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Review

Stress and perceived social isolation (loneliness)

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ABSTRACT

Background: Perceived Social Isolation or loneliness, a cognitive state with negative effects on health, is a global problem.

Objectives: Treatment of diagnosed loneliness is mostly through its physical (cardiovascular) and/or mental (depression, anxiety) health consequences, with limited success. Desired solitude is considered a means to wellbeing by Mindfulness-Based Stress Reduction (MBSR), Evidence exists for the relevancy of developing stress-related medical factors which have demonstrated a prodromic or causal role in loneliness, depression and hopelessness. Consequently, presently unexplored direct medical treatment of biological factors in loneliness becomes an option.

Data sources: We searched medical and psychological databases including PubMed, PsycINFO and Cochrane from 1975 thru May 2018 with the keywords, no limits, pursuing related links. Studies identified: 373. Studies considered: 42.

Study eligibility criteria: Studies indicating causal and correlational links between stress and loneliness were considered as to relevancy and study quality.

Results: Data indicate that both loneliness and solitude may be caused by or correlate with biological factors resulting from psychological (life quality) and medical (health) factors including circulating stress hormones, immune system components and the glutamate system.

Limitations: Causal and correlational links between stress and loneliness are under-researched and study size is generally small. Most research is correlational and study criteria diverse. This review is partly descriptive.

Conclusions and implications of key findings: Forty years of incidental research give indications as to a co-causal or prodromic role for stress in loneliness.

Early medical and psychological stress treatment should be combined for incipient and clinical loneliness.

1. Introduction

All the lonely people, where do they all come from? The Beatles. 1966.

1.1. What we know

Causes and characteristics of suffering loneliness or enjoying solitude are increasingly found to be relevant for health and wellbeing. Loneliness, also termed Perceived Social Isolation (PSI), has become of worldwide concern, having more negative impact on health than obesity, and affecting all groups from adolescents to especially the elderly. Loneliness is recognized as a clinically relevant cognitive state with demonstrated negative effects on physical and mental health (van Beljouw et al., 2014). It was qualified as a modern-day epidemic by Fortune[1], The New York Times,[2] The Guardian[3] and The Times.[4] The United Kingdom named a "minister of Loneliness" in 2018.[5] Treatment of loneliness has limited success and is mostly indirect by way of the medical treatment of related health conditions such as cardiovascular problems, and its mental health consequences by way of psychosocial approaches or medication, generally antidepressants or anxiolytics. The opposite state of mind is solitude or Perceived Desired Social Distance (PDSD), that is, enjoying being more alone, a condition also clinically relevant as providing possible beneficial effects on health. Stress-

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[1] http://fortune.com/2016/06/22/loneliness-is-a-modern-day-epidemic/.
[2] http://www.nytimes.com/2016/09/06/health/lonliness-aging-health-effects.html.
[3] https://www.theguardian.com/commentisfree/2016/oct/12/neoliberalism-creating-loneliness-wrenching-society-apart.
[4] http://www.thetimes.co.uk/tto/life/article4716455.ece.
[5] https://www.theguardian.com/society/2018/jan/23/tracey-crouch-minister-loneliness-friends-powerful-vested-interests.

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reduction programs such as Mindfulness-Based Stress Reduction (MBSR) often aim at creating a certain degree of PDSD and finding (more) "alone time" with which to regain or maintain emotional balance, thus valuing solitude.

1.2. Questions we address

Our concern was to consider current evidence on the question "Can stress treatment prevent or reduce loneliness? ". A variety of studies indicate that stress is causally related to loneliness and it is hypothesized that changes produced in the hypothalamic-pituitary-adrenocortical (HPA) axis affect health (Brown, Gallagher, & Creaven, 2017). The mechanism is at work not only in the elderly but across age groups (Drake, Sladek, & Doane, 2016), and was found to have a variety of sources, some related to ageing, but all related to a perceived loss of proper capacities or qualities. Nevertheless, some studies also suggest a direct causal role of stress in loneliness. In 1985, Glaser (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985) published a series of studies on stress, loneliness and herpes, finding that the higher stress levels of the lonelier subjects in their student cohort affected their immune system noticeably, thus providing evidence of a causal stress-loneliness-health relationship. High-loneliness subjects had significantly higher EBV antibody titers than low-loneliness subjects. As the authors observed: "We have now (1984, in 4 studies) shown a significant association between loneliness and competency of the immune response across two very different populations, medical students and psychiatric inpatients, on four different direct or indirect measures of cellular immunocompetency". Their results indicate that stress is intimately associated with loneliness. Recent studies go a step further and find a solid positive association, with a possibly reciprocate (Jaremka et al., 2014) thus also causal pathway through abnormal activity of the HPA axis as a major component of the endocrine system (Edwards, Bosch, Engeland, Cacioppo, & Marucha, 2010; Hawkley, Masi, Berry, & Cacioppo, 2006; Hawkley, Cole, Capitanio, Norman, & Cacioppo, 2012; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). A British study points at stress being a condition for clinical loneliness (Stone, Evandrou, & Falkinghamm, 2013).

