Trends in Cognitive Sciences

Feature Review

The Neurobiology of Social Distance

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Never before have we experienced social isolation on such a massive scale as we have in response to coronavirus disease 2019 (COVID-19). However, we know that the social environment has a dramatic impact on our sense of life satisfaction and well-being. In times of distress, crisis, or disaster, human resilience depends on the richness and strength of social connections, as well as on active engagement in groups and communities. Over recent years, evidence emerging from various disciplines has made it abundantly clear: perceived social isolation (i.e., loneliness) may be the most potent threat to survival and longevity. We highlight the benefits of social bonds, the choreographies of bond creation and maintenance, as well as the neurocognitive basis of social isolation and its deep consequences for mental and physical health.

Highlights

From babies to the elderly, psychosocial embedding in interpersonal relationships is crucial for survival.

Insufficient social stimulation affects reasoning and memory performance, hormone homeostasis, brain grey/white matter connectivity and function, as well as resilience to physical and mental disease.

Feelings of loneliness can spread through a social network, causing negatively skewed social perception, escalating morbidity and mortality, and, in older people, precipitating the onset of dementia (e.g., Alzheimer's disease).

The Problem of Social Isolation

Humans, like all monkeys and apes, are intensely social. As an unsurprising consequence, most of us find social deprivation stressful. Social isolation, or a lack of social opportunity, gives rise to a sense of loneliness. Directly or indirectly, this feeling has many wide-ranging consequences for our psychological well-being as well as for our physical health, even our longevity. In short, loneliness kills people. The neuroscientist John Cacioppo argued that the sense of loneliness has evolved as an alarm signal to ensure that we remain firmly embedded within our social cocoon [1–3].

In 2019, the World Health Organization declared that loneliness is a major health concern worldwide [4]. In many metropolitan cities around the globe, >50% of people already live in single-person households. The UK recently appointed its first Minister of Loneliness. The feeling of loneliness has been found to spread from person to person through social networks [3]. Once lonely, humans can become trapped in a psychological downward cycle that can be difficult to escape from. This is in part reinforced by a skewed perception of negative cues and social threat from others, or the expectation of being socially excluded by others. The biased world-view leads to escalated suicide rates [5,6], among other consequences. This 'learned social helplessness' can be dangerous because, among all existing species, we depend longest on other individuals.

We explore here the neurobiology of social isolation and the consequences it has for our health and psychological well-being. First, we outline the evidence for the many benefits of social interaction. We then consider why one cannot have an unlimited number of friends, even though they are highly beneficial. Next, we briefly survey the behavioral patterns that play a central role in creating and maintaining strong social bonds. Finally, we examine key neurobiological mechanisms underlying social interplay, and the impact that social deprivation has on them.

Why Social Bonds Are Good For You

There is now accumulating evidence that friendships are a *conditio sine qua non* for health quality [7–14]. The tighter someone is embedded in a network of friends, the less likely they are to become ill. The higher your social capital, the faster you get better if you fall ill, the quicker you recover from surgery, and the longer you will live.

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Previous research [15] collated 148 epidemiological studies (~300 000 people in total) to identify common factors that influence mortality. In the specific case of death due to cardiovascular disease, the three factors with by far the biggest effect were (i) the frequency of social support from others, (ii) how well integrated the person was into their social network, and (iii) whether the patient gave up smoking – two, arguably even three, social reasons. By contrast, the factors that doctors are conventionally most concerned about all had much less impact on survival rates. Key factors included obesity, diet, alcohol consumption, how much exercise was taken, drug treatments prescribed, and local air pollution. These authors conducted a follow-up analysis of 70 studies of longevity in older people, which followed ~3.5 million people over an average of ~7 years [16]: social isolation, living alone, and feeling lonely increased the chances of dying by ~30%, even after accounting for age, sex, and health status.

Many other studies have shown that social isolation (though not self-reported feelings of loneliness) was a significant predictor of the risk of death. For example, a longitudinal analysis of ~6500 British men and women aged 50–59 years [17] found that being socially isolated increases the risk of dying in the next decade by ~25%. Quantitative analysis of nearly ~400 000 married couples in the American Medicare database revealed that, for men, the death of their spouse increased their own chances of dying in the immediate future by 18%. The death of the husband in turn increased the wife's risk of dying by 16% [18].

Similar effects on morbidity rates have been found with respect to social support. A series of elegant prospective studies using data from the Framingham Heart Study [19,20] found that the chances of becoming happy, depressed, or obese were all strongly mirrored by similar changes in the closest friend. There was a smaller significant effect due to the behavior of the friend's friend. A detectable effect was even present due to the friend of a friend's friend, but nothing beyond. This contagion phenomenon was especially strong if the friendship was reciprocal (i.e., both individuals recognized each other as a friend). If the friendship was not mutual, the social contagion effect was negligible. The investigators also documented a strong effect of 'geographical contagion'. If you have a happy friend who lives within a radius of 1 mile, you are 25% more likely to be happy. In addition, you are 34% more likely to be happy if your next-door neighbor is happy.

Social Contagion Spreads in the Wider Community

People who belong to more groups are less likely to experience bouts of depression. Such findings emerged from the UK Longitudinal Study of Ageing (ELSA) that repeatedly profiled around ~5000 people from the age of 50 years onwards. Previous research showed [21] that depressed people reduce their risk of depression at a later time-point by almost a quarter if they join a social group such as a sports club, church, political party, hobby group, or charity. Indeed, joining three groups reduced the risk of depression by almost two-thirds.

On a more general note, surveys on social visits to pubs, social evening dinners, or regular attendance at religious services converged on one core conclusion: people who engaged in any of these activities typically had more friends, were happier, and felt more satisfied with their life. Such individuals were more immersed in their local community and trusted their neighbors more [22–24]. The causal directionality was difficult to pin down in these cases because of the cross-sectional nature of the data. Nevertheless, path analysis provided some indication that intensity of social exchange was the candidate driver.

