically requires a better understanding of the brain structural and functional neural changes related to chronic feeling of social isolation.

Brain Structural Adaptations Associated with Loneliness

Prolonged periods of social isolation have been linked to broad changes in brain morphology. For instance, participants of a 14-months long Antarctica expedition exhibited significant reductions in brain-derived neurotrophic factor concentrations and gray matter volume in the dorsolateral and orbitofrontal cortex and hippocampus compared to controls [56]. While these findings are consistent with animal studies showing an association between social isolation and hippocampal neurogenesis [57], it is also conceivable that the expedition-related changes are a byproduct of sensory deprivation. Previous studies also observed that larger and more diverse social networks positively correlate with amygdala volume [58], but a recent study failed to replicate this association [59]. Along these lines, a rare patient with bilateral amygdala damage showed a normal size and complexity of her social network [60], indicating that an intact amygdala is not necessary to maintain social relationships or at least can be compensated for [61]. Several years after the first assessment of the social network, the

82 woman with amygdala lesion developed severe treatment-resistant depression along with a
83 reduction in the size of her social network, and she reported strong feelings of loneliness [62],
84 demonstrating that the experience of loneliness may not require an intact amygdala either.
85 However, recent large scale brain morphology studies suggest that there are sex-dependent
86 brain volume effects of loneliness, especially in the amygdala and the ventromedial prefrontal
87 cortex (vmPFC) [63]. Smaller amygdala volumes were detected for lonely men, but not lonely
88 women, and this pattern was reversed for the vmPFC volume. Thus, prospective longitudinal
89 studies are required to monitor sex-specific morphological changes that accompany chronic
90 loneliness. Sex and loneliness interactions are not restricted to brain structural effects. It has
91 been found that lonely individuals display stronger functional communication in the default
92 mode network (DMN) and this loneliness-related effect was more prominent in men than
93 women [64].

94 Furthermore, individual differences in loneliness correlated with gray matter density in the left
95 posterior superior temporal sulcus and this association was mediated by social perception
96 skills [65]. Interestingly, the correlation remained significant after controlling for trait anxiety
97 and social network size, thus providing further support for the notion that loneliness and social
98 anxiety are characterized by distinct neural phenotypes [66] and for the dissociation of
99 loneliness and social isolation. Importantly, loneliness has also been linked to altered neural
100 processing in various neurocognitive domains (cf. **Figure 1**), including negative cognitive
101 biases, sensory processing, executive functioning, reward-related processes, and memory.

102

103 **Negative Cognitive Biases**

104 It has been hypothesized that the maintenance of loneliness is fueled by negative cognitive
105 biases which make positive social interactions less rewarding and may foster even more social
106 withdrawal [13, 67]. Mechanistically, lonely individuals may be more likely to perceive social
107 stimuli as threatening and to evaluate themselves and others more negatively [15]. Feelings
108 of alienation may result from larger self-other dissimilarity of activation patterns in the medial

prefrontal cortex [68]. Furthermore, loneliness is associated with reduced interpersonal trust and a preference for larger social distances from unfamiliar others and this behavioral phenotype is paralleled by reduced trust-associated activity in the anterior insula. Importantly, blunted functional connectivity between the anterior insula and occipito-parietal regions predicts diminished affective and oxytocinergic responses to positive social interaction [69]. Given that the anterior insula plays a key role in self-awareness and interoceptive processing [70], we hypothesize that the negative cognitive biases in loneliness are mediated by an external attention focus due to reduced generation of or sensitivity to internal physiological signals in social situations [71]. Further supporting evidence for this notion comes from a study showing that insula responses to emotional faces mediate the association between alexithymia and subjective isolation stress [45]. Increased functional connectivity of the DMN [64] and overall increased network integration between the DMN and the attentional and visual networks in lonely subjects [72] may reflect exaggerated rumination during rest [73]. In addition, loneliness may affect synchronization during social interactions, such that lonely people may require stronger activation of their observation execution system including the inferior frontal gyrus (IFG) and the inferior parietal lobule for alignment to compensate for some deficiency in their synchronization ability [74]. Further studies are warranted to probe possible causal pathways of how disrupted interoceptive processes and impaired synchronization may lead to social withdrawal and the chronicity of loneliness.