Apart from a direct effect of PSI on circulating glucocorticoids levels, loneliness is associated with glucocorticoid resistance, a diminished response to transduced glucocorticoid signals, smaller neutrophil to monocyte and neutrophil to lymphocyte ratios in white blood cells, thus indicative of biological chronicity because of social isolation (Cole, 2008; Hanke, Powell, Stiner, Bailey, & Sheridan, 2012; Xia & Li, 2017). Dopamine is known to be related to loneliness (Matthews et al., 2016) and, recently, the glutamate system was found to be involved, even inter-individually. Sterley et al. (2018) established that transmitted stress has the same lasting effects on glutamate synapses as authentic stress, thus can contaminate stress from one individual to others which is reflected in corticotropin releasing hormone (CRH) neuron activity. In another animal study, Lewis (2016) that dopaminergic neurons mediate sociability and cause loneliness when social isolation is present.

In view of the results of current research that confirms and amplifies Glaser's findings of a positive relationship between loneliness and stress (Segrin, McNelis, & Pavlich, 2017), we hypothesize the already indicated inverse mechanism: *perceived social isolation is (co-)caused by biological factors, specifically circulating diurnal stress hormones and immune system components.* If so, a specific approach to treating loneliness through treating stress becomes a possibility, based upon the individually varying but generally established neuroimmunoendocrine communication problems (Cruces, Venero, Pereda-Pérez, & De la Fuente, 2014).

PSI, being a negative cognitive state, as well as other negative cognitive states such as hopelessness, would be related to a person's negative cognitive style, causing a more negative interpretation of life events and thus, with age, accumulating more stress, leading to stress-induced depression (Southwick, Vythilingam, & Charney, 2005). The amount of resilience or cognitive coping a person possesses or develops is a biological and cognitive factor in this process. The accumulation of stress that is resistant to coping, accounts for increased negative health effects in older individuals.

The mechanisms of stress-induced negative cognitive states are several. The observed stress-related immune reactions act on neuronal organs that are conditioned by genetic, epigenetic or hormonal factors. Age is arguably the first epigenetic factor to consider. Studies found the bidirectional relationship between the neuroendocrine and immune systems to have far-reaching influences and intimate connections with loneliness (Abelson, Khan, Liberzon, Erickson, & Young, 2008; Jaremka et al., 2014; Lewis, 2016; Reiche, Morimoto, & Nunes, 2005; Sterley et al., 2018). These correlations as presently experimentally established approach evidence of a causal relationship independent of age but especially in less resilient cohorts such as the elderly and are sufficient clinical reason for intent-to-treat. In mental health, there is no such thing as simple direct causality, and clinical decisions are heavily dependent upon correlated evidence. Present data confirm an intimate relationship between stress and loneliness that, in both causal and consequential form, warrants action.

1.3. Information sources

We did several searches with different combinations of the keywords, e.g. in Pubmed until June 2018 with

- Perceived social isolation, stress, hormone
- Perceived social isolation, loneliness, stress
- Loneliness, stress, factors, health

In total 373 studies came up. Similar searches in PsychInfo and Cochrane. In total 42 studies were considered.

1.4. Collected data classification

Study characteristics and results were too diverse to offer enough basis for statistical analysis and a descriptive allocation of data was decided upon. The following subject categories were selected:

1 Subclinical and clinical loneliness
2 Connectedness, de facto isolation and perceived loneliness
3 Cohorts at risk of loneliness
4 Loneliness in the brain
5 Sources and effects of solitude
6 Diagnostic and treatment options for loneliness

2. Subclinical and clinical loneliness

"Alone" is a fact and "lonely" is a feeling. Thus, social connectedness is defined by quality and not by numbers, which makes screening for loneliness centre on individual perception, hence Perceived Social Isolation. Loneliness may undo both mental balance and clarity, resulting in conscious and subconscious stress. In contrast, desired solitude may reduce stress, enhance mental balance and clarity.

