Psychotherapy and Psychosomatics

Editorial

Psychother Psychosom 2022;91:227–237
DOI: 10.1159/000524157

Received: January 15, 2022
Accepted: March 16, 2022
Published online: May 2, 2022

Chronic Loneliness: Neurocognitive Mechanisms and Interventions

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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 (ICBT) 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]. This conceptualization is in line with earlier epidemiological studies differentiating between "availability" and "adequacy" of social support. Increased mortality and risk of cardiovascular diseases have been linked to less perceived adequacy of social support [11–14]. 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 [15]. Loneliness can be seen as a social equivalent to hunger, such that the feeling

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of loneliness triggers the need to form new social relationships, in the same way as hunger triggers the need to eat [16–18]. 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 [19]. Clearly, the effects of acute loneliness are distinct from the impact of chronic loneliness [20, 21]. 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 [22], possibly reflecting the evolutionary desire to form social bonds. Although previous studies found that acute social exclusion elicits activations in neural pathways overlapping with those mediating physical pain such as the dorsal anterior cingulate cortex (ACC) and may lead to severe distress [23, 24], a recent meta-analysis did not detect reliable activation in the dorsal ACC in acute social exclusion but rather found robust engagement of the ventral ACC, posterior insula, posterior cingulate cortex, and lateral prefrontal regions with further co-activation analyses demonstrating a functional co-variance with large-scale networks that resembled the default mode network (DMN) topography [25]. Nevertheless, acute social isolation should not be confused with chronic loneliness, which exerts more harmful effects such as strongly increased mortality in comparison to acute social isolation [26]. Chronic loneliness may function as a continuous psychological stressor which increases the allostatic load, characterized as the wear and tear resulting from chronic overreactivity of stress systems [27, 28]. Several studies linked satisfactory social relationships to reduced allostatic load [29–31]. Allostatic overload is associated with poor health and should be assessed with an integrated approach including not only clinimetric criteria but also biomarkers [32]. Several large-scale studies showed that common genetic variants contribute to loneliness in a range from 4 to 27% [33–35]. Therefore, loneliness seems to interact with a complex system consisting of individual biology, as well as psychosocial status and may lead to a form of biosocial pathogenesis [36, 37]. Given that the COVID-19 pandemic and the necessary measures of social distancing may facilitate the transition from acute to chronic loneliness [38], interventions in vulnerable populations [39] may help to reduce the allostatic load and therefore prevent the 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 major public health concerns [40–43]. Increasing evidence suggests associations between chronic loneliness and an impaired integrity of the immune system, including reduced numbers of natural killer cells [44, 45] and diminished immune responses to acute stressors [46] in lonely individuals. Chronic loneliness has also been linked to heightened blood pressure [47, 48] and an increased risk for coronary heart diseases and stroke [49, 50]. In addition, feelings of social isolation are a risk factor for obesity [51–53] and impaired sleep quality [54, 55]. Sleep deprivation in turn can trigger feelings of loneliness, starting a self-reinforcing cycle of social withdrawal [56]. 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 [57, 58] and is associated with higher levels of depressive symptoms [59, 60], anxiety [61, 62], and psychosocial stress [63]. Furthermore, patients with substance abuse [64–66], borderline personality disorder [67, 68], and schizoid personality disorder [69] report more loneliness and social disconnection than healthy controls. In addition, loneliness is a potential risk factor for post-traumatic stress disorder [70, 71] and enhances intrusive thoughts after trauma exposure [72, 73]. 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-month long Antarctica expedition exhib-

