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Review article

Brain-body interactions underlying the association of loneliness with mental and physical health

Lisa Quadt[a,b,c,1,*], Giulia Esposito[a,d,1,*], Hugo D. Critchley[a,b,c], Sarah N. Garfinkel[a,b,c]

[a] Department of Neuroscience, Brighton and Sussex Medical School (BSMS), University of Sussex, Falmer, BN1 9RY, UK
[b] Sackler Centre for Consciousness Science, University of Sussex, Falmer, BN1 9RR, UK
[c] Sussex Partnership NHS Foundation Trust, Brighton, BN2 3EW, UK
[d] Department of Psychology, Royal Holloway University of London, Egham, TW20 0EX

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ABSTRACT

Loneliness can be operationalized as the actual or perceived absence of those social relationships that serve to meet basic emotional needs. In contrast to solitude, a chosen state of being without company, loneliness is associated with negative affect and emotional distress. Loneliness can have detrimental effects on mental and physical wellbeing, expressed as an increased risk of morbidity and mortality. Higher rates of loneliness are observed in patients suffering from chronic health conditions, mental health conditions, cardiovascular problems, and neurodivergent populations, including autistic individuals. While the link between poor health and loneliness is established, the identification of relevant underlying mechanisms is a difficult endeavor. In this narrative review, we provide an overview of published research and related literature describing the manifold interactions between loneliness, affective symptomatology, neural and embodied processing relevant to physical health, mental health, and neurodiversity. We propose a framework that can inform the identification of psychophysiological mechanisms underlying the link between loneliness and affective symptomatology that may represent interventional targets to mitigate the associated cycle of biopsychosocial morbidity.

1. Introduction

In recent years, research on loneliness has attracted growing attention, not least by the demonstration that lonely individuals are at higher risk for mental and physical health conditions carrying high societal costs. These include depression (Cacioppo et al., 2010; Domènech-Abella et al., 2019; Santini et al., 2015), anxiety (Anderson and Harvey, 1988), psychotic disorders (Lim et al., 2018; Michael and Park, 2016), cardiovascular conditions (Winterton and Quintana, 2019), chronic health conditions (Barlow et al., 2015), and immunological/inflammatory changes (Moieni et al., 2015a). Additionally, neurodivergent individuals with conditions including autism are now recognized as having greater vulnerability to the distress evoked by social isolation and to negative physical consequences associated with loneliness (Ee et al., 2019; Stickley et al., 2017).

In sum, increased self-report of loneliness is associated with higher morbidity and mortality. Such links have been investigated in recent meta-analyses. It was reported that the negative impact of loneliness on mortality was consistent across 35 articles included in a systematic review, and this relationship was found across gender and age groups (Rico-Uribe et al., 2018). The relationship between loneliness and depression has also been the object of investigation in a recent meta-analysis, in which loneliness was shown to consistently have moderate effects on depressive symptoms across studies regardless of sampling strategies, publication type and publication year (Erzen and Çikrikci, 2018). Thus, with the growing amount of research and interest in identifying possible mechanisms by which loneliness impacts on health, the present work sets out to provide a broader view of the literature on the effects of loneliness on both physical and mental health.

In this narrative review, we provide an overview of the current literature on the multi-directional interactions between loneliness, loneliness distress, affective symptomatology, emotional processing and interoceptive control. We highlight interoception as the sensory interface between the dynamic regulation of the internal physiological state of the body and the neurocognitive (mental) processes that support motivational behaviors, affective and emotional feelings, and even an integrated sense of selfhood: Interoception is an umbrella term encompassing body-to-brain communication through distinct neural and

* Corresponding authors at: Trafford Centre, University of Sussex, BN1 9RY, Brighton, UK.
E-mail addresses: L.Quadt@sussex.ac.uk (L. Quadt), Giulia.Esposito@rhul.ac.uk (G. Esposito).
[1] Lisa Quadt and Giulia Esposito contributed equally to writing this paper

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Table 1
Short glossary of the most common terms and measurement instruments.

Term	Meaning	Instrument	Direct/Indirect
Loneliness	The perceived state of having few meaningful social relationships	UCLA Loneliness Scale	Indirect
		Social Functioning Questionnaire	Direct
		de Jong Gierveld Loneliness Scale	Indirect
Loneliness Distress	The upset caused by the perceived absence of intimate social relations	–	–
Social Isolation	A low number of meaningful social contacts	UCLA Loneliness Scale	Indirect
		Social Functioning Questionnaire	Direct
		de Jong Gierveld Loneliness Scale	Indirect
Solitude	The chosen state of being alone	–	–

humoral channels, the neural representation and integration of this afferent information, the impact of these representations on perceptive, cognitive and behavioral processes, and the psychological expression of these bodily representations as conscious sensations, emotional feelings and affective states (Craig, 2003; Critchley, 2004; Quadt et al., 2018). Importantly, interoception is intrinsically linked with affective states, to the extent that some theories posit a direct relationship between bodily and emotional changes (James, 1884; Schachter and Singer, 1962). Correspondingly, bodily and emotional processes share neural architecture (Zaki et al., 2012), with the insular cortex as a hub for interoceptive mechanisms and conscious affect (Critchley et al., 2004).

After reviewing evidence from psychophysiology, self-report and neuroimaging research on the impact of loneliness on mental and physical health, we formulate a model of loneliness, loneliness distress, and affective symptomatology based upon aberrant predictive interoceptive processing. Matthews and Tye (2019) put forward the hypothesis that there are coordinated adaptations across discrete neural circuits that function to maintain "social homeostasis". We aim to pick up this hypothesis and extend the concept to a proposed model of social allostasis. This model addresses how the predictive engagement of neural circuits, interoceptive pathways, and autonomic mechanisms interact to navigate the complex social environment.

1.1. Terminology and methodology

The term 'loneliness' can be quite elusive, with different explicit and implicit definitions used in everyday language, and also in academic research on the effects of loneliness. For this reason, it makes sense to delineate the most important terms and outline how we will use them in this review.

One commonly used definition describes loneliness as the actual or perceived absence of meaningful social relationships in an individual's life (Cacioppo et al., 2010; Petitte et al., 2015; Weiss, 1973). Therein, however, lies the crux, as the quantity of social contacts does not necessarily define the quality of social relationships. Efforts are therefore often made to keep these apart conceptually, for example by distinguishing emotional loneliness (the perceived lack of meaningful attachment) from social loneliness (the lack of membership to a group, Weiss, 1973), or social isolation (a low number of social contacts). In this manner, the philosopher Paul Tillich wrote: "Loneliness expresses the pain of being alone. Solitude expresses the glory of being alone" (Tillich, 1959). Although there is a common understanding that loneliness reflects psychological distress, scientific investigations into loneliness tend not to incorporate measures of both emotional loneliness and social loneliness/isolation. This conceptual distinction between quality and quantity of social relationships is not explicitly represented in most scientific measures of loneliness.

The most commonly used instrument to measure loneliness is the UCLA Loneliness Scale (Russell, 1996). The 20 items of the scale indeed focus on the subjective perception of loneliness (e.g., "How often do you feel that there are people you can turn to?", "How often do you feel that your relationships with others are not meaningful?"). Many studies use a shorter version of the UCLA Loneliness Scale, an 8-item questionnaire (ULS-8, Hays and DiMatteo, 1987), or the Social Function Questionnaire (SFQ, Tyrer et al., 2005). In the latter, out of the eight questions, only one directly asks about loneliness ("I feel lonely and isolated from other people"), some questions only indirectly touch upon social connections (e.g., "I get on well with my family and other relatives"), and others not at all (e.g., "I enjoy my spare time"). However, in all questionnaires, the vast majority of questions do not make clear the distinction between chosen solitude and involuntary distress at being lonely. Therefore, while the UCLA Loneliness scales and SFQ remain the most widely used self-report measures (for which there is general agreement that they measure loneliness in terms of being upset about being alone), neither explicitly asks whether perceived instances of social isolation actually cause distress.

To reflect these important distinctions, we will use the term 'social isolation' to reflect a low number of social relationships (Weiss, 1973) 'solitude' to reflect the chosen state of being alone (Tillich, 1959), 'loneliness' as the perceived state of having few meaningful social relationships (Cacioppo et al., 2010), and 'loneliness distress' as the upset caused by the perceived absence of intimate social relations (Quadt et al., 2019b)(see Table 1).

1.2. The neuroscience of loneliness

Neuroscientific approaches to the investigation of loneliness and its representation or impact within the human brain have grown over the past decade. Despite increasing knowledge of the neural correlates that underpin social perception and cognition (Adolphs, 2009; Lieberman, 2013), the neurobiological basis and consequences of loneliness are much less well understood. Approaches to investigate the neural correlates of loneliness in humans include task-based and resting-state functional neuroimaging as well as structural neuroimaging, although the evidence for connectivity, functional, and structural changes in lonely individuals is sparse and often discrepant, possibly due to different sampling strategies, both in terms of the number of participants and different age groups tested (Duzel et al., 2019). In addition, animal models offer valid platforms to explore the cellular and molecular mechanisms through which loneliness can impact brain structure and function.

Task-related brain imaging, now mostly using functional magnetic resonance imaging (fMRI), is a widely adopted strategy to define proximate mechanisms underlying individual differences in affective reactivity. Here, with appropriate experimental design, inferences concerning loneliness can be made from patterns of neural response to social and non-social stimuli across lonely and non-lonely individuals. At the cortical level, evidence suggests involvement of visual, attentional, and emotion-related neural systems (Cacioppo and Ortigue, 2011). However, there are conflicting findings regarding regional neural responses to social stimuli in lonely and non-lonely individuals that make it challenging to draw definitive conclusions about the differential contributions of specific brain areas. For instance, one study reported an attenuation of activation within the ventral striatum in lonely versus non-lonely individuals during the processing of pleasant social stimuli, suggesting reduced representation (and feelings) of

reward in response to positive social images (Cacioppo et al., 2009). However, another study later reported an amplification of ventral striatal activation to the same stimuli in lonely individuals, compatible with a form of 'social craving' (Inagaki et al., 2016). More recently, a functional imaging study of younger and older adults reported no association between loneliness and ventral striatal activation in response to pleasant social images of strangers or depictions of loneliness (D'Agostino et al., 2019). Such contradictions extend to related areas of social neuroscience, for example, increased amygdala activation was previously observed to track larger social network size in young adults (Von Der Heide et al., 2014), yet this finding was not replicated in a more recent fMRI investigation (D'Agostino et al., 2019).

