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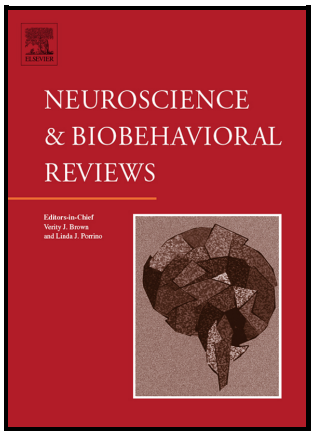

A translational neuroscience perspective on loneliness: Narrative review focusing on social interaction, illness and oxytocinTranslational neuroscience on loneliness

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Submission to *Neuroscience and Biobehavioral Reviews*

Title: A translational neuroscience perspective on loneliness: Narrative review focusing on social interaction, illness and oxytocin

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Abstract

This review addresses key findings on loneliness from the social, neurobiological and clinical fields. From a translational perspective, results from studies in humans and animals are included, with a focus on social interaction, mental and physical illness and the role of oxytocin in loneliness. In terms of social interactions, lonely individuals tend to exhibit a range of

abnormal behaviors based on dysfunctional social cognitions that make it difficult for them to form meaningful relationships. Neurobiologically, a link has been established between loneliness and the hypothalamic peptide hormone oxytocin. Since social interactions and especially social touch regulate oxytocin signaling, lonely individuals may have an oxytocin imbalance, which in turn affects their health and well-being. Clinically, loneliness is a predictor of physical and mental illness and leads to increased morbidity and mortality. There is evidence that psychopathology is both a cause and a consequence of loneliness. The final section of this review summarizes the findings from social, neurobiological and clinical perspectives to present a new model of the complex construct of loneliness.

Introduction

While there have been several definitions of loneliness, many described it in terms of causes, hence obscuring the actual experience of being lonely (McKenna-Plumley et al., 2023). In response, a recommended definition of loneliness from the Global Initiative on Loneliness and Connection defines loneliness as "a subjective unpleasant or distressing feeling of a lack of connection to other people, along with a desire for more, or more satisfying, social relationships" (Badock et al., 2022, p. 19). This definition expresses the subjective perception and the emotional suffering of being socially isolated. Loneliness is not necessarily correlated with objective measures such as social isolation or social network size (Badcock, Adery, & Park, 2020; Tiwari, 2013). It is also a major risk factor for mental and physical illness, such as increased risk for depression, anxiety, cognitive decline, dementia and coronary heart disease (Cacioppo, Hawkley, & Thisted, 2010; Herrman et al., 2022; Holwerda et al., 2014; Shankar et al., 2013; Valtorta et al., 2018). It is therefore of immense social relevance to understand the roots and consequences of loneliness. An extensive meta-analysis of 345 studies found that loneliness has substantially increased in emerging adults during the last 43 years (Buecker et al., 2021). However, a review about loneliness across historical time and geographic space (Luhmann, Buecker, & Rüsberg, 2022) suggests a more nuanced view of macro-level factors on loneliness. The authors argue that although variables related to objective social isolation have indeed increased in the past half-century, cross-temporal meta-analyses about changes in loneliness over time report inconsistent findings. While a general statement about the temporal trends of loneliness is difficult, the drastically increasing share of older people in the general population in Western societies due to low fertility rates is well documented (Sciubba, 2020), therefore loneliness can be assumed to be more prevalent in the future, emphasizing the need for research in this field. In addition to human studies, research also uses animal studies to study the neurobiological mechanisms of loneliness.

As loneliness is a complex construct, it is best understood from an interdisciplinary perspective. This review article intends to discuss loneliness on the basis of social and clinical neuroscience. While several previous reviews about the topic of loneliness (e.g., Finlay & Schaefer, 2022; Lam et al., 2021; Vitale & Smith, 2022) primarily argued from a perspective of neuroscience, the present review also aims to incorporate relevant clinical and social aspects for a more interdisciplinary approach. In addition, the present article has a stronger focus on specific influencing factors on loneliness, i.e., social interaction (such as social touch), illness (mentally and physically) and the role of oxytocin.

For this narrative review, we conducted a literature search for peer-reviewed publications about the topic of loneliness, specifically with regard to social interaction, social touch, mental illness, physical illness and oxytocin. Both human and animal studies were included due to the translational scope of this review. Online data bases PubMed, ScienceDirect, PsycInfo and Google Scholar were screened in October and November 2023 for articles mainly published during the last 10 years. The following inclusion criteria were used: (1) empirical studies and reviews published in English language scientific journals, (2) use of a validated scale for assessing loneliness, and (3) statistical analysis examining the relationship of loneliness and variables of interest. RoB assessments for individual studies were not part of this review. Central key words were loneliness, social interaction, touch, mental illness, psychological disorder, psychopathology, physical illness, and oxytocin. Included studies were from the fields of neuroscience, psychiatry and psychology.

The article is divided into the following sections: The first section discusses loneliness from a behavioral perspective, with specific emphasis on social interactions. The second section is neurobiologically oriented and discusses the link between the oxytocin system and loneliness. The third section covers the clinical field and discusses the link between loneliness and psychopathology on one hand and physical illness on the other hand, especially discussing potential causes and consequences. The final section summarizes the central results and sets them in relation to each other by synthesizing a new model of loneliness.

1. Impaired social interaction in loneliness

Extant research has consistently demonstrated a significant connection between loneliness and deficits in social behavior, that hinder the capacity of lonely individuals (especially when chronically lonely) to initiate and sustain meaningful relationships. Loneliness is associated with heightened negative emotional experiences during interpersonal interactions (Hawkley & Cacioppo, 2003) and self-reported reductions in relationship satisfaction, increased conflict, and decreased self-disclosure and emotional intimacy (Mund et al., 2020). Moreover, it is associated with decreased engagement in prosocial acts in comparison to their non-lonely counterparts (Gest et al., 2001; Woodhouse et al., 2012), with difficulties in establishing trust with others (Lieberz et al., 2022), and with impairments in the capacity to achieve synchronization with peers in tasks involving movement coordination (Saporta et al., 2023). Furthermore, evidence suggests that loneliness is related to negative social biases, such as the tendency to focus on negative rather than positive social cues (Cacioppo & Hawkley, 2009; Cacioppo et al., 2016), influencing individuals' perceptions of the social environment, and leading them to anticipate a lack of support and assistance. Additionally, lonely individuals perceive greater cognitive distance between themselves and their friends, also in relation to memory biases (Kokici et al., 2021; Kokici et al., 2023), and prefer greater physical distance from others (Layden et al., 2018; Saporta et al., 2021). Finally, it has been shown that individuals experiencing loneliness report reduced positive evaluations of social interactions, and exhibit attenuated brain activity associated with reward when exposed to positive social stimuli (Lieberz et al., 2021). These findings point to a tendency of hypo-sociality among lonely individuals, which may explain the diminished quality of interpersonal interactions and a reduced quantity of relationships.

