

Social Withdrawal, Loneliness, and Health in Schizophrenia: Psychological and Neural Mechanisms

Daniel Fulford^{*1,2}, and Daphne J. Holt^{*3,4}

¹Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA, USA; ²Psychological and Brain Sciences, Boston University, Boston, MA, USA; ³Department of Psychiatry, Harvard Medical School, Boston, MA, USA; ⁴Massachusetts General Hospital, Boston, MA, USA

*To whom correspondence should be addressed; Daniel Fulford, 635 Commonwealth Ave. Boston, MA 02215, USA; tel: 617-358-2889, e-mail: dfulford@bu.edu; Daphne J. Holt, 149 13th St. Charlestown, MA 02129, USA; tel: 617-726-5610, e-mail: dholt@mg.harvard.edu

Background and Hypothesis: Some of the most debilitating aspects of schizophrenia and other serious mental illnesses (SMI) are the impairments in social perception, motivation, and behavior that frequently accompany these conditions. These impairments may ultimately lead to chronic social disconnection (ie, social withdrawal, objective isolation, and perceived social isolation or loneliness), which may contribute to the poor cardiometabolic health and early mortality commonly observed in SMI. However, the psychological and neurobiological mechanisms underlying relationships between impairments in social perception and motivation and social isolation and loneliness in SMI remain incompletely understood. **Study Design:** A narrative, selective review of studies on social withdrawal, isolation, loneliness, and health in SMI. **Study Results:** We describe some of what is known and hypothesized about the psychological and neurobiological mechanisms of social disconnection in the general population, and how these mechanisms may contribute to social isolation and loneliness, and their consequences, in individuals with SMI. **Conclusions:** A synthesis of evolutionary and cognitive theories with the “social homeostasis” model of social isolation and loneliness represents one testable framework for understanding the dynamic cognitive and biological correlates, as well as the health consequences, of social disconnection in SMI. The development of such an understanding may provide the basis for novel approaches for preventing or treating both functional disability and poor physical health that diminish the quality and length of life for many individuals with these conditions.

Impairments in perceptual and motor processes involved in social interactions and experiences, including deficits

in social perception, motivation, and behavior, are known predictors of functional disability in serious mental illness (SMI; eg, schizophrenia and other disabling psychiatric disorders).^{1–3} Such impairments may also be linked to the experience of “social disconnection” in SMI. Social disconnection is often defined simply and objectively as social *isolation* (ie, having a lower-than-average number of relationships and interactions⁴). A more subjective form of social disconnection is *loneliness*, which has been defined as a perceived discrepancy between the actual and desired levels (quantity and/or quality) of social bonds.^{5–7} Both forms of social disconnection are common among people with SMI.

Importantly, an accumulation of evidence, from studies conducted both in the general population and in people with SMI, has shown that social disconnection is strongly associated with poorer cardiometabolic health,⁸ impaired immune function,⁹ and overall reductions in lifespan.^{8,10} In fact, in SMI, living alone is a stronger predictor of early mortality (which is on average 20 years lower in people with SMI than in the general population¹¹) than smoking or metabolic syndrome.³ These findings raise the question of whether the poor health outcomes associated with SMI may be in part attributable to the experience of isolation and loneliness and their widespread effects throughout the body. Thus, a better understanding of the mechanisms underlying the high levels of social disconnection frequently experienced by people with SMI may lead to the development of novel treatments that could ameliorate some of the serious consequences of these experiences.

To further this goal, in this narrative review, we present a testable model of the psychological and neural mechanisms of social disconnection in SMI, based on a synthesis

of published behavioral and neurobiological data and theoretical models of isolation and loneliness derived primarily from studies conducted in general population samples and animal research. We then summarize evidence for a link between social disconnection and adverse health outcomes and discuss implications for intervention development.

Social Disconnection: Individual Differences and Levels of Analysis

Although much remains unknown about how loneliness and isolation interact and contribute to one another over time, both within and between individuals, the 2 constructs are typically only modestly correlated ($r \sim 0.20$),^{12–14} suggesting that loneliness is not merely a function of inadequate amounts of social contact. Studies have shown that people may experience high levels of both loneliness and isolation, little of either, or one without the other. For example, in a survey study conducted in New Zealand of over 18 000 people, a small proportion (5.7%) reported high levels of both isolation and loneliness; roughly one-third reported elevated loneliness but little isolation, and 7% reported little loneliness but substantial isolation (with the remaining $\sim 50\%$ reporting an absence of both loneliness and isolation).¹⁵ Such distinct expressions of social disconnection highlight the importance of accounting for individual differences in mechanism-focused studies.

It is also clear that the different forms of social disconnection are not static phenomena; the relationship between the frequency and quality of social contacts and the subjective experience of loneliness can vary within people dynamically over time.^{16–19} However, in the majority of prior studies, social disconnection has been most frequently assessed at the “trait” (stable) level, using questionnaires that measure social activity level or loneliness as a more general, dispositional experience (eg, “How often do you feel disconnected from others?”), often without specifying a time frame. However, fluctuations in social connection can be measured using ecological momentary assessment (EMA) methods, with questionnaire items analogous to their dispositional counterparts (eg, “I am alone,” “I feel left out”) but applied on a shorter time scale (ie, in the moment or over a period of hours).²⁰ Despite a large degree of relative stability at the dispositional level,^{20–22} assessment of momentary variation allows for identification of time-varying predictors of these experiences that can inform models of the etiology and maintenance of social disconnection, as well as intervention design.^{18,23,24}

Psychological and Cognitive Mechanisms of Social Disconnection

Research to date has identified several potential psychological and cognitive mechanisms contributing to social

disconnection in the general population,²⁵ of which are likely relevant in SMI as well. Loneliness is moderately correlated with symptoms of depression and social anxiety,^{26–28} and may predict increases in these symptoms prospectively.²⁷ Also, subclinical paranoia is associated with loneliness in the general population,²⁹ and lonely individuals exhibit diminished interpersonal trust^{30,31} which has been linked to specific patterns of brain activity.³⁰ These correlational findings suggest that an underlying bias or set of beliefs in lonely individuals regarding the negative intentions of others, potentially associated with the presence of various forms of psychopathology, may lead to maladaptive interpretations of social situations, ultimately leading to social disconnection. Loneliness itself, then, may contribute to cognitive biases that exacerbate this disconnection.

To make sense of these findings, cognitive and evolutionary frameworks of the etiology and maintenance of loneliness and isolation have been proposed and tested. Cognitive perspectives suggest that a perceived discrepancy between actual and desired social connection leads to the experience of loneliness. These perceptions may arise from stable beliefs or personality characteristics related to feelings of diminished self-worth and self-blame^{28,32} rather than objective experiences of social isolation, which contribute to social withdrawal and disconnection over time. In an evolutionary framework, acute loneliness is believed to serve as a signal that one’s current social bonds are insufficient in number or quality, which initially stimulates motivation and subsequent actions that aim to increase the level of social contact. However, chronic social disconnection can lead to a state of hypervigilance to social threats (ie, fear of rejection or negative appraisals of others), which may represent an adaptive, defensive response that may protect the individual from the real dangers associated with lacking social protection.⁴ This adaptive response can manifest as social amotivation, reflected behaviorally as social withdrawal in the context of the anticipation of aversive social experiences.

These models are supported by studies showing that loneliness is associated with a greater attentional bias toward threatening social cues^{4,33,34} and greater memory for negative social events.³⁵ Additional evidence for the presence of these stable biases in lonely people comes from studies of interpersonal distance.^{30,36–38} In healthy adults, loneliness is associated with preferences for larger interpersonal distance, after controlling for gender, marital status, objective social isolation, anxiety, and depression.³⁶ In a study conducted during the coronavirus disease 2019 pandemic, preferences for larger interpersonal distance were associated with chronic loneliness, while acute, situational loneliness was linked with preferences for smaller interpersonal distances.³⁸ These findings are consistent with the notion that an acute deficit in social bonds facilitates social approach behavior (ie,

smaller interpersonal distances), whereas chronic deficits lead to greater sensitivity to the possibility of negative outcomes of social interactions and self-protective avoidance of others. Larger interpersonal distances have also been associated with lower social motivation and greater social withdrawal in both healthy and SMI populations.³⁹

Overall, these findings suggest that stable negative cognitive biases contribute to the etiology of loneliness and behaviors that may perpetuate it. Importantly, such cognitive and psychological mechanisms may lead to loneliness through their dampening effects on social motivation and the resulting social withdrawal, leading to a self-reinforcing cycle that may exacerbate loneliness over time. Such self-reinforcing drivers of loneliness are likely to be “transdiagnostic” to a large extent (ie, present in SMI, as discussed below, and other clinical populations), although further research is needed to confirm this prediction.