People may prefer being alone to being with others. Solitude can therefore be a positive state, something desired. Loneliness, however, is a state that overcomes and envelops a person in a negative way. It does not seem to depend on a specific level of social connectedness. People may be lonely in a crowd, with their family, or all by themselves. Loneliness has been described as the dissatisfaction with the discrepancy between desired and actual social relationships, but many slightly different definitions exist (Peplau & Perlman, 1982, in their Table 1.1). Thus, loneliness is a personal and negative state, something a person suffers. It makes one quasi-social, that is, not fitting in completely, in part because they feel inadequate connecting with others,

and perceive others to be uninterested in connecting with them. Having many social intimates does not necessarily resolve loneliness. In contrast to the at times positive effects of desired solitude, loneliness was found to prevent happiness and to determine quality of life.

Since the 1970s, differences between loneliness and solitude have been studied and condensed in textbooks (Coplan & Bowker, 2014; Peplau & Perlman, 1982). Generally, both conditions are considered exclusively psychological and subjective, contrary to our hypothesis of a biological mechanism. Symptoms vary in time and perception. Solitary people may consciously value solitude. But a clinically relevant reduced social integration may go consciously unnoticed (or be psychologically suppressed) by the lonely, as do the health risks involved. PSI is a confirmed factor for psychiatric and psychological problems such as anorexia, drug abuse, depression and suicide, and physical problems such as heart conditions (Valtorta, Kanaan, & Gilbody, 2016), diabetes (Whisman, 2010) and dementia (Zhong, Chen, & Conwell, 2016). Loneliness affects quality of life, but lonely persons may deny its presence or its impact.

Research on the causes of why people may prefer (more) solitude has identified wildly different subconscious or biological reasons for desiring solitude, amongst these having phobias or having a higher intelligence (IQ). Intelligent people who socialize less may consider themselves to not be lonely, but rather in the positive mood state called solitude. It is proposed that they prefer solitude because of a lesser dependency on others (Li & Kanazawa, 2016). Individuals of higher intelligence experienced lower life satisfaction when socializing more frequently with friends. This last study looked at 15,000 adults, aged 18–28. On another line, the Economics of Happiness propose that more intelligent persons socialize less because they focus on other, more rewarding and longer-term objectives. However, regardless of personal interpretations, less social connectedness in objective terms in the long term was found to affect health negatively (Holt-Lunstad et al., 2015). In general, these apparent and sometimes contradictory factors at work in loneliness and solitude leave open the possibility of biologic mechanisms.

The growing worldwide tendency towards pursuing more solitude, because of the increasing and pursued value of the individual, is resulting in more “living alone” whilst maintaining other forms of social connectedness (Klinenberg, 2012). As said, this positively regarded tendency does not necessarily improve the negative health effects of objectively being alone.

3. Connectedness, de facto isolation and perceived loneliness

Whether the lives of the *de facto* lonely are affected *in general*, whatever their perceived opinion of being alone, is of clinical interest because of its health consequences. The solitary intelligent showed to have a better life expectancy than the lonely depressed (Li & Kanazawa, 2016). However, and rather counter-intuitively, a meta-analysis (Holt-Lunstad, Smith, & Baker, 2015) found that both *de facto* but not perceived, as well as perceived social isolation were associated with an increased risk of early mortality, that is, both objective and subjective social isolation produced a similar negative influence on life expectancy, although more so when older than 65. This argues for a sociobiological origin of social isolation, which questions our earlier suggestion that desired solitude is good and unwanted loneliness, bad. The origins of the types of stress, relevant for PSI are being discovered. Ageing may produce perceptible cognitive impairment, which has proven to be a (co) cause of loneliness (Burholt, Windle, Morgan, & on behalf of the CFAS Wales team, 2017). It also may produce physical complaints, such as muscle tension and pain, which in turn cause stress that contributes to loneliness (Glaros, Marszalek, & Williams, 2016). Digestion problems, proper of ageing, contributed to PSI (Rémond et al., 2015), whereas a lower interest in sex, romance and love contributed as well to PSI. However, not only the ageing suffer from stress related to fertility problems and notions of perceived social isolation, as a study on the psychological experiences of women with infertility demonstrated (Donkor, Naab, & Kussiwaah, 2017). Upon ageing, but also upon experiencing medical problems at whatever age, higher psychological distress associated with lower immune function is produced and resulted in higher loneliness and depression (Engeland et al., 2016). Sleeping problems, specifically insomnia, proved a predictor of loneliness (Horn et al., 2017).