Task-related fMRI investigations of loneliness are potentially problematic because, rather than directly addressing trait loneliness, they emphasize the measurement of neural responses to different stimuli in the moment, and therefore concern state, rather than trait, loneliness (Yi et al., 2018). Other approaches are arguably more appropriate: For example, resting state fMRI measures the strength and coordinated pattern of communication between centers across the brain from dynamic fluctuations in indices of 'spontaneous' neural activity (Biswal et al., 1995). Such measures are well suited to tracking individual differences in cortical processing and may thus provide a better measure of functional brain architecture associated with trait loneliness (Yi et al., 2018). Using Granger Causality, higher loneliness scores have been associated with relatively weaker influence of the 'dorsal attention network' (which includes the superior and inferior frontal gyrus, superior and inferior parietal gyrus, middle occipital gyrus, postcentral gyrus, and supramarginal gyrus) on activation within the 'ventral attention network' (which includes the supramarginal, superior, middle and inferior temporal gyrus, and inferior frontal gyrus, Vossel et al., 2012). Similar claims are made for a decrease in causal influence from a predominantly subcortical 'affective' network (including putamen, amygdala, caudate, and pallidum; Price, 2003) to the visual cortical network (that includes extrastriatal regions in middle occipital gyrus, calcarine fissure, fusiform gyrus; Greicius et al., 2007; Tian et al., 2017). These findings can be interpreted in light of previous studies that indicate, in lonely individuals, weaker reactivity to positive social pictures within the affective network and increased reactivity to negative pictures within the visual network when compared to non-lonely individuals (Cacioppo et al., 2009), indicating that impaired processing of social cues in lonely individuals may render them more attentive to negative as opposed to positive social stimuli (Tian et al., 2017).

In addition to functional neuroimaging studies, loneliness has been associated with more specific correlates in measures of brain structure. For example, one voxel-based morphometry study in young adults reported lower gray matter (GM) volume in the region of the posterior superior temporal sulcus (pSTS) of lonely as opposed to non-lonely participants (Kanai et al., 2012). The pSTS is implicated in the early stages of social perception (Allison et al., 2000), hence the observed lower pSTS GM volume was also observed to predict poorer performance on a social perception task. Nevertheless, loneliness did not predict social perception ability. One interpretation is that, rather than mediating the feeling of loneliness *per se*, abnormalities within the pSTS impact basic social perception skills, which may then contribute to the feeling of loneliness. Moreover, the directionality of these relationships remains to be determined, since it is unclear whether loneliness determines GM volume reductions in the pSTS, or whether lower pSTS volume leads to impaired social skills and, consequentially, to loneliness (Kanai et al., 2012). Moreover, as the authors point out in their discussion, it is likely that structural changes in additional regions are also associated with higher levels of loneliness, and that some associations may have failed to be identified due to the small sample size employed. Accordingly, a later study with a much larger sample size (766 young adults) has in fact reported white matter density reductions in regions besides the pSTS, including the bilateral inferior parietal lobule (IPL), right anterior insula (AI), posterior temporoparietal junction (pTPJ), dorsomedial prefrontal cortex (dmPFC) and rostrolateral prefrontal cortex (RLPFC) (Nakagawa et al., 2015). On the other hand, a more recent investigation of the structural correlates of loneliness in older adults (N = 319) did not report any changes in volume within the pSTS (Duzel et al., 2019). Voxel-based morphology revealed decreased GM volume associated with increasing ratings of loneliness within amygdalo-hippocampal complex (left anterior amygdala, hippocampus, left parahippocampal cortex, left posterior parahippocampal gyrus) and left cerebellum. When including age as a covariate, the analysis revealed that, while older participants reporting higher loneliness displayed reduced GM volumes in the dlPFC, amygdala, hippocampus, and ACC, younger participants displayed higher volumes in these regions, suggesting that loneliness exerts stronger negative effects on brain structure with advanced age (Duzel et al., 2019). Thus, it is possible that, in association with high levels of loneliness, age-related changes in brain structure may account for the different findings observed in studies employing younger and older adults, and further longitudinal investigations will be necessary to provide a clear picture of the long-term effects of loneliness on brain structure in otherwise healthy individuals. While these changes were associated with loneliness, they did not predict objective social network size. Region of interest (ROI)-based analysis, based on data from previous functional neuroimaging studies of loneliness, on the other hand, revealed negative associations between loneliness and GM volume within the dlPFC, hippocampus, insula, and anterior cingulate cortex (Duzel et al., 2019), key regions implicated in both emotion regulation and self-reflective processes (Johnson et al., 2006).

Human behavioral and neuroimaging approaches, which can provide a direct indication of structural and functional correlates of loneliness, can be complemented by insights from animal studies investigating the neurobiological implications of social deprivation at the level of cellular/molecular mechanisms. However, loneliness is different from social isolation. While animal studies can model the effects of social isolation, e.g. by changing the housing conditions of animals and separating them from cage mates, the subjective experience of self-reported loneliness and loneliness distress cannot be studied in animals. Nevertheless, both loneliness and loneliness distress are likely not unique to humans, rather they may represent a trans-species discrepancy between the desired and actual social relations that can also affect other animals (Cacioppo et al., 2015). While preclinical studies of the effects of social isolation are abundant and often report altered dopamine signaling (Fabricius et al., 2010; Hall et al., 1998; Yorgason et al., 2016), the neurobiological consequences of loneliness in animal models remains underexplored, likely due to the challenges associated with recapitulating such subjective feelings in animals. Preliminary findings, however, point to a role of dopaminergic neurons within the dorsal raphe nucleus (DRN) in the expression of loneliness (Matthews et al., 2016). Using in vivo calcium imaging to measure responses of DRN dopamine neurons in mice, neuronal activity was observed to increase during social contact following previous social isolation. Furthermore, photoactivation of DRN dopaminergic neurons favoured social preference in group-caged rodents, while activating these neurons in the absence of a social target was aversive, and photoinhibition prevented the social-seeking behaviours that were typically observed following isolation. These findings suggest that these neurons may detect and/or resolve disparity between the desired and actual social environment of the animal, and that their activation may represent a loneliness-like state, where a negative affective state drives increased seeking of social contact (Matthews et al., 2016). More recently, however, increased firing of DRN dopaminergic neurons was observed not only in single-housed male mice upon first encounters with female intruders, but also in response to non-social salient stimuli, suggesting that the activity of at least some sub-populations of DRN dopaminergic neurons may not be specific to social engagement (Cho et al., 2017), thus calling for further investigations into their specific contribution to the feeling of loneliness in animal models.

1.3. Demographic overview

The experience of feeling lonely can affect individuals of all age groups, although much research on loneliness focuses on its expression within elderly populations (Matthews et al., 2019). However, some age groups seem to be more strongly affected than others. Loneliness appears to be particularly prevalent among younger and older, relative to middle-aged adults (Lauder et al., 2004; Richard et al., 2017). Recently, survey data from the Environmental Risk Longitudinal Twin Study in the UK, in which loneliness was measured at age 18 in 2232 individuals, showed that about 30 % of young people report feeling lonely at least sometimes, with a small percentage (5–7 %) reporting feelings of loneliness with much higher frequency (Matthews et al., 2019).

The same study found that individuals with higher loneliness scores were also more likely to have a diagnosis of conditions such as ADHD, anxiety, and depression, and carry a higher risk for substance (alcohol and cannabis) misuse and self-harm (Matthews et al., 2019). A large-scale survey with over twenty thousand US-American individuals aged 18 or older also reported a large prevalence of loneliness among younger individuals. Overall, younger individuals reported higher loneliness scores when compared with individuals over the age of 65 (Bruce et al., 2019). Moreover, even though young adults report larger social network size compared to late middle-aged adults, they report feeling lonely and isolated for twice as many days (Child and Lawton, 2019). Despite the evidence on the relative prevalence of loneliness across different age groups, large-scale longitudinal studies to address the question of how chronic loneliness affects quality of life throughout the lifespan are lacking. Furthermore, additional factors may contribute to a higher incidence of loneliness in different populations, such as lower socioeconomic status or living without a partner (Bruce et al., 2019).

As discussed in the next sections, loneliness also appears to be more prevalent in individuals suffering from chronic physical conditions, neurological disorders, hearing and vision impairments, as well as mental health conditions, including depression, anxiety, and psychosis. This speaks for a need to determine how loneliness relates to such conditions, and the extent to which it is implicated in the neural and physiological mechanisms that underlie them.

2. Loneliness and mental health conditions

To limit the scope of this narrative review, we have chosen to focus on four mental health conditions for which substantial evidence is available: depression, anxiety, psychotic disorders, and suicidality. This is not to say, however, that there are not relevant associations between loneliness and other mental health conditions. A novel approach in psychiatry defines psychological and psychiatric conditions as inherently social, which suggests that loneliness and loneliness distress may play a vital role in all mental health conditions (Schilbach, 2016). Others have provided evidence for an association between loneliness and addiction (Åkerlind and Hörnquist, 1992), eating disorders (Levine, 2012), disordered sleep (Simon and Walker, 2018), and Borderline/Emotionally Unstable Personality Disorder (Liebke et al., 2017).

2.1. Depression

Depressive episodes are marked by persistent affective and cognitive symptoms, including low mood, irritability, restlessness, pervasive negative rumination, and intense feelings of hopelessness (ICD-10, 2016). Somatic symptoms like psychomotor slowing, a leaden feeling in the extremities, and aches and pains also occur frequently in depressed patients and are independent of cultural context (Kirmayer, 2001; Tylee and Gandhi, 2005). Behavioral changes often accompany depressive episodes. Most notably, patients show so-called sickness behaviors that include fatigue, reduced food and fluid intake, anhedonia, and social withdrawal (Dantzer et al., 2008). Sickness behaviors are a stereotyped behavioral pattern that may have evolved as a defensive response to infectious threats to the organism, reducing bodily strain (e.g., fatigue), and risk of infection through social isolation (Miller, 1964). Combined with research indicating heightened levels of inflammation in depressed individuals (Dantzer et al., 2008; Harrison et al., 2009b), sickness behaviors in depression may be part of an initially adaptive response that becomes maladaptive when regulatory mechanisms fail to revert the organism back to equilibrium (Quadt et al., 2018). Social isolation might therefore be part of an autonomic reaction at the onset of depression, fostering feelings of loneliness that frequently co-occur with other depressive symptoms. However, it is widely acknowledged that loneliness and depression often go hand in hand, yet the exact temporal and causal relationship between the two states remains elusive.

The co-occurrence of depression and loneliness is common, to the extent that some diagnostic tools include feelings of loneliness as a defining characteristic of a depressive episode (e.g., Centre for Epidemiologic Studies Depression Scale [CES-D], Radloff, 1977). Despite this regular comorbidity, studies show that depression and loneliness are statistically separable (Cacioppo et al., 2006a, b) and functionally distinct (Adam et al., 2006; Hawkley et al., 2006). Depression can be conceptually separated from loneliness, in that depression concerns general feelings, while loneliness expresses how people feel specifically about their social connections (Weiss, 1973).