Sensory Processing

Loneliness-induced hypervigilance can be observed in a shift of visual and auditory attention to negative or threating stimuli. These changes in sensory processing could be induced by alterations in the dorsal and ventral attention networks [72, 75]. Furthermore, there appears to be a bidirectional relationship between tactile processing and loneliness. Touch deprivation during COVID-19-related restrictions has been linked to higher anxiety and greater loneliness [76], but loneliness also positively correlated with touch avoidance [77]. The excitatory

transcranial direct current stimulation to the right IFG slowed responses to observed touch in lonely individuals [77], indicating that the IFG may contribute to the perpetuation of loneliness by enhancing the avoidance of positive social cues. Likewise, olfactory impairment can severely disrupt close relationships [78]. Loneliness is higher in participants who experienced childhood maltreatment, which correlates with amygdala hyperreactivity and hippocampal deactivation in response to social stress odors [79]. Whether and how loneliness may affect the sensory integration of multiple modalities is still elusive.

Executive Functioning and Cognitive Control

Loneliness is a risk factor for cognitive decline and dementia in older individuals, but evidence for an association between loneliness and impaired executive functioning across the life span is scarce. Attentional regulation was reduced in lonely individuals in a dichotic listening task [80] and loneliness was associated with significantly reduced odds of physical activity [33], which may reflect decreased cognitive control. Acute social exclusion has been found to impair self-regulation, possibly because it makes excluded people less inclined to make the effort to control impulses [81, 82]. It has been hypothesized that reduced functional connectivity of the right middle/superior frontal gyrus to the cingulo-opercular network during rest may reflect diminished executive functioning in loneliness [83], but future studies are needed to test a causal relationship between loneliness and executive functioning.

Reward-Related Processes

The activation patterns evoked by acute social isolation in the ventral tegmental area is similar to the craving-related activation pattern observed after fasting [14]. By contrast, dissociable responses were evident in the striatum, with fasting enhancing responses to food cues in the nucleus accumbens and social isolation increasing responses to social cues in the caudate nucleus. Cacioppo et al. showed reduced ventral striatum (VS) activity in lonely individuals

while viewing pleasant pictures with social connotation [84], but other studies found no significant correlation between loneliness and VS responses to pleasant social stimuli [85], nor between loneliness and striatal dopamine synthesis capacity in healthy controls or patients with autism spectrum disorder [86]. These contradictory findings may be reconciled by taking the familiarity of the social context into account. For instance, another functional magnetic resonance imaging study reported selectively increased VS responses to images of close others compared to strangers in lonely individuals, possibly reflecting fear of alienation or rejection [12].

Memory and Working Memory

In line with the above-mentioned association between loneliness and cognitive decline, several studies have reported loneliness-related declines in episodic, semantic, and working memory in older adults [87-89]. In patients with major depressive disorder, loneliness had no significant effect on working memory performance, but it was linked to increased functional connectivity between the dorsolateral prefrontal cortex and inferior parietal cortex, indicating that loneliness may be associated with altered neural regulatory functioning in self-referential processing [90]. Of note, a recent study found that loneliness may influence trauma memory in a sex-dependent manner. Specifically, lonely men, but not lonely women, exhibited more intrusive thoughts after experimental trauma and this phenotype was related to amygdala hyperreactivity during both fear conditioning and habituation processes, suggesting that the limbic system is a potential target for interventions that increase social connectedness [55].

Therapeutic Interventions for Loneliness and Integration with Neurocognitive Mechanisms

A recent meta-analysis showed that psychological interventions were more effective than measures to increase access to other people to improve the perceived quality of social

connections [91]. For example, cognitive-behavioral therapies targeting maladaptive cognition can reduce loneliness levels and the elevated blood pressure associated with loneliness in older individuals [92, 93]. Furthermore, mindfulness training has been demonstrated to be effective in reducing loneliness and related pro-inflammatory gene expression [94-96]. Further studies have focused on designing and evaluating internet- or tele-delivered approaches that may facilitate more scalable and accessible interventions for chronic loneliness. A recent randomized controlled trial compared internet-based cognitive behavioral therapy (ICBT) and internet-based interpersonal psychotherapy (IIPT) and demonstrated a significantly greater efficacy of ICBT than IIPT in reducing loneliness [2]. Similarly, a short-term tele-delivered intervention that aimed at facilitating social connectedness showed promising results in older adults by reducing feelings of loneliness and depression [97]. Overall, there is growing evidence that behavioral and psychological interventions targeting loneliness are an effective way to increase the feeling of social connectedness and additionally reduce harmful health effects. Despite increasing evidence demonstrating the efficacy of behavioral interventions for loneliness, the brain-based mechanisms mediating interventional effects have not been examined. Future prospective studies are needed to differentiate predisposing brain alterations that render individuals vulnerable to chronic loneliness from alterations as a consequence of prolonged loneliness and those that normalize during the course of successful treatment. Moreover, a better understanding of the neurocognitive mechanisms mediating chronic loneliness opens up novel opportunities to enhance the efficacy of loneliness interventions by targeting the underlying brain circuits. Loneliness-related functional and structural brain changes are evident in various neural circuits of social and affective brain systems, including limbic regions such as the amygdala, hippocampus and the anterior insula, as well as striatal, prefrontal, and temporal regions (cf. **Figure 2**). Alterations in the underlying brain circuits have been associated with detrimental effects of loneliness in various functional domains, which appear to be distinct from the consequences of depression [98] and social anxiety [66]. Therapy outcomes may be improved when interventions focus on multiple functional domains and the related neural targets. For instance, accumulating evidence from basic research and