All these up to now not necessarily considered relevant problems for the onset of loneliness indicate its indivualistic nature.

The resulting stress, although perceived, may remain unidentified for several reasons. Apparently, stress produced by non-perceived social isolation may be perceived subconsciously or not consciously. The Sterley study (2018) explains the synaptic mechanism of the neurobiological projection of stress from one individual to another. These authors affirm that “interactions, however, can also transmit stress to the naive individual. Indeed, behavioral and endocrine changes in partners of stressed individuals offer proof that some parameters associated with stress map from one individual to others in the group. This physiological mimicry of stress by the naive individual prompted us to hypothesize that social interactions may also transmit persistent synaptic changes, or metaplasticity, from one individual to another”.

Holt-Lundstad’s review established the overall and relative magnitude of social isolation and loneliness, examining possible moderators. Data were sought on mortality as affected by 1) loneliness, 2) social isolation, or 3) living alone, without looking at motives, however. Mortality increased by 29%, 26%, and 32%, respectively. The meta-analysis included 70 studies with 3,407,134 participants, over 7 years. It thus found no differences between objective and subjective social isolation, gender, length of follow-up, and world region, but initial health status and age were relevant. The authors observed that "Living alone, having few social network ties, and having infrequent social contact are all markers of social isolation", not expressly differentiating, however, between persons who consciously desired fewer social network ties, as opposed to persons longing for social connectedness, the difference being relevant as to levels of perceived and non-perceived stress. They qualified: "Loneliness is the perception of social isolation, or the subjective experience of being lonely, and thus involves necessarily subjective measurement."

However, a Japanese study did measure the differential effects of solitude on positive and negative affect, controlling for loneliness. Its data demonstrate that a preference for solitude decreased negative affect and promoted emotional well-being (Toyoshima & Sato, 2015). For gerontology it is important to note that the probability of negative health consequences through the accumulation of perceived and non-perceived loneliness increases with time. Early medical attention of causal factors such as stress is required.

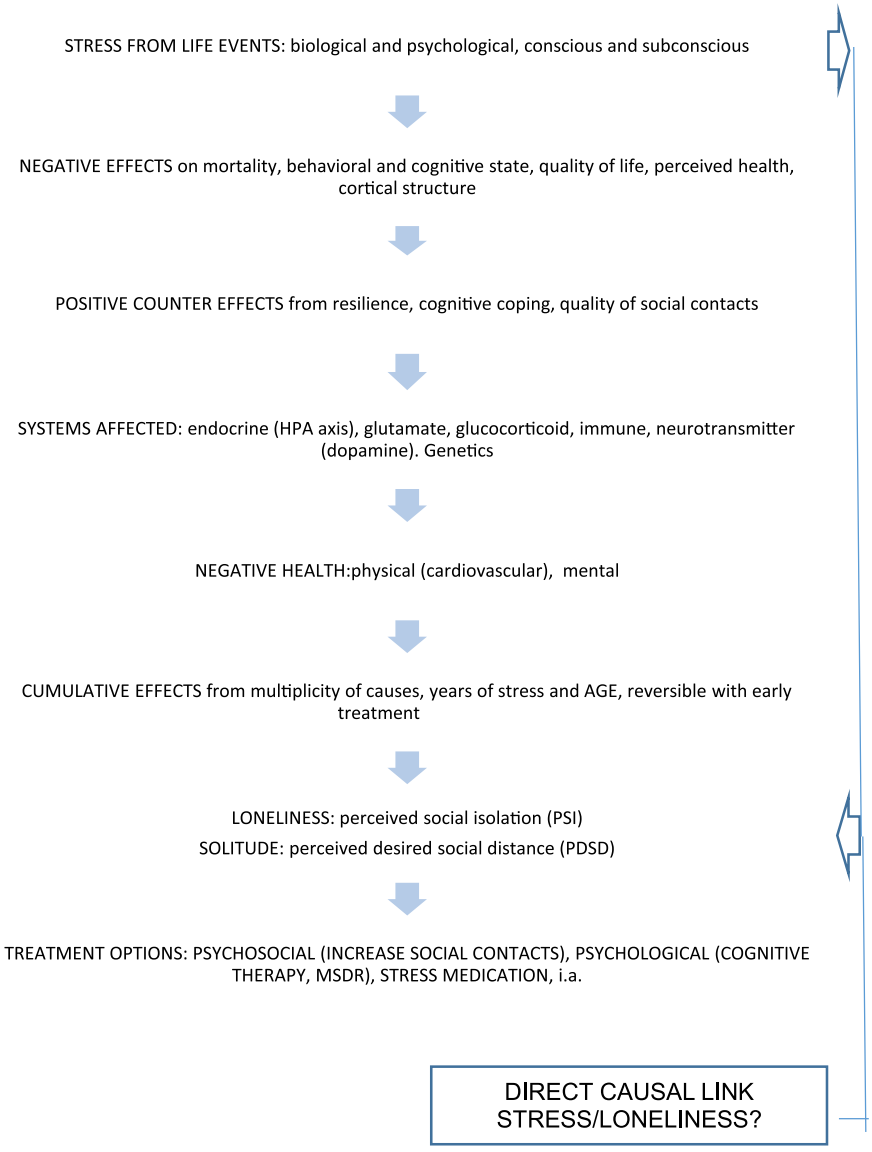
As we said at the beginning, loneliness and solitude, though different phenomena, influence health status and well-being both in a negative and in a positive way. As Glaser found, and was confirmed since then, a discriminating factor may be (persistent) biological stress. Aiming to further define this notion, studies have tried to establish the characteristics and the relative incidence of lonely and of solitary people. Objective social isolation, both intentional and accidental, proved to not be significantly correlated to loneliness (Coyle & Dugan, 2012; Perissinotto & Covinsky, 2014).