Several longitudinal studies now demonstrate that increased scores on self-report measures of loneliness predict both the onset of, and symptomatic changes during, depressive episodes (Cacioppo et al., 2006a, 2010; Cacioppo et al., 2006b; Jaremka et al., 2014). Importantly, loneliness is found to put people at much higher risk of depression than social isolation (Cornwell and Waite, 2009; VanderWeele et al., 2011), indicating that the subjective perception and evaluation of social relationships plays an important role in offsetting depressive episodes. In a longitudinal study (van Winkel et al., 2017) applying the Experience Sampling Method (ESM, Myin-Germeys et al., 2009) to track depression, it was found that social company was judged more negatively after feeling lonely, and this predicted the frequency with which company was subsequently avoided. Additionally, trait loneliness predicted the transition into a depressive episode even after controlling for sub-clinical depression at baseline. These results suggest that the negative appraisal of social relationships and the subsequent withdrawal from social contact may play a role in the onset of depression (van Winkel et al., 2017).

Structural and functional neuroimaging studies have enhanced our understanding of neural mechanisms underpinning depressive symptoms. Prefrontal regions, most notably the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), and anterior cingulate cortex (aCC), interact with subcortical centers associated with the processing and representation of reward, notably the nucleus accumbens in the ventral striatum, and with regions implicated in motivational learning, notably the amygdalo-hippocampal complex (Rive et al., 2013). Genome-wide association studies have identified a set of genes associated with a decrease in calbindin-positive interneurons in depressed patients (Kim and Webster, 2010). Similar gene expression patterns within the dlPFC are reported in association with levels of loneliness 5 years ante-mortem, suggesting molecular mechanisms by which loneliness contributes to neurobiological changes in brain areas associated with depression (Canli et al., 2018).

However, little is known regarding how the brain changes specifically in relation to interactions between loneliness and depression. To date, few studies have directly investigated such changes, and most primarily focus on elderly populations with late-life depression. Older individuals with recurrent late-life depressive episodes are observed to report higher levels of loneliness (even compared to those with single depressive episodes). This was also reflected in structural differences within left striatal areas (putamen, caudate, and pallidum, Sin et al., 2018). In fact, GM volume positively correlated with loneliness in the single episode subgroup, and negatively in the multiple episode

subgroup, suggesting that loneliness interacts with depressive symptoms to compromise further the structural integrity of striatal reward-related circuitry (Sin et al., 2018). A recent study investigating both functional and structural changes in relation to loneliness in individuals with late-life depression, on the other hand, revealed no significant structural connectivity differences in depressed versus control participants. However, functional connectivity within areas of the default mode network (DMN, middle frontal gyrus, posterior cingulate, middle and inferior temporal gyrus) and the cortico-striatal network (including lateral orbitofrontal and thalamus) positively correlated with loneliness scores in depressed participants (but negatively in healthy controls) when processing negative affective stimuli (Wong et al., 2016). These findings remain consistent with reports of impaired down-regulation of the DMN in depressed patients when viewing negative stimuli (Sheline et al., 2009), and with impairment of cortico-striatal connectivity and reward processing in depression (Heller et al., 2009). Additional research is needed to establish whether and how loneliness determines and/or exacerbates structural and functional changes associated with depression.

From a clinical perspective, it is important to consider research that shows the effectiveness of treating loneliness in the context of depression. Social isolation reduces responsiveness to standard treatment of depression (Trivedi et al., 2005), making the alleviation of isolation a promising target of interventions. Indeed, two recent longitudinal intervention studies confirm that facilitating meaningful social interaction effectively prevents and reduces depressive symptoms and relapse rates (Cruwys et al., 2013, 2014). Although joining more social groups led to larger improvements in depressive symptomatology, identification with a social group and a feeling of belonging crucially best predicted positive outcomes. However, for those participants with an existing history of depressive disorders, being a member of a larger number of social groups proved to be a more powerful predictor of remission than for those without a history of depression (Cruwys et al., 2013). In summary, although subjective feelings of loneliness are more predictive of the occurrence of depression than the objective number of social connections, increased exposure to meaningful social contacts may help to prevent and treat depressive symptomatology through regulating and hindering negative biases that maintain negative affect and cognitions.

2.2. Anxiety disorders

Social withdrawal and peer rejection increase feelings of loneliness in childhood (Boivin et al., 1995), and loneliness occurring as a result of peer rejection in pre-kindergarten children is associated with higher anxious/depressed symptoms during adolescence, suggesting a mediating effect of loneliness in the relationship between social rejection early in life and subsequent development of mental disorders (Fontaine et al., 2009). Loneliness is a recognized risk factor in the development and maintenance of social anxiety. In particular, the relationship between peer acceptance and social inclusion, loneliness and social anxiety has been investigated in children and adolescents, with a recent meta-analysis revealing positive longitudinal associations between loneliness and social anxiety (Maes et al., 2019). One fMRI investigation (Jarcho et al., 2019) employed a 'virtual school paradigm', where participants learn associations between social evaluations and virtual peers providing the evaluation. Virtual peers classified as 'mean' always provide negative social evaluations; peers classified as 'nice' always provide positive social evaluations; and 'unpredictable' virtual peers provide positive and negative evaluations 50 % of the time, respectively (Jarcho et al., 2019). Children experiencing high levels of peer victimization report more loneliness and social dissatisfaction. High victimization also correlates with increased right amygdala reactivity to positive evaluations, suggesting a possible link between social distress, loneliness, and social anxiety symptoms prompted by heightened amygdala responses to social stimuli (Jarcho et al., 2019).

Links between loneliness and social anxiety have also been reported in other age groups. A recent longitudinal study with over 1000 participants aged 18–87 measured loneliness over a period of six months and revealed that early state loneliness predicted later state social anxiety, as well as paranoia and depression (Lim et al., 2016). The relationship between social anxiety and loneliness appears to be bi-directional, such that earlier state social anxiety also predicts later state loneliness (Lim et al., 2016). A high-performance electroencephalographic (EEG) study, which included participants aged 18–44, reported differences in event-related potentials between lonely and non-lonely participants. Although the study did not report significant differences in self-reported social anxiety between lonely and non-lonely individuals, possibly because this only included healthy university students, the neuroimaging results provide interesting insights into brain mechanisms underlying processing of social stimuli in lonely vs. non-lonely individuals (Cacioppo et al., 2016). According to an evolutionary theory of loneliness, lonely individuals display heightened attention for social threat during the *early* stages of processing of social stimuli (Cacioppo et al., 2015). Results from this EEG investigation provide supporting evidence to the following claims: in contrast to non-lonely participants, who displayed common brain microstates early (60 − 248 ms) during processing of social and non-social threat, lonely individuals displayed differences in processing of social and non-social threat stimuli in the first 116 ms of information processing. In addition, social threat elicited differential activation of regions associated with attention, self-representation, and threat perception, including the inferior and superior temporal gyrus, dlPFC, parahippocampus, supramarginal gyrus, and possibly amygdala and insula (Cacioppo et al., 2016).

Despite the compelling evidence linking loneliness to social anxiety across various age groups, research on the relationship between loneliness and other forms of anxiety remains scarce. While theoretical approaches suggest that loneliness leads to a generalized hypervigilant state, with consequences that affect physical as well as mental health (Hawkley and Cacioppo, 2010), more studies are needed to establish clear links to anxiety. Longitudinal investigations including both behavioral and structural/functional neuroimaging approaches will be necessary to determine how loneliness affects the brain, and the extent to which these changes are associated with an increased risk of anxiety disorders.

2.3. Psychotic disorders

Psychosis represents a symptom of several psychiatric, neurodevelopmental and neurologic conditions, being the defining feature of schizophrenia spectrum disorders (Ffytche et al., 2017; Heckers et al., 2013; Holtzman et al., 2013). Psychotic symptoms negatively impact an individual's ability to seek social interactions and to maintain close relationships, with both positive (e.g. hallucinations) and negative (e.g. anhedonia) symptoms reported to negatively influence social activities (Rabinowitz et al., 2013). While the effect of loneliness on depressive and anxiety symptomatology is now widely recognized (Cacioppo et al., 2010), the relationship between loneliness and psychotic disorders remains largely underexplored (Badcock et al., 2015).

The 'social defeat hypothesis' attempts to identify social isolation and loneliness as risk factors for developing psychosis (Selten and Cantor-Graae, 2005), drawing from evidence revealing that migrants (both first and second generation) are more at risk of developing schizophrenia. This trend is reported to be largely independent from the country of origin, thus suggesting causes that go beyond genetic or biological factors (Cantor-Graae and Selten, 2005). However, while the theory addresses possible links between social adversity, social isolation and psychosis, it does not account for the experience of subjective loneliness, as an individual who faces social adversity or isolation does not necessarily experience loneliness (Lim et al., 2018).

Given the high percentage of individuals suffering from psychotic disorders reporting feeling lonely, with loneliness affecting over 80 %

of individuals with psychosis (Stain et al., 2012), identifying potential mechanisms by which loneliness affects the onset and worsening of psychotic symptoms is of crucial importance. Insights come from an investigation in which loneliness predicted symptoms of subjective thought disorder and loss of pleasure (anhedonia) in individuals with a diagnosis of a psychotic disorder (including schizophrenia, schizoaffective disorder, depressive psychosis, and bipolar disorder with psychotic features), and poorer cognitive functions, indexed by lower digit symbol coding scores in individuals who reported feeling more lonely (Badcock et al., 2015). There are associations between anhedonia and impairments of processes such as reward evaluation, decision-making, anticipation and motivation, with severity of anhedonia negatively correlating with activity in frontal-executive areas including the orbitofrontal cortex, ventromedial and dorsolateral PFC in schizophrenic patients (Harvey et al., 2010; Park et al., 2009). It is thus possible that loneliness may contribute to the further worsening of cognitive functions and contribute to maintaining subjective thought disorder and anhedonia in individuals with different forms of psychosis (Badcock et al., 2015). However, since this study only assessed loneliness by means of a single question asking participants whether, in the past 12 months, they had felt lonely (and to rate their answer on a 4-point scale, rather than employing a more psychometrically valid scale), it is difficult to generalize its findings to other studies in the literature.

Another theoretical approach to the relationship between social isolation and symptoms of psychosis is the 'social deafferentation hypothesis' of schizophrenia (Hoffman, 2007). According to this hypothesis, plastic re-organization of cortical areas involved in social cognition takes place following experiences of social withdrawal, thus yielding hallucinations and delusions with social content that carry emotional value, resembling phenomena like visual hallucinations following loss of vision, or phantom limbs following amputations (Hoffman, 2007). Understanding one's body and its boundaries is crucial for the ability to distinguish self from others, and is therefore essential for adaptive social functioning (Park and Nasrallah, 2014; Petkova et al., 2011). Interestingly, loneliness has been associated with a greater incidence of hallucinations in individuals with Alzheimer's disease (AD) and healthy elderly controls (El Haj et al., 2016), possibly indicating that loneliness may determine the onset of psychotic symptoms even in the absence of an underlying neurological or psychiatric condition. Self-disturbances and anomalous bodily experiences often accompany schizophrenia, and susceptibility to induced proprioceptive illusions, including the Pinocchio Illusion (Lackner, 1988), in which the experience that one's nose is growing is generated, is reported to be higher in individuals with schizophrenia. These findings extend the social deafferentation hypothesis to tactile sensations and suggest that social isolation also contributes to aberrant sensations across exteroceptive and proprioceptive dimensions (Michael and Park, 2016).