Recent work has also uncovered how the biases that underlie social disconnection may manifest in daily life. For example, EMA work has shown that greater levels of stable, trait-level loneliness are associated with daily social experiences of lower quality or intimacy.⁴⁰ Loneliness, then, may reflect limited experiences of (or opportunities for) *meaningful* social connections.⁴¹ Also, momentary increases in loneliness predict subsequent experiences of emotional hypervigilance (eg, fear, hostility).¹⁸ Consistent with the cognitive and evolutionary models of loneliness, such hypervigilance to social threat could increase sensitivity to cues signaling interpersonal rejection, inhibiting social motivation, and leading to social withdrawal. Individuals who are overly vigilant to potential social threats at a given moment may be more likely to avoid social interaction out of fear of rejection or exclusion, or due to diminished interest in engaging in potentially aversive interactions, thus contributing to a cycle of isolation and loneliness over time. Over the long term, underlying cognitive biases that contribute to the onset of loneliness may themselves intensify because of social isolation. Among people with SMI, this process may be especially detrimental given existing social impairments, which may further interfere with adaptive processes that could interrupt a cycle of chronic disconnection.

Social Disconnection in SMI

Individuals with SMI tend to be both more socially isolated and lonelier than the general population.^{42,43} While the causes of social isolation and loneliness in people with SMI are complex and not fully understood, there is evidence that social disconnection in SMI is not merely an inevitable byproduct of impairments in functioning associated with these illnesses; rather, it may represent a core feature of the psychopathology, with wide-ranging impacts on health and well-being.⁴⁴

Specifically, people with psychotic disorders tend to have small social networks,^{1,45} and frequently report poor

relationship *quality* and high levels of loneliness, which is at least one standard deviation higher than in the general population.^{7,46} Only a small percentage of individuals with SMI are meaningfully employed or have long-term romantic partners.^{47,48} Also, people with SMI report high rates of stigma and perceived rejection, which appear to contribute to social isolation.^{49,50} A commonly held misconception is that people with psychotic disorders do not want relationships; in reality, they consistently cite “improved relationships” as a key treatment goal.^{51–53} Thus, social disconnection in SMI likely reflects having a lower number of relationships characterized by high intimacy.⁵⁴

As described above, one contributor to loneliness in the general population is an elevated sensitivity to negative social evaluation; this bias appears to contribute to loneliness in SMI as well. Symptoms of depression, anxiety, and paranoia, which are also maintained by negative cognitive biases, are associated with loneliness in SMI.⁵⁰ Additional factors, such as perceived discrimination and low self-esteem, have also been identified as correlates of loneliness in SMI.⁵⁵ Moreover, a heightened sensitivity to threat can play an insidious role in reducing the capacity to experience social pleasure, promoting withdrawal behaviors that can perpetuate isolation and loneliness and worsen social impairments that contribute to further isolation and loneliness.¹

Further support for the role of negative cognitive biases in the experience of loneliness is provided by 2 EMA studies of people with schizophrenia; in both studies, higher dispositional (trait-like) loneliness at baseline was associated with significantly lower self-reported quality (ie, intimacy, positive affect) of social interactions in daily life,^{23,56} consistent with similar findings in the general population.⁴⁰ In the one study to date that measured momentary loneliness in people with schizophrenia, reports of loneliness were not lower on average when people were around others vs. alone; loneliness was lower; however, when people were interacting with intimate others (eg, friends or family) compared to when they were alone or with strangers.²³ These findings are consistent with other EMA studies that have found a greater degree of social avoidance and withdrawal in people with SMI, despite reports of higher positive affect in the presence of others vs. when alone.⁵⁷

Thus, greater chronic loneliness in SMI may manifest as hypervigilance to social threat/rejection and social avoidance, which may result in a diminished social drive (lack of interest in or motivation to engage in social interactions). In turn, this diminished social motivation could lead to greater objective isolation over time.¹ This model is consistent with related models of social withdrawal in SMI, including those highlighting the role of defeatist attitudes in negative symptoms, and the impact of stigma and rejection on social information processing.^{3,58} Additional research is needed to determine the extent to which cognitive processes associated with prolonged

loneliness contribute directly to diminished social motivation, as well as how these processes unfold in the context of daily social interactions.

In addition, given the heterogeneity in illness presentation across SMI populations, including the roughly 25% experiencing low social interest/drive who meet criteria for the “deficit syndrome” of schizophrenia,^{59,60} there is clearly a subgroup of people with SMI that are generally uninterested in social connection, and thus objectively isolated but not lonely. In future research, it will be important to characterize such subgroups and individual expressions of isolation and loneliness more fully within SMI populations.

Neurobiological Mechanisms of Social Disconnection

Although little is currently known about the specific brain circuits associated with social isolation and loneliness in SMI, some clues have emerged from neuroimaging studies conducted in the general population. For example, objective isolation has been associated with a smaller volume,^{61,62} lower gray matter density,⁶³ reduced responsiveness,⁶⁴ and reduced connectivity⁶⁵ of the amygdala, a region of the medial temporal lobe known to be involved in social behavior⁶⁶ that is altered in disorders characterized by social functioning deficits (eg, schizophrenia and autism).^{67–70} One cannot infer a causal relationship between a lower amygdala volume, connectivity, or function and social isolation, however; social isolation may be associated with lower levels of stimulation of brain networks involved in social perception (eg, in the perception of human faces) which could result in atrophy of those areas. This second possibility is in fact consistent with evidence from studies in rodents and non-human primates showing reductions in cellular proliferation and myelination of the amygdala, as well as the hippocampus and prefrontal cortex, following social isolation.⁷¹

Neuroimaging studies have identified a large number of brain networks and regions that may be altered in individuals who experience chronic loneliness (see ref. ^{71–73} for comprehensive reviews of this literature). Differences in volume or activation of brain regions involved in emotional and social processing have been linked with higher levels of loneliness, or have been observed in lonely compared to non-lonely individuals. For example, loneliness has been linked to differences in the functioning of the striatum (which includes the caudate, putamen, and nucleus accumbens), with findings of decreased striatal responses to socially rewarding stimuli⁷⁴ and during trust-related decisions³⁰ in lonely individuals. In addition, several studies have identified greater activation or connectivity of attentional systems involved in monitoring the environment, such as the ventral attention and salience networks (ie, including the anterior insula and anterior cingulate cortex), in association with loneliness.^{71,75}

These findings may be linked to the heightened vigilance to social threats observed in lonely individuals.

In addition, several studies have shown that the volume and connectivity of the default network, a group of interconnected brain regions that are involved in introspection, autobiographical memory, and social cognitive processes,^{76,77} are altered in lonely compared to non-lonely individuals.^{78,79} For example, one study that conducted analyses of the UK Biobank dataset ($N = \sim 40,000$) found that several default network regions were larger and exhibited increased within-network functional connectivity in lonely, compared to non-lonely, individuals,⁷⁸ and a follow-up study found related changes in the hippocampus.⁸⁰ These findings may be linked to a greater tendency of lonely (compared to non-lonely) individuals to engage in internally focused cognitive processes that rely on these regions, such as rumination and reviewing the past (ie, retrieving autobiographical memories), and mental simulations of social interactions and conversations. These processes may also represent compensatory mechanisms that attempt to reproduce aspects of experiences of social intimacy that have been lost.⁸¹

These findings in nonclinical populations raise the question of whether prior observations of abnormalities in medial temporal lobe, striatal, attentional, or default network neural systems in schizophrenia^{82–85} could be attributable, at least in part, to the effects of chronic loneliness or isolation. Future studies can investigate this question further, ideally using longitudinal designs.

Also, there are several important caveats to consider when attempting to interpret this literature, including the potentially confounding effects of symptoms of depression and anxiety that are often associated with loneliness (accounted for in some but not all studies) and the challenge of distinguishing between the effects of chronic vs. acute loneliness and causes vs. effects of social disconnection. However, as discussed further below, understanding both the neural and larger systemic correlates of different types of social disconnection may facilitate the development of testable models, which can be used ultimately to validate novel treatments.