Thus, study results as to the importance of effective social interaction are conditioned in the sense that:

1 Solitude is a desired state of Perceived Desired Social Distance, or reduced social contact.
2 Loneliness, or Perceived Social Isolation, is a negative state of mind, largely independent of the real level of social connectedness.

As we saw earlier, the amount of social interaction does have relevancy, irrespective of positive or negative perception, as:

Table 1
(CO)Causal flow from stress to loneliness.



1 Both solitude and loneliness may negatively affect health and life quality
2 A subjective need for solitude or a subjective experience of loneliness are related to both the mental state and the neurobiological condition of the individual.

This implies that a person's perception of life will change on account of changing circumstances, experiences or treatment, which will have consequences for biological stress levels.

4. Cohorts at risk of loneliness

A considerable number of studies aimed to establish the specific risk for loneliness per age group. One (N = 16,132) confirmed that loneliness affects the old, probably because of decreasing social interaction and reduced income. But peaks in loneliness were measured in early (30 s) and mid (50 s) adulthood which could not be explained by commonly supposed risk factors, such as income, gender, health and number of social contacts (Luhmann & Hawkley, 2016). This result differs from other, earlier studies in which loneliness demonstrated a nonlinear U-shaped distribution, with those aged under 25 years and those over 65 years having the highest levels of loneliness, although for the first cohort the *quantity* of social contacts was buffering and for the second cohort the *quality* was a protective factor (Victor & Yang, 2012), indicating that loneliness selectively relates to different aspects of the social circumstances of the individual, but depending on age, thus of a developmental nature. Importantly, the relationship between measured stress markers and loneliness was also confirmed in middle-aged men and women (Steptoe et al., 2004) and in other age groups. As a result, loneliness remains of prime importante for the aged but does relate to stress in earlier periods of life. It may be an important prodromic factor for the confirmed negative health consequences in the general aged population.

None of these studies measured "desired solitude" (PDSD), but only "objective solitude", referring to the number and duration of social contacts, and distance from neighbours and family (Borg, Fagerström, & Balducci, 2008). In a longitudinal study comparing negative correlations of loneliness with objective social disconnectedness, loneliness predicted depression but not vice versa, and this temporal association was not attributable to demographic variables, objective social isolation, dispositional negativity, perceived psychological stress, or social support (Cacioppo, Hawkley, & Thisted, 2010). In this last study,

measurements were indicative of cardiovascular health risks (i.e., BMI, systolic blood pressure (SBP), cholesterol levels, glycated haemoglobin concentration, and maximum oxygen consumption (Hawkley & Cacioppo, 2010). These are, however, also indicators of (chronic) stress. The authors hypothesized a Loneliness Model, which explains chronic stress as the result of lonely individuals feeling unsafe which sets off implicit hypervigilance for (additional) social threats in the environment. Later studies as to heart disease found similar results, with an important mediating role for stress (Christiansen, Larsen, & Lasgaard, 2016). Said Loneliness Model is not in conflict with our hypothesis as to stress having a double role: as a cause as well as a consequence of loneliness.