On the other hand, research exploring the capacity of lonely individuals to participate in social interactions suggests that, in certain situations, loneliness is linked to an increased desire for social connection (Kanterman et al., 2022). Studies that focus on increased craving for social connection are based on theoretical formulations holding that loneliness, similar to hunger for food, devolved to signal weak social connections, motivating individuals to seek social bonds (Cacioppo et al., 2014). Consistent with this approach, it was found that lonely individuals attempt to regain social connections and exhibit more prosocial behavior specifically in public situations (Huang et al., 2016). Likewise, it was shown that there is an increased craving for social connection represented by higher activity in the reward system when viewing close others compared to strangers (Inagaki et al., 2016). Interestingly, Tomova et al. (2020) showed that acute social isolation of ten hours results in increased motivation to seek contact, which is accompanied by midbrain responses to social cues which are similar to neural responses to food cues when hungry, suggesting that there is indeed a physiological crave for connection. As such, when social needs are not being met, an increase in other forms of reward-consumption is evident, such as elevated intake of sugary beverages (Henriksen et al., 2014) or engaging in substance abuse (Ingram et al., 2020). These results indicate that lonely individuals may also exhibit hyper-sociality, which raises the question of what are the factors that determine their behavior during social interactions.

Two such main factors are safety cues and whether the experience of loneliness is acute (situational) or chronic (prolonged). First, research has shown that social approach can be upregulated among lonely individuals with high propensity to avoid social situations in the presence of stimuli deemed as safe. Lucas et al. (2010) demonstrated that exposing lonely individuals to acceptance cues in the form of vignettes portraying a secure and inclusive social context, increases social motivation during subsequent social interactions when compared to non-lonely individuals. Kanterman et al. (2022) demonstrated that lonely individuals exhibit a greater willingness to invest effort into securing inclusion in social interactions when the expenditure of effort is minimal, but this inclination diminishes when the required effort is substantial. This is substantiated by evidence of heightened reward-related brain activity when exposed to familiar individuals as opposed to unfamiliar ones (Inagaki et al., 2016). Hence, contextual factors such as whether the social environment is safe or not influence the social behavior of lonely individuals in a dynamic manner.

Second, research shows that acute loneliness related to COVID 19 lockdowns correlates with an increased preference for interpersonal proximity, while chronic loneliness is associated with an augmented inclination for interpersonal distance (Saporta et al., 2021). In a situational loneliness context, it appears that approach motivation intensifies, propelling lonely individuals toward reconnection and hyper-alignment. Conversely, in the case of chronic loneliness, characterized by its enduring nature, avoidance motivation and hypo-alignment become more prominent, resulting in difficulties in interpersonal connection. Additional research indicates that lonely individuals may exhibit challenges in adapting their movements to those of their interaction partner, coupled with heightened activation in the observation-execution system (Saporta et al., 2023). This heightened neural activity possibly signifies increased cognitive effort when attempting to synchronize with others, possibly due to inability to regulate approach and avoidance properly.

Similarly to human studies, animal studies also contribute to the study of social interaction, allowing translational research. Previous studies have shown that animals have the ability to act socially cooperative in order to solve tasks, such as elephants (Plotnik et al., 2011), rats (Avital, Aga-Mizrachi, & Zubedat, 2016), mice (Shin & Ko, 2021) and non-human great apes (Melis & Rossano, 2022). This need for social interaction and mutual benefit allows findings comparable to social interaction in humans. There is also evidence of self-recognition in a mirror-recognition task in elephants, apes and dolphins. Their similarity of responses is interpreted as cognitive evolution related to complex sociality and cooperation (Plotnik, de Waal, & Reiss, 2006). Due to the comparability between humans and certain animals in social cognition and behavior, this review applies a translational perspective.

Overall, the evidence of social impairment among individuals experiencing loneliness suggests that, contingent upon the situational context, loneliness can manifest as either an intensified inclination towards engagement (hyper-approach) or an enhanced propensity for withdrawal (hyper-avoidance). These behavioral tendencies may be shaped by a multitude of factors, among which the perceived safety or threat of the environment, as well as the nature of the loneliness experienced - whether it is transient and situational or persistent and chronic - play pivotal roles. This framework supports with the herding theory of loneliness posited by Shamay-Tsoory and Kanterman (2024), wherein loneliness is conceptualized as a dysregulation within the approach-avoidance and alignment mechanisms. Furthermore, this interpretation is congruent with the theoretical model proposed by Cacioppo et al. (2014), which posits that hyper-approach behaviors in lonely individuals may serve as compensatory strategies aimed at mitigating feelings of loneliness through enhanced social engagement. Conversely, hyper-avoidance behaviors may function as adaptive defenses, safeguarding against potential social threats or the risk of rejection that could intensify the experience of loneliness.

2. Link between the oxytocin system and loneliness

While there are several biological systems contributing to loneliness, the present review focuses on the neuropeptide oxytocin (OT), as it is well known for its role in promoting affiliative, social seeking and pair bonding behavior. It increases trust, regulates stress, facilitates emotion recognition, increases prosocial behavior, and attenuates loneliness (Cacioppo et al., 2015; Kosfeld et al., 2005). Therefore, current research highlights OT system as a key component in understanding the complex neurobiological mechanism of loneliness. Here, we will dissect how loneliness imprints the changes in the functioning of OT circuits, leading to altered behavior. We will mainly focus on the effects of subjective social isolation / loneliness on OT system in adults, since little research has been done on younger age groups.

2.1. How loneliness imprints on OT system

Social isolation modulates the OT system directly by increasing the density of OT producing cells in the paraventricular nucleus of the hypothalamus (PVN). In addition, elevated OT serum levels have been found in socially isolated animals (Harvey et al., 2019). Both changes are seemingly contradictory to the typical anxiolytic view on OT (Hylin et al., 2022). However, due to its prominent role in social bonding and stress responses, OT might play a compensatory or adaptive role in the context of social deprivation. In other words, an increase

in OT could be a biological attempt to counteract the stress and emotional deficits caused by isolation. Another adaptive role of increased OT production during social isolation may be to modulate sensory circuits and plasticity (Grinevich & Stoop, 2018b; Mitre et al., 2018), thus to enhance the processing and salience of social stimuli in response to social deprivation (Choe et al., 2015; Oettl et al., 2016). Conversely, in chronic state of loneliness, human studies showed that OT plasma levels are lower (Jobst et al., 2016) indicating that physiology of OT system functions as an adaptive mechanism on the long range too.

Other than the expression of OT itself, another factor influencing its function is the presence of the OT receptor (OTR). It is well known that OT receptors (OTRs) are broadly expressed in the central nervous system, and their influence on social behavior varies depending on brain region. Interestingly, different studies have shown that OT modulates behavior differently in socially affiliated vs isolated individuals. This is probably due to differential sensitivity of OT system under various conditions. Studies have reported altered OT neuron population, changes in OTR distribution, expression levels on both mRNA and protein level, and binding affinities of OTRs in social isolation (Vitale & Smith, 2022). Specific form of loneliness has been observed through a loss of loved ones, usually a romantic partner. In naturally monogamous prairie voles, isolation from a partner has resulted in downregulation of OTR expression in both males and females, yet in females the OT secretion was also higher, indicating a more effective buffering mechanism (McNeal et al., 2014; Pournajafi-Nazarloo et al., 2013).