The impetus to access social capital in the wider community [7] extends beyond humans. There is now a wealth of evidence from long-term field studies of wild baboons that socially well-connected females experience less harassment by other monkeys [7,23], have lower levels of cortisol stress hormones [25,26], faster wound healing [27], produce more offspring, and live longer [28–31]. Such ramifications of social capital appear to hold up across a diversity of species, including chimpanzees [32], macaques [33–35], feral horses [36,37], and dolphins [38].

Loneliness and the Immune System

A key underlying reason for these effects, at least in humans, is likely that loneliness impairs the immune system and reduces resistance to diseases and infections. Research has found [39] that freshmen students who reported feeling lonely had a reduced immune system response when they were given a flu vaccine compared to students who felt socially well engaged. Moreover, those students with only four to 12 close friends had significantly poorer responses than those with 13–20 friends. These two effects seemed to interact with each other: having many friends (a large social group of 19 or 20 friends) seems to buffer against a weakened immune response. Nevertheless, feeling lonely and having few friends results in a particularly poor immune defense. Other investigators [40] used data from the Framingham Heart Study to show that people with fewer contacts in their social network had elevated serum fibrinogen concentrations. By contrast, people enjoying many social contacts had low fibrinogen levels. Fibrinogen plays an important role in blood clotting when a blood vessel has been ruptured, and also facilitates wound healing and tissue repair more generally: high concentrations thus signal poor health. Endorphins constitute a core component of the psychoendocrine mechanisms underpinning friendship (Box 1). Other research has found [41] that social bonds stimulate the release of the body's natural killer cells, one of the white blood cells of the innate immune system whose core function is to destroy harmful bacteria and viruses.

People who are more socially integrated have better-adjusted biomarkers for physiological function, as indexed by lower systolic blood pressure, lower body mass index, and lower levels of C-reactive protein – the latter being another molecular response to inflammation. This insight was evident in each of four age groups (adolescents, young adults, middle age, and old age) based on data from four large longitudinal American health databases [42]. The investigators found that, in adolescence, lack of social engagement had as big an effect on risk of inflammation as lack of physical activity. In old age, lack of friends had a bigger effect on risk of hypertension than the usually cited clinical causes such as diabetes. Even more worrying, the effects of social relationships on these physiological measures of good health during adolescence and young adulthood can persist into old age. In a longitudinal study of 267 males, for example, research found [43] that the more socially integrated a child was at 6 years of age, the lower their blood pressure and body mass index (a measure of fatness) two decades later. This result held up when they controlled for race, body mass index in childhood, parental socioeconomic status, childhood health, and extraversion.

Box 1. How Endorphins Create Friendships

Primates service their relationships through social grooming. Grooming triggers the endorphin system in the brain through a very specific neural system: the afferent CT fibers [163]. These axon bundles have receptors at the base of most hair follicles, have the unusual properties of being unmyelinated (and hence are very slow, especially compared to the pain receptors in the skin), have no return motor loop (unlike pain and other proprioceptive neurons), respond to a very specific stimulus (light slow stroking at ~2.5 cm per s), and directly trigger the endorphin reward system [164]. Although humans no longer have the full fur covering that encourages social grooming, we still have the receptors and instead use physical contact in the form of touching, stroking, caressing, and hugging as a means for strengthening social ties in our closer relationships [165,166].

Physical touch is intimate, and hence limited mainly to close family and friends (see Figure 2 in main text). To bond our wider range of relationships as well as our more intimate ones, humans exploit several behaviors that also trigger the endorphin system. These joint activities include laughing [167,168], singing [169,170], dancing [171,172], feasting [22], and emotional storytelling [53]. An important feature of all these behaviors is that behavioral synchrony seems to ramp up the level of endorphin release [172,173].

Social isolation may well have pervasive effects on brain connectivity. If rats are socially isolated when young (a condition that can give rise to feelings of loneliness in humans), neural function and plasticity are altered [44–47]. In particular, episodes of social isolation can irretrievably alter the function of the prefrontal cortex (the part of the brain that is central to managing our social relationships; see below), as well as its axon myelination (the laying down of the fatty sheaths around neurons that enable them to transmit signals faster and more efficiently) [44]. Although short periods of loneliness in humans rarely have any long-term adverse outcomes, persistent loneliness escalates the risk of Alzheimer's disease and depression [48,49]. Loneliness also leads to poor sleeping habits, with adverse psychological and physiological secondary consequences [50].

What Limits the Number of Friends?

The fact that friends can have such dramatic effects on our health and well-being may lead us to suppose that the more friends we have, the better. However, the number of friends and family relationships we can manage at any given time is limited by cognitive constraints to ~150 [51,52]. There is, however, considerable individual variation, and social network sizes range approximately between 100 and 250. Several fairly conventional factors are responsible for this variation: age (younger people typically have larger social networks than older people [53]), sex (females usually have larger social networks than males [53,54], although this does vary with age [55]), personality (extraverts have larger social networks than introverts [56]; women who score high on the neuroticism personality dimension have fewer acquaintances than those who score lower in that trait [57]).

Friendships, however, require the investment of considerable time to create and maintain. The emotional quality of a friendship depends directly on the time invested in a given social link [57–59]. One prospective study estimated that it takes ~200 h of face-to-face contact over a 3 month period to turn a stranger into a good friend [60]. Conversely, the emotional quality of a relationship declines rapidly (Figure 1) if contact rates drop below those appropriate to the relationship quality [61].

Time resources, however, are naturally limited: we devote only ~20% of our day to direct social interaction (excluding business-related interactions), equivalent to about 3.5 h per day [62]. Given that our relationships are not all of equal value to us (friends serve a variety of different functions [63,64]), we allocate our valuable time across our social network in such a way as to maximize the different benefits that friends of different quality provide [65]. This dynamic results in a specific social fingerprint that is unique to each of us [66].