A general limitation arising from the current literature on the relationship between loneliness and psychotic disorders appears to be the lack of longitudinal investigations assessing how loneliness may impact the development of a psychotic disorder in individuals with or without additional risk factors, such as genetic vulnerability. While a picture is emerging regarding how loneliness poses an additional burden on the quality of life of individuals with psychosis (Switaj et al., 2018), the mechanisms by which it contributes to symptoms of psychosis remain poorly understood.

2.4. Suicidality

Suicidal behavior is a complex biopsychosocial process that includes thoughts, plans and attempts to end one's own life. It is the leading cause of death for middle-aged males in the UK (Samaritans, 2019), with close to 800 000 people world-wide dying by suicide every year, thus now being a priority of the World Health Organization (WHO, 2019). Similarly to loneliness, suicidal behavior is called a world-wide epidemic that occurs in low- and high-income countries across all age groups (Naghavi, 2019).

Loneliness is significantly associated with an increased risk of mortality and it is possible that suicidal behavior plays an important role in this association. However, there is little research investigating how loneliness and suicidality are linked. Some existing studies focus on specific age groups, finding that adolescents (Garnefski et al., 1992), middle-aged (Miret et al., 2014), and elderly individuals (Li et al., 2016) are vulnerable to both loneliness and suicidal behavior. However, there are only few population-wide studies that show a positive correlation between loneliness and suicide. Drawing on data from the Quebec Health Survey in 1987 (Boyer et al., 1992), an early study shows that prevalence of suicidal behavior increases with the degree of both subjective loneliness and having fewer social relationships, i.e., objective loneliness (Stravynski and Boyer, 2001). Gender differences were found across lifespan, with a stronger link between loneliness and suicidal ideation in men than women. It should be noted, though, that the measures of loneliness in this survey are very sparse, with two questions enquiring about marital status and whether the individual has friends ("objective measure of loneliness"), and only one question used to establish subjective feelings of loneliness ("How often do you feel alone?"). Nevertheless, the contribution of loneliness to suicidal behavior has been recognized in several studies and across different countries (Conroy and Smith, 1983; McKinnon et al., 2016; Osgood, 1991; Peck, 1983) using more thorough self-report measures.

Analysis of the Adult Psychiatric Morbidity Survey (McManus et al., 2009), in which over 7000 households in the UK were interviewed, checked for a link between loneliness and suicidal behavior across multiple factors (Stickley and Koyanagi, 2016). More specifically, the study set out to disentangle the complex relationship between loneliness, common mental disorders (CMD) such as anxiety and depression, and suicidal behavior, since the role of each of these components is unclear. Research on the association between the three has hitherto been conflicting, with one study stating that loneliness is a crucial factor in suicide attempts independent of depression (Wiktorsson et al., 2010), while others report that the link between loneliness and suicidal ideation is fully mediated by depression (Lasgaard et al., 2011). The analysis of the population-wide survey shows that higher rates of loneliness (as measured with the Social Functioning Questionnaire) are indeed related with a higher prevalence of suicidal ideation and attempts. Regarding the role of CMD and loneliness for risk of suicidal behavior, it was found that being lonely without CMD, and CMD without being lonely was associated with elevated odds of engaging in suicidal behavior. However, being lonely with a CMD increased the odds significantly, showing that the combination of both creates the largest risk.

Although poor mental health exacerbates suicidal behavior in a lonely person, it is important to understand how loneliness affects suicidal behavior independently of the presence of mental illness (Stickley and Koyanagi, 2016). One potential mediator might be stress; not only are lonely individuals prone to perceiving life as more stressful (Hawkley and Cacioppo, 2003, 2007), chronic stress is also related with increased suicidal behavior (Feskanich et al., 2002; Grover et al., 2009).

A recent narrative meta-analysis found that the main social constructs that are associated with suicidal outcomes (i.e., ideation and attempt) are having no partner or partners, living alone, social isolation, feeling lonely, feeling alienated from others, and feeling not to belong (Calati et al., 2019). Interestingly, the subjective feeling of loneliness appeared to have the strongest impact on both suicidal ideation and suicide attempts. This finding is corroborated by a systematic, integrative meta-analysis showing that although structural/quantitative social relationships do have an effect on suicidal behavior in elderly individuals, the function and quality of social relationships is much more predictive of suicidal ideation and attempt (Chang et al., 2017).

Given these findings, it appears that meaningful social relationships

indeed are a protective factor against suicidal behavior and that interventions against loneliness could be a promising strategy to reduce suicidal ideation, plans, and attempts.

3. Loneliness and neurodiversity

Autism Spectrum Conditions (ASC) and Attention Deficit and Hyperactivity Disorder (ADHD) are terms for a cluster of neurodevelopmental phenotypes. Autistic individuals often present with stereotypical and restricted behavioral patterns, altered sensory reactivity, and non-typical social and emotional processing (Frith, 2014). ADHD individuals typically display inattentiveness, hyperactivity and impulsiveness according to the Diagnostic Statistical Manual (DSM-V, 2016). Both neurodiversities are linked with an increased risk for mental and physical health conditions, such as depression (Hollocks et al., 2019), anxiety (Fuller-Thomson et al., 2016; Joshi et al., 2013), chronic pain conditions (Baeza-Velasco et al., 2018; Stickley et al., 2016), and immunological challenges (Casavant et al., 2012; Marchezan et al., 2018). There is an increasing number of research showing that autistic and ADHD adults are significantly more likely to feel lonely than neurotypical adults (Mazurek, 2014; Stickley et al., 2017).

3.1. ADHD and loneliness

There are very few studies with partially conflicting results that investigate a potential connection between ADHD and loneliness. In children and adolescents, no link between diagnosis of ADHD (Houghton et al., 2015) or presence of ADHD symptoms (Diamantopoulou et al., 2005) was found. However, a longitudinal study showed that young adults who were diagnosed with ADHD as children reported high rates of loneliness (Weiss and Hechtman, 1993). In older adults with ADHD, the diagnosis was linked to increased loneliness, but not social isolation (Michielsen et al., 2015).

Despite the sparse evidence, more research into ADHD and loneliness is vital, given that individuals diagnosed with ADHD are more prone to conditions previously linked with increased loneliness (Stickley et al., 2017). Studies with ADHD adults have shown that they often experience decreased social satisfaction in the form of poorer quality of relationships (Das et al., 2012), difficulties in marital relationships (Eakin et al., 2004), and poor social support (Brod et al., 2012). Individuals with ADHD are also more vulnerable to mental health conditions such as depression and anxiety (Kessler et al., 2006). Although the exact pathways remain unclear, a recent study shows that depressive symptomatology and loneliness are highly correlated in a sample of elderly ADHD individuals, indicating the potential importance of depression for a link between ADHD symptoms and loneliness (Michielsen et al., 2015). Drawing on a nationally representative sample of the UK through the Adult Psychiatric Morbidity Survey (McManus et al., 2009), ADHD symptomatology and symptom severity is strongly associated with loneliness scores, even after full adjustment for potentially confounding factors (Stickley et al., 2017). This association is, in accordance with previous studies, partially mediated by the presence of common mental health conditions such as depression, anxiety and obsessive-compulsive disorder. Importantly, even those with fewer symptoms and milder symptom severity were still significantly more likely to experience high scores on loneliness measures.

3.2. Autism and loneliness

There is substantial evidence that autistic children and adolescents show higher rates of loneliness than their neurotypical peers (Bauminger et al., 2008; Orsmond et al., 2004; van Asselt-Goverts et al., 2015; Whitehouse et al., 2009). In young autistic individuals, self-reported anxiety correlated with levels of loneliness (White and Roberson-Nay, 2009). Specifically, autistic children and adolescents report feeling more lonely and display higher levels of social anxiety compared to both clinical and non-clinical controls (Deckers et al., 2017). Loneliness is reported to correlate negatively with social skills and social competence, and to correlate positively with social anxiety in both autistic children and adolescents and neurotypical controls (Deckers et al., 2017). However, loneliness in autistic adults is much less researched. Recent large-scale studies suggest that rates of loneliness are up to four times higher in autistic than non-autistic adults (Mazurek, 2014; National Autistic Society, 2018). Data from 220 autistic and 146 non-autistic adults, gathered in the Australian Longitudinal Study of Adults with Autism (ALSAA), furthermore shows elevated rates of loneliness in autistic adults, where the presence of an autism diagnosis contributed the greatest variance in loneliness scores (Ee et al., 2019). The number of support persons in their social network significantly correlated with loneliness scores in non-autistic participants, while dissatisfaction with social support was more significant in autistic participants. Anxiety was highly correlated with loneliness in autistics, but not non-autistics, pointing to an important role of mental health conditions in this association. A qualitative analysis of comments from autistic participants revealed high inter-individual variation in the conceptualization of loneliness; where some participants scored high of items of the ULS-8 such as “I feel like I lack companionship”, they did still not perceive themselves as lonely as not socializing was their choice.

The hitherto neglected topic of how autistic adults understand loneliness has recently been explored in a small-sample qualitative study using focus groups and individual interviews (Elmose, 2019). Previously, it was reported that autistic children and adolescents typically conceptualize loneliness in non-affective terms, referring to more socio-structural dimensions like being alone or having no one to play with (Bauminger and Kasari, 2000). When asked about social challenges and support in daily life, autistic adults view themselves as profoundly isolated and having difficulty initiating interaction, but still longing for intimacy and connection (Causton-Theoharis et al., 2009; Müller et al., 2008). In accordance with these findings, four major recurring themes are proposed supported by a study using phenomenological-based thematic analysis (Elmose, 2019). The four themes include experience of loneliness, being autistic, discrepancies in social relationships, and ease of interaction. Similar to neurotypicals, loneliness was mostly seen as a distressing emotion of an absence that is not within one’s control, and associated with feelings of depression. All themes suggest that there is a profound experience of disconnection from the neurotypical world, where feelings of not being accepted and not belonging pose a great risk factor for loneliness. The inherent difference between autistic and non-autistic individuals may contribute to feelings of loneliness, often starting in early childhood for autistic children. Research shows that differences in communication-style, non-verbal social interactive cue processing, and emotional expression goes both ways between autistic and non-autistic individuals, although a much larger research effort has been made to explain how autistics misunderstand non-autistics, not adequately reflecting the issue from an autistic viewpoint (Milton and Bracher, 2013). The discrepancy in mutual understanding and reciprocity in communication between autistic and non-autistic individuals has been described as the ‘double empathy problem’ (Milton, 2012), and is likely one reason for autistic people reporting a large number of negative social experiences that further social withdrawal and negative mental health outcomes (Ee et al., 2019). A recent review (Milton et al., 2018) summarizes research on the double empathy problem and concludes that, rather than being a deficit in autistic communication skills, breakdown of communication and subsequent isolation of autistic individuals is a two-way street.