2.2. Effects of intranasal OT administration on sociability

Early research on OT and sociability upon intranasal OT administration showed that it influences perception of interpersonal relationships, with its effect strongly adhering to social, and not nonsocial settings (Hurlemann et al., 2010). This has been further confirmed in a fMRI study which showed increased activity in specific brain regions (amygdala, hippocampus, parahippocampal gyrus and putamen) during social feedback. Additionally, there was enhanced connectivity between the amygdala and the insula, as well as the caudate (Hu et al., 2015). Therefore, OT may increase the salience and reward value of anticipated social feedback, by increasing functional connectivity and responsiveness in emotional memory processing (Cardoso et al., 2014; Hu et al., 2015). Similarly, Rimmelle and colleagues showed that OT selectively increases participant's feelings of familiarity to a face (Kéri & Benedek, 2009; Rimmele et al., 2009).

OT also influences emotion recognition and empathy (Lischke et al., 2012). Research indicates that a single dose of OT enhances the ability to recognize emotions in faces, particularly happiness and fear (Fischer-Shofty et al., 2013; Shahrestani et al., 2013). This effect is consistent across various types of facial cues, such as masked or dynamic expressions, and under OT, individuals are able to detect emotions at lower intensities and pay more attention to faces than with a placebo (Prehn et al., 2013). OT also makes individuals more likely to focus on happy expressions over angry ones and slows down their response time to ambiguous emotions, while improving their overall accuracy in identifying such emotions (Di Simplicio et al., 2009). These findings reveal that characteristic behavioral changes in psychopathology of loneliness - such as heightened sensitivity to social cues, reduced trust with negative

anticipation and perception of everyday interpersonal interactions (Cacioppo, J. T., and Patrick, 2008; Gable, 2006; Hawkley et al., 1995), have a neurobiological basis in OT system.

2.3. Social touch and loneliness

The tendency of lonely individuals for social distancing and their diminished benefit from interpersonal relationships may be attributed to dysregulated processing of social touch. Impairments in multisensory integration in the insular cortex (IC), as well as dysregulation of OT release, may induce a negative bias towards the social touch context, preventing lonely individuals from benefiting of such experiences (Devine et al., 2020). It is well known that OT neurons project to the primary (S1) and secondary (S2) somatosensory cortices, and anterior insula - a key region for multisensory integration and interoception, as well as interpreting the context of affective touch processing (McGlone et al., 2014). In patients with PTSD and history of childhood maltreatment, an extensive dysfunction of this network has been observed: reduced connectivity between the insula and other cortical areas involved in sensorimotor processing and increased connectivity of the posterior insula (PI) with limbic and brainstem regions involved in evoking instinctual defensive responses (Harricharan et al., 2021). As a result, individuals become hyper-reactive upon experiencing social touch, creating a bias towards perceiving it as threatening and aversive (Maier et al., 2020), and leading to an overall avoidance behavior. Moreover, there is evidence that OT contributes to the integration of multiple senses across various sensory fields (Maier et al., 2018, 2020), and it is significantly involved in shaping social behaviors that depend on sensory inputs (as discussed by Grinevich & Stoop, 2018). Therefore, a malfunction in OT pathways could hinder the combined sensory processing involved in social forms of touch. This is further sustained by the research from Riem et al. (2020) and Maier et al. (2020), showing OT can influence the way social touch is processed. The altered processing of social touch can in turn impact the effect of OT release and create a loop of negative reinforcement. Altogether, we can conclude that impaired OT system can anchor the lonely phenotype and can act both as a trigger or perpetual force in chronic loneliness, joint with other psychiatric conditions.

It was also found that tactile stimulation similar to social touch activates tachykinin-1 OT pathways in rats, thereby promoting social interaction (Yu et al., 2022). In humans, the effect of OT was shown to be dependent on an individual's perception of social touch. As somatosensory stimuli are delivered by social touch and regulate OT, this neuropeptide plays a crucial role in social interactions (Tang et al., 2020). Interpersonal touch induces the release of OT (Kreuder et al., 2017), also OT modulates the pleasantness of social touch (Scheele et al., 2014) and antinociceptive effects of touch-based social support (Kreuder et al., 2019).

Moreover, studies have consistently shown that individuals with trauma history tend to have weaker reactions, both in their behavior and brain activity, to positive rewards, (Lokshina et al., 2021; Seidemann et al., 2021; Teicher et al., 2016) which in turn could contribute to inability to experience satisfaction from social interactions, leading to feelings of disconnection and loneliness.

2.4. Complex interplay of OT and dopamine system in social reward

Social interactions are neurobiologically driven by the reward system - activated by dopaminergic projections from ventral tegmental area (VTA) to ventral striatum and higher-

order brain region, including insular cortex (IC). This mechanism is highly coordinated with the release of OT and serves a purpose of creating and maintaining enjoyable and meaningful relationships (Vitale & Smith, 2022). This functional connection is known to be impaired in lonely individuals e.g. the function of IC is reduced in socially isolated individuals (Morr et al., 2021). Appropriate functioning of IC is crucial for generating predictions about social environment and adjusting behavioral response according to novel social stimuli. When presented with a novel situation, IC integrates extero-and interoceptive inputs from thalamus and visceromotor regions and encodes the prediction of the outcome, specifically by action of insular "prediction" neurons (Rogers-Carter et al., 2018). OT is known to modulate the function of these neurons, via OT projections to the rostral agranular insula - an area necessary for recognizing affective state of social conspecifics and driving social avoidance of stressed conspecific in rodents (Quattrocki & Friston, 2014). As OT production is increased in socially isolated animals (Grippo et al., 2007), it could disrupt the normal processing in IC. This in turn can lead to increased attention and hypervigilance during social encounters and therefore contribute to lonely individual's preference for greater physical distance (Knobloch & Grinevich, 2014; Vitale & Smith, 2022). Inadequate prediction on the behavior of conspecific can likely result in focusing on negative social cues and anticipation of lack of support and assistance. Altogether, this can contribute to experiencing relationships as less satisfying and rewarding, overall resulting in social avoidance.

Lonely individuals do not perceive social interaction as rewarding as their non-lonely counterparts. In fact, research shows reduced social motivation and relationship satisfaction, leading to overall reduced social intimacy and reinforced loneliness pattern (Hu et al., 2015). Positive effect of OT on bonding behavior seems to be reward-based, as it depends on dopaminergic pathways. For example, OT was found to support passive stress-coping following partner-separation in voles, via its action in the nucleus accumbens (Bosch et al., 2016). In the perpetuating cycle of psychopathology of loneliness, impairment of OT system creates difficulties in forming and maintaining meaningful and satisfactory bonds (Patin, Scheele, & Hurlemann, 2018). Also, OT neurons extensively project to dopaminergic regions, such as the VTA -specifically, and activation of OTRs in the VTA is essential for social reward experience (Borland et al., 2018; Vitale & Smith, 2022). Thus, OT might enhance dopamine's involvement in social attention by making social cues more appealing.