Social Disconnection and Cardiometabolic Health

If social disconnection affects brain structure and function (or is driven by such changes), it is probably unsurprising that it appears to have wide-ranging effects throughout the rest of the body as well. Prior research has unequivocally shown that physical well-being is enhanced by social connectedness. For example, social contact (ie, with conspecifics) is associated with an increased life span across many animal species, including bees, ants, rodents, and non-human primates.⁸⁶ Similarly, social isolation and loneliness predict poor health outcomes in humans, including early mortality. Specifically, a recent meta-analysis revealed that social isolation and loneliness

are related to a 29% and 26% increased risk, respectively, of mortality over time.⁸⁷ While data suggest that both isolation and loneliness contribute to poor health in the general population, the precise contributions and mechanisms underlying these relationships are unclear. In a prospective examination of over 30 000 men,⁸⁸ of those who were unmarried with a small social network had a 90% increased risk of cardiovascular death compared to those who were married with a larger network. The socially isolated men were also more than twice as likely to die from an accident or suicide, or to experience a stroke. A later study of this cohort examined both objective isolation and loneliness independently, finding stronger relationships between poor health (ie, cardiovascular disease, inflammation) and loneliness than with social isolation.⁸⁹ Also, a recent longitudinal study showed that older adults who were both isolated and lonely were at highest risk of mortality over time.⁹⁰

Data on the contribution of isolation and loneliness to cardiometabolic disease in people with SMI specifically are currently limited. However, in a large survey in Australia, loneliness was linked with metabolic syndrome in people with psychotic disorders.¹⁰ In another study, loneliness in individuals with schizophrenia was associated with high blood pressure and elevated Hemoglobin A1C.⁹¹

Several potential mechanisms have been proposed to account for the relationships between social isolation, loneliness, and health outcomes. Time spent with healthy others (friends, acquaintances, and family) may serve to promote healthy habits, including healthy eating and physical activity. A stronger social network may also serve to improve access to helpful health-related information, transportation to healthcare providers, and other resources (eg, financial).¹³ Also, loneliness is linked to depression and other forms of psychopathology that are associated with worse health outcomes.^{92,93}

Recent evidence suggests, however, that at least some portion of the associations between physical health and loneliness may arise from a *direct relationship* between loneliness and the physiological responses to stress generated by the body. Loneliness increases sympathetic nervous system activity and inflammatory responses,⁹⁴ and has been shown to interfere with immune function, increasing susceptibility to infection.⁹⁵ Loneliness is also associated with insomnia and poor sleep quality,^{37,96} which has been linked to disrupted immune and cardiovascular function and impaired glucose regulation.⁹⁶

Although the mechanisms underlying these associations remain incompletely understood, the “social homeostasis” model,^{86,97} which synthesizes findings of animal research and human behavioral data, proposes that loneliness represents the subjective manifestation of a physiological signal indicating the presence of a deficit in the availability of protective social bonds (see [figure 1](#) for a schematic illustration of this model). This signal

represents one component of a complex response (which includes a multi-system stress response) designed to restore homeostasis for the organism relative to their “set point” in expected level or quality of social bonds. This set point in social connection is similar to other set points that control homeostatic signals generated by the body to promote survival, such as the experience of hunger or fatigue, which trigger behaviors aimed at correcting deficits in caloric intake or sleep that may threaten well-being. Thus, the acute psychological signal of loneliness is thought to serve the purpose of generating behaviors that then correct a detected deficit in social connection relative to the individual’s set point.

If the deficit in social bonds that triggers a cascade of stress-related mediators is not corrected, the hypothalamic-pituitary-adrenal axis and immune system activation associated with this state of loneliness can become chronic, similar to other states of persistently elevated stress. Chronic social disconnection accompanied by these physiological derangements (elevated stress and immunological responses) may then negatively impact cardiometabolic health over time, possibly similar to the way that chronic states of elevated stress due to other types of environmental adversity (poverty, maltreatment, and neighborhood effects) can be detrimental to physical health.¹⁰¹

This state of social disconnection and related activation of systemic and neural stress responses can become self-sustaining over time in part due to the relationship (present in some individuals) between chronic loneliness and an increased vigilance or sensitivity to social threat/rejection, which paradoxically interferes with the individual’s ability to seek out the social supports that would correct this deficit.

Responses to Changes in “Social Homeostasis” and Implications for SMI

Matthews and Tye proposed that the social homeostatic system has three components: A detector, control center, and effector ([figure 1A](#)). In this model, when there is a reduction in the level of social connection, the detector identifies a change in the quantity or quality of social bonds, and the control center compares this quantity to the set point in social connection for the individual. If a deficit is detected, the effector system is engaged to correct this deficit by generating the subjective, conscious state of loneliness (and the accompanying systemic stress response), followed by the motivation and subsequent behaviors that may lead to an increase in social contact and connection. The effector system may also heighten attention to the environment to facilitate detection of social resources as well as threats. If the deficit in social bonds is corrected by the social approach-related actions triggered by the effector system, feedback about the new, no-longer-deficient state is then sent back to the detector,