Taken together, neurodivergent individuals are not only much more vulnerable to mental health conditions associated with loneliness, but also experience loneliness and negative social contact more often than neurotypicals. These findings suggest that affective symptomatology and loneliness are tightly correlated and that future interventions need to consider not only the higher likelihood of mental illness, but also

increase awareness about neurodiversity in neurotypicals to warrant mutual respect and acceptance.

4. Loneliness and physical health

4.1. Cardiovascular health

Perceived social isolation determines an increased vigilance for social threat associated with reductions in health-related behaviours, poorer quality of sleep, and increases in stress (Hawkley and Cacioppo, 2010). These can, in turn, affect peripheral physiology through neuroendocrine (e.g. increased cortisol levels) and autonomic dysregulation, with enhanced sympathetic activity and parasympathetic withdrawal (Steptoe and Kivimäki, 2012). The detrimental effects of loneliness on physical health are well-documented, with recent meta-analyses reporting a 30 % increased risk for stroke, myocardial infarction, and mortality in individuals reporting feeling lonelier (Holt-Lunstad et al., 2015; Steptoe et al., 2013; Valtorta et al., 2016).

One of the mechanisms by which loneliness impacts physical health is a reduction in one's ability to self-regulate emotions, thoughts, and behaviors. Lonely individuals tend to associate the social world with threatening situations (Hawkley and Cacioppo, 2010) and are less inclined to perform physical activity (Hawkley et al., 2009). Reduced self-control that accompanies loneliness has also been suggested as a contributing risk factor for alcohol abuse (Akerlind and Hornquist, 1992). Other studies, however, have failed to identify differences in health behaviors between high and low loneliness individuals (Cacioppo et al., 2002).

Social isolation during childhood and adolescence predicts both adult social isolation and increased cardiovascular risk factors in adulthood, including BMI, systolic blood pressure, and high-density lipoprotein (HDL) cholesterol levels (Caspi et al., 2006). Studies have also found positive relationships between loneliness and increased systolic blood pressure (SBP) in middle-aged adults, where the rate of blood pressure increase over a four-year period was significantly increased by trait loneliness (Hawkley et al., 2006; Hawkley and Cacioppo, 2010). Evidence indicates that elevated total peripheral resistance (TPR) in individuals aged 30–49 predicts rises in SBP in late adulthood (Franklin et al., 1997), and individuals who report feeling lonelier also display elevated TPR (Hawkley and Cacioppo, 2003). Therefore, it is suggested that loneliness-mediated rises in TPR represent a candidate mechanism for the acceleration in the rate of increase in SBP in lonely individuals at older ages (Hawkley and Cacioppo, 2010).

Neuroendocrine changes can occur as a result of chronic loneliness, and are regarded as key contributors to cardiovascular morbidity associated with long-term chronic loneliness (Hawkley and Cacioppo, 2010). These mechanisms include increases in hypothalamic-pituitary-adrenocortical (HPA) axis activation, which, as discussed below, contributes to glucocorticoid resistance and increased inflammatory responses. Altered HPA activity and resulting increases in pro-inflammatory processes are in turn associated with cardiovascular problems including hypertension, atherosclerosis, and coronary artery disease (Girod and Brotman, 2004; Nijm and Jonasson, 2009; Whitworth et al., 2001). A second mechanism is thought to involve over-activation of the sympathetic nervous system (SNS). High levels of epinephrine and norepinephrine are measured in lonely middle-aged and older adults (Cole et al., 2015b; Hawkley et al., 2006), and similar results indicating increased sympathetic activity are reported in monkeys (Capitanio et al., 2019). Given the well-documented links between hypertension and cardiovascular alterations and increased SNS activity (Grassi, 2010), such findings provide early insights on the mechanisms by which loneliness exerts its detrimental effects on cardiovascular physiology. Oxytocin is one potential 'upstream' regulator of social interaction and autonomic cardiac control. Released during social interaction (Grewen et al., 2005), oxytocin is linked to loneliness by the identification of oxytocin receptor polymorphisms in humans associated with higher degrees of both social and emotional loneliness (Lucht et al., 2009).

When investigating the effects of intranasal oxytocin on autonomic cardiac control in healthy individuals, Norman et al. (2011), found that loneliness, here measured using the UCLA loneliness scale, predicted high-frequency heart rate variability (HF-HRV) responses. HF-HRV is a product of respiratory sinus arrhythmia (RSA), which signals changes in the tonic inhibitory control of vagal parasympathetic activity, such that, with inspiration, inhibitory vagal control is reduced, and heart rate increased (Grossman and Taylor, 2007). This is a good indicator of cardiac autonomic function (Berntson et al., 1997, 1993). Social interactions have been reported to have positive effects on HRV. For example, married individuals display higher levels of HF-HRV (Randall et al., 2009), and HRV is increased in shy individuals (who generally display lower HRV levels) during social interactions with close others (Schwerdtfeger et al., 2020). In response to intranasal administration of oxytocin, individuals with lower scores on the UCLA loneliness scale displayed significant increases in HF-HRV, as opposed to individuals with high loneliness scores, who did not display significant responses compared to the placebo group (Norman et al., 2011). On the other hand, upon oxytocin administration, decreases in pre-ejection period (PEP), which indexes increased sympathetic cardiac control (Berntson et al., 1997), occurred independently of loneliness scores. Together, these results suggest that, for lonely individuals, oxytocin-mediated autonomic cardiac control is shifted from a co-activation of autonomic branches towards a selective sympathetic activation, highlighting a potential mechanism by which a perceived lack of social interactions may impact cardiovascular health (Norman et al., 2011). Conversely, the degree of social integration in international students over time after arrival in their host country has been associated with changes in heart rate and HF-HRV (Gouin et al., 2015). While loneliness, here measured using the UCLA scale, did not predict changes in HF-HRV or HR, bivariate correlations revealed that high levels of social integration predicted increases in HF-HRV over time, whereas low levels of social integration were associated with higher HR and lower HF-HRV 2- and 5-months post-arrival. Reduced HF-HRV has been associated with cardiovascular disease, cardiac events in individuals with no previous history of cardiac problems (Hillebrand et al., 2013), as well as predicting future development of cardiovascular disease (Stein et al., 2008). Thus, the observed changes in HF-HRV in lonely individuals support the notion that reduced autonomic regulation plays a role in the deleterious effects of loneliness on cardiovascular health.

However, the exact mechanisms by which social isolation and loneliness impact cardiovascular health remain elusive. As recently suggested, providing clear distinctions between different aspects of social isolation, in relation to different types of social bonds (e.g. spousal or friendship relationships), will be necessary to elucidate potential mechanisms by which loneliness affects cardiovascular health, and whether differential effects occur depending on the type and number of relationships compromised (Winterton and Quintana, 2019).

4.2. Chronic health conditions

One theoretical framework formulates possible pathways by which loneliness leads to physical illness (Hawkley and Cacioppo, 2010). Chronic conditions such as diabetes, cardiovascular disease, and migraine are linked to loneliness, despite sparse empirical evidence about how loneliness mechanistically affects physical health (Christiansen et al., 2016). Besides some evidence for a directional effect from loneliness to chronic health problems, several studies report the effects that chronic health conditions have on both social isolation and loneliness. In children and adolescents, having a chronic physical condition may render inclusion in a peer group more challenging. For instance, children and adolescents with a chronic condition are at risk of school absenteeism (Emerson et al., 2016), and present lower quality

friendships, less peer acceptance, and less support from peers (Martinez et al., 2011; Pinquart and Teubert, 2012). This, in turn, may lead to increased feelings of loneliness (Heinrich and Gullone, 2006). A recent meta-analysis investigated loneliness in children and adolescents with chronic conditions including neurological disorders, visual and hearing impairments, haematological conditions, cancer, endocrine diseases and heart conditions. This investigation revealed significant associations between loneliness and chronic illness, particularly neurological conditions and visual/hearing impairments, possibly due to the higher communication difficulties in children and adolescents with such diagnoses (Maes et al., 2017).

Given the growing evidence on the long-term effects of loneliness on both physical and mental health, it would be interesting for future longitudinal analyses to investigate whether loneliness in young individuals with chronic illness is linked to further physical health problems later in life, as well as to a higher incidence of mental disorders. This need is further supported by studies reporting a linear increase in loneliness in individuals with chronic health conditions over an eight-year longitudinal investigation (Barlow et al., 2015). This study also found that health-related self-protection, which includes psychological processes that aim at ameliorating emotional well-being in the context of health threats, such as positive re-appraisal and reducing self-blame (Heckhausen et al., 2013), appeared to mitigate the effects of chronic illness on the experience of loneliness (Barlow et al., 2015).

How loneliness relates to three chronic conditions (migraine, cardiovascular disease, and diabetes) has been investigated in some detail (Christiansen et al., 2016). Here, loneliness was assessed using the Danish version of the three-item loneliness scale ('How often do you feel isolated from others?'; 'How often do you feel you lack companionship?'; 'How often do you feel left out?'; Hughes et al., 2004), based on the revised UCLA loneliness scale. In order to characterize possible relationships between loneliness and chronic health conditions, the study assessed the effect of moderating factors, including smoking, poor diet, physical inactivity, high stress, poor sleep quality and duration, and alcohol consumption (Christiansen et al., 2016). Such moderators mediated significant relationships between loneliness and diabetes, migraine, and cardiovascular disease, suggesting that loneliness exerts its detrimental effects on health via indirect, rather than direct, pathways. Because stress appeared to be the strongest predictor of poor health in relation to loneliness, it is possible that it plays a unique role in poor health outcomes in lonely individuals (Christiansen et al., 2016).

Further supporting the role of health-related behaviors in the detrimental effects that loneliness has on physical health, the English Longitudinal Study of Ageing reported that physical activity was lower in older adults with high levels of social isolation, independent of other factors including mobility limitations and depressive symptoms, although a relationship was not observed between sedentary behaviors and loneliness (Schrempft et al., 2019). Another study investigated the structural (living with or without a partner; degree of contact with family and friends; which could be translated to social isolation according to the terminology of the present review) and functional (degree to which one feels to be able to count on help from others in case of illness, which could reflect loneliness as described in the present review) aspects of social relations in individuals with type 2 diabetes (Hempler et al., 2013). Although a causal relationship between social isolation/loneliness and diabetes was not identified, the study reported that individuals with type 2 diabetes were more likely to live without a partner, less likely to have contacts with family and friends, and less certain that they could receive support from others in case of illness (Barlow et al., 2015).

A recent correlational study found significant relationships between loneliness and depression in cancer patients and reported that depression and loneliness were predictors of mortality among patients. However, when accounting for depressive symptoms, high loneliness surprisingly predicted low mortality in cancer patients (D'ippolito et al., 2017). Although such a relationship will need further validation, these findings indicate that loneliness distress, and subsequent development of depressive symptoms, rather than loneliness itself, contributes to poorer prognosis in cancer patients. Similar investigations should be carried out in other clinical populations to obtain clearer insights on the effects of social isolation, loneliness, and loneliness distress on the prognosis of diverse health conditions.