Another important aspect contributing to diminished sense of reward upon engaging is social interaction is the impairment in the activity of mirror neuron network (MNN). Social processing, specifically fear processing and empathy, depends on the activity of MNN, which is known to be strongly regulated by OT system (De Coster et al., 2014). Interestingly, the evidence shows that being imitated by others increases OT secretion and activates anterior right insula (Aoki et al., 2014). The same effects have been observed upon the intranasal OT administration in patients with autism spectrum disorder, indicating a possibly reciprocal relationship between OT and the MNN to increase prosocial behavior (Andari et al., 2016). On the other hand, social synchrony and cooperative behavior have also been known to rely on MNN based social processing, as shown in studies of intimate romantic partners and military veterans (Levy et al., 2016). In both studies, it is shown that synchronous social interactions evoke heightened endogenous OT release, increasing reciprocity and emotion transmission of social information (Spengler et al., 2017). As previously mentioned, lonely individuals display

impairment in synchrony behavior, which also relies on MNN network. This could further contribute to subjective feelings of failing to socially adjust within the concept of reciprocating necessary relationships' behavior.

2.5. OT-mediated regulation of limbic system in loneliness

The phenomenon of hypervigilance of lonely individuals towards social cues and lack of trust could be attributed to reduced ability of the salience network to override limbic hyperactivity and elevated alertness. OT modulates emotional functions of amygdala and hypothalamus, and regulates stress levels through the effects on hypothalamic-pituitary-adrenal (HPA) axis (Vitale & Smith, 2022). OT directly influences the activity of HPA axis via release of CRH from parvocellular neurons in PVN, triggering a cascade of ACTH secretion from pituitary, and finally adrenal gland-derived corticosteroids, which in negative feedback loop shuts down the neuroendocrine stress response (Neumann, Krömer, et al., 2000). However, research indicates that OT may suppress HPA axis function normally, but during stress experience facilitates HPA activity. For example, blocking OT receptors in basal conditions resulted in increased production of ACTH and vice versa in stress conditions (Neumann, Krömer, et al., 2000; Neumann, Wigger, et al., 2000). Although OTR expression does change under isolation conditions, studies on manipulation of OTRs across OT projection regions have not been studied yet in this context; and would be necessary to further confirm the varying behavioral effects of loneliness in response to altered functioning of OT system.

3. Loneliness, psychopathology and physical illness

3.1 Loneliness and mental disorders

3.1.1 Association between loneliness and mental illness

Generally speaking, loneliness is associated with psychological problems and psychological distress (Meltzer et al., 2013). Social isolation and loneliness are more prevalent in people with mental illness than in the general population (Caple et al., 2023). Evidence shows that loneliness increases risk of physical and mental illness as well as mortality; for instance, participants rated as most lonely were more likely to be placed in psychiatric hospitals than less lonely participants (Prince et al., 2018). Loneliness has been associated with several mental disorders. Diagnoses frequently mentioned are major depression, anxiety, personality disorders including borderline personality disorder, schizophrenia, alcoholism, bulimia (Mushtaq et al., 2014; Wang et al., 2018). For major depression, social isolation or loneliness is considered the second most prevalent symptom after depressed mood or sadness in Western cultures and also one of the most central symptoms in non-Western cultures. Thus, there is consensus across cultures that loneliness is a hallmark symptom of major depression (Herrman et al., 2022). Risk factors for loneliness include lower socioeconomic status, education level, mental and physical health as well as major negative life events (death, disease, trauma) (Lim, Eres, & Vasan, 2020). In people with psychotic disorders, loneliness is extremely common (80% of patients reported loneliness) and has been identified as one of the main risk factors. Patients have rated loneliness as one of the most significant obstacles in recovery (Badcock et al., 2020).

Loneliness at baseline was significantly associated with symptom severity in major depression and anxiety, affective symptoms, self-rated recovery and health-related quality of life after a 4-month period in patients (Wang et al., 2018). There may also be variation in how loneliness is perceived in otherwise healthy individuals versus individuals with mental illness; that is, added to being subjective, symptoms and progression of mental illness may interact with loneliness to create very specific and extremely varied experiences of loneliness (Badcock et al., 2020).

There is generally a strong association between loneliness on one hand and suicide / suicidal ideation on the other hand. Also, loneliness is a predictor of suicidal ideation and / or behavior in select populations, such as females as well as ages 16-20 and >55 (McClelland et al., 2020). A general population survey showed that the association between feelings of loneliness and suicidal ideation / attempts in adults remains significant after adjusting for common mental disorders (Stickley & Koyanagi, 2016).

During the COVID-19 pandemic, the link between loneliness and psychological distress became apparent across all age groups. A study found that 43% of respondents who scored above defined cutoffs criteria for loneliness, showed a strong association with greater depressive symptoms and suicidal ideation (Killgore et al., 2020). Singles and people with a psychiatric diagnosis were most affected by social distancing rules during the pandemic. A link between loneliness and major depression as well as anxiety symptoms was found (Hoffart, Johnson, & Ebrahimi, 2020).

While loneliness has been shown as a risk factor for psychological disorders, it must be acknowledged that loneliness itself can be an integral part of the experience of being mentally ill. Loneliness as a risk-factor as well as a byproduct of mental disorders highlights the complex nature of this association.

3.1.2 Mediators between loneliness and mental illness

Lonely persons tend to exhibit a hypervigilance to social threat and their subdued reactions to positive social situations, which diminishes other people's interest to interact with them (Cacioppo & Hawkley, 2009). This leads to a vicious cycle, as the resulting reactions of other people in turn reinforce the negative perception of lonely people (Hawkley & Cacioppo, 2010). Negative emotions, often chronic in nature, play a crucial role in development and maintenance of psychopathology. As loneliness is a negative emotion by itself, it was found to have a significant influence on major depression (Erzen & Cikrikci, 2018). This mechanism of self-fulfilling prophecy shows that there is a bidirectional influence between loneliness and negative social cognitions.

Social support has been shown to be a partial mediator for the association between loneliness and anxiety, major depression, and somatic symptoms (Hutten et al., 2021), and is considered a protective factor against major depression (Marx et al., 2023). Greater social support has been shown to be associated with better subjective quality of life in schizophrenic and schizoaffective patients, whereas less social support is a predictor of greater symptom severity and worse remission in depressed patients, as well as patients with anxiety or bipolar disorders (Wang et al., 2018). Social exclusion has been indicated to cause psychological pain not unlike physical pain and significantly predicted loneliness and mental health issues in adolescents (Arslan, 2021).

Other possible mediators, which might explain the association between loneliness and mental health, are self-efficacy or self-esteem: Fortuna et al. (2022) investigated loneliness and its association with health behaviors in people with serious mental illness, including depressive disorder, schizophrenia spectrum disorder, bipolar disorder and posttraumatic stress disorder. It was found that high levels of loneliness were associated with low levels of self-efficacy to manage chronic diseases and psychological well-being, therefore possibly contributing to early mortality in these disorders. Hawkley and Cacioppo (2010) developed a model to explain the association between loneliness and psychopathology. Loneliness influences people's perception of social interactions negatively, generating the expectation of social interactions to go poorly and thereby creating a self-fulfilling prophecy. The result is low self-esteem, social withdrawal, and other negative effects on mental health.