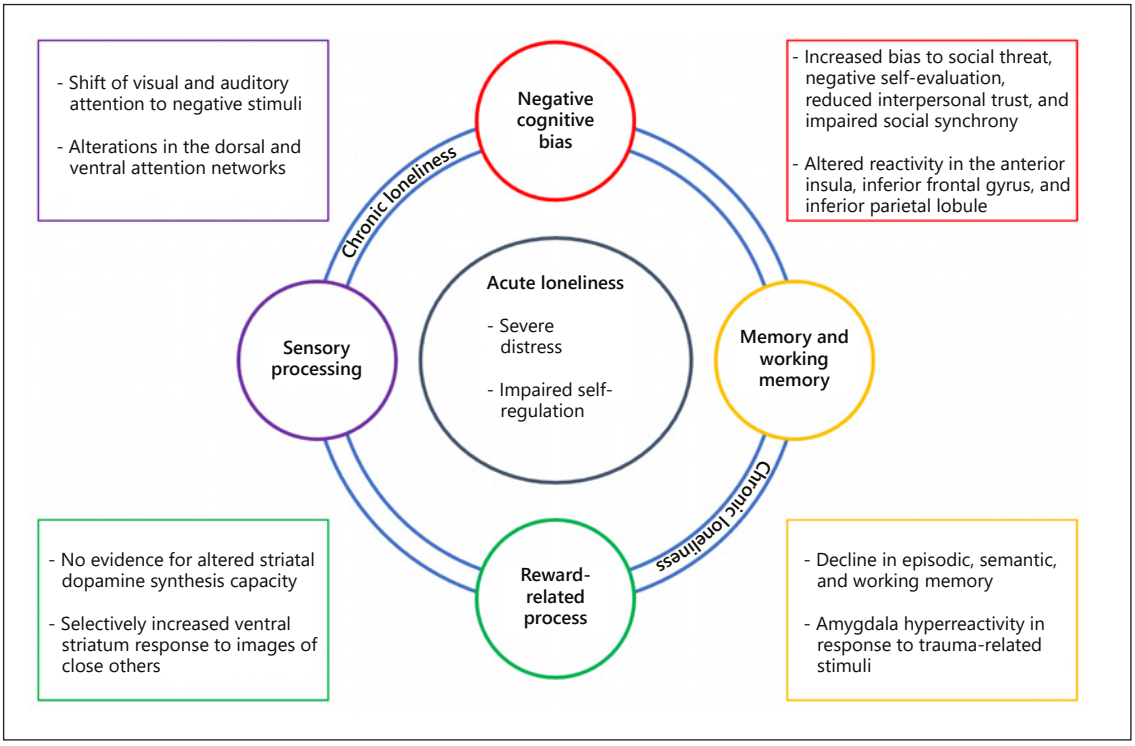

Fig. 1. Theoretical model illustrating the impact of acute and chronic loneliness. Acute effects of loneliness are shown in the inner circle. Chronic loneliness may affect functional domains which are illustrated in the outer circles. Exemplary findings for the domains are listed in the circles: negative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

ited significant reductions in brain-derived neurotrophic factor concentrations and gray matter volume in the dorsolateral and orbitofrontal cortex and hippocampus compared to controls [74]. While these findings are consistent with animal studies showing an association between social isolation and hippocampal neurogenesis [75], 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 [76], but a recent study failed to replicate this association [77]. Along these lines, a rare patient with bilateral amygdala damage showed a normal size and complexity of her social network [78], indicating that an intact amygdala is not necessary to maintain social relationships or at least can be compensated for [79]. Several years after the first assessment of the social network, the woman with amygdala lesion developed severe treatment-resistant depression along with a reduction in the size of her social network, and she reported strong feelings of loneliness [80], demonstrating that the experience of loneliness may not require an intact amygdala either. However, recent large-scale brain morphology studies suggest that there are sex-dependent brain volume effects of loneliness, especially in the amygdala and the ventromedial prefrontal cortex (vmPFC) [81]. Smaller amygdala volumes were detected for lonely men, but not lonely women, and this pattern was reversed for the vmPFC volume. Thus, prospective longitudinal studies are required to monitor sex-specific morphological changes that accompany chronic loneliness. Sex and loneliness interactions are not restricted to brain structural effects. A recent large databank study found that lonely individuals display volume deviations and functional communication changes in the DMN, identifying the DMN as a key component of perceived social isolation [82]. Interestingly, this loneliness-related effect was more prominent in men than women.

Furthermore, individual differences in loneliness correlated with gray matter density in the left posterior superior temporal sulcus, and this association was mediated by social perception skills [83]. Interestingly, the correlation remained significant after controlling for trait anxiety and

social network size, thus providing further support for the notion that loneliness and social anxiety are characterized by distinct neural phenotypes [84] and for the dissociation of loneliness and social isolation. Importantly, loneliness has also been linked to altered neural processing in various neurocognitive domains (Fig. 1), including negative cognitive biases, sensory processing, executive functioning, reward-related processes, and memory.

Negative Cognitive Biases

It has been hypothesized that the maintenance of loneliness is fueled by negative cognitive biases which make positive social interactions less rewarding and may foster even more social withdrawal [17, 85]. Mechanistically, lonely individuals may be more likely to perceive social stimuli as threatening and to evaluate themselves and others more negatively [19]. Feelings of alienation may result from larger self-other dissimilarity of activation patterns in the medial prefrontal cortex [86]. 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 [87]. Given that the anterior insula plays a key role in self-awareness and interoceptive processing [88], 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 [89]. 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 [63]. Additionally, the DMN has been recently identified as a key system involved in loneliness through large-scale UK biobank studies. Increased functional connectivity of the DMN [82] and overall increased network integration between the DMN and the attentional and visual networks in lonely subjects [90] may reflect exaggerated rumination during rest [91]. Furthermore, it has been suggested that negative cognitive biases such as the expectation of more negative social interactions may be based on the association between loneliness and distinct divergences in the structural covariation of DMN and hippocampus subregions [92].