4.3. Immunology

Poor physical health has been suggested to be associated with disruptions in inflammatory regulation and exacerbation of inflammatory responses that occur as a result of loneliness (Shankar et al., 2011). The interaction between social behaviors and inflammation is thought to be bi-directional. Inflammatory responses play a role in shaping behavior by signals sent from inflammatory cytokines onto, for example, afferent vagal nerves (Goehler et al., 1997). These inflammatory signals elicit 'sickness behaviors' such as sleepiness, fatigue, and social withdrawal (Dantzer and Kelley, 2007). The effects of inflammation on social behavior are well-documented in animal models, and include, for example, social withdrawal from unfamiliar animals but increased contact with familiar cagemates in both female and male rats (Yee and Prendergast, 2010). In humans, inflammation has been reported to increase feelings of social disconnection (here described as loneliness) as well as sensitivity to both positive and negative social stimuli in humans (Moieni et al., 2015c; Muscatell et al., 2016). The effect of social isolation and loneliness on inflammation, on the other hand, is suggested to be a preventive response mechanism of the body to an increased vulnerability to wounding and infection that arises from lack of protection from others. Inflammation is not only regulated peripherally, but also neurally, resulting in increased immune system activation when the environment signals an increased risk for wounding and infection (Eisenberger et al., 2017). This is achieved by a dual mechanisms: chronic stress leads to repeated activation of SNS fibers that innervate lymph nodes and coordinate immune responses (Sloan et al., 2007), together with continuous activation of the HPA axis and glucocorticoid outputs, which in turn lose efficiency at down-regulating inflammatory responses via glucocorticoid resistance (Avitsur et al., 2001).

In an effort to determine possible biological mechanisms by which loneliness may contribute to poor physical health and mortality, Cole et al., 2007 investigated the differential expression of genes associated with chronically high levels of *subjective* social isolation. Their investigation revealed a highly activated, proliferative phenotype in circulating leukocytes (indexed by over-expression of genes involved in cell growth and differentiation and cell cycle progression, such as *ERG1* and *CDC25)*, doubled levels of C-reactive protein (CRP, a marker for systemic inflammation), decrease in glucocorticoid receptor (GR) target genes (indexing glucocorticoid resistance) and increase in nuclear factor (NF)-κB target genes (indexing increased transcription of pro-inflammatory cytokines). These results were indicative of a shift towards pro-inflammatory states and impairments in the GR-mediated anti-inflammatory effects. Other studies have investigated the relationships between inflammation and sensitivity to social isolation. This measure represents a composite score obtained from the UCLA loneliness scale, the Experiences in Close Relationships Questionnaire (anxious attachment subscale), the Brief Fear of Negative Evaluation Questionnaire, and the Merhabian Sensitivity to Rejection Scale (Moieni et al., 2015a), which, according to the terminology laid out in the present review, can be viewed as a composite measurement of loneliness and loneliness distress. Such studies document that, rather than baseline levels of circulating pro-inflammatory mediators, what is exacerbated in individuals with high as opposed to low sensitivity to social isolation is the inflammatory response to a stressor, and this is especially documented in young adults (Moieni et al., 2015a). Recently, administration of a *Salmonella typhi* capsular polysaccharide vaccine

was shown to elicit an increase in IL-6 which was positively correlated with scores on the UCLA Loneliness Scale (Balter et al., 2019).

The interaction between inflammation, sensitivity to social isolation, and depressive symptoms is consistent with the 'social signal transduction hypothesis' of depression, whereby increased social-environmental stress drives increased inflammation, which results in depression (Slavich and Irwin, 2014). In a sample of 115 healthy adults, depressed mood was increased by infusion of an endotoxin (*E. coli*), with the increase being moderated by baseline levels of sensitivity to social isolation. In addition, high levels of sensitivity to social isolation determined an increase in endotoxin-induced activation of pro-inflammatory transcription control pathways (AP-1 and NF-κB) (Irwin et al., 2019).

While *subjective* loneliness is generally associated with changes in immune system activation, more so than the *objective* size of the social network (Cole et al., 2007), an opposite trend is also seen, where objective social isolation, rather than self-reported loneliness, predicts increased CRP levels indicating inflammation (Shankar et al., 2011). Despite the evidence, because studies reporting relationships between loneliness and inflammation often only assess objective or subjective social isolation (Balter et al., 2019; Heffner et al., 2011), it is essential for future research to investigate concurrently the impact that both dimensions have on inflammation.

5. Loneliness in a social allostasis model

5.1. The social homeostasis model of social isolation

From an evolutionary perspective, social isolation and loneliness can be seen as both adaptive and maladaptive mechanisms, depending on the context of the individual. A classic evolutionary model of loneliness posits that the feeling evolved to ensure survival and reproduction of the human species, where offspring go through a long period of dependency to caregivers (Cacioppo et al., 2006a), and where even short amounts of time without group protection could mean substantial risk to harm from predators. According to this model, the negative affect associated with loneliness serves as a mechanism to draw the individual back to its group where it is safer from environmental threats. Neuroscientific findings that identify overlapping brain regions for physical and social pain (Eisenberger et al., 2003) are taken as evidence for the claim that social pain is interpreted similarly to (and can be just as threatening to) the organism as physical pain. Loneliness, from this perspective, is an initially adaptive affective response to the potential threats of social isolation. However, social isolation can be beneficial to the individual in the case of illness, where isolating oneself from external sources of additional infection is advantageous. In this case, social isolation is an initially adaptive behavioral response as part of sickness behaviors (Dantzer et al., 2008). Loneliness distress can be seen as a signal to return to the group after recovery and seek reconnection.

A novel model of loneliness adapts and extends these claims, positing that the negative affect related with loneliness is triggered by an adaptive response to perceived social deficits (Matthews and Tye, 2019). In this 'social homeostasis model', the organism detects that a specific set point associated with social needs is not met, which elicits control systems to trigger appropriate behavioral responses that will lead the system back to the set point. The evidence reviewed for this model is mainly based on findings from small animals, but suggestions are made that similar mechanisms can be found in humans. In the remainder of this chapter, we will lay out the social homeostasis model as it is suggested for humans and then introduce an alternative model of loneliness, loneliness distress and affective symptomatology as an aberrant process of predictive social allostasis.

The social homeostasis model considers three different neural and behavioral response patterns to social isolation. These initially adaptive reactions are suggested to underlie disease states associated with loneliness when their intended short-term engagement is prolonged (Matthews and Tye, 2019). These homeostatic responses to social deficits are hypervigilance and/or heightened arousal, social motivational mechanisms, and passive coping for self-protection.

The classic evolutionary model of loneliness (Cacioppo et al., 2006a) assumes that loneliness originated to promote hypervigilance to guard against potential threats to the socially isolated individual. This claim is supported by empirical findings showing that humans with increased self-reported loneliness also show increased anxiety (Ginter et al., 1994; Stednitz and Epkins, 2006), and heightened responses to aversive social stimuli (Cacioppo et al., 2016). In both rodents and humans, acute social distress like isolation or exclusion recruits fast-acting mechanisms that regulate arousal, vigilance and attention. As reviewed above, a major system involved in reactions to social isolation is the HPA axis. While its activation is deemed adaptive in the short-term to prepare the individual for potential threats, chronic HPA axis activation leads to poor regulation of daily cortisol output associated with self-reported loneliness in humans (Adam et al., 2006; Doane and Adam, 2010). Corticotropin-releasing factor (CRF) pathways initiate neuroendocrine responses to social isolation, and in rodents activate social connection-seeking behaviors (Füzesi et al., 2016). In humans, it is suggested that HPA axis, CRF pathways and LC noradrenergic systems play a role in the increased arousal, attention and vigilance associated with loneliness.

Social deficits activate a "social monitoring system" with the purpose of increasing attention towards socially relevant information (Gardner et al., 2005). Additionally, reward processing dopaminergic systems that facilitate social behavior and the hypothalamic oxytocin system are suggested to be engaged in motivating the individual to seek social reconnection in the case of isolation and loneliness (Matthews and Tye, 2019). Lonely humans may exhibit increased negative affect (Cacioppo et al., 2006b), with reduced sensitivity to physical noxious stimuli and attenuated emotional sensitivity (DeWall and Baumeister, 2006). These patterns are suggested to be strategies for protection against emotional distress associated with loneliness.

The social homeostasis model furthermore includes findings on immunological reactions to social isolation, where perceived isolation leads to increased pro-inflammatory activity as a preparation for potential physical injury and as a consequence of the decreased risk of contagious viral infections (Eisenberger and Cole, 2012; Eisenberger et al., 2010b). Importantly, there appears to be a bi-directional relationship between immunological response and loneliness, as changes to the immune system predict loneliness (Cole et al., 2015b).

Discussing the subjective nature of social experience, the authors point out that there is an important difference between actual and perceived social isolation, and that the latter is what is repeatedly found to be associated with increased morbidity and mortality (Matthews and Tye, 2019). They conclude that a model of social homeostasis for humans needs to account for this subjective assessment of social experience; an aspect that is strongly dependent upon internal bodily signals and interoceptive processes. It is this aspect we will pick up in order to develop our model of loneliness, loneliness distress and their relation with affective symptomatology.

5.2. The basics: interoceptive predictive processing and allostasis

We will base our model on previous proposals on the flexible and predictive nature of interoceptive processing and emotional regulation (Quadt et al., 2019a, 2018), which we will briefly review in this section. This model will be enriched with the notions of allostasis, allostatic load/overload (McEwen, 1998; McEwen and Stellar, 1993), and the recent characterization of psychosocial stress as uncertainty within the free energy principle (Peters et al., 2017).[2]

[2] We would like to thank two anonymous reviewers for their insightful and

Interoceptive predictive processing (Barrett and Simmons, 2015; Clark, 2016; Seth and Critchley, 2013) is based upon the general hypothetical framework of *predictive processing* (Clark, 2013) or *predictive coding* (Friston, 2012; Hohwy, 2013), a popular algorithmic theory about cortical organization and neural function. Given the basic assumption that the brain only has indirect access to environmental and bodily states, an inference process is required to arrive at the most probable hidden cause of the multitude of sensory signals. Filtering out regularities on different temporal and spatial timescales, noise and irregularities are cancelled out (Hohwy, 2013). Underlying this process is the generation of predictive models of the most likely incoming sensory signals and the improvement of model probability through feedback loops that are steered by error signals (i.e., the mismatch between predicted and received signal). Prediction errors function in two distinct ways that result either in generating perception (i.e., perceptual inference, where error signals update predictive models) or in generating action (i.e., active inference, where error signals elicit changes in behavior, Friston, 2012). Within cortical hierarchies, timescales from slow to fast signal processing differ with respect to their degree of abstraction; where concrete sensory signal properties are computed at lower, fast levels, highly abstract regularities are represented on slower, higher levels of this hierarchy (Hohwy, 2010). Within this dynamic cascade of top-down and bottom-up information, both prediction errors and predictive models undergo precision estimation and optimization by the reduction or increase the synaptic gain of error units (Friston, 2010). The overarching goal of these complex processes is to steer the organism towards adaptive responses to external and internal stimuli and efficient navigation of behavior and experience (Friston, 2009).