Nonetheless, there are some broadly consistent patterns: a 40% share of our time is devoted to our five closest friends and family, and a further 20% to the 10 next closest individuals. In other words, 60% of the 3.5 hours a day we spend in social interaction are devoted to only 15 people. Social partners in the outermost layers of the social network each receive only 30 s of our time per day on average. This gives rise to a very distinctive layering to our social networks in which the layers have a characteristic fractal pattern: the innermost layers of closest friends is very small (typically five people) but intense, the outermost (~150) very large but more casual [67,68]. It is that inner circle of five closest friends and family that seems to matter most in terms of the buffering of both loneliness and disease.

Geographical distance also imposes strong constraints on the organization of friendship. The '30 minute rule' provides an empirical reminder that people are less willing to visit friends and family who live more than 30 minutes away – no matter whether that involves travel on foot, by bicycle, or by car [69]. Cutting across this effect is the influence of genetic relatedness:

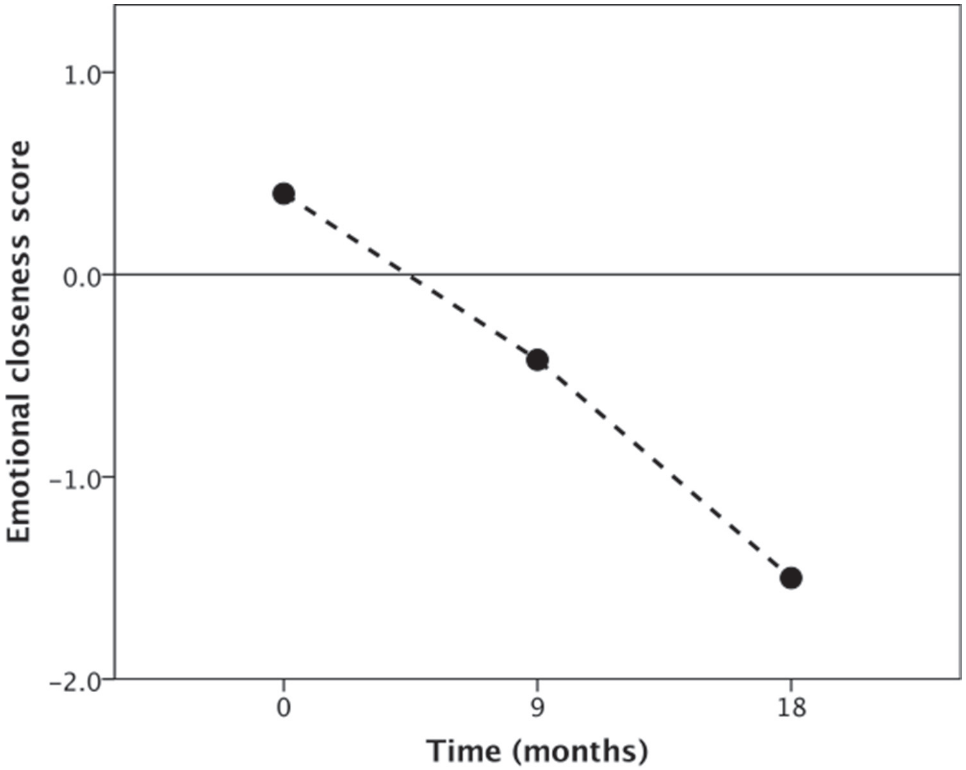

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Figure 1. Emotional Closeness Depends on Contact Frequency. Change in mean emotional closeness (indexed by a 1–10 analog scale) to all members of the extended family (unfilled dots) and all the friends they had at the start of the study (filled dots) over 18 months after the participant had moved away from home (at month 6) and could no longer meet with these individuals in person. Emotional closeness at the start of the study is set at 0 for both groups. Reproduced, with permission, from [61].

the kinship premium (i.e., the strong mutual benefits that kinship typically affords) incentivizes us to travel an extra mile to maintain contact with family than we are with friends [70].

While the role of close contacts such as friends is pivotal, other regular contacts can also meaningfully contribute to one's social capital. Previous authors [71] famously claimed that weak – as opposed to strong or close – ties provide important sources of external information. Analyses of information flow in social networks suggest that sources outside the 50 closest friendships offer few benefits [72]. Other benefits of interaction with more loose social ties can, of course, include heightened subjective well-being and a sense of belonging to the local community [73]. However, as is often the case in such studies, it is crucial to precisely define the meaning of weak versus strong ties because all weak ties belonged to the same community (a student class). Regular interaction with different people at the periphery of social networks can give rise to heightened perceived social and emotional fulfillment in ways that act as psychological buffers [24], although this might depend on personality or social style [74].

Online versus Offline Social Interaction

Social-affective processes in the presence of others take a different form than in their physical absence. Already in a nursery, if a baby starts to cry, other nearby babies hear the distress signal and typically also start to cry by mere emotional contagion. In addition to utterances and prosody, humans tend to align their communication towards each other by imitating vocabulary, grammar, mimics, and gestures. For instance, humans tend to unconsciously synchronize their facial expressions even with people who are directing their gaze at someone else [75]. Such subliminal motor and emotional resonance is typically found to be intrinsically rewarding [76]. On the positive side, contagion processes can uplift an individual's happiness through people not only within the close neighborhood but also miles apart [19]. On the negative side, loneliness also spreads rapidly through an individual's social interaction partners, thus affecting even friends of friends of friends [77,78].