Social disconnectedness showed to be relevant for health in the long term for both loneliness and solitude, but it does not automatically provoke perceived isolation, at least not without an additional component being present. Perceived isolation appeared to be somewhat more informed by personality and factors such as neuroticism, shyness and cognitive schemas. Some twin studies indicate that nearly half of the variation in loneliness is genetically determined (Boomsma, Cacioppo, & Muthén, 2007), but that is not the subject of our hypothesis. As said earlier, in the past loneliness had long shown to be only weakly correlated with social connectedness (Fees, Martin, & Poon, 1999). But social disconnectedness and perceived isolation were found to have separate though distinct associations with physical and mental health (Cornwell & Waite, 2009) where, for instance, although loneliness is a predictor of depression in adults, solitude is not. These correlations indicate a positive influence on health of *desired* social disconnectedness, but *not* a negative influence on loneliness of depression (only the other way around). These data therefor suggest that in clinically relevant loneliness another factor may be decisive, such as stress. See Table 1.

5. Loneliness in the brain

Mental health has related physiological causes and consequences. Independent of any ties to depression and self-reported and thus *perceived* stress, loneliness has been found to independently correlate with (continuously) higher levels of stress hormones, i.e. circulating cortisol levels (Doane & Adam, 2010; Matias, Nicolson, & Freire, 2011), as well as with the levels of pro-inflammatory substances. Cortisol levels may fluctuate strongly over the day, and lower early levels appeared to relate to loneliness, as do higher overall levels. One may be a consequence, the other a cause. It is important to keep in mind that perceived stress does not necessarily correlate with higher cortisol levels. These levels may be lower (Faresjö et al., 2013), normal (Hirvikoski, Lindholm, Nordenström, Nordström, & Lajic, 2009) or higher, depending on the case (Pruessner, Hellhammer, & Kirschbaum, 1999). Stress reduction programs, such as those that are mindfulness-based (MBSR) reportedly result in reduced loneliness. Similar stress-reducing effects on leukocytes were measured after practicing Yoga or yogic meditation (Black, Cole, & Irwin, 2013; Naveen, Varambally, & Thirthalli, 2016). However, possible proof of a causal relationship between stress and loneliness was found when reported loneliness associated with upregulated pro-inflammatory NF-κB-related gene expression in circulating leukocytes, also an indicator of stress, and was found downregulated at post-treatment (Creswell, Irwin, & Burklund, 2012). In an interesting cross-species study as to the reciprocity between stress and loneliness, the increasing effect loneliness has on stress fight-or-flight signalling was measured, reportedly indicating that loneliness makes the subject more sensitive to stress and its health effects. The authors conclude: “Leukocyte gene expression and loneliness appear to have a reciprocal relationship, suggesting that each can help propagate the other over time” (Cole et al., 2015), thus confirming what was known already: that loneliness is not only a probable cause of stress but also one of its consequences. Recent meta-analysed treatments are mainly socio-psychological, and aimed at detecting maladaptive social cognition. However, they do confirm the relevance of leukocytes in social isolation (loneliness) (Masi, Chen, & Hawkley, 2011). In studies on the health consequences of social isolation, endogenous glucocorticoids were found to elevate circulating neutrophils, and suppress lymphocytes and monocytes, in direct proportion to circulating cortisol levels (Cole, 2008). Different types of loneliness had different effects on cortisol (Doane & Adam, 2010) which indicates what we said before: loneliness is an individual and complex phenomenon as to its relationship to stress. The consequences of high circulating cortisol were measured short and long-term. Imaging techniques confirmed the damaging effects of chronic hypercortisolism on the brain, and a (partial) reversibility of damages through early treatment (Resmini, Santos, & Webb, 2016). These negative effects increased in subjects with diagnosed loneliness, confirming the role of the HPA axis in mediating the effects of loneliness on the neuroendocrine system. Much earlier evidence as to a causal role of (non-perceived) stress comes from the cited Glaser group study showing that non-psychotic psychiatric inpatients who experienced loneliness had higher urine levels of cortisol than inpatients who had experienced more social support (Kiecolt-Glaser et al., 1984). This result was independent of the influence of stressful life events, as those did not have any impact on the findings.