PP is formulated as an instance of a larger principle, namely the Free Energy Principle (Friston and Stephan, 2007). Different organisms face different homeostatic challenges. While cats may survive on their own rather early in life, humans depend on social relationships in several ways. These necessary circumstances can be expressed in a probabilistic way – being alone in an ally is a more probable state for young cats than children to find themselves in. This implies that if a system moves out of its expected or probable set of states, this state will be – in information theoretical terms – surprising, as it is unexpected. For an organism to survive, it must strive to minimize surprise and stay within the range of expected states as much as possible. More formally, the probability of internal and external states must have low entropy, where entropy is a measure of disorder and uncertainty (Friston, 2010). By minimizing prediction error and thereby uncertainty, PP instantiates the Free Energy Principle (Clark, 2013).

In the more specific case of interoceptive predictive processing (IPP), it is hypothesized that predictions about internal states are generated in visceromotor regions within the prefrontal (caudal visceromotor-prefrontal cortex [VMPFC]/orbitofrontal cortex [OFC]), anterior/mid cingulate cortices and anterior insula cortex (AIC, Barrett and Simmons, 2015). These predictive signals are compared to internal viscerosensory input that ascends from the nucleus of the solitary tract (NTS), parabrachial nucleus and thalamus, arriving at the primary interoceptive cortex, i.e., mid/posterior insular cortex (Barrett et al., 2016). Reduction of the error signal is either reached through perceptual inference which implies a change in feeling state, or active inference, involving autonomic or behavioral responses.

Ultimately, this predictive interoceptive system adapts to anticipated demands and deviations in an effort to efficiently regulate needs and resources. Prior experience, contextual information and the current state of the organism inform the generation of predictions, and the comparison between predicted and actual incoming internal signal in accordance with precision estimations serve the goal of keeping the organism within the expected range of integrity (Quadt et al., 2018). The flexible adaptation to internal and external changes are crucial in this process that can be conceptualized as “allostasis” or “predictive regulation” (Sterling, 2012).

5.3. Loneliness as social allostatic load

We propose that social allostasis is a predictive mechanism encompassing neural, physiological, autonomic and interoceptive processes with the goal of steering perception, emotions and social behavior in an adaptive manner. In healthy individuals, the complex and dynamic interaction between external and internal needs and resources is balanced by the engagement of appropriate neural and autonomic systems that shape the control of bodily states and behavior. Feeling states arise and fluctuate in concert with the dynamic regulation of internal states and as adaptive responses to social stimuli. Navigating the social environment is of importance to humans for a variety of reasons. From a phylogenetic perspective, groups provided much needed protection from environmental threats, but at the same time social isolation as a sickness behavior ensured limited exposure to infectious threats from others. Ontogentically, humans rely on caregivers for survival for a long timespan, thus separation from others can be seen as an inherent threat. Keeping an organism alive and well therefore requires a flexible and context-sensitive balance of withdrawal and seeking connection.

The research reviewed here shows that loneliness as social stress are associated with decreased health in a vast variety of conditions and is linked with increased morbidity and mortality. This suggests that the internal mechanisms reacting to and steering social interaction are of an equally large and wide variety. Similar to the social homeostasis model, we assume that the over-activation of initially adaptive mechanisms ultimately underlies increased morbidity and mortality associated with loneliness. Social allostatic load expresses the metabolic effort of the system to steer itself back into a range of expected states, for example, finding companionship, re-building social relationships, asking others for help. If these efforts do not resolve stress, and engagement of originally short-term mechanisms is prolonged, interoceptive impairments and ultimately negative affective symptomatology are the consequence.

Importantly, the social allostatic process is not without cost to the organism. The successful and adaptive coordination of neural, neuroendocrine, immunological and autonomic systems to ensure homeostatic balance demands a considerable amount of metabolic energy (Juster et al., 2010). The strain on the system of this concerted effort is expressed in the term “allostatic load” (McEwen, 1998), referring to the ‘wear and tear’ of the body during repeated allostatic activation as a response to stress. When exposed to chronic stress, allostatic load can turn into “allostatic overload”, which is the point at which morbidity and mortality start to threaten the organism as a consequence of prolonged and now exhausted activation of adaptive mechanisms (McEwen and Wingfield, 2003).

Many reviews have summarized the role of poor social relationships and psychosocial stress on allostatic load (e.g., Beckie, 2012; Juster et al., 2010; McEwen and McEwen, 2015), and stress was recently reframed as uncertainty within the larger concept of the Free Energy Principle (Peters et al., 2017). When circumstances change for an organism, new adaptations need to be made, which elicits an acute stress response involving ACC, amygdala, midbrain and brainstem nuclei (Barrett and Simmons, 2015). Initial reactive HPA-axis secretion of glucocorticoids activates energetic resources for fight-or-flight responses, recruiting neuroendocrine, immune and inflammatory systems (Juster et al., 2010). These so-called primary mediators, which include norepinephrine, epinephrine, cortisol, dehydroepiandrosterone sulfate, insulin-like growth factor-1, and interleukin-6 affect organs and tissues, and allow for quick adjustments to preserve systemic integrity (Beckie, 2012; Juster et al., 2010; McEwen and Wingfield, 2003). In PP terms, neural models of the world must be adjusted to the internal and/or external changes if they no longer adequately predict sensory input.

(*footnote continued*)
helpful comments on this manuscript, but especially our model.

This first systemic reaction to psychosocial stressors represents a hypervigilant state activated via descending projections from the ACC-amygdala complex to the locus coeruleus (LC) in the brain stem. Here, norepinephrine boosts information transmission at cortical synapses (Aston-Jones and Cohen, 2005), again increasing the brain's energy demand (Harris et al., 2012b). The selective enhancement of sensory information transmission can improve and adjust internal models to a now changed environment and thereby habituate and consolidate systemic responses (Mather et al., 2016). Additionally, the ACC descends projections to the HPA-axis where cortisol is released, passing the blood-brain barrier and binding to glucocorticoid receptors and mineralcorticoid receptors in neuronal populations located in the amygdala, cerebral cortex and hippocampus (Harris et al., 2012a). However, if no appropriate update is found and stress continues, ACC-transmitted error signals prevail, signaling continued entropy (uncertainty). The ACC-amygdala-complex remains in a hyperaroused and –vigilant state, which requires heightened energy output through the allostatic network, i.e., sympathetic nervous system and HPA-axis (Hitze et al., 2010). If these acute responses do not resolve uncertainty and stress becomes chronic, allostatic load grows and burdens the organism.

These primary allostatic effects now lead to secondary outcomes of systemic dysregulation of cardiovascular, inflammatory and metabolic markers. As a response to the over- or underproduction of primary mediators, these systems alter their function, which can lead to subclinical levels of cardiovascular (e.g., blood pressure, heart rate, heart rate variability), metabolic (e.g., high- and high density lipoprotein cholesterol, glucose, insulin), and immune (c-reactive protein, fibrinogen) parameters (McEwen, 1998). Finally, the wear and tear leads to allostatic overload and can cause systemic damage manifesting itself as cardiovascular disease, chronic pain, cognitive dysfunction, or depressed mood (Peters et al., 2017). Tertiary outcomes then refer to the stage of allostatic overload, where the cluster of physiological efforts to return the system to homeostasis (allostatic load) manifests as mental and physical health decrease, poor quality of life and increased risk of mortality (Juster et al., 2010).

5.4. The burden of loneliness distress: social allostatic overload

Perceptual content within predictive processing is proposed to be steered by the estimated precision of prior experience and incoming sensory signals (Clark, 2018; Hohwy, 2012). It is proposed that interoceptive inference plays a role in the occurrence of affective symptoms; when interoceptive signals are unexpected, they reach conscious awareness (Van den Bergh et al., 2017). Bodily sensations, according to this proposal, are interpreted as symptoms when the predictive model with the highest probability contains information representing disease-related causes. Negative or anxious affect could therefore result from aberrant social allostatic mechanisms that fail to return the system to the desired state of social connection; as expectations on higher levels, based on systemic needs, fail to accurately predict social stimuli, large prediction errors ensue and populate consciousness as negative affect signaling that needs are not met. Importantly, failure to return the system to more desirable social states may also and even primarily rely on external circumstances, where no social support system is available or has been removed due to loss, re-location, ongoing bullying, or other causes that are not within the control of the individual.

However, how does perceived isolation from meaningful social connections elicit negative affect? The classic model of loneliness suggests that perceived social isolation is the starting point of a vicious cycle, in which the initial hypervigilance for social threats leads to confirmatory attentional, memory and behavioral biases (Cacioppo et al., 2014). These biases in turn lead to increased negative behavioral displays, social interactions and affect, causing the social environment to withdraw from the individual and thereby increasing social isolation. This cascade of negativity is underpinned by the activation of neurobiological mechanisms that increase morbidity and mortality. The focus of this model is on the overall effects of perceived social isolation, where negative affect is both consequence and cause for loneliness. The social homeostasis model suggests that the prolonged engagement of mechanisms normally recruited for short-term adaptations plays a vital role in the negative consequences of perceived isolation (Matthews and Tye, 2019). In our model, we will concentrate on the effects of loneliness and loneliness distress on affective symptomatology.

When adopting the notion of stress as uncertainty, the subjective experience of controllability takes on major relevance. Stress research shows that the perception of controllability of a stressful event is tightly related to the negative impact on the individual (e.g., Dickerson and Kemeny, 2004; Henderson et al., 2012; Maier and Seligman, 2016). Beliefs about uncertainty have been shown to mediate the magnitude of individual stress responses, and the adaptability of beliefs about uncertainty improves prediction of future outcomes (De Berker et al., 2016). This indicates that habituation to stressful experiences through the perception and judgment of uncertainty and controllability leads to more adaptive responses. Arguably, social stressors are not always in the control of an individual and can easily be perceived as uncontrollable. The perception of social stress as outside of one's control may therefore not only causes the onset of the allostatic stress response, but may play a major role in the maintenance of social allostatic overload. Where habituation to stressors does not occur, allostatic load keeps increasing until it leads to systemic damage (Peters et al., 2017).

Particularly when associated with sickness behaviors as a response to increased inflammatory signals, aberrant social allostatic processes that are associated with imbalanced emotional processing may drive affective symptoms of depression via social allostatic overload. The experimental manipulation of inflammatory levels (Eisenberger et al., 2010a; Harrison et al., 2009a; Rosenkranz et al., 2005) reveals interoceptive pathways that are neurally mediated via a discrete set of neural circuits, including basal and posterior ventromedial thalamus, dorsal mid and posterior insula (Harrison et al., 2009c). The ensuing increase in inflammation leads to the display of sickness behaviors, and specific functional changes within interoceptive brain regions can be identified for different components of these behaviors. While the subgenual cingulate appears to underlie change in mood (Harrison et al., 2009a), the insula is implicated in the subjective experience of social disconnect (Harrison, 2017). The loss of interest in social interactions is associated with an increase in right anterior insula metabolism (Hannestad et al., 2012). Importantly, these are the same regions that underlie emotional and affective regulation, supporting the notion that inflammation, through interoceptive processing, enhances mechanisms that are associated with feelings of loneliness, social disconnect and the impairment of social cue processing (Moieni et al., 2015b).