proof-of-concept studies suggests that targeting hormonal systems such as the oxytocin or vasopressin system may have the potential to facilitate social functioning in relevant domains in both, healthy individuals as well as patients with mental disorders [99]. A single intranasal dose of oxytocin reduced aversive anticipation in high anxious individuals [100] and prevented sensitization towards angry faces [101] via reducing amygdala reactivity. Furthermore, oxytocin was found to enhance approach behavior towards positive social stimuli by modulating responsivity of the anterior insula [102, 103]. Both, single-dose administrations of oxytocin and vasopressin may enhance the salience of social stimuli and decrease reactivity towards negative social feedback [104, 105]. Although neuropeptide treatment effects in these domains may vary as a function of dosage [106, 107], treatment expectation [108-110], and sex [111-113], the adjunct administration in combination with behavioral interventions may represent a promising venue to enhance the efficacy of loneliness interventions.

Conclusion

Taken together, loneliness is a crucial and modifiable risk factor for physical and mental health. A better understanding of the neural underpinnings of social (dis)connectedness can help boost the efficiency of loneliness interventions not only in healthy participants but also in patients with mental disorders.

Conflict of interest statement

The authors report no competing biomedical financial interests or personal affiliations in connection with the content of this manuscript.

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M.M., X.L., R.H., B.B and D.S. all made substantial contributions to the conception of this paper. M.M. and D.S. drafted this paper, and X.L. and B.B. contributed critical revisions for intellectual content. All of the authors had final approval of all of the submitted versions, and all are in agreement to be accountable for all aspects of this work.