Stress was found to have an aggravating effect on health problems when combined with loneliness. In a large study, $N = 7074$, stress had a (much) larger effect on sleep problems if the subject reported loneliness (Lazar, Kerr, & Wasserman, 2005). As said earlier, the reverse hypothesis was investigated in a study $N = 8593$, that showed high stress to trigger adverse health effects especially in lonely subjects (Christiansen et al., 2016). The data confirm loneliness to have not only a psychological but also a distinct physical and stress-originated content (with an important genetic component), together differentiating happy social isolation from sad social isolation, solitude from loneliness (Cacioppo et al., 2000).

Stress and loneliness can be visibly documented. The brain physically reflects when it is vulnerable or resistant to loneliness. Stress reduction through meditation has been found to thicken and strengthen the anterior (frontal) cingulate cortex and the insula over time. These regions are involved with controlled attention, empathy and compassion, which meditation was found to improve (Aanes, Hetland, Pallesen, & Mittelmark, 2011; Kang, Jo, & Jung, 2013). Meditators had less cortical thinning with aging. An even larger group of structures may be involved, as the distributed neuronal pool of dorsolateral, prefrontal and parietal cortices, hippocampus, temporal lobe, anterior cingulate, striatum, and pre- and postcentral gyri is brightened on functional MRI/Positron Emission Tomography studies during meditation, relaxation and spiritual or religious experiences (Fischl & Dale, 2000; Leung, Chan, & Yin, 2013). The first study cited referred to measured cortical thickening resulting from different mental or physical exercises, all producing similar results. Consequently, persons with genetically thicker cortical structures would be more resistant to loneliness because of being less susceptible to stress. In general, meta-analyses on the effects of meditation still express many methodological concerns (Fox, Dixon, & Nijeboer, 2016).

In sum, current research finds loneliness to be a consequence of stress through complex biological, psychological, social and genetic factors, and treatment options will be depending on each of these angles.

6. Sources and effects of solitude

The above describes possible sources, forms and effects of loneliness. Solitude is generally seen as the opposite of loneliness. Their relationship and possible common origins have been commented but not well studied. Loneliness has negative effects on health and well-being. The hypothetical positive effects on health of solitude warrant further scientific exploration. Recent studies suggest that perceived benefits of solitude could be in part imaginary, as some people may

expect solitude to be a more positive state than social contact, something found to be not true (Epley & Schroeder, 2014). However, the "imaginary benefits" of a positive attitude on stress and loneliness did give rise to real benefits when older and lonely adults were induced to positive self-appraisal (Fischl & Dale, 2000). Induced "health-related self-protection", such as positive reappraisals or avoiding self-blame, was reflected over time in diurnal cortisol secretion and higher levels of C-reactive protein (CRP). The longitudinal study ($N = 122$) measured diurnal cortisol levels at baseline and 2-year follow-up, and levels of CRP at 6-year follow-up. Significant long-lasting associations were found between self-protection attitude and lower cortisol levels, but only in lonely adults and not in controls. Similarly, the role of adult self-esteem was found to inversely correlate with diurnal cortisol and, through it, with loneliness (Liu, Wrosch, & Miller, 2014). Nevertheless, lifestyle arguably influences diurnal cortisol levels more, with both psychological (self-esteem) and physiological (longer sleep) changes having a positive influence that reflected in reduced loneliness (Rueggeberg, Wrosch, & Miller, 2012). The positive effects of more solitude that were measured in adolescents improved emotional state and adjustment, as a strategic retreat complementing social experience (Larson, 1997). Here, solitude acted in adolescents as a "detoxifier" of social tension, through reducing stress and reducing vulnerability to loneliness.

7. Diagnostic and treatment options for loneliness

Perceived Social Isolation or loneliness, not being a mental disorder, a psychopathology or a medical condition, must be considered a health problem precursor or prodrome and, as such, warrants the health professional's attention, especially in gerontology. Screening for loneliness has become a standard tool in ageing and older populations. Overall, however, the timely diagnosis of loneliness is a pending issue that critically depends on local protocols (American Academy of Social Work & Social Welfare, 2015; Taylor, Herbers, Talisman, & Morrow-Howell, 2016). These protocols usually manage information of the following kind:

A

- A Habitual screening in at-risk populations, often defined by advanced age which leaves unattended other at-risk groups mentioned above;
- B Detection by cross-referencing with medical conditions and psychological disorders that are known to relate to loneliness, which leaves out not-yet manifest prodromal conditions and thus hampers prevention;
- C Diagnosis of "clinical" loneliness only after clinical symptoms appear, thus omitting attention to manifest but not-yet-clinical conditions.