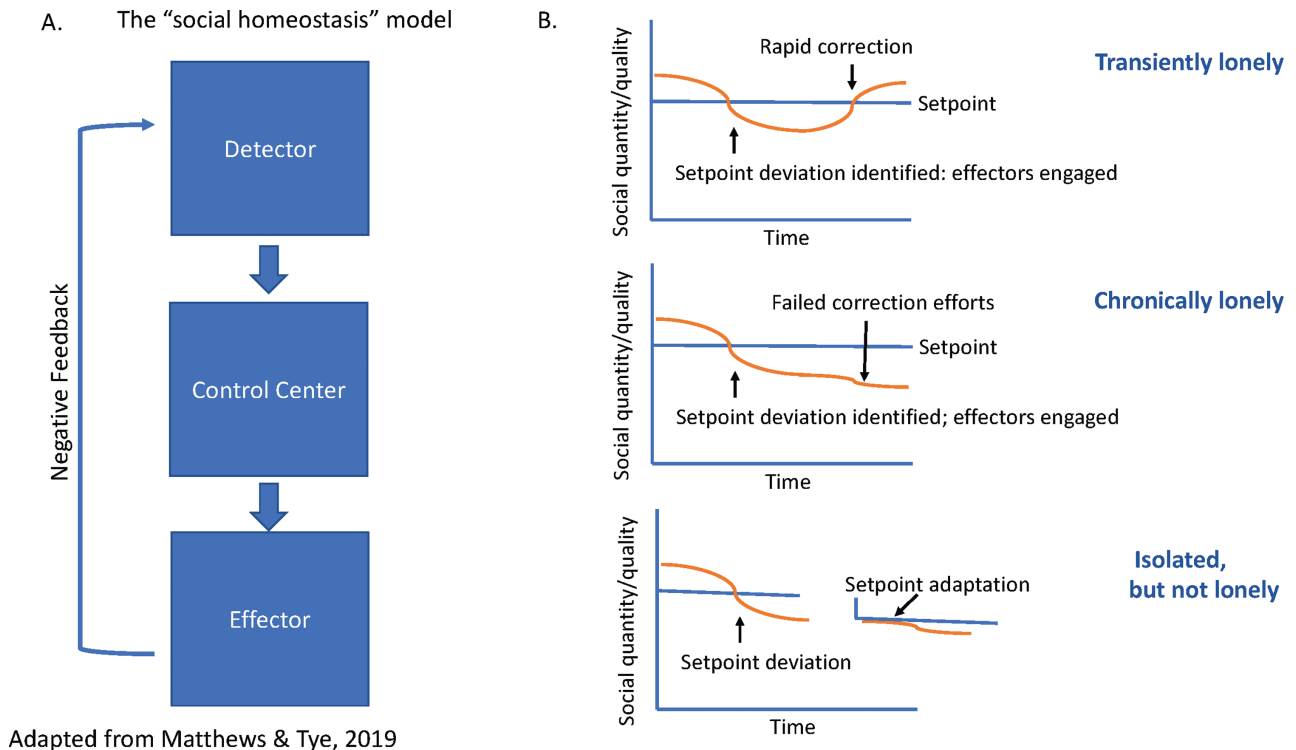


Fig. 1. A schematic of the social homeostasis model, as proposed and developed by Matthews and Tye,⁸⁶ is presented (figure adapted with permission from⁸⁶). Although the neural correlates of these components of this model are unknown, we speculate that the Detector function in this system may rely on brain networks involved in social perception, such as the amygdala and other areas of the “social brain.”⁹⁸ The Control Center may engage brain regions that track social knowledge and memories, such as the hippocampus, the temporal-parietal junction, and the default network, to compare the individual’s current social state with stored expectations. Thus, the Effector System may have several components, perhaps including brainstem projections from the ventral tegmental area, dorsal raphe nucleus, and locus coeruleus, that are stimulated by the hypothalamus, which drives changes in mood, vigilance, and systemic changes in sympathetic nervous system activity and immune system mediators. This is consistent with findings of rodent studies that have shown that social isolation leads to activation of the hypothalamic-pituitary-adrenal axis (HPA) axis via the release of corticotropin-releasing factor by the paraventricular nucleus of the hypothalamus. Thus, the Effector System may generate the psychological signal of loneliness and in parallel a physiologic stress response, with increases in activity of the HPA axis and sympathetic nervous system activity involving the release of glucocorticoids such as cortisol, and epinephrine, as well as increases in the release of pro-inflammatory cytokines and other immunological mediators, such as interleukin-6, C-reactive protein and fibrinogen.^{99,100} The activity of the ventral tegmental area and dorsal raphe nucleus dopaminergic neurons may signal both the aversive state of isolation and the rewarding aspects of social contact via distinct projections to the amygdala, striatum, and prefrontal cortex. Loneliness is also associated with a shift in immune function, with enhanced pro-inflammatory activity but a reduced antiviral response, which is thought to prepare an individual for the infections most likely to be encountered when alone (ie, bacterial infections sustained through physical injury but fewer socially transmitted viral infections⁹). Thus, taken together, this model proposes, based on a large body of animal research, that a multi-system response is generated by the brain to respond to discrepancies between expected or desired and actual levels of social bonds, which serves to correct a survival-threatening state of reduced social contact and support.

and the corrective process is then inhibited until a new deviation is detected. However, if the deficit is not corrected, then this system may be persistently “turned on.”

Thus, if this system is working well, small perturbations in social connectedness are rapidly corrected, and individuals spend most of their daily life near their set point (figure 1B, top panel). However, if a deviation from this social connection set point is not corrected, persistent engagement of the Effector System may occur, which can lead to damage to cardiovascular and metabolic systems, inhibition of social motivation, and the development of maladaptive behaviors such as social withdrawal (figure 1B, middle panel). Lastly, a

third scenario may arise if a deviation occurs early in neurodevelopment (during a period of plasticity in this system), when a consistently low quantity or quality of social bonds may lead to a change in the individual’s set point. In this case, a state of social connection that was previously assessed as deficient may no longer register as a deviation from the setpoint. Such a set point shift could also occur following major losses at later points in life (eg, marital separation, death of a loved one).¹⁰² In individuals with “low” set points, isolation may not trigger loneliness or lead to the negative cardiometabolic effects of social disconnection (figure 1B, bottom panel).

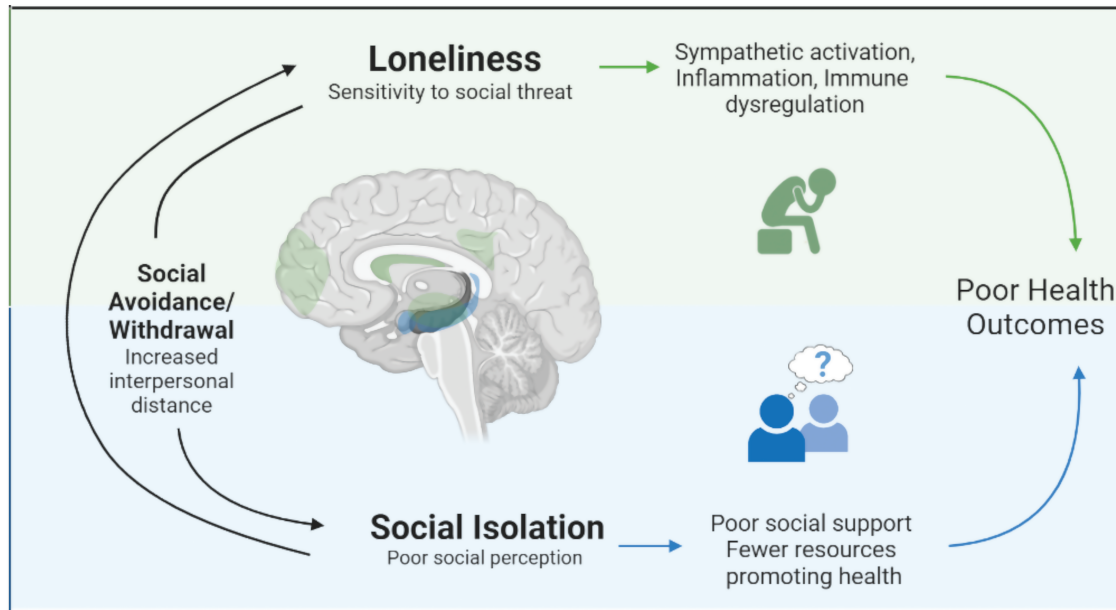


Fig. 2. A schematic diagram illustrating the proposed model of this review, incorporating some of the psychological, behavioral, and health correlates of isolation and loneliness in serious mental illnesses (SMI), is shown. Although there is a rapidly growing body of work uncovering important correlates of social disconnection and their associations with health outcomes, the complex and dynamic nature of social isolation and loneliness suggests a multi-method approach will be critical to answering the unresolved questions about the mechanisms of social disconnection in SMI. Studies including assessment of both stable and dynamic correlates of social disconnection at multiple levels of analysis (psychological, behavioral, and neural), combined with measures of health outcomes, collected in longitudinal designs, could inform the development of new interventions that could reverse some of the adverse psychological and systemic consequences of isolation and loneliness.

Individuals with or without SMI may exhibit each of the three expressions of social homeostasis illustrated in figure 1, but the two characterized by fewer social contacts (ie, chronic loneliness, or social isolation without loneliness) may be more common in SMI than in the general population. This social homeostasis model could provide one framework that could be useful for identifying in individuals with SMI: (1) an individual's set point in their expectations or desire for social connection, and (2) potential causes for "correction failures" after set point deviations. For example, in light of the impairments in social cognition and social skills in SMI that are frequently present even before the onset of illness,^{103–105} chronic disconnection early in life could result in a lower-than-average set point that persists throughout the life course.

Potential Mechanisms Through Which Social Disconnection Impacts Health in SMI

A model that synthesizes known and hypothesized relationships among psychological, cognitive, and neural mechanisms of social disconnection in SMI is presented in figure 2. First, we propose that impairments in the function of the amygdala and hippocampus (regions of the medial temporal lobe [MTL]) lead to poor social perception (ie, impairments in perceptual processes involved in social cognition such as facial affect recognition) in SMI,

which then gives rise to social *isolation*. (Alternatively, less frequent engagement of the MTL in social perception-related processes, due to social isolation, may lead to impairments in MTL functioning, due to "lack of use" and subsequent experience-dependent modification or atrophy of the MTL.) In support of this prediction is the evidence that poor social perception is linked to impairments in psychosocial functioning in SMI.^{106,107}

Secondly, the experience of *loneliness* may be triggered by a larger network of brain regions involved in perceiving social information and mediating social interactions (see figure 1 legend), such as the default network, medial temporal lobe structures, the striatum, and anterior insula.^{30,75,78,79} These regions play key roles in reward processes and detection of salient information in the environment. In addition, the circuitry involved in the generation of the subjective state of loneliness likely includes the midbrain and hypothalamus, given the involvement of these areas in stress responses and homeostatic processes.⁸⁶

A specific response of brain networks involved in social perception and reward may represent the measurable manifestation (as quantified by conventional brain imaging techniques such as functional magnetic resonance imaging) of the long-term effects of a persistent homeostatic signal, involving the release of stress and inflammatory response mediators, that indicate that the individual's baseline requirement for closeness with others has not been met.^{97,108,109} In addition to the experience of

loneliness, this neural response may be accompanied by discomfort in the presence of others (due to anticipated rejection) and a need for greater physical distance from others (interpersonal space),^{36,38} as well as a bias towards a greater allocation of attention to social threat (ie, rejection)¹⁸ during social interactions. In some individuals, such biases could then lead to diminished social motivation, social avoidance, and isolation.