Depressed mood is associated with the negative appraisal of social company and the withdrawal from others (van Winkel et al., 2017). These findings fit with the hypothesis that depression is associated with a "locked-in" state of the brain, where negative assumptions about the environment are not corrected due to reduced exposure to potentially corrective stimuli and insensitivity to prediction errors containing corrective information (Barrett et al., 2016). In combination with the enlisting of sickness behaviors to conserve energy, this may lead to inefficient energy regulation that could underlie negative affect and biases the organism towards social withdrawal and general avoidance behaviors (Schwartenbeck et al., 2015). More specifically, dysfunction in visceromotor cortical regions, where interoceptive prediction errors are claimed to originate, may cause imbalances in responses to bodily needs through overpredicting metabolic energy demands (Nieuwenhuizen and Rutters, 2008). Ensuing HPA axis overactivity will then increase pro-inflammatory cytokines and cause changes in the endocrine and immune system (Barrett and Simmons, 2015). Ultimately, this process leads to aberrant coupling of interoceptive predictions and inputs at the thalamocortical level and may result in an increase in interoceptive prediction errors. In an attempt to down-regulate these noisy error signals through precision units leaves them

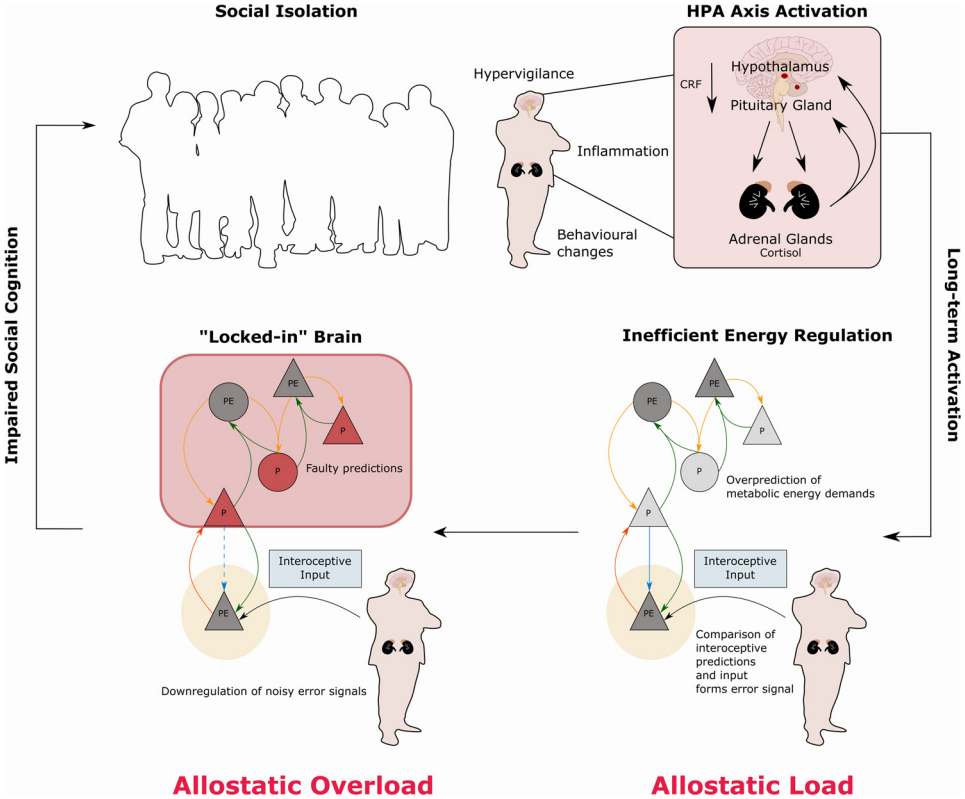

Fig. 1. Social Allostasis.
This figure outlines the social allostasis model. Social isolation leads to HPA axis activation, which, if prolonged, results in aberrant predictive processing of interoceptive signals. Overprediction of metabolic energy demands causes large and noisy interoceptive errors, which are subsequently downregulated. This dysregulation leaves predictions largely impenetrable to potentially corrective error signals, thus resulting in a "locked-in" brain state. Resulting impaired social cognition in turn causes further social isolation, perpetuating the cycle of loneliness.

less likely to influence and change predictions. The system is now "locked-in", as sensitivity to prediction errors decreases, enabling faulty predictions to maintain the high demand of metabolic energy (Stephan et al., 2016). When the endocrine and immune system have reached their limit, depression ensues as a result of enlisting sickness behaviors to conserve energy (Barrett et al., 2016). In the case of loneliness, this process might set in as a result of HPA axis overactivity to shield against potential threats. Distress and negative affective symptomatology set in when the system does not revert to equilibrium, but stays "locked-in".

5.5. Breaking the cycle: mechanisms, causes and interventions

It remains an open empirical question how increased loneliness and loneliness distress are causally linked to higher mortality and morbidity. It is unclear whether external, social-environmental factors leading to feelings of loneliness distress set in motion the allostatic process that ultimately leads to systemic damage, or whether chronic allostatic load precedes feelings of loneliness and – through sickness behaviors such as social withdrawal – causes loneliness and distress. It is also possible that both social stressors (e.g., loss of a loved one, exposure to bullying) and internal stressors (e.g., onset of a depressive episode) can set in motion the allostatic process that is not resolved, which again might have either external or internal reasons.

A recent meta-analysis discusses the mechanistic and causal role of loneliness in psychotic disorders (Michalska da Rocha et al., 2018). While it is confirmed that loneliness and psychotic symptoms are significantly interrelated, the causal structure of these relationships remains unclear. However, there is some evidence that loneliness – through elicitation or exacerbation of negative affect and low self-esteem – might play a role at the onset or at subclinical stages of psychosis (Garety et al., 2001). Others suggest a self-perpetuating cycle where psychotic symptoms foster isolation and disconnect from potentially helpful contacts and support, and loneliness enables the maintenance of symptoms through low self-esteem and negative affect, which in turn increase isolation (Gayer-Anderson and Morgan, 2013; van der Werf et al., 2010).

Data from randomized controlled trials shed some light on how to break the cycle of loneliness, negative affect and further isolation. When compared to the effectiveness of Active Cognitive Therapy, Befriending showed equal improvements in both positive and negative symptoms (Jackson et al., 2008). Befriending consists of the simple practice of the therapist talking with the patient about general things in their life, or jointly participating in activities when verbal interaction proves difficult for the patient (Sensky et al., 2000). Furthermore, subjective increase in quality of life and self-reported recovery in patients diagnosed with schizophrenia or schizoaffective disorder was positively correlated with social support, and negatively correlated with feelings of loneliness. In a population of depressed patients, interventions counteracting social withdrawal and enabling meaningful social contact alleviated depressive symptomatology and may even prevent relapse (Cruwys et al., 2013, 2014). These findings suggest that the exposure to social stimuli might indeed counteract the "locked-in" state of the brain and facilitate the correction of negative assumptions, thus breaking the vicious cycle of perpetuating negative feelings of loneliness.

However, a meta-analysis comparing different types of interventions in different designs found that those addressing maladaptive social cognition via Cognitive Behavioral Therapy-based interventions showed the greatest reduction in loneliness scores (Masi et al., 2011). It is concluded that increasing opportunities for social contact does not necessarily lead to an increase in meaningful relationships that would alleviate feelings of loneliness. Furthermore, these results speak for an important role of aberrant social cognitive mechanisms in contributing to feelings of loneliness, such as negative evaluations of the social environment, being stuck in a hypervigilant state that is caused by heightened perceptions of social threat, and memory biases towards negative social events (Masi et al., 2011).

We suggest that, in line with the evidence reviewed here, feelings of loneliness and loneliness distress can play a causal role for the onset and maintenance of mental and physical health problems. The underlying

mechanisms involve the recruitment and, most importantly, exhaustion of processes adapted to shield the individual from stressors. Although interventional studies show that improved social cognitive processing alleviates feelings of loneliness, the exact temporal and causal relationships between loneliness, physical and mental health are yet to be determined. The detrimental effects of loneliness on health are likely complex and multifaceted, where chronic illness – mental and physical – can lead to social withdrawal, setting the vicious cycle in motion, or where extended social stress leads to chronic illness via social allostatic overload (Fig. 1).

6. Conclusion and future research

Loneliness and loneliness distress are phenomena that appear across all age groups and cultures. Given the evolutionary importance of belonging to a group, being distressed by the perceived or actual lack of social contact appears like a reasonable response. However, as shown in this narrative review, the effects of prolonged loneliness can be detrimental to the entire organism. The impact of loneliness on an individual includes not just maladaptive behavioral patterns, but appear to initiate a cascade of complex body-brain interactions that make the whole organism more vulnerable to mental and physical health conditions. It is thus of utter importance to clarify the causal directions between social isolation, negative feelings of loneliness, and brain and body responses. This review aimed at giving an impression of the current state of research on that topic.

While research on loneliness and its impact on health is growing, there are many important areas still to explore. Our model of social allostasis proposes how affective symptomatology arises as a consequence of loneliness. This model, however, is based on research on neurotypical individuals with mental and physical health conditions and as such does not necessarily apply to neurodivergent individuals. It is an open question whether the same interoceptive and allostatic processes are involved in the impact of loneliness in neurodivergent individuals, or whether their heightened loneliness rates are due to more socio-structural reasons. One possibility, for example, is that they are exposed to social isolation more often due to the double empathy problem, which neurotypicals are usually less likely to be concerned with. However, once social isolation sets in, are the same processes involved in generating vulnerability to disease in neurotypical and neurodivergent individuals? More empirical research is needed to reveal the reasons for heightened loneliness in neurodiversity, their specific notion of loneliness and loneliness distress, and how these relate to the increased vulnerability to health conditions.

In the case of neurotypical individuals with depression, only a subset of depressed individuals shows signs of heightened inflammation as a potential factor for their symptoms (Harrison, 2017), and there is a potential role of inflammation-induced mechanisms fostering feelings of loneliness and associated affective symptomatology. This leads to an empirical question that, to our knowledge, has not been investigated yet: Are depressed individuals with inflammatory issues lonelier and more distressed by social isolation than those without inflammatory markers of depression? The answer to this question could provide further hints about the role of inflammation and interoceptive pathways that are involved in affective symptomatology linked with loneliness distress and depression.

From a clinical perspective, only few studies have investigated potential interventions to minimize loneliness and its negative effects. One way to break the vicious cycle of social isolation, social withdrawal and negative affect appears to be the exposure to meaningful social interaction. However, additional research is necessary to examine whether interventions have long-term positive effects and whether these effects can reverse potential damage that is already done.

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