Loneliness is also often stigmatized (Cacioppo & Cacioppo, 2018) both by the lonely individuals themselves as well as their social environment. Added to the stigma about mental illness that is still common in societies worldwide, the combination of social withdrawal by the lonely individual and social exclusion from the social environment can further aggravate the loneliness an individual experience (Badcock et al., 2020).

Both acute and chronic stress can cause loneliness, which in turn leads to other negative health outcomes, indicating a bidirectional influence. It is also associated with poor sleep quality and poor functioning during the day like fatigue and low energy, as well as poorer cardiometabolic health and strokes. Lonely people suffer from more depressive symptoms and there is a strong association of loneliness with suicidal ideation and suicide attempts (Gomboc et al., 2022). Doane and Thurston (2014) investigated associations between daily stress levels, sleep quality and loneliness in adolescents. They found evidence of bidirectional and dynamic influence between these measures, as high stress negatively affected sleep quality and loneliness served as a mediator between these two factors. McHugh and Lawlor (2013) found that perceived stress mediates the association between loneliness and sleep quality in older adults.

3.1.3 Loneliness across the lifecycle

Loneliness, especially long-term loneliness, is an important issue across the entire lifespan. Particularly loneliness during childhood seems to be a major risk factor for psychological problems even in adulthood. A longitudinal study of 1.420 subjects showed that childhood loneliness was associated with adult self-reported anxiety and depressive outcomes, thus there are long-term mental consequences of loneliness during childhood (Xerxa et al, 2023). Moreover, women abused in childhood were found to be lonelier than women who were not abused (Mushtaq et al., 2014). In adolescents, loneliness has been found to be associated with a higher prevalence of later mental illness (Arslan, 2021); this is especially relevant as the late teens / early 20s are often the period of onset for disorders such as major depression or psychoses, where loneliness plays an important role as a risk factor.

Evidence points to an association between loneliness and depressive symptom, especially later in life (Herrman et al., 2022). A review of ten studies (Van As et al., 2021) found that loneliness affects up to 43% in the elderly, with numbers varying across studies. The longitudinal association between loneliness and depressive symptoms was examined in this particular age group. These studies all showed a significant and positive association. While

some studies showed a longitudinal effect of loneliness on depressive symptoms, others showed that an unfavorable clinical course of major depression is also associated with loneliness, i.e., the influence between those two factors is mutual.

3.1.4 A shared biological basis for loneliness and psychopathology?

Genetic correlation studies showed a strong role of genetic influences in the co-occurrence of major depression and loneliness. In the E-Risk (Environmental Risk) Longitudinal Twin Study, loneliness and social isolation were correlated with major depression. The authors conclude that since the same genes influence loneliness and major depression, both phenotypes co-occur and interventions should target both (Matthews et al., 2016). This finding is in line with other work, which has identified several candidate genes linked to loneliness (Spithoven et al., 2019). However, possibly because loneliness is a complex construct and genes contribute to loneliness indirectly rather than directly, findings have varied and so far and were only replicable for the OT receptor gene (Goossens et al., 2015). Some of the genes put forth by these studies are also implied in affective and schizophrenia spectrum disorders (Kim et al., 2022; Marx et al., 2023), suggesting a polygenic overlap between loneliness and mental disorders that even extends to cardiovascular risk factors via shared genetic pathways (Rødevand et al., 2021).

Inflammatory processes have been indicated in loneliness, associating loneliness with increased levels of C-reactive protein CRP, fibrinogen and Interleukin-6 (IL-6) (Smith et al., 2020). Possibly suggesting common pathways, the same inflammatory markers have been found to be elevated in major depression and schizophrenia (Kim et al., 2022; Marx et al., 2023).

The gut microbiome has been suggested to play an important role in mental disorders as well as loneliness via modulating inflammatory pathways, vagal nerve signaling and secondary metabolites. Studies on this issue found higher levels of Alistipes and Parabacteroides and lower levels of Prevotella and Coprococcus bacteria in loneliness as well as in major depression and schizophrenia (Kim et al., 2022; Marx et al., 2023; McGuiness et al., 2022; Kelly et al., 2021) compared to healthy controls.

Research into the neural underpinnings of loneliness has identified changes to structural and functional brain architecture between individuals with loneliness compared to non-lonely individuals. Those changes partially overlap with those that have been found in studies on major depression and schizophrenia (Lim et al., 2020).

Using EEG, Cacioppo, Balogh, and Cacioppo (2015) found that lonelier people are extremely vigilant to negative social cues such as words or images, indicating an altered functioning of dorsolateral prefrontal cortex and precuneus compared to healthy controls. In line with this finding, MRI-based neuroimaging studies show altered white and gray matter structure as well as functioning across a range of regions in the brain, including the dorsolateral and dorsomedial prefrontal cortices, amygdala, medial and inferior frontal gyri, temporal lobe, and ventral striatum (Lam et al., 2021; Lim et al., 2020) when comparing lonely people to control participants. In the same vein, Düzel et al. (2019) showed that elderly lonelier individuals exhibited smaller gray matter volumes across the amygdala, hippocampus and cerebellum. Some of these structural and functional changes to brain connectivity, like the

changes in the frontoparietal network, amygdala or hippocampus, are shared between loneliness and disorders such as major depression and schizophrenia.

There have also been findings that suggest go-between effects, e.g. neuroticism, which has been reported to act as moderator between loneliness and major depression and which has a very strong genetic basis and also mediates the relation between loneliness and gray matter volume in dorsolateral prefrontal cortex (Kong et al., 2015).

3.2 Loneliness and physical / neurological disorders

Over the last years, there has been mounting evidence that loneliness is not only associated with psychological states and psychiatric disorders, but also physical conditions, including cardiovascular diseases (CVD), dementia, and type 2 diabetes.

3.2.1 Loneliness and cardiovascular diseases

When considering the relationship between loneliness and physical conditions, CVD is the most researched disease complex. Although some studies find equivocal results, ample research points into the direction of the considerable association between loneliness and the occurrence of CVD. Furthermore, loneliness appears to negatively impact the further course of the disease.

Following results were mostly derived from long-term epidemiological cohort studies prior to the disease onset under inspection and presented after controlling for demographic, behavioral or psychological factors. Loneliness was associated with an increased risk of CVD independent of established risk factors (Bu et al., 2020; Foti et al., 2020; Golaszewski et al., 2022; Hu et al., 2021; Vallée, 2023; Valtorta et al., 2018), with around 30% increase of risk (Bu et al., 2020; Christiansen et al., 2021) and, in terms of magnitude, was an even stronger predictor for CVD than lifestyle risk factors in patients with diabetes (Wang et al., 2023). In a UK Biobank study loneliness amplified the risk of an acute myocardial infarction, but was not related to a rise in mortality following such an event (Hakulinen et al., 2018).

One study pointing to a potential mechanism how loneliness could influence cardiovascular health was performed by Roddick and Chen (2021). Heart rate variability (HRV) was investigated in 316 healthy women with different levels of loneliness. Greater chronic loneliness could predict a reduced resting HRV and blunted HRV reactivity to a cognitive challenge as well as a stronger increase in HRV following an induction of state loneliness.