Critically, a chronically elevated systemic stress response occurring as a consequence of a persistent difference between the *expected* and *actual* level of social connection¹¹⁰ is predicted to impact cardiometabolic health (eg, lead to dyslipidemia, hypertension) in SMI over time. In addition, chronic social isolation likely also leads to poor health outcomes because of the associated reduced availability of health-promoting supports and resources. Moreover, the combined effects of high levels of both loneliness and isolation—common in SMI—could result in particularly poor cardiometabolic outcomes.

Implications for Intervention

If core aspects of the proposed model (figure 2) are confirmed by ongoing and future research, novel approaches for intervention could follow. Identifying behavioral antecedents of fluctuations in social isolation and loneliness within individuals in the context of daily life could uncover targets for cognitive and behavioral interventions, particularly those that can be delivered “just-in-time” by mobile technologies (eg, smartphone apps). Addressing underlying cognitions that may contribute to a cycle of behaviors and self-reinforcing beliefs that perpetuate loneliness could represent a key component of a treatment plan aimed at reducing social disconnection.

Furthermore, behavioral correlates of social disconnection, such as abnormalities in personal space preferences and social perception, could represent components of a phenotype of social isolation and loneliness in SMI that could be employed as an intermediate target of early detection and intervention strategies. Addressing the unique contributors to social isolation and loneliness in SMI, and the relationships of each to functional and health outcomes, will be important as well. For example, if objective social isolation results in fewer health-promoting behaviors due to limited social support or available resources, then treatments that target such isolating behaviors should have the added benefit of directly improving health, broadly speaking. On the other hand, interventions that target the cognitive underpinnings of loneliness, perhaps through reductions of maladaptive beliefs regarding anticipated social rejection, could theoretically reduce the direct negative impacts of such perceptions on social motivation and the ability to generate behaviors that correct deficits in levels or quality of social bonds. Such a correction could then “turn off”

the damaging physiological processes that adversely impact cardiometabolic health.

Summary and Conclusions

This narrative review summarized some of what is currently known about the psychological, cognitive, and neural correlates of social disconnection, as well as some of the recent studies of the moment-to-moment changes in these experiences, and how social disconnection may contribute to poor physical health over time in SMI. Extending the concept of social homeostasis, we presented a mechanistic model of social isolation and loneliness in SMI that could provide one working framework for future investigations. In addition, novel interventions could be deployed to target its different components, both to test the model’s validity (its proposed sequence of mechanisms) and to identify a range of potential approaches for reversing the negative consequences of social disconnection in SMI. Targeting isolation and loneliness in SMI may represent one less explored avenue for treating or preventing the poor physical health and diminished quality of life that remains all too common in this population.

Acknowledgments

We acknowledge the following funding sources in preparing this manuscript. We also thank Renata Botello for her help in preparing figure 2.

Funding

National Institute of Mental Health (NIMH) R01MH109562, R01MH122367, R01MH125426, and R01MH127265.

References

1. Fulford D, Campellone T, Gard DE. Social motivation in schizophrenia: how research on basic reward processes informs and limits our understanding. *Clin Psychol Rev*. 2018;63:12–24. doi: [10.1016/j.cpr.2018.05.007](https://doi.org/10.1016/j.cpr.2018.05.007)
2. Botello R, Gill K, Mow JL, et al. Validation of the Social Effort and Conscientious Scale (SEACS) in Schizophrenia. *J Psychopathol Behav Assess*. 2023. doi: [10.1007/s10862-023-10031-1](https://doi.org/10.1007/s10862-023-10031-1)
3. Green MF, Horan WP, Lee J, McCleery A, Reddy LF, Wynn JK. At Issue: Social Disconnection in Schizophrenia and the General Community. *Schizophr Bull*. 2017;44:242–249. doi: [10.1093/schbul/sbx082](https://doi.org/10.1093/schbul/sbx082)
4. Cacioppo JT, Hawkley LC, Ernst JM, et al. Loneliness within a nomological net: an evolutionary perspective. *J Res Person*. 2006;40(6):1054–1085.
5. Stain HJ, Galletly CA, Clark S, et al. Understanding the social costs of psychosis: the experience of adults affected by psychosis identified within the second Australian national