Reading others' faces – impossible during a conventional phone call – may be an evolutionarily conserved means for exchanging pivotal information that coevolved with the corresponding decoding machinery in brain and behavior responses (see next section). Faces offer a plethora of social information about the sex, age, ethnicity, and emotional expressions of an individual, and potentially about their intentions and mental state (all of which influence the strength of the bond between two individuals [59]). Throughout development, learning and maturing critically hinge on the joint attention of two individuals on the same object [79,80]. Such mentalizing and eye gaze processes have been repeatedly linked to the higher associative and striatal reward circuitry [79,81–83]. Some authors even argue that the importance of such facets of interpersonal exchange may explain why humans developed wide and white sclera in the eyes – that are more easily visible than in most animals [84]. What may lead to greater vulnerability to predators for some species (by making the individual and her intentions more apparent and thus exploitable) may have boosted learning and cooperation in human primates [85,99]. Such evolutionary adaptations facilitate how humans automatically represent the (visual) perspective of nearby others. Making statements about objects in the physical environment may take longer, as a result of interference, if another person also present has partial or different knowledge of these same objects [86].

Although primate societies are driven by visual signals and immediate encounters, humans have also evolved elaborate means to interact at large geographical distances. Virtual face-to-face contact by video chat, such as via Skype or Zoom, is becoming increasingly common. Its rated quality of social interaction with friends has outperformed that of (non-visual) telephone and text-only communication channels via SMS, WhatsApp, or e-mail [87]. Other authors have reported broadly similar effects for familial relationships, in so far as they found a negligible benefit from video-based channels [88]. Compared to actual interpersonal encounters, there are a surprising number of psychological constants in how humans entertain and juggle with social relationships in digital environments. For example, the upper bound of ~150 contacts (see above), as well as the structure of these networks, appears to hold across both the real world and a variety of virtual online contexts [53,68,89,90], suggesting that group size in today's society is still governed by the same principles as when we were hunter-gatherers. Indeed, several neuroimaging studies (e.g., [51,91]) broadly confirm that our online social networks correlate with the volumes of the same core brain regions that resonate with the size of our offline networks [52,92].

These constancies suggest that lively virtual social interaction may similarly entrain faculties such as memory and concept generation. Conversely, a paucity of social interaction and loneliness may have deleterious effects on the cognitive and memory systems. It is conceivable that enhancement or decline of cognitive and neural reserve may be mediated by analogous pathways that potentially involve dendritic arborization in the hippocampal and prefrontal regions [49]. The need for personalized interactions may already be reflected in the way that stock market traders sometimes add coded numbers to money transfers (e.g., 10 000 467 instead of 10 000 000 shares) as a potential replacement for the recognition of somebody's unique facial identity instead of remaining anonymous [93,94]. This attractor for a full range of face-to-face cues during social interactions may explain why emojis have become so popular: they replace the important emotional signals in the absence of the ostensive facial cues that we use for the interpretation of utterances in the face-to-face environment.

These considerations raise the important question of how the brain implements toggling between real-world social interactions and virtual or imagined social interaction in the absence of physical contact [79]. The right temporoparietal junction was proposed as a key switching relay between two antagonistic classes of neurocognitive processes: those more anchored in one's current external sensory environment, and more stimulus-independent processes that rely on internally generated information [95]. This idea was later substantiated by a multimodal neuroimaging study in 10 000 humans [96]: the right and left temporoparietal junction explained most variation in functional coupling changes between all major brain networks. Hence, these two association cortex regions may help to mediate shifts of focus from the person in front of you to a person you are texting with on the phone, and who is out of sight or touch (Figure 2).

Taken together, evidence of digital communication suggests that this new medium does not in fact change the general pattern of our social interactions or the numbers of people we contact [68,89,90,97]. The sizes of the layers in our social networks are unchanged by using digital media or virtual communication. In addition, the frequencies with which we contact people in each social layer are strikingly similar in the online and offline worlds. Some digital vehicles, however, lack the communicative richness of real face-to-face interactions: when asked to rate their satisfaction with interactions with their five closest friends each day, participants rated face-to-face and Skype interactions as equally satisfying, and both as significantly more satisfying than interactions with the same individual by phone, text messaging, SMS messaging, e-mail, or text-based social media such as Facebook [87].

Strong and Thin Social Networks are Manifested in Brain Circuitry

Human and non-human primates predominantly live in groups to minimize external ecological threats, including predators, raiding by neighbors, and environmental hazards. Advanced forms of cooperation are rare in non-primate species [98,99], and these probably emerged in non-

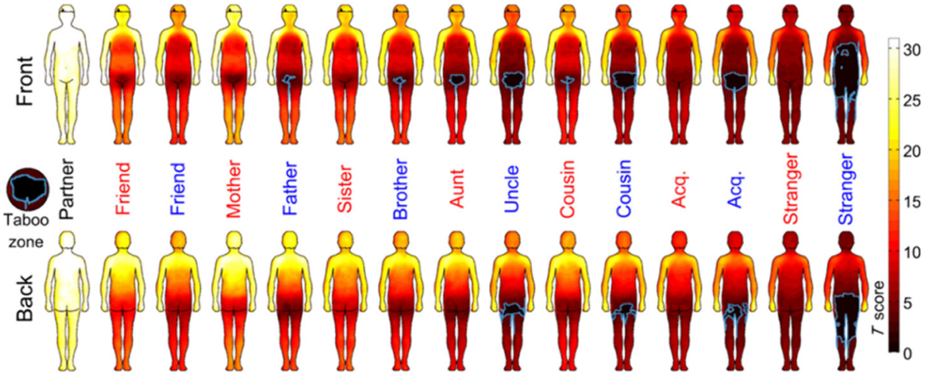

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Figure 2. Quantitative Map of How Much Social Touching Is Allowed for Different Body Regions. In 1368 people from several countries, this study investigated the permissibility of social touch [165]. The authors showed that human social touch is particularly dependent on the nature of the relationship. The topography of accepted social touching depends on many factors, including (i) emotional relationship, (ii) type of interpersonal bond including kinship, (iii) sex, and (iv) power dynamics. Close acquaintances and family members are touched for more different reasons. Culture influence, measured in five countries, was small. Female, rather than opposite-sex, touch was evaluated as being more pleasant, and it was consequently allowed on larger areas of the body. Reproduced, with permission, from [165]. Abbreviation: Acq, acquaintance (distant).

human primates several million years ago. Today, the average human spends up to 80% of waking hours in the presence of others [100,101]. Investing cognitive resources in keeping track of friends, family, and colleagues is highly demanding – more costly than contemplating the physical facts of the more static environment [102,103]. Not only time-limits (see above) but also neurocognitive limits (e.g., [104]) effectively constrain how close one can be to how many individuals. Nevertheless, how is regular social stimulation reflected in neurobiology?