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 [93]. 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 and Executive Functioning

Loneliness-induced hypervigilance can be observed in a shift of visual and auditory attention to negative or threatening stimuli. These changes in sensory processing could be induced by alterations in the dorsal and ventral attention networks [90, 94]. 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 [95], but loneliness also positively correlated with touch avoidance [96]. The excitatory transcranial direct current stimulation to the right IFG slowed responses to observed touch in lonely individuals [96], 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 [97]. Loneliness is higher in participants who experienced childhood maltreatment, which correlates with amygdala hyperreactivity and hippocampal deactivation in response to social stress odors [98]. Whether and how loneliness may affect the sensory integration of multiple modalities is still elusive. In addition, 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 [99], but evidence for an association between loneliness and impaired executive functioning across the life span is scarce.

Reward-Related Processes

The activation patterns evoked by acute social isolation in the ventral tegmental area are similar to the craving-related activation pattern observed after fasting [18]. 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. [100] showed reduced ventral striatum (VS) activity in lonely individuals while viewing pleasant pictures with social connotation, but other studies found no significant correlation between loneliness and VS responses to pleasant social stimuli [101], nor between loneliness and striatal dopamine synthesis capacity in healthy controls or patients with autism spectrum disorder [102]. 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 [16].

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 [103–105]. 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 [106]. 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 [73]. Furthermore, the above-mentioned alterations in hippocampus-DMN covariation may reflect the neurobiological basis for an increased negative memory retrieval [92]. Interestingly, these alterations seem to have distinct links to genetic components of loneliness [92, 107].

Neurocognitive Mechanisms Underlying Loneliness-Related Vulnerability

The current lack of longitudinal studies probing the trajectories of loneliness-associated neural changes hamper conclusions about causal mechanisms. However, given the strong involvement of the DMN in loneliness, it is conceivable that DMN dysregulation also contributes to the detrimental health effects of loneliness. For instance, loneliness has consistently been associated with cognitive decline in patients with Alzheimer's disease [57, 58], and DMN dysregulation has not only been linked to Alzheimer pathology and cognitive decline [108, 109], but also to psychiatric disorders such as substance abuse [110], depression [91, 111], and post-traumatic stress disorder [112, 113]. Perceived social isolation could therefore influence different pathologies by changing the structural and functional integrity of the DMN.

A second possible mechanism mediating detrimental health effects of loneliness could be based on disrupted interoceptive processes. Loneliness has been linked with an "attentional switch" leading to a shift in the direction of heightened exteroceptive attention rather than interoceptive processes which may foster the negative cognitive bias in loneliness [89]. A perceptual insensitivity to the modulation of interoceptive signals has been observed across several common psychiatric disorders such as depression and anxiety disorder [114, 115]. This way, loneliness-dependent activity and connectivity changes in the anterior insula may reflect heightened subjective isolation stress and could convey increased vulnerability in lonely individuals to psychological disorders [63, 87].

Furthermore, amygdala hyperreactivity might be another mechanism underlying the elevated prevalence of psychiatric disorders in high-lonely individuals. Recently, we found amygdala hyperreactivity and increased intrusive thought formation after trauma exposure in high-lonely men [73]. Heightened amygdala reactivity predicts depressive [116] and post-traumatic stress disorder symptoms [117]. Furthermore, amygdala connectivity with the DMN is decreased in patients with major depressive disorder [118]. All of these hypothesized neurocognitive mechanisms might be possible targets for specific therapeutic interventions to reduce loneliness-related vulnerability, but rigorous randomized clinical trials are required to probe causal effects.

Therapeutic Interventions for Loneliness and Integration with Neurocognitive Mechanisms

Social interventions should be considered in new therapeutic concepts to effectively reduce feelings of loneliness. Several studies support the effectiveness of social interventions in a non-clinical environment [119–122]. Intervention types range from group-based physical