- survey of psychosis. *Aust N Z J Psychiatry*. 2012;46(9):879–889. doi: [10.1177/0004867412449060](https://doi.org/10.1177/0004867412449060)
6. Badcock JC, Shah S, Mackinnon A, et al. Loneliness in psychotic disorders and its association with cognitive function and symptom profile. *Schizophr Res*. 2015;169(1-3):268–273. doi: [10.1016/j.schres.2015.10.027](https://doi.org/10.1016/j.schres.2015.10.027)
 7. Eglit GML, Palmer BW, Martin AS, Tu X, Jeste DV. Loneliness in schizophrenia: construct clarification, measurement, and clinical relevance. *PLoS One*. 2018;13(3):e0194021. doi: [10.1371/journal.pone.0194021](https://doi.org/10.1371/journal.pone.0194021)
 8. Fortuna KL, Brusilovskiy E, Snethen G, Brooks JM, Townley G, Salzer MS. Loneliness and its association with physical health conditions and psychiatric hospitalizations in people with serious mental illness. *Soc Work Ment Health*. 2020;18(5):571–585. doi: [10.1080/15332985.2020.1810197](https://doi.org/10.1080/15332985.2020.1810197)
 9. Cole SW, Levine ME, Arevalo JMG, Ma J, Weir DR, Crimmins EM. Loneliness, eudaimonia, and the human conserved transcriptional response to adversity. *Psychoneuroendocrinology*. 2015;62:11–17. doi: [10.1016/j.psyneuen.2015.07.001](https://doi.org/10.1016/j.psyneuen.2015.07.001)
 10. Badcock JC, Mackinnon A, Waterreus A, et al. Loneliness in psychotic illness and its association with cardiometabolic disorders. *Schizophr Res*. 2019;204:90–95. doi: [10.1016/j.schres.2018.09.021](https://doi.org/10.1016/j.schres.2018.09.021)
 11. Correll CU, Solmi M, Croatto G, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry*. 2022;21(2):248–271. doi: [10.1002/wps.20994](https://doi.org/10.1002/wps.20994)
 12. Cacioppo JT, Hawkley LC, Berntson GG. The anatomy of loneliness. *Curr Dir Psychol Sci*. 2003;12(3):71–74.
 13. Cornwell EY, Waite LJ. Measuring social isolation among older adults using multiple indicators from the NSHAP study. *J Gerontol B Psychol Sci Soc Sci*. 2009;64B(suppl 1):i38–i46. doi: [10.1093/geronb/gbp037](https://doi.org/10.1093/geronb/gbp037)
 14. Reinhardt JP, Boerner K, Horowitz A. Good to have but not to use: differential impact of perceived and received support on well-being. *J Soc Pers Relatsh*. 2006;23(1):117–129. doi: [10.1177/0265407506060182](https://doi.org/10.1177/0265407506060182)
 15. Hawkins-Elder H, Milfont TL, Hammond MD, Sibley CG. Who are the lonely? A typology of loneliness in New Zealand. *Aust N Z J Psychiatry*. 2018;52(4):357–364. doi: [10.1177/0004867417718944](https://doi.org/10.1177/0004867417718944)
 16. Goldman AW, Compernelle EL. Personal network size and social accompaniment: protective or risk factor for momentary loneliness, and for whom? *Soc Ment Health*. 2023;13(1):23–44. doi: [10.1177/21568693221142336](https://doi.org/10.1177/21568693221142336)
 17. Doane LD, Adam EK. Loneliness and cortisol: momentary, day-to-day, and trait associations. *Psychoneuroendocrinology*. 2010;35(3):430–441. doi: [10.1016/j.psyneuen.2009.08.005](https://doi.org/10.1016/j.psyneuen.2009.08.005)
 18. Meng J, Wang X, Wei D, Qiu J. State loneliness is associated with emotional hypervigilance in daily life: a network analysis. *Pers Individ*. 2020;165:110154. doi: [10.1016/j.paid.2020.110154](https://doi.org/10.1016/j.paid.2020.110154)
 19. Awad R, Shamay-Tsoory SG, Palgi Y. Fluctuations in loneliness due to changes in frequency of social interactions among older adults: a weekly based diary study. *Int Psychogeriatr*. 2023;35:1–11. doi: [10.1017/S1041610223000133](https://doi.org/10.1017/S1041610223000133)
 20. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J Pers Assess*. 1996;66(1):20–40. doi: [10.1207/s15327752jpa6601_2](https://doi.org/10.1207/s15327752jpa6601_2)
 21. Lin CY, Tsai CS, Jian CR, et al. Comparing the psychometric properties among three versions of the UCLA loneliness scale in individuals with schizophrenia or schizoaffective disorder. *Int J Environ Res Public Health*. 2022;19(14):8443. doi: [10.3390/ijerph19148443](https://doi.org/10.3390/ijerph19148443)
 22. Zawisza K, Galas A, Tobiasz-Adamczyk B, et al. The validity of the instrument to evaluate social network in the ageing population: the collaborative research on ageing in europe social network index. *Clin Psychol Psychother*. 2014;21(3):227–241. doi: [10.1002/cpp.1860](https://doi.org/10.1002/cpp.1860)
 23. Culbreth AJ, Barch DM, Moran EK. An ecological examination of loneliness and social functioning in people with schizophrenia. *J Abnorm Psychol*. 2021;130(8):899–908. doi: [10.1037/abn0000706](https://doi.org/10.1037/abn0000706)
 24. van Roekel E, Verhagen M, Engels RCME, Scholte RHJ, Cacioppo S, Cacioppo JT. Trait and state levels of loneliness in early and late adolescents: examining the differential reactivity hypothesis. *J Clin Child Adolesc Psychol*. 2018;47(6):888–899. doi: [10.1080/15374416.2016.1146993](https://doi.org/10.1080/15374416.2016.1146993)
 25. Larson R, Csikszentmihalyi M. Experiential correlates of time alone in adolescence. *J Pers*. 1978;46(4):677–693. doi: [10.1111/j.1467-6494.1978.tb00191.x](https://doi.org/10.1111/j.1467-6494.1978.tb00191.x)
 26. Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychol Aging*. 2006;21(1):140–151. doi: [10.1037/0882-7974.21.1.140](https://doi.org/10.1037/0882-7974.21.1.140)
 27. Lim MH, Rodebaugh TL, Zyphur MJ, Gleason JFM. Loneliness over time: the crucial role of social anxiety. *J Abnorm Psychol*. 2016;125(5):620–630. doi: [10.1037/abn0000162](https://doi.org/10.1037/abn0000162)
 28. Vanhalst J, Soenens B, Luyckx K, Van Petegem S, Weeks MS, Asher SR. Why do the lonely stay lonely? Chronically lonely adolescents' attributions and emotions in situations of social inclusion and exclusion. *J Pers Soc Psychol*. 2015;109(5):932–948. doi: [10.1037/pspp0000051](https://doi.org/10.1037/pspp0000051)
 29. Contreras A, Valiente C, Vázquez C, et al. The network structure of paranoia dimensions and its mental health correlates in the general population: the core role of loneliness. *Schizophr Res*. 2022;246:65–73. doi: [10.1016/j.schres.2022.06.005](https://doi.org/10.1016/j.schres.2022.06.005)
 30. Lieberz J, Shamay-Tsoory SG, Saporta N, et al. Loneliness and the social brain: how perceived social isolation impairs human interactions. *Adv Sci*. 2021;8(21):2102076. doi: [10.1002/advs.202102076](https://doi.org/10.1002/advs.202102076)
 31. Spithoven AWM, Bijttebier P, Goossens L. It is all in their mind: a review on information processing bias in lonely individuals. *Clin Psychol Rev*. 2017;58:97–114. doi: [10.1016/j.cpr.2017.10.003](https://doi.org/10.1016/j.cpr.2017.10.003)
 32. Qualter P, Vanhalst J, Harris R, et al. Loneliness across the life span. *Perspect Psychol Sci*. 2015;10(2):250–264. doi: [10.1177/1745691615568999](https://doi.org/10.1177/1745691615568999)
 33. Cacioppo S, Bangee M, Balogh S, Cardenas-Iniguez C, Qualter P, Cacioppo JT. Loneliness and implicit attention to social threat: a high-performance electrical neuroimaging study. *Cogn Neurosci*. 2016;7(1-4):138–159. doi: [10.1080/17588928.2015.1070136](https://doi.org/10.1080/17588928.2015.1070136)
 34. Bangee M, Harris RA, Bridges N, Rotenberg KJ, Qualter P. Loneliness and attention to social threat in young adults: findings from an eye tracker study. *Pers Individ*. 2014;63:16–23. doi: [10.1016/j.paid.2014.01.039](https://doi.org/10.1016/j.paid.2014.01.039)
 35. Cacioppo JT, Hawkley LC. Perceived social isolation and cognition. *Trends Cogn Sci*. 2009;13(10):447–454. doi: [10.1016/j.tics.2009.06.005](https://doi.org/10.1016/j.tics.2009.06.005)
 36. Layden EA, Cacioppo JT, Cacioppo S. Loneliness predicts a preference for larger interpersonal distance within intimate space. *PLoS One*. 2018;13(9):e0203491. doi: [10.1371/journal.pone.0203491](https://doi.org/10.1371/journal.pone.0203491)
 37. Ben Simon E, Walker MP. Sleep loss causes social withdrawal and loneliness. *Nat Commun*. 2018;9(1):3146. doi: [10.1038/s41467-018-05377-0](https://doi.org/10.1038/s41467-018-05377-0)