In monkeys [105,106] and in humans [51,52,107,108,187], various indices of sociality and measures of social network size are robustly associated with specific regions of the neocortex. These same regions are responsible for processing social information such as predicting others' intentions [92,109]. At least some of these brain–behavior associations may be cross-culturally consistent in humans, as evidenced by a structural neuroimaging study in the USA and China [110]. Whole-brain analyses have repeatedly highlighted a relationship between the ventromedial prefrontal cortex and measures of social network complexity or social competence [92,105,109,111–113]. The ventromedial prefrontal cortex and striatal nucleus accumbens have been found to play a key role in both social reward behaviors and the amount of social stimulation in humans [112] and other mammals (e.g., [44,47]). Functional neuroimaging has shown that these neural correlates are also implicated in tracking others' popularity status in real-world social networks [114]. Similarly, positron emission tomography has shown that, in humans, the density of μ-receptors for β-endorphin, especially in the ventromedial prefrontal cortex, correlates with social attachment style, for which endorphins are probably more important than other neuropeptides [115]. Other evidence, such as in a functional neuroimaging study on maintenance and manipulation of social working memory [104], has also related the dorsomedial prefrontal cortex to social network properties. There are similar correlations for social cognitive skills such as mentalizing that are crucial to maintaining functional social relationships [116–118].

Analyses of social richness and brain morphology in humans tend to identify a neural network involving the prefrontal cortex, including several parts of the so-called default mode network, as being crucial for managing social networks (e.g., [113]). This major brain network of the higher association cortex has probably recently expanded in primate evolution [119]. Its constituent regions are often thought to support several of the most sophisticated neurocognitive processes [120,121]. In monkeys, there is evidence that experimental manipulation of social group size results in adaptations in the volume of frontal brain regions – the posterior superior temporal sulcus or temporoparietal junction –as well as the amygdala and other parts of the limbic system [105,106]. In humans, there is evidence for structural coupling between social network size measured by number of online friends and parts of the default mode network, including the hippocampus [51]. From a clinical perspective, functional connectivity alterations in the default mode network have been demonstrated as a consequence of feelings of loneliness in younger adults [122]. Moreover, the default mode network is especially vulnerable in normal cognitive aging [123], and is among the main brain circuits impacted by neuropathology in Alzheimer's disease [124,125].

Complementing higher associative regions of the human social brain [126], the volume of the amygdala is larger in individuals with more extensive social networks in humans [52,107]. Amygdalar functional connectivity was also reported to increase in canonical brain networks implicated in face perception and approach-avoidance behavior [107]. Indeed, previous authors reported [127] that a patient with complete bilateral amygdala lesions lacked a sense of appropriate personal space *vis-à-vis* other people (Figure 3). This patient exhibited no discomfort when at close distances from another person, even to the point of touching the other's nose – despite the fact that their conceptual understanding of people's private physical space was intact. By contrast, healthy individuals typically show amygdalar activation in response to close personal

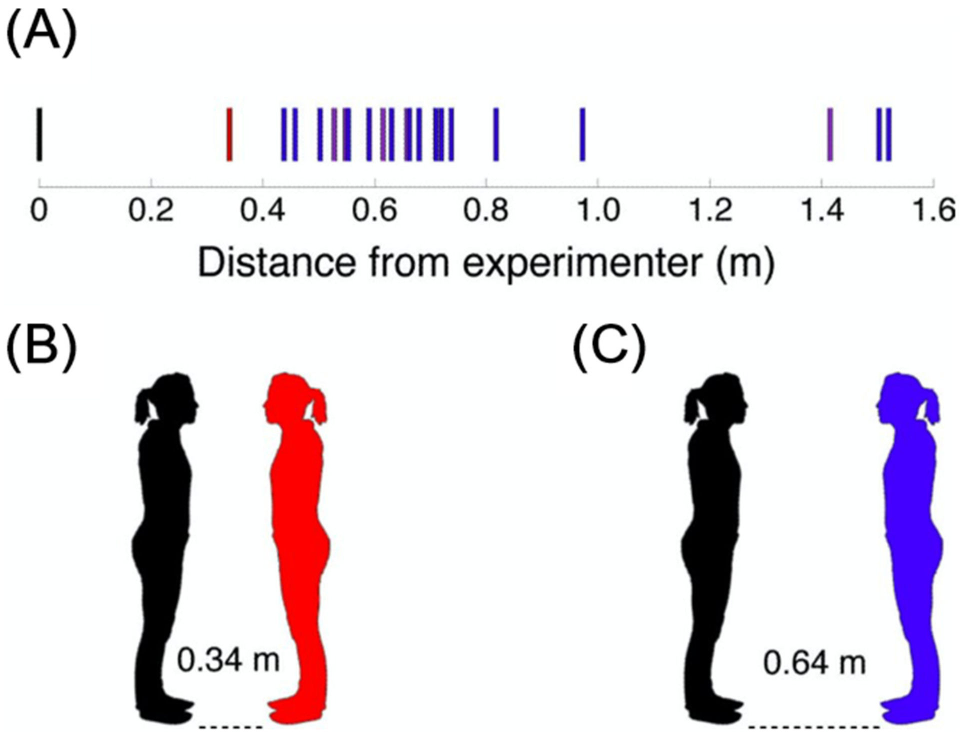

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Figure 3. Amygdala Damage Leads to Disturbed Management of One's Comfort Zone. The scale in (A) shows the chin-to-chin distance between experimenter and participant. A patient with bilateral amygdala lesion (B, red line and image) preferred closer distance to the experimenter (C, black image), without expressing any sense of discomfort, compared to 15 matched neurotypical controls (blue lines and image). The authors also report fMRI data [127] confirming that neural activity responses in the amygdala are implicated in the management of one's personal space. This observation is in line with other studies of amygdalar involvement in various approach–avoidance decisions, such as social judgments of attractiveness or trustworthiness from other's faces (e.g., [82,83,93]). Reproduced, with permission, from [127].