Habitually, the "current practice" or "assessment protocol" in use will consider treatment only if clinically identifiable symptoms are present (scenario C). Even then, loneliness may be considered habitual in certain populations such as the aged and considered "normal", thus little or no treatment will be applied. Consequently, any clinical manifestations may then be treated only indirectly, thus not as result of loneliness but as resulting from a loneliness-related medical or mental health condition.

Even the more comprehensive protocols existing in several countries do not necessarily lead to identifying and specifically treating loneliness, less so the symptoms and indicators typical of its prodromal stages. Treatment options are limited in scope and efficacy. The importance of paying attention to stress in its medical and biological manifestations as a precursor of PSI is under-recognized.

The data reflected above indicate that treatment of loneliness should include habitually screening for stress in at-risk-cohorts, i.e. adolescents and young adults up to 28 years, men but especially women over 60 years, and single persons with reduced social contacts irrespective of age. Screening would comprise short psychological tests and verification of relevant neurotransmitter levels thru symptom assessment, as well as early and day cortisol.

8. Discussion

We summarize that, since Glaser's et al. studies in the '80 s established a reciprocal relationship between stress markers and loneliness, a considerable body of research supports the hypothesis that the origin of loneliness has a biological, stress-related component. Such a causal component would explain several clinical aspects of loneliness and of solitude that have been producing seemingly contradictory results in existing studies, specifically as to the differential influence between perceived and non-perceived stress. As we mentioned, social isolation may be perceived in the positive sense of "solitude" and may even be actively sought but, nevertheless, a person's isolation *de facto* did affect life expectancy. It is tempting to look for a protective role of solitude through lower stress and inflammation or autoimmune levels, but the long term negative influence on life expectancy that was found in subjects with lower social connectedness, even if that Perceived Positive Social Distance was desired, points at an underlying psychobiological stress-related mechanism.

We saw that, in several studies, the short-term negative effect on health as produced by PSI/loneliness links higher circulating stress-related factors with short and medium term negative effects from cortisol, neutrophil and leukocyte levels as well as with long-term negative effects on the very structure of the brain. A recent cross-sectional Dutch study ($N = 426$) found that lower (thus not higher) cortisol levels at awakening were relevant for loneliness (Schutter et al., 2017). However, cortisol levels noticeably fluctuate over the natural day so both lower early levels and higher general levels are relevant. Moreover, cortisol is not the only relevant circulating factor.

Based on what is known at present, we find sufficient data as to a causal role of stress that would justify the use of an extended biological protocol when screening for loneliness. In turn, a treatment protocol should maintain treatments such as psychological/psychosocial stress reducing programs that were found efficient, but also should consider direct medical treatment to reduce chronic stress, thus aimed at normalizing circulating glucocorticoid, leukocyte and other relevant immune system levels.

As a conclusion, we found consistent and increasing evidence to initially support the hypothesis that stress has a co-causal role in loneliness. The presence of identified and detectable biological and medical factors in ensuing psychological manifestations, facilitates an early detection of chronic stress in loneliness-prone populations. As to treatment, not only the usual (and mostly secondary) psychological or psychosocial treatments are to be considered. Medical treatment of relevant stress-related biological factors could produce early results at less economic and emotional cost. Normalizing circulating levels may contribute to reducing or delaying the development of clinically relevant loneliness. Existing medical treatment options aimed at controlling persistent stress and immune-related factors should be investigated as to their specific efficacy in perceived loneliness.

These interpretations of results have limitations. First and foremost, most studies take loneliness to be a consequence of stress, and more recent studies consider a reciprocal presence, but few specifically investigate the causal role of stress in loneliness. The ones that do – as cited above – should be replicated and extended.

In future research, not only stress and loneliness, but also desired and objective solitude should be differentiated as to circulating levels of stress-related factors. The question we raised at the beginning: "Can medication prevent or reduce loneliness" is especially relevant for future gerontologic research. Present research suggests that controlling for stress in the aging population may reduce or prevent manifest loneliness and this needs to be further established. Furthermore, side-

effects of available medication for stress reduction depend upon age and would benefit from studies as to alternatives.

Finally, data suggest that loneliness may “incubate” in pre-geriatric populations through the stress caused by life changes as identified above. Screening for stress in that age group may give the early warning system needed.

Conflicts of interest

No conflicts of interest.

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