Mediators of loneliness and CVD

In a systematic review by the American Heart Association several mediators between loneliness, social isolation and cardiovascular and brain health have been identified, encompassing behavioral, psychological and physiological factors (Cené et al., 2022). Behavioral factors with a significant association with loneliness included smoking behaviors and reduced physical activity. The strongest psychological factor that showed a negative relationship with cardiovascular health is major depression (Cené et al., 2022). The association between loneliness and CVD might even be related to inflammatory processes, as a systematic review and meta-analysis showed a strong relationship to the inflammatory marker IL-6 (Smith et al., 2020). Reduced sleep and poor sleep quality might present additional physiological modulators of CVD.

3.2.2 Loneliness and cancer

In similar manner as in CVD, loneliness seems to be related cancer. A large meta-analysis has provided the strongest evidence so far that loneliness can negatively impact the health outcome in cancer patients. In their analysis, Wang et al. (2023) examined prospective data from 2,205,199 individuals including 476,404 patients with cancer and found loneliness not only increased all-cause mortality significantly, but also mortality in cancer patients. Furthermore, loneliness was associated with mortality, but also the incidence of cancer in a cohort of middle-aged Finnish men even after adjusting for lifestyle- and health-related covariates (Kraav et al., 2021). Though, there seem to be differential effects on different types of cancer. Similarly, the prevalence of loneliness in cancer patients varies between cancer types, age groups, cultures and circumstances ranging from 6 to 52% (Dahill et al., 2020; Howden et al., 2022; Pilleron et al., 2023; Smith et al., 2024).

The experience and effects of loneliness can prevail beyond the active phase of cancer. In their systematic review of qualitative studies investigating loneliness in cancer survivors, Raque-Bogdan et al. (2019) identified several social layers of loneliness: apart from the individual level, cancer survivors experiences loneliness from their social support system (e.g., in form of avoidance), the healthcare system (e.g. unmet needs after treatment), and society (e.g., stigma and pressure to experience growth after cancer). Such social constraints can negatively influence cancer-related symptoms and loneliness was found to mediate the effect of these constraints on symptoms such as pain interference, cognitive impairments and fatigue (Adams et al., 2018; Jaremka et al., 2014; Sleight et al., 2023).

Given the profound negative effects loneliness can have on the physical and mental health outcome in cancer survivors, there is a need for the development of interventions targeting loneliness as there are only limited interventions available so far (McElfresh et al., 2021).

3.2.3 Loneliness and dementia

In recent years, there has been growing evidence that loneliness has important implications in the development and course of dementia. Several studies determined an increased risk of developing dementia in individuals experiencing loneliness in long-term cohort studies (Freak-Poli et al., 2022; Kuiper et al., 2015; Lazzari & Rabottini, 2022; Peavy et al., 2022; Rafnsson et al., 2020; Salinas et al., 2022; Shibata et al., 2021; Sutin et al., 2020; Zhou, Wang, & Fang, 2018) although the results are mixed (Penninkilampi et al., 2018; Shen et al., 2022). The risk of developing dementia in lonely individuals was elevated by 50% - 60% (Sundström et al., 2020; Sutin et al., 2023). Furthermore, loneliness seems to strongly impact the quality of life in patients with dementia (Carbone et al., 2022).

Preclinically, greater loneliness was associated with lower global cognitive function and several facets of cognition (Harrington et al., 2023). Moreover, the rate of cognitive decline appeared to vary as a function of loneliness (Lara et al., 2019), pointing to loneliness as an important risk factor that should be scanned for in at-risk populations for dementia.

But loneliness does not only negatively affect patients with dementia, but seems to expand to caregivers of patients suffering from dementia (Hsu et al., 2023; Peavy et al., 2022), presenting an even more widespread problem in our modern societies.

3.2.4 Loneliness and type 2 diabetes

Evidence on the relationship between loneliness and diabetes is scarce, but there seems to be a growing research interest in the last couple of years. As of now, evidence points to an association between loneliness and diabetes (Christiansen et al., 2021; Foti et al., 2020; Henriksen et al., 2023; Kobos et al., 2021), also after controlling for demographic, psychological and behavioral factors. Corno and Burns (2022) even investigated the direction of the association between loneliness and functional limitations among patients diagnosed with diabetes type 2 from the U.S. Health and Retirement Study. Interestingly, the results suggest a bidirectionality with higher levels of loneliness being related to subsequently higher levels of functional limitations and vice versa. Thus, loneliness appears not only to increase the risk of developing type 2 diabetes, but also to aggravate the disease by secondary mechanisms (McCaffery et al., 2020).

3.2.5 Mediators of loneliness and physical health

Several factors have been identified as potential mediators of loneliness and physical health, encompassing physiological, behavioral, psychological, and social processes (F. Wang et al., 2023).

In a systematic review by the American Heart Association several mediators between loneliness, social isolation and cardiovascular and brain health have been identified, encompassing behavioral, psychological, and physiological factors (Cené et al., 2022). Similar factors have been identified for cancer (Wang et al., 2023) Behavioral factors with a significant association with loneliness included smoking behaviors and reduced physical activity, similarly for cancer (Smith et al., 2024). The strongest psychological factor that showed a negative relationship with cardiovascular health is major depression (Cené et al., 2022). The association between loneliness and CVD might even be related to inflammatory processes, as a systematic review and meta-analysis showed a strong relationship to the inflammatory marker IL-6 (Smith et al., 2020). Reduced sleep and poor sleep quality might present additional physiological modulators of physical health.

Physiological Factors

One major factor in contributing to the adverse health effects of loneliness is stress. Chronic stress from biological or psychological sources can affect various systems. Loneliness can activate the HPA axis and stimulate the release of cortisol and can start endocrinologic, immunologic and inflammatory, and metabolic cascades (Dai et al., 2020; Hawkley & Cacioppo, 2003; Smith et al., 2020; Smith et al., 2024; Wang et al., 2023) that disrupt homeostasis and interfere regenerative processes from a cellular to a behavioral level.

Interaction with mental health

Loneliness is strongly connected to mental health, as described in chapter 3.1. Moreover, mental health is often affected in severe physical illnesses like cancer. Depression and anxiety significantly increase the risk of developing cancer, cancer-specific mortality, as

well as all-cause mortality in cancer patients (Wang et al., 2020). Loneliness can further exacerbate this detrimental relationship.

Behavioral risk factors

Behavioral factors with a strong association with loneliness include smoking behaviors and reduced physical activity, reduced fruit and vegetable intake and other dietary choices, alcohol consumption, and adherence to medication plans (Cené et al., 2022; Malcolm et al., 2019; Smith et al., 2024; Steptoe et al., 2013). These health-adverse behaviors might promote and aggravate the existing physical problems. Additional mental health problems can further decrease the ability to carry out health-promoting behaviors.

Social isolation and level of care

Although the experience of loneliness is not necessarily preceded by social isolation or a small social network, social isolation can be one causal factor of loneliness. Being socially isolated can negatively impact the level of care. Having a large and strong social network on the other hand often leads to a better quality and greater quantity of care especially through informal care provided by close family and friends (Steptoe et al., 2013; Wang et al., 2023).