proximity. In a similar vein, the grey matter volume of the amygdala correlates negatively with social phobia [128]. The amygdala may hence be necessary to trigger the strong emotional reactions normally associated with personal space violations, thus regulating interpersonal distance in humans.

Such existing reports on the social brain often seemed to be in conflict about whether they highlight the prefrontal cortex or the amygdala of the limbic system. This apparent discrepancy was reconciled in a recent population neuroimaging study [129]: social traits such as daily exchanges with family, friends, and work colleagues were associated with brain morphology in ~10 000 UK Biobank participants. Particularly prominent findings were reported in the limbic system, where regional volumes varied consistently with various indicators of social isolation. Less socially stimulated participants showed volume effects in various parts of the social brain including the ventromedial prefrontal cortex and the amygdala, in addition to the nucleus accumbens of the reward circuitry. Volume effects in these regions were reported for several markers of brittle social integration, such as living in a socially 'emptier' household, knowing fewer individuals with whom to regularly share experiences and concerns, and feeling unsatisfied with one's friendship circles, as well as having grown up without brothers or sisters and being unhappy with one's family situation [129]. This analysis also demonstrated wide-ranging sex differentiation in how traits of social isolation are linked to brain morphology. These findings underscore evidence from animals for a sex-specific coevolutionary relationship between the primate brain and social complexity (the social brain hypothesis [130,131]).

The perspective of brain network integration in loneliness was investigated in a seminal neuroimaging study of intrinsic functional connectivity in ~1000 humans [122]. Careful analysis showed that feelings of loneliness especially affect the neural communication strength between the limbic system and the default mode network, as well as the communication strength inside the default mode network. As a particularly discriminatory pattern for loneliness, impoverished functional modularity was found for the default mode network and its interacting brain networks. By contrast, a positive sense of one’s meaning in life was linked to strengthened functional differentiation of the canonical network ensemble. The collective evidence led the investigators [122] to argue that the default mode network and its coupling partners represent a neural signature reflecting one’s own purpose in life versus sense of social disconnection to others.

Neurocognitive Consequences of Social Isolation

According to estimates by the United Nations Children's Fund (UNICEF), ~140 million children worldwide live deprived of parents who could provide comfort and support. About 8 million of these children grow up in institutions without the socioemotional context of a regular family. In one of the earliest randomized clinical trials of its kind, orphans raised in institutions were systematically compared to orphans who were later welcomed into a foster home [132]. Abandoned children were randomly assigned either to remain under the care of the institution or to transition to the care of foster parents. Their cognitive trajectories were monitored over several years. Those children who remained in the institution showed significantly lower development indices and lower IQs (of ~70 [132]) than the adopted orphans. Being deprived of social bonds with caregivers also led to a pernicious reduction in grey and white matter tissue and lower fiber tract integrity as evidenced by brain MRI [132]. Institutional rearing was also shown to exacerbate the decay of the telomeres in cell nuclei [133,134]. These protection caps normally prevent chromosome deterioration, which acts like a cellular sand clock of aging. Their shortening has major consequences for various biological pathways and health outcomes.

The younger the children were when adopted by a foster family, the better their later cognitive performance [135]. Impoverished cognitive domains include memory and executive function: for orphans who transitioned to a foster home, some cognitive facets remained below average throughout later life (e.g., short-term visual memory and attention allocation). Other cognitive dimensions (e.g., visual–spatial memory and spatial working memory) caught up with a normal trajectory at age 16 [132]. Such unique evidence underlines the fact that lack of socioemotional context in early life severely impedes brain development and maturation of the cognitive repertoire, which can be partially mitigated by developing social bonds to non-genetic parents (Box 2).

Early psychosocial deprivation also shows intergenerational effects, which are probably mediated through maternal and epigenetic effects [136]. Social isolation in childhood leads to molecular annotations of DNA (such as methylation or phosphorylation of the histones that provide the structure for DNA strands) that are passed on to influence how children cope with stress and in turn determine how they raise their own children. For instance, in rats, socioemotional experience as a pup has an impact on how the rat’s own pups later deal with stress and high anxiety levels [137]. Epigenetic regulation of gene transcription is involved in how maternal care promotes the rat pup’s brain development and cognitive maturation. More licking and grooming by the mother increases protein expression of the *Grm1* gene in the pup’s hippocampus. This upregulated gene transcription leads to greater availability of glutamate receptor proteins in hippocampal cells for interneuronal signaling [138]. In humans, a longitudinal neuroimaging study indeed showed that

Box 2. The Essential Role of Social Closeness in Babies

In baby primates, close social interaction is not only beneficial but also crucial for maturation and resilience. Experiments in baby monkeys showed that upbringing in social isolation during the first years causes a variety of social deficits. When separated early from their mothers, baby monkeys showed strong symptoms of social withdrawal: self-hurting behavior such as biting, stereotypical and repetitive motor behavior, excessive avoidance behavior towards others, and poor social and maternal skills as adults. When separated later from their mothers, baby monkeys tended to indiscriminately approach unknown monkeys without fear [174].