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Figures

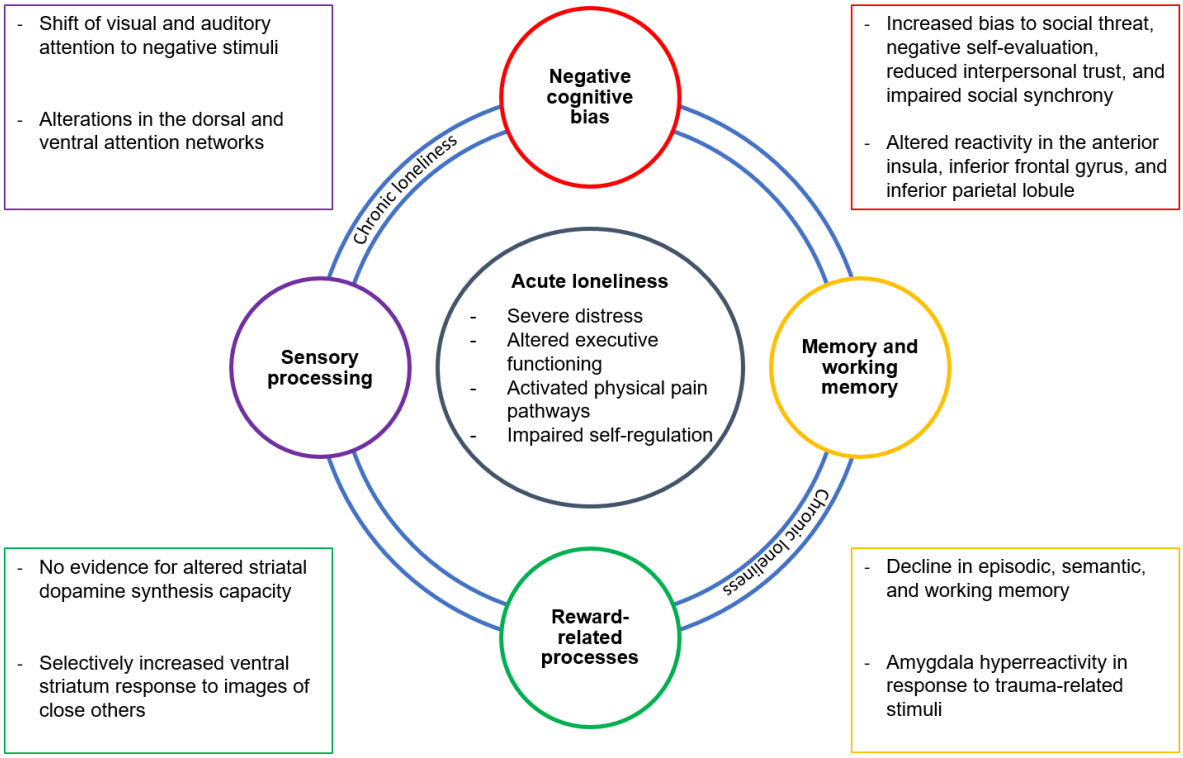

Fig. 1. Theoretical model illustrating the impact of acute and chronic loneliness. Acute effects of loneliness are shown in the inner circle. Chronic loneliness may affect functional domains which are illustrated in the outer circles. Exemplary findings for the domains are listed in the boxes: negative cognitive biases (red), memory and working memory (yellow), reward-related processes (green), and sensory processing (purple).

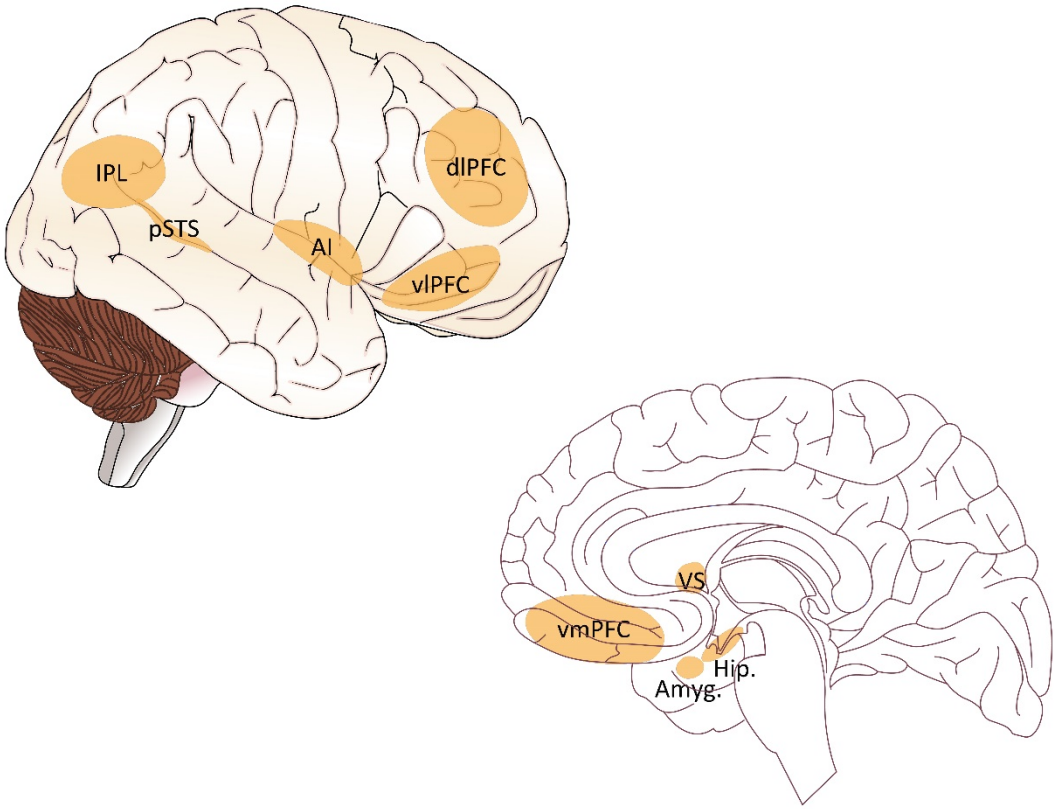

Fig. 2 Illustration of brain areas involved in loneliness. Chronic loneliness has been associated with functional and structural changes in various neural circuits of social and affective brain systems, including limbic regions such as the amygdala, hippocampus and the anterior insula, as well as striatal, prefrontal, and temporal regions Abbreviations: Amyg, amygdala; dlPFC, dorsolateral prefrontal cortex; Hip, hippocampus; IPL, inferior parietal lobule; AI, anterior insula, VS, ventral striatum; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex, pSTS, posterior superior temporal sulcus. Source of the brain template picture used to display the brain regions from https://scidraw.io/ (shared under the creative commons license CC-BY license).