4. Integration of findings

In the following, the above-mentioned translational findings for loneliness from the social, neurobiological and clinical fields are summarized and integrated into a common framework. Interconnections between these domains are highlighted to discuss loneliness as a cause and consequence. Also, clinical implications of this basic science research for possible treatment options are suggested.

4.1 Mutual influences of social deficits, illness and OT on loneliness

The reported social skills deficits and negative social cognitions in lonely people complement existing models of loneliness showing an unbalanced OT system and an association with illness, both assumed to be linked to a lack of social interaction. There is consistent evidence that lonely people have deficits in their social behavior. In parallel, quality of their interactions and quantity of their relationships are reduced. This impairment in social behavior is both influenced by dysfunctional social cognitions, such as a negativity bias (Cacioppo & Hawkley, 2009; Cacioppo et al., 2016), as well as by neurobiological deviations of the OT system (Harvey et al., 2019; Jobst et al., 2016; Vitale & Smith, 2022). Results point to a bi-directional influence between these two. As described, the perception of social interactions in lonely people is negatively distorted and influences their expectations of social outcomes, hindering them to escape loneliness. Also, loneliness sustains social impairment, as being lonely deprives them of receiving positive social feedback to disprove their aversive social perceptions. The OT system, in turn, is modulated by social interaction (Cacioppo et al., 2015; Maier et al., 2020; Riem et al., 2020). A prolonged lack of social interaction (e.g., social touch) dysregulates the OT system and this negatively affects processes necessary for establishing relationships (e.g., social seeking, pair bonding, trust, emotional recognition),

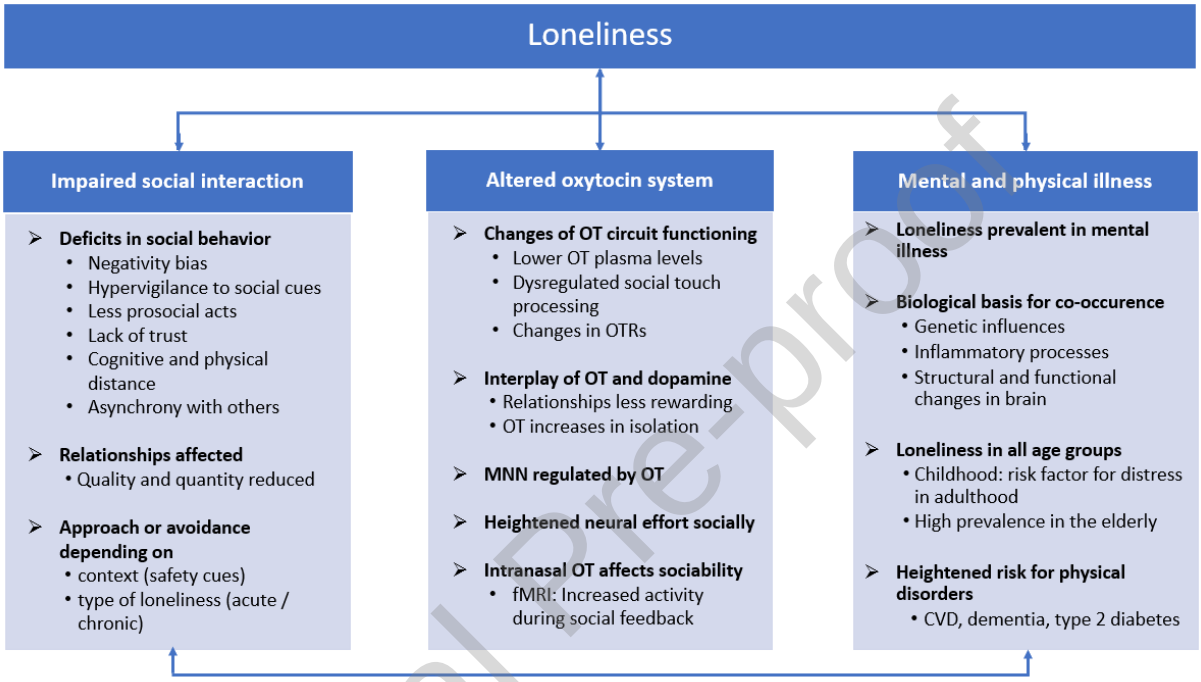
leading to loneliness as a consequence. A link of the OT system to social perception could be demonstrated by intranasal administration of OT, influencing social perception in a positive way, e.g. focusing on happy facial expressions over angry ones (Di Simplicio et al., 2009; Hurlemann et al., 2010). There is also evidence demonstrating that social touch triggers endogenous central OT release (Tang et al., 2020). The impaired reward system in lonely people, which is coordinated with the release of OT, can be positively influenced by such intervention.

Regarding the associations between loneliness, psychopathology and physical illness, many of the studies mentioned before have shown that loneliness has a detrimental effect on mental health across different age groups ranging from childhood to the elderly, either directly or possibly as a mediator (Fortuna et al., 2022; Hutten et al., 2021; Meltzer et al., 2013; Van As et al., 2021; Xerxa e al., 2023). Also, loneliness also appears to increase the risk of adverse physical health events such as cardiovascular diseases, dementia, stroke, and diabetes and additionally leads to reduced health maintaining behaviors such as physical activity, therapeutic adherence, and diet to restrict or counteract the fatal sequelae of these diseases (Roddick & Chen, 2021; Christiansen et al., 2021; Sutin et al. 2023). In the opposite direction, mental illness can lead to loneliness through social stigma, (self-) isolation or quite simply as a result of anxiety-induced avoidance behavior, evident in social withdrawal or altered perception of social cues (Cacioppo & Cacioppo, 2018; Cacioppo & Hawkley, 2009; Maier et al., 2020). Underlying neurobiological mechanisms can overlap between loneliness and psychopathology, suggesting shared biological pathways (Düzel et al., 2019; Kim et al., 2022; Marx et al., 2023; Matthews et al., 2016). Social impairment in psychopathology is well established, such as in major depression (Herrman et al., 2022). As stated above, behavioral changes in psychopathology of loneliness also have a neurobiological basis in the OT system. An impaired OT system can act both as a trigger or perpetual force in chronic loneliness in connection with psychiatric conditions. Also, the presence of these health conditions seems, in turn, to negatively affect the social well-being of the respective patients as well, therefore, initiating a downwards spiral of deteriorating health and reduced quality of life (Christiansen et al., 2021). Overall, rather than a causal or unidirectional relationship, the literature in this field indicates that there is a bidirectional relationship between loneliness on one hand and psychopathology and physical illness respectively on the other hand, i.e. that each factor can be both cause and effect, which can perpetuate a vicious circle. While loneliness shows substantial overlap with mental disorders and physical disease, it is not inevitably correlated to those and future research has to specify under which circumstances loneliness co-occurs with disease. The argument can be made that loneliness is a factor in most mental illnesses, which illustrates the necessity for psychiatry to focus on the social inclusion of the patients.