38. Saporta N, Scheele D, Lieberz J, Stuhr-Wulff F, Hurlemann R, Shamay-Tsoory SG. Opposing association of situational and chronic loneliness with interpersonal distance. *Brain Sci.* 2021;11(9):1135. doi: [10.3390/brainsci11091135](https://doi.org/10.3390/brainsci11091135)
39. Zapetis SL, Nasirivanaki Z, Luther L, Holt DJ. Neural correlates of variation in personal space and social functioning in schizophrenia and healthy individuals. *Schizophr Bull.* 2022;48(5):1075–1084. doi: [10.1093/schbul/sbac052](https://doi.org/10.1093/schbul/sbac052)
40. Hawkley LC, Preacher KJ, Cacioppo JT. Multilevel modeling of social interactions and mood in lonely and socially connected individuals: the MacArthur social neuroscience studies. In: Ong AD, van Dulmen MHM, eds. *Oxford Handbook of Methods in Positive Psychology. Series in positive psychology.* Oxford, UK: Oxford University Press; 2007:559–575.
41. Winkel M van, Wichers M, Collip D, et al. Unraveling the role of loneliness in depression: the relationship between daily life experience and behavior. *Psychiatry.* 2017;80(2):104–117. doi: [10.1080/00332747.2016.1256143](https://doi.org/10.1080/00332747.2016.1256143)
42. Yanos PT, Stefanic A, Tsemberis S. Psychological community integration among people with psychiatric disabilities and nondisabled community members. *J Commun Psychol.* 2011;39(4):390–401. doi: [10.1002/jcop.20441](https://doi.org/10.1002/jcop.20441)
43. Gayer-Anderson C, Morgan C. Social networks, support and early psychosis: a systematic review. *Epidemiol Psychiatr Sci.* 2013;22(2):131–146. doi: [10.1017/S2045796012000406](https://doi.org/10.1017/S2045796012000406)
44. Badcock JC, Adery LH, Park S. Loneliness in psychosis: a practical review and critique for clinicians. *Clin Psychol Sci Pract.* 2020;27(4):e12345. doi: [10.1111/cpsp.12345](https://doi.org/10.1111/cpsp.12345)
45. Mueser KT, Bellack AS, Douglas MS, Morrison RL. Prevalence and stability of social skill deficits in schizophrenia. *Schizophr Res.* 1991;5(2):167–176.
46. Bellack AS, Mueser KT, Gingerich S, Agresta J. *Social Skills Training for Schizophrenia: A Step-by-Step Guide.* 2nd ed. New York, USA: Guilford Press; 2004.
47. Marwaha S, Johnson S. Schizophrenia and employment. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39(5):337–349. doi: [10.1007/s00127-004-0762-4](https://doi.org/10.1007/s00127-004-0762-4)
48. Agerbo E, Byrne M, Eaton WW, Mortensen PB. Marital and labor market status in the long run in schizophrenia. *Arch Gen Psychiatry.* 2004;61(1):28–33. doi: [10.1001/archpsyc.61.1.28](https://doi.org/10.1001/archpsyc.61.1.28)
49. Lincoln SH, Johnson T, Winters A, Laquidara J. Social exclusion and rejection across the psychosis spectrum: a systematic review of empirical research. *Schizophr Res.* 2021;228:43–50. doi: [10.1016/j.schres.2020.11.056](https://doi.org/10.1016/j.schres.2020.11.056)
50. Lim MH, Gleeson JFM, Alvarez-Jimenez M, Penn DL. Loneliness in psychosis: a systematic review. *Soc Psychiatry Psychiatr Epidemiol.* 2018;53(3):221–238. doi: [10.1007/s00127-018-1482-5](https://doi.org/10.1007/s00127-018-1482-5)
51. Auslander LA, Jeste DV. Perceptions of problems and needs for service among middle-aged and elderly outpatients with schizophrenia and related psychotic disorders. *Community Ment Health J.* 2002;38(5):391–402. doi: [10.1023/a:1019808412017](https://doi.org/10.1023/a:1019808412017)
52. Pinfold V, Sweet D, Porter I, et al. Improving community health networks for people with severe mental illness: a case study investigation. *NIHR Journals Library.* 2015;3. <http://www.ncbi.nlm.nih.gov/books/NBK276549/>. Accessed March 8, 2020.
53. Morgan VA, Waterreus A, Jablensky A, et al. People living with psychotic illness in 2010: the second Australian national survey of psychosis. *Aust N Z J Psychiatry.* 2012;46(8):735–752. doi: [10.1177/0004867412449877](https://doi.org/10.1177/0004867412449877)
54. Cuthbert BN. The PRISM project: social withdrawal from an RDoC perspective. *Neurosci Biobehav Rev.* 2019;97:34–37. doi: [10.1016/j.neubiorev.2018.08.006](https://doi.org/10.1016/j.neubiorev.2018.08.006)
55. Świtaj P, Grygiel P, Anczewska M, Wciórka J. Experiences of discrimination and the feelings of loneliness in people with psychotic disorders: the mediating effects of self-esteem and support seeking. *Compr Psychiatry.* 2015;59:73–79. doi: [10.1016/j.comppsy.2015.02.016](https://doi.org/10.1016/j.comppsy.2015.02.016)
56. Mote J, Gard DE, Gonzalez R, Fulford D. How did that interaction make you feel? The relationship between quality of everyday social experiences and emotion in people with and without schizophrenia. *PLoS One.* 2019;14(9):e0223003. doi: [10.1371/journal.pone.0223003](https://doi.org/10.1371/journal.pone.0223003)
57. Mote J, Fulford D. Ecological momentary assessment of everyday social experiences of people with schizophrenia: a systematic review. *Schizophr Res.* 2019;216:56–68. doi: [10.1016/j.schres.2019.10.021](https://doi.org/10.1016/j.schres.2019.10.021)
58. Grant PM, Beck AT. Defeatist beliefs as a mediator of cognitive impairment, negative symptoms, and functioning in schizophrenia. *Schizophr Bull.* 2009;35(4):798–806.
59. Kirkpatrick B, Buchanan RW, McKenny PD, Alphas LD, Carpenter WT. The schedule for the deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Res.* 1989;30(2):119–123.
60. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry.* 2001;58(2):165–171. doi: [10.1001/archpsyc.58.2.165](https://doi.org/10.1001/archpsyc.58.2.165)
61. Bickart KC, Wright CI, Dautoff RJ, Dickerson BC, Barrett LF. Amygdala volume and social network size in humans. *Nat Neurosci.* 2011;14(2):163–164. doi: [10.1038/nn.2724](https://doi.org/10.1038/nn.2724)
62. Von Der Heide R, Vyas G, Olson IR. The social network: size is predicted by brain structure and function in the amygdala and paralimbic regions. *Soc Cogn Affect Neurosci.* 2014;9(12):1962–1972. doi: [10.1093/scan/nsu009](https://doi.org/10.1093/scan/nsu009)
63. Kanai R, Bahrami B, Roylance R, Rees G. Online social network size is reflected in human brain structure. *Proc Biol Sci.* 2012;279(1732):1327–1334. doi: [10.1098/rspb.2011.1959](https://doi.org/10.1098/rspb.2011.1959)
64. Dziura SL, Thompson JC. Social-network complexity in humans is associated with the neural response to social information. *Psychol Sci.* 2014;25(11):2095–2101. doi: [10.1177/0956797614549209](https://doi.org/10.1177/0956797614549209)
65. Bickart KC, Hollenbeck MC, Barrett LF, Dickerson BC. Intrinsic amygdala–cortical functional connectivity predicts social network size in humans. *J Neurosci.* 2012;32(42):14729–14741. doi: [10.1523/JNEUROSCI.1599-12.2012](https://doi.org/10.1523/JNEUROSCI.1599-12.2012)
66. Adolphs R. What does the amygdala contribute to social cognition? *Ann N Y Acad Sci.* 2010;1191(1):42–61. doi: [10.1111/j.1749-6632.2010.05445.x](https://doi.org/10.1111/j.1749-6632.2010.05445.x)
67. Hennessey T, Andari E, Rainnie DG. RDoC-based categorization of amygdala functions and its implications in autism. *Neurosci Biobehav Rev.* 2018;90:115–129. doi: [10.1016/j.neubiorev.2018.04.007](https://doi.org/10.1016/j.neubiorev.2018.04.007)
68. Anticevic A, Van Snellenberg JX, Cohen RE, Repovs G, Dowd EC, Barch DM. Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. *Schizophr Bull.* 2012;38(3):608–621. doi: [10.1093/schbul/sbq131](https://doi.org/10.1093/schbul/sbq131)
69. Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biol Psychiatry.* 2012;71(2):136–145. doi: [10.1016/j.biopsych.2011.09.007](https://doi.org/10.1016/j.biopsych.2011.09.007)