Reports of human children in some crowded Russian and Romanian orphanages have painted a strikingly similar picture: socially and emotionally abandoned children showed either forward–backward rocking tics and social escape, or overly strong attachments, analogously to neglected baby monkeys [175]. These cases invigorated the then-contested claim that mother–child bonds are indispensable for normal development, and that foster-care parents can compensate many of these needs [132,158,176,177]. Disruption of social interplay during critical developmental periods impacts negatively on cognitive, verbal, social, and motor performance, and predisposes to mental health issues. In other words, early neglect remains measurable in brain and behavior in later life.

The socioemotional dialogue between caregiver and baby is mediated in several important ways. Mothers speak to their offspring in 'baby talk', which potentially evolved only recently in humans [178]. Accompanied by direct face-to-face exchanges, these communication bouts with characteristic vocabulary and prosody promote infant developmental milestones. The interpersonal stimulation grabs the baby’s attention, she gains weight faster, modulates her emotional state, and enhances various health outcomes. Mother–infant communication is also delivered through direct skin-to-skin contact [164]. Postnatal touching bolsters mother–infant bonding, alleviates anxiety, and provides intrinsic pleasure through endorphin release [179–181]. Throughout life, and independently of geography, primate societies are orchestrated by the creation, curation, and cultivation of social bonds though purposeful social closeness.

social support from the mother promotes volume growth trajectories in the hippocampus, and predicts socioemotional development and emotion regulation in early adolescence [139].

In young rhesus monkeys, loss of social contact with the mother leads to behavioral aberrations that last into adulthood. Such social isolation was shown to entail downregulated dendritic growth in the prefrontal cortex and reduced gene expression in the amygdala [140]. Social adversity undergone by children with institutional upbringing led to disturbed functional connectivity between the prefrontal cortex and the amygdala [141]. Such perturbed brain maturation through social deprivation may be mediated by glucocorticoids, which are known to be inhibited by maternal care in primates [142]. Hence, maternal care is a crucial enrichment of the social environment that promotes neural maturation, expression of growth hormones, and synaptogenesis in various brain circuits. By contrast, social neglect leads to disturbed social attachment, as well as to increased aggression and hyperactivity, that may last lifelong [143,144]. How vulnerable an individual is to parental deprivation is subject to complex nature–nurture interactions that appear to be strongly conditioned on personality and overall genetic endowment [145,146].

Rats separated early from their mothers were impaired in adult life in emotion regulation and arousal management [147]. Early socioemotional isolation of rat pups affected whether these rats later showed healthy responses to stress by mounting adequate cortisol levels [148]. Hormones of the hypothalamic–pituitary–adrenocortical (HPA) axis are an important endocrine mechanism of stress neurobiology that plays a key role in social isolation. In baboon monkeys, infant survival is jeopardized for mothers who are more socially isolated and not well integrated into their local communities, including reduced ties to sisters, adult daughters, and other mothers [149]. Monkey mothers with a thinner social network are less likely to have infants which themselves have high fitness [28]. Female baboon monkeys with a larger close social circle of grooming partners have healthy cortisol levels and typically deal better with stressful situations [25,26,150]. When one of these strong social bonds is disrupted, such as when a close member of the social group is killed by predators, cortisol titers rise in the blood. Such monkeys then tend to seek out new connections to 'repair' the lost link in their social network [151].

A lower than usual cortisol level in the morning is indicative of extended stress periods in adults [152]. The same diurnal cortisol dynamic is frequently observed in disturbed child–caregiver relationships [153]. In rhesus monkeys, a depressed hormone response has been observed after repeated separations from the mother. The same observation has been reported for children who were moved between several caregivers. An intact child–caregiver relationship probably provides a stress reserve to adrenoreceptor responses so that children get over stressful episodes quicker [154,155]. After undergoing adversity in early childhood, such as emotional or physical neglect, maltreatment, or maternal separation, enhancement of the child–caregiver relationship can mitigate the effects of previous hits to the HPA system. Early disturbance in important social relationships is linked to dysfunctional cortisol hemostasis in adult life [156]. In some neglected children, ensuing problems and behavioral disruptions can even be exacerbated in adult life [157]. Abnormal blood cortisol levels can potentially be prevented, mitigated, or restored by family-based therapy and other interventions [158]. Nonetheless, dysregulated diurnal cortisol levels are further linked to various mental disorders including major depression, substance abuse, and post-dramatic stress disorder [152], in addition to stress-mediated effects on the immune, cardiovascular, and metabolic systems [159,160].

Further insight into the neurobiology of social isolation has also been derived from rigorous experiments with adult primates (Box 3). In one study, 20 monkeys were separated from others to live alone for 1.5 years [161]. Subsequently, monkeys were reintegrated into social groups of four monkeys housed together. Repeated positron emission tomography (PET) scanning revealed increased levels of dopamine D_2 receptors in the basal ganglia, which include key nodes of the reward circuitry (see above), after being socially housed. This neurochemical adaptation in the monkeys' brain circuitry was apparent after as few as 3 months of social rehabilitation [161]. The authors also reported several differences in respect of social integration and social rank: monkeys of higher rank were groomed more by others. By contrast, subordinate monkeys spent more time by themselves. As a behavioral consequence, the lower-rank monkeys were also significantly more willing to self-administer cocaine, and this may also relate to heightened drug abuse in lonely humans [162]. Such molecular imaging evidence shows that changing from social deprivation to an environment with constant social stimulation causes neural remodeling in the dopaminergic neurotransmitter pathways in non-human primates, and this may be clinically relevant for substance abuse disorders in humans.