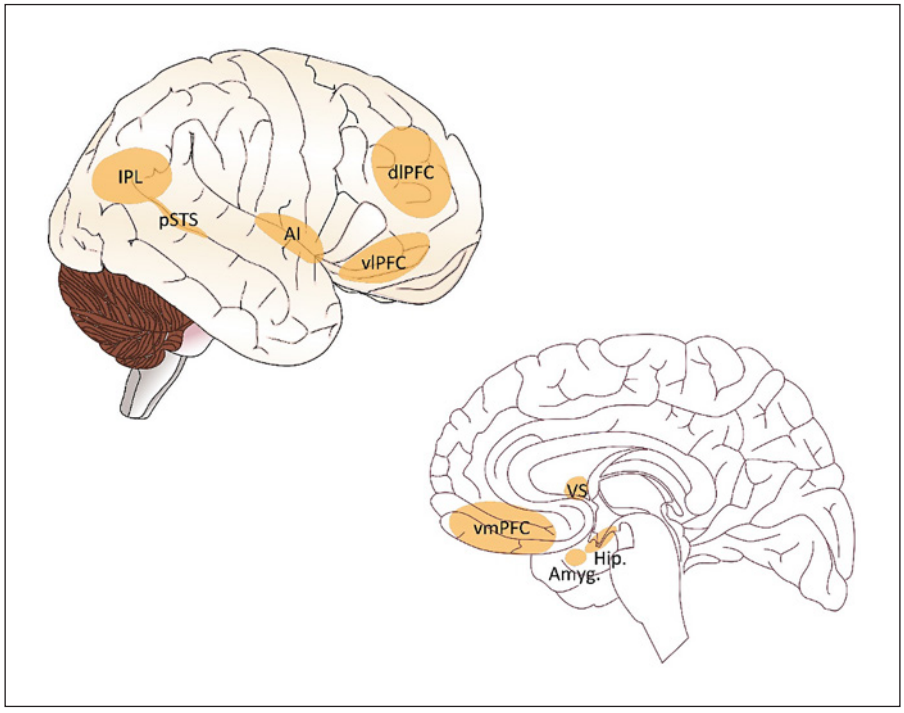

Fig. 2. Illustration of brain areas involved in loneliness. Chronic loneliness has been associated with functional and structural changes in various neural circuits of social and affective brain systems, including limbic regions such as the amygdala, hippocampus, and the anterior insula, as well as striatal, prefrontal, and temporal regions. 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).

activities [123–125], internet and app-based group interventions [126–128] to the use of robotic agents [129, 130]. In addition, a positive social climate and community programs can further prevent loneliness [131–133]. 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 [134]. For example, cognitive-behavioral therapies targeting maladaptive cognition can reduce loneliness levels and the elevated blood pressure associated with loneliness in older individuals [135, 136]. Furthermore, mindfulness training has been demonstrated to be effective in reducing loneliness and related pro-inflammatory gene expression [137–139]. 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 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 [140]. CBT and group therapy sessions also significantly increased social support and decreased depression scores after coronary heart disease [141]. Nevertheless, one-to-one peer support did not significantly reduce readmission rates in the year after discharge from inpatient psychiatric care [142], indicating that more specific interventions may be required. 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. Based on the notion of loneliness as biosocial pathogenesis, longitudinal studies are required to distinguish whether loneliness-related neural changes reflect damage as a direct consequence of excessive exposure to this stressor or adaptive processes which shape the brain in an experience-dependent plastic manner to cope with the negatively perceived social environment [36]. Similar approaches lead to a better understanding of the neural mechanisms in childhood maltreatment and should be adapted in future loneliness research [143].

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 (Fig. 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 [144] and social anxiety [84]. 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 and patients with mental disorders [145]. A single intranasal dose of oxytocin reduced aversive anticipation in high anxious individuals [146] and prevented sensitization towards angry faces [147] via reducing amygdala reactivity. Furthermore, oxytocin was found to enhance approach behavior towards positive social stimuli by modulating responsivity of the anterior insula [148, 149]. Both single-dose administrations of oxytocin and vasopressin may enhance the salience of social stimuli and decrease reactivity towards negative social feedback [150, 151]. Although neuropeptide treatment effects in these domains may vary as a function of dosage [152, 153], treatment expectation [154–156], and sex [157–159], the adjunct administration in combination with behavioral interventions may represent a promising venue to enhance the efficacy of loneliness interventions. Likewise, the endogenous oxytocin response to positive social interactions seems to be attenuated in high-lonely individuals [87], but repeated exposure to situations that have been found to induce the release of endogenous oxytocin such as massage, choir singing, or interpersonal synchronized behavior may reinstate normal neurohormonal responses [160–162].

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 have no conflicts of interest to declare.

Funding Sources

Dr. Scheele is supported by an Else-Kröner-Fresenius-Stiftung grant (2017_A35).

Author Contributions

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. A preprint of the manuscript has been posted on the Psyarxiv repository (DOI: 10.31234/osf.io/r4f9e).

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