70. Pinkham AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophr Res*. 2008;99(1-3):164–175. doi: [10.1016/j.schres.2007.10.024](https://doi.org/10.1016/j.schres.2007.10.024)
71. Finley AJ, Schaefer SM. Affective neuroscience of loneliness: potential mechanisms underlying the association between perceived social isolation, health, and well-being. *J Psychiatr Brain Sci*. 2022;7(6):e220011. doi: [10.20900/jpbs.20220011](https://doi.org/10.20900/jpbs.20220011)
72. Lam JA, Murray ER, Yu KE, et al. Neurobiology of loneliness: a systematic review. *Neuropsychopharmacol*. 2021;46(11):1873–1887. doi: [10.1038/s41386-021-01058-7](https://doi.org/10.1038/s41386-021-01058-7)
73. Zovetti N, Rossetti MG, Perlini C, Brambilla P, Bellani M. Neuroimaging studies exploring the neural basis of social isolation. *Epidemiol Psychiatr Sci*. 2021;30:e29. doi: [10.1017/S2045796021000135](https://doi.org/10.1017/S2045796021000135)
74. Cacioppo JT, Norris CJ, Decety J, Monteleone G, Nusbaum H. In the eye of the beholder: individual differences in perceived social isolation predict regional brain activation to social stimuli. *J Cogn Neurosci*. 2009;21(1):83–92. doi: [10.1162/jocn.2009.21007](https://doi.org/10.1162/jocn.2009.21007)
75. Layden EA, Cacioppo JT, Cacioppo S, et al. Perceived social isolation is associated with altered functional connectivity in neural networks associated with tonic alertness and executive control. *Neuroimage*. 2017;145(Pt A):58–73. doi: [10.1016/j.neuroimage.2016.09.050](https://doi.org/10.1016/j.neuroimage.2016.09.050)
76. Buckner RL, DiNicola LM. The brain's default network: updated anatomy, physiology and evolving insights. *Nat Rev Neurosci*. 2019;20(10):593–608. doi: [10.1038/s41583-019-0212-7](https://doi.org/10.1038/s41583-019-0212-7)
77. Yeshurun Y, Nguyen M, Hasson U. The default mode network: where the idiosyncratic self meets the shared social world. *Nat Rev Neurosci*. 2021;22(3):181–192. doi: [10.1038/s41583-020-00420-w](https://doi.org/10.1038/s41583-020-00420-w)
78. Spreng RN, Dimas E, Mwilambwe-Tshilobo L, et al. The default network of the human brain is associated with perceived social isolation. *Nat Commun*. 2020;11(1):6393. doi: [10.1038/s41467-020-20039-w](https://doi.org/10.1038/s41467-020-20039-w)
79. Baek EC, Hyon R, López K, Du M, Porter MA, Parkinson C. Lonely individuals process the world in idiosyncratic ways. *Psychol Sci*. 2023;34:09567976221145316. doi: [10.1177/09567976221145316](https://doi.org/10.1177/09567976221145316)
80. Zajner C, Spreng RN, Bzdok D. Loneliness is linked to specific subregional alterations in hippocampus-default network covariation. *J Neurophysiol*. 2021;126(6):2138–2157. doi: [10.1152/jn.00339.2021](https://doi.org/10.1152/jn.00339.2021)
81. Zhou X, Sedikides C, Wildschut T, Gao DG. Counteracting loneliness: on the restorative function of nostalgia. *Psychol Sci*. 2008;19(10):1023–1029. doi: [10.1111/j.1467-9280.2008.02194.x](https://doi.org/10.1111/j.1467-9280.2008.02194.x)
82. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res*. 2001;49(1-2):1–52. doi: [10.1016/s0920-9964\(01\)00163-3](https://doi.org/10.1016/s0920-9964(01)00163-3)
83. McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends Neurosci*. 2019;42(3):205–220. doi: [10.1016/j.tins.2018.12.004](https://doi.org/10.1016/j.tins.2018.12.004)
84. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol*. 2012;8:49–76. doi: [10.1146/annurev-clinpsy-032511-143049](https://doi.org/10.1146/annurev-clinpsy-032511-143049)
85. Menon V, Palaniyappan L, Supekar K. Integrative brain network and salience models of psychopathology and cognitive dysfunction in schizophrenia. *Biol Psychiatry*. 2022;S0006-3223(22):01637–01637. doi: [10.1016/j.biopsych.2022.09.029](https://doi.org/10.1016/j.biopsych.2022.09.029)
86. Matthews GA, Tye KM. Neural mechanisms of social homeostasis. *Ann N Y Acad Sci*. 2019;1457(1):5–25. doi: [10.1111/nyas.14016](https://doi.org/10.1111/nyas.14016)
87. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10(2):227–237.
88. Kawachi I, Colditz GA, Ascherio A, et al. A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA. *J Epidemiol Community Health*. 1996;50(3):245–251. doi: [10.1136/jech.50.3.245](https://doi.org/10.1136/jech.50.3.245)
89. Cacioppo JT, Cacioppo S. Social relationships and health: the toxic effects of perceived social isolation. *Soc Person Psychol Compass*. 2014;8(2):58–72. doi: [10.1111/spc3.12087](https://doi.org/10.1111/spc3.12087)
90. Ward M, May P, Normand C, Kenny RA, Nolan A. Mortality risk associated with combinations of loneliness and social isolation. Findings from The Irish Longitudinal Study on Ageing (TILDA). *Age Ageing*. 2021;50(afab004):1329–1335. doi: [10.1093/ageing/afab00](https://doi.org/10.1093/ageing/afab00)
91. Trémeau F, Antonius D, Malaspina D, Goff DC, Javitt DC. Loneliness in schizophrenia and its possible correlates. An exploratory study. *Psychiatry Res*. 2016;246:211–217. doi: [10.1016/j.psychres.2016.09.043](https://doi.org/10.1016/j.psychres.2016.09.043)
92. Mehta KM, Yaffe K, Covinsky KE. Cognitive impairment, depressive symptoms, and functional decline in older people. *J Am Geriatr Soc*. 2002;50(6):1045–1050. doi: [10.1046/j.1532-5415.2002.50259.x](https://doi.org/10.1046/j.1532-5415.2002.50259.x)
93. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord*. 2002;72(3):227–236. doi: [10.1016/s0165-0327\(01\)00413-x](https://doi.org/10.1016/s0165-0327(01)00413-x)
94. Cacioppo JT, Hawkey LC, Norman GJ, Berntson GG. Social isolation. *Ann N Y Acad Sci*. 2011;1231(1):17–22. doi: [10.1111/j.1749-6632.2011.06028.x](https://doi.org/10.1111/j.1749-6632.2011.06028.x)
95. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. *JAMA*. 1997;277(24):1940–1944. doi: [10.1001/jama.1997.03540480040036](https://doi.org/10.1001/jama.1997.03540480040036)
96. Kurina LM, Knutson KL, Hawkey LC, Cacioppo JT, Lauderdale DS, Ober C. Loneliness is associated with sleep fragmentation in a communal society. *Sleep*. 2011;34(11):1519–1526. doi: [10.5665/sleep.1390](https://doi.org/10.5665/sleep.1390)
97. Atzil S, Gao W, Fradkin I, Barrett LF. Growing a social brain. *Nat Hum Behav*. 2018;2(9):624–636. doi: [10.1038/s41562-018-0384-6](https://doi.org/10.1038/s41562-018-0384-6)
98. Mow JL, Gandhi A, Fulford D. Imaging the “social brain” in schizophrenia: a systematic review of neuroimaging studies of social reward and punishment. *Neurosci Biobehav Rev*. 2020;118:704–722. doi: [10.1016/j.neubiorev.2020.08.005](https://doi.org/10.1016/j.neubiorev.2020.08.005)
99. Grant N, Hamer M, Steptoe A. Social isolation and stress-related cardiovascular, lipid, and cortisol responses. *Ann Behav Med*. 2009;37(1):29–37. doi: [10.1007/s12160-009-9081-z](https://doi.org/10.1007/s12160-009-9081-z)
100. Smith KJ, Gavey S, Riddell NE, Kontari P, Victor C. The association between loneliness, social isolation and inflammation: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2020;112:519–541. doi: [10.1016/j.neubiorev.2020.02.002](https://doi.org/10.1016/j.neubiorev.2020.02.002)
101. Coplan JD, Andrews MW, Rosenblum LA, et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci U S A*. 1996;93(4):1619–1623. doi: [10.1073/pnas.93.4.1619](https://doi.org/10.1073/pnas.93.4.1619)

102. Coan JA, Sbarra DA. Social baseline theory: the social regulation of risk and effort. *Curr Opin Psychol.* 2015;1:87–91. doi: [10.1016/j.copsyc.2014.12.021](https://doi.org/10.1016/j.copsyc.2014.12.021)
103. Piskulic D, Liu L, Cadenhead KS, *et al.* Social cognition over time in individuals at clinical high risk for psychosis: findings from the NAPLS-2 cohort. *Schizophr Res.* 2016;171(1–3):176–181. doi: [10.1016/j.schres.2016.01.017](https://doi.org/10.1016/j.schres.2016.01.017)
104. Green MF, Bearden CE, Cannon TD, *et al.* Social cognition in schizophrenia, part 1: performance across phase of illness. *Schizophr Bull.* 2012;38(4):854–864. doi: [10.1093/schbul/sbq171](https://doi.org/10.1093/schbul/sbq171)
105. Pinkham AE, Penn DL, Perkins DO, Graham KA, Siegel M. Emotion perception and social skill over the course of psychosis: a comparison of individuals “at-risk” for psychosis and individuals with early and chronic schizophrenia spectrum illness. *Cogn Neuropsychiatry.* 2007;12(3):198–212. doi: [10.1080/13546800600985557](https://doi.org/10.1080/13546800600985557)
106. Fett AKJ, Viechtbauer W, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev.* 2011;35(3):573–588.
107. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* 2015;16(10):620–631. doi: [10.1038/nrn4005](https://doi.org/10.1038/nrn4005)
108. Kleckner IR, Zhang J, Touroutoglou A, *et al.* Evidence for a large-scale brain system supporting allostasis and interoception in humans. *Nat Hum Behav.* 2017;1(5):1–14. doi: [10.1038/s41562-017-0069](https://doi.org/10.1038/s41562-017-0069)
109. Quadt L, Esposito G, Critchley HD, Garfinkel SN. Brain-body interactions underlying the association of loneliness with mental and physical health. *Neurosci Biobehav Rev.* 2020;116:283–300. doi: [10.1016/j.neubiorev.2020.06.015](https://doi.org/10.1016/j.neubiorev.2020.06.015)
110. Saxbe DE, Beckes L, Stoycos SA, Coan JA. Social allostasis and social allostatic load: a new model for research in social dynamics, stress, and health. *Perspect Psychol Sci.* 2020;15(2):469–482. doi: [10.1177/1745691619876528](https://doi.org/10.1177/1745691619876528)