Box 3. Loneliness and Aging in Human Adults

Among the many consequences of loneliness on body and mind, the scarcity of social contact encourages drug compensation and substance-use behavior, such as alcoholism, possibly via non-social rewards triggering dopaminergic neurotransmitter pathways [161]. At the genetic level, loneliness was shown to entail underexpression of anti-inflammatory genes involved in the glucocorticoid response and overexpression of genes related to proinflammatory immune responses [182]. Fortunately for future clinical intervention, loneliness may be a modifiable determinant in healthy aging [11].

As people grow older, the social network typically becomes smaller – naturally diminishing the cognitive stimulation through frequent and intense social interaction on a daily basis, thus potentially reducing the neural reserve. Over the past century, the average human lifespan in developed nations has increased by nearly three decades. However, older people are also reported to show a decline in their capacity to take other people's point of view, as demonstrated in three separate mentalizing tasks [161]. These authors showed that social cognition deficits were related to decreased neural activity responses in the medial prefrontal default mode network [161]. This capacity is likely to be particularly important when introspecting the minds of other people who are not physically present – where social cues such as facial expressions, mimics, and gestures are missing.

Both limited social stimulation and weakening social reflection capacities relate to the sense of loneliness in complex and important ways [13]. Once lonely, bias for negative information processing of cues from others hinders social rehabilitation in a downward cycle [4,183]. Many recent studies have corroborated the corpus of empirical evidence that feelings of loneliness escalate the risk of certain neurological diseases in later life, especially Alzheimer's disease [49].

Concluding Remarks

We are social creatures. Social interplay and cooperation have fuelled the rapid ascent of human culture and civilization. However, social species struggle when forced to live in isolation. The expansion of loneliness has accelerated in the past decade. As one consequence, the UK has launched the ‘Campaign to End Loneliness’ – a network of over 600 national, regional, and local organizations that aim to create the right conditions for reducing loneliness in later life. Such efforts speak to the growing public recognition and political will to confront this evolving societal challenge. These concerns are likely to be exacerbated if there are prolonged periods of social isolation imposed by national policy responses to extraordinary crises such as COVID-19.

Social deprivation in childhood and in late adulthood both impact on neurobiological architecture and functional organization. The ensuing loss of social and cognitive capacity has significant public health consequences. On the individual scale, this can result in people becoming less socially engaged and, hence, at greater risk of developing antisocial behavior. The result is likely to be a drain on the public purse, either in terms of caring for individuals in psychological and physical decline or of the incarceration of disorderly individuals. If social isolation during development happens on a sufficiently large scale, it is likely to have significant consequences for community stability and social cohesion (see Outstanding Questions).

These prospects should encourage us to search for means to mitigate possible negative backlash. We offer some suggestions in Box 4. Additional insight into stress-responsive brain systems will be imperative to tailor clinical decision making and therapeutic interventions to single individuals. There is also a dire need for additional longitudinal research on the HPA axis and the cortisol response to psychological stressors.

Box 4. How To mitigate the Large-Scale Costs of Social Isolation?

Social isolation at a massive scale risks creating cohorts of individuals who are less socially functional. It may therefore be important to identify ways of mitigating the worst of the effects so as to alleviate the consequences. The following possible countermeasures may be worth exploring.

One promising intervention would involve creating opportunities where mutual social support relationships (friendships) can develop naturally. One cannot, however, force people to become friends: both parties need to be willing to devote resources to each other in a context where the time budget available for social engagement is limited [184,185] and there are competing friendship interests [66]. However, by providing more opportunities for people to meet in congenial environments, new friendships may blossom.

Social neuroscientists [186] undertook a longitudinal intervention study of 332 matched adults who underwent regular training sessions. Several months of cognitive training improved empathy for others’ affective state or perspective-taking of others’ mental state, which resulted in structural remodeling in brain regions belonging to the social brain network, including the frontoinsular network and the default mode network. Daily affective training resulted in thickening of the right anterior and mid-insula, with correspondingly enhanced compassion ratings. Different training regimes correlated with different brain regions. There is an urgent need for further research to explore therapeutic interventions using training of social capacities in socially deprived humans.

One important lesson is that joining clubs can have important benefits in reducing both a sense of loneliness and psychological or psychiatric conditions [21]. One obvious solution is to encourage vulnerable individuals to join social groups and communities that suit their interests and abilities. Establishing a wide range of such clubs is likely to be much cheaper than paying for carehomes and prisons.

Singing is known to have a dramatic, immediate effect on creating a sense of social engagement and elevating psychological well-being (the 'ice-breaker effect' [169]). Vulnerable individuals could be encouraged to join choirs and community singing groups. Encouragement and funding may need to be invested in establishing a network of choirs.

Use of video-embedded digital communication is likely to gain in importance. This is especially true where family and friendship groups can meet in the same virtual space. The visual component of the interpersonal encounter appears to play a key role in creating a more satisfying experience of digital social media [87].

Outstanding Questions

Why and how do feelings of loneliness cause or accelerate the onset of neurodegenerative diseases, and of Alzheimer’s disease in particular? It is urgent to narrow this knowledge gap because reducing (perceived) social isolation among older adults is an actionable public health concern.

What further refinements of online digital media might improve people’s function in creating and maintaining friendships, especially for the housebound? It is insufficiently known which types of modern medium best mimic the neurocognitive facets that underlie real social interaction.

Which neurobiological mechanisms explain how the default mode network and its connections to subordinate brain systems support higher social capacities, and contribute their decline in social deprivation? This higher associative brain network needs to be more completely understood, especially regarding the congruencies and idiosyncrasies between healthy aging trajectories, the experience of social isolation, and vulnerability to neurodegenerative pathologies. In terms of progress towards causal understanding, putting a premium on longitudinal studies holds unprecedented promise.

Across the entire lifespan, to what extent does reduced social stimulation or too few social contacts diminish the general capacities of the cognitive repertoire? How much do people struggling with cognitive load have issues maintaining many active social relationships? New insight in this chicken-and-egg problem will shed light on the etiopathology of loneliness, and may usher in new intervention strategies.

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