It can be argued that impaired social interaction, the OT system and illness are interconnected in lonely people and recognizing these links is central to understanding the complex construct of loneliness. **Figure 1** incorporates central results and the interplay between social impairment, an irregular OT system and psychopathology / physical illness in a common model for understanding loneliness. In contrast to previous models about loneliness, this one specifically points out the interplay between social interaction, the OT system and illness. It predicts that these areas are interconnected and in order to understand loneliness, it is necessary to consider them together. The model would be refuted if it can be shown that a long-term lack

of social interaction would not impact the OT system and health, which would contradict the consensus in research. Future studies should focus on the interconnections between these three central domains contributing to loneliness, specifying the conditions under which loneliness is cause or consequence.

Figure 1: Translational model for loneliness summarizing central findings on social interaction, OT and illness.



Legend:
OT: oxytocin; OTRs: oxytocin receptors; MNN: mirror neuron network; CVD: cardiovascular disease

The findings of human and animal studies complement each other in a translational way. The subjective perception of distress about isolation, which defines loneliness, can only be articulated in human studies, while understanding of the OT system is based to a significant part on animal studies. Biological intervention strategies are leaning on translation from animal models. Therefore, human and animal studies contribute different insights to the complex construct of loneliness. As mentioned, social impairment goes along with several biological correlates, such as attenuated brain activity to positive social stimuli (Lieberz et al., 2021), midbrain responses to social cues during hyper-sociality in acute loneliness (Tomova et al., 2020), reward-related brain activity to familiar persons compared to unfamiliar ones (Inagaki et al., 2016) and fMRI showing increased activity in certain regions during social feedback (Hu et al., 2015). However, major influence on social interaction and perception can be attributed to the OT system.

Furthermore, the distinction between acute and chronic loneliness is crucial, as social behaviors and the underlying neurobiological functioning can be quite opposite between these two. This type of loneliness influences social interaction behavior (hypo- or hyper-sociality), OT plasma levels (lower in chronic state) and extent of mental or physical disease. While many study results describe loneliness in general, a further distinction for type of loneliness seems adequate. A potential mechanism by which loneliness may result in negative health effects is

physiological reactivity to acute stress (Brown, Gallagher, & Creaven, 2017). As a biobehavioral response to stress in females, the "tend-and-befriend" response (involving nurturant activities and building of social networks) has been described and human as well as animal studies point to OT as at its core (Taylor et al., 2000).

An apparent contradiction in findings concerns the role of evolution in loneliness. According to evolutionary theory, loneliness can be viewed both as an outcome and as a predictor of health-related outcomes (Goossens et al., 2015). As stated above, current perspectives on loneliness emphasize its important role in evolution, acting as a warning signal that social connections are lacking and as motivation to seek social bonds (Cacioppo et al., 2014). On the other hand, chronic loneliness tends to be accompanied by deficits in social interaction that impede initiating and maintaining social connections. Also, as stated, loneliness is associated with an unbalance in the OT system and lonely people do not perceive social interaction as rewarding, which leads to reduced motivation to seek social connections and perceived relationship satisfaction. In sum, while they are positive qualities associated with loneliness, negative effects appear when loneliness is sustained over longer time. The same apparent contradiction can also be pointed out with regard to anxiety. While normal anxiety serves an evolutionary purpose to defend against threats, anxiety disorders can be seen as a dysregulation of normal defensive responses (Marks & Nesse, 2001). Future research should aim to specify why some persons are vulnerable to negative effects of loneliness, which counteracts the evolutionary purpose, e.g. by examination of a possible genetic predisposition.

4.2 Clinical implications of basic loneliness research

There are several implications for potential treatment options. In the following, psychotherapeutic, social and pharmacological interventions are discussed.

Regarding psychological interventions, as loneliness is an integral part in a multitude of mental disorders, it is recommended to incorporate loneliness into the treatment plan. There is evidence for psychotherapy to achieve a significant reduction in loneliness, tough one superior form of intervention could not be identified (Beckers et al., 2022). A meta-analysis examining 28 studies concluded that loneliness across the life span could be significantly reduced by psychological interventions. The same authors reviewed 31 studies, concluding that cognitive behavioral therapy was the most commonly applied intervention (Hickin et al., 2021). As loneliness is characterized by individual differences, personalized approaches to treatment are recommended. However, it is poorly documented how psychological interventions are tailored (Badock et al., 2023). The high co-occurrence between mental health problems and loneliness shows that psychotherapy is appropriate in case of comorbidity with a mental disorder, such as major depression. To address loneliness early would allow possible prevention of mental and physical disease.

In social regard, as chronic loneliness is characterized by negative social cognitions and deficits in social behavior, a psychoeducation to change cognitions and social skills training should improve social competency. Participation in supported socialization and community-based group activities may help affected persons to feel less lonely (Dingle et al., 2022; Mann et al., 2017). A review examining interventions targeting loneliness identified new technologies and community engagement as promising tools for treating social isolation and loneliness among older individuals (Poscia et al., 2017). Studies in animals and humans also show the

intrinsic need and benefit for social cooperation. As social interaction and social touch produce OT, which is crucial for the reward system, it is clinically promising to involve lonely persons in tasks of social cooperation and interaction.

Regarding pharmacological interventions, to stimulate the dopaminergic system (reward system), which shows strong interplay with OT, allows to mitigate adverse effects of loneliness. As a clinical implication, an unbalanced OT system and correlated negative emotions should be improved by social interactions. Neurobiologically, intranasal application of OT can induce positive emotions and have a positive effect on social perception (Hurlemann et al., 2010), showing the clinical application potential of OT as an intervention to address loneliness, e.g. to counteract the negativity bias prominent in lonely people. Intransal OT could even improve social functioning in people with autism spectrum disorders (Huang er al., 2021). Likewise, as there is an interplay between OT and dopamine (Borland et al., 2018; Vitale & Smith, 2022), medications targeting the dopamine system could be promising, especially in connection with mental disorders. However, more research regarding the effect of intranasal OT application on loneliness is needed, as a positive effect of OT cannot always be replicated. Berger et al. (2023) could not find a significant effect of intranasal OT application on trait-like loneliness and perceived stress in contrast to a psychological intervention, tough there was a significant effect on state loneliness within sessions and bonding between group members. Future studies have to specify the exact conditions under which intranasal OT application can have an effect on loneliness.

Practically, addressing loneliness (particular in the elderly) has been suggested as a key preventive intervention for major depression (Herrman et al., 2022). In recent years, there has been a push in clinical practice towards recognizing loneliness as a social issue in its own right, but also as an important aspect of treatment that needs to be considered when conceptualizing treatment plans, but that trend is still in its early stages. Loneliness considerably increases the risk for psychiatric morbidity, therefore early detection and intervention are crucial. More work is needed both in research into the underlying mechanisms of loneliness as well as into how to treat it effectively, both on its own and as part of clinical psychiatric care.

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Highlights

- Lonely people show social impairment in cognitions (e.g., negativity bias, hypervigilance to social cues) and behavior (e.g., avoidance)
- A dysregulated oxytocin system in lonely people, which affects their social functioning, serves as a neurobiological mechanism of loneliness
- Loneliness considerably increases the probability for psychiatric and physical morbidity and vice versa
- Loneliness can be both a cause and consequence of these three interconnected domains (social impairment, dysregulated oxytocin system and illness)
- This review incorporates neurobiological, psychological and behavioral results into a new translational model for loneliness explaining mutual influences