

# Social isolation and the brain in the pandemic era

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Intense sociality has been a catalyst for human culture and civilization, and our social relationships at a personal level play a pivotal role in our health and well-being. These relationships are, however, sensitive to the time we invest in them. To understand how and why this should be, we first outline the evolutionary background in primate sociality from which our human social world has emerged. We then review defining features of that human sociality, putting forward a framework within which one can understand the consequences of mass social isolation during the COVID-19 pandemic, including mental health deterioration, stress, sleep disturbance and substance misuse. We outline recent research on the neural basis of prolonged social isolation, highlighting especially higher-order neural circuits such as the default mode network. Our survey of studies covers the negative effects of prolonged social deprivation and the multifaceted drivers of day-to-day pandemic experiences.

Humans, like all anthropoid primates, are intensely social. There is now considerable evidence that interindividual differences in social embeddedness affect a variety of health and fitness indicators. In humans, the single best predictor of physical health and well-being, as well as future longevity, is the number and quality of close friendships, with the more conventional suspects (such as diet, obesity, alcohol consumption and air quality) ranking a distant second<sup>1,2</sup>. Indeed, the frequency of social engagement predicts psychological health and well-being<sup>3</sup>, self-rated feelings of happiness, satisfaction with life, and trust in one's local community<sup>4</sup>.

The COVID-19 lockdowns of the past two years were a global stress test—large-scale social deprivation in a more dramatic extent and form than ever before in recorded history. At the peak of public health restrictions, >3.6 billion people worldwide were subject to government-imposed stay-at-home orders. On the individual scale, we know that we respond poorly to isolation. However, existing psychological and neuroscience research had little to say about the possible consequences of mass isolation. By contrast, there have been many large-scale epidemiological studies of the effects of social deprivation in the elderly<sup>5</sup>. Almost all of these investigations yielded evidence for detrimental effects on cognitive capacity, psychological and physical well-being, and even longevity. It is clear that the chronic experience of

social isolation escalates the risk of depression and dementias, as well as cardiovascular disease and certain types of cancer<sup>6–8</sup>.

The present review provides a frame of reference that can help to situate current and future findings on mass social isolation by incorporating established knowledge on human sociality and its underlying neurobiological mechanisms. To this end, we first place human sociality within the broader context of anthropoid primate sociality, with its behavioural and neurobiological determinants. Our aim is to provide a more grounded explanation as to why the neurobiology of human sociality takes the form it does. We then survey some of the unfolding evidence with direct relevance to the neurobiological and psychological consequences of the large-scale lockdown during COVID-19 and subsequent social rehabilitation.

## The neurobiology of primate sociality

Anthropoid primates exhibit a form of bonded sociality that is rarely encountered among other mammals or birds<sup>9,10</sup>. Primate sociality typically involves stable social groups based on dyadic relationships that can last a lifetime. These modes of interaction are reinforced by specific behaviours such as social grooming<sup>11</sup> and involve constant visual monitoring of social partners<sup>12</sup> that are the context for the regular exchange of social support<sup>13</sup>. In both humans and the most intensely

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social non-human primates (including pair-bonded species such as titi and owl monkeys, and the baboons, macaques and great apes), these relationships are characterized by a level of emotional intensity that is reflected in an apparent desire to be in close spatial proximity to the social partner<sup>12,14</sup>. Just as in humans, close relationships with other individuals are known to provide substantial health benefits: individuals who have more grooming partners recover faster from injuries, live longer, are more fertile and have offspring that are more likely to survive to reproductive age.

In anthropoid primates, social relationships of this kind are formed and maintained by a dual-process mechanism that exploits two separate neural systems in the brain<sup>15</sup>. One is an emotional (or 'raw feels'<sup>16</sup>) component built on the endorphin system, mediated by social grooming (as a form of social 'soft touch'), which may be closely related to brain correlates of social support in humans (see below). The other component is a more explicitly self-aware form of higher-level cognition<sup>17</sup> that involves developing a conceptualized understanding of a relationship, which may be closely related to brain correlates of loneliness in humans (see below). The first neural system creates a psychopharmacological environment that incentivizes two bonded individuals to stay together over time. This in turn allows them to build relationships of trust, obligation and reciprocity via the second neural system. Other neurotransmitters (for example, serotonin and dopamine) and neurohormones (for example, oxytocin and testosterone) play important roles in the management of behaviour<sup>18</sup>. However, it is possible that none contribute to the formation of bonded relationships in the specific way that endorphins do<sup>19–22</sup>. If true, this may largely be a consequence of the fact that endorphins have a much longer half-life than the other chemicals<sup>22</sup>.

In primates, but not other avian and mammal orders, social group size is tied to brain volume (the social brain hypothesis)<sup>10,23,24</sup>. This evolutionary perspective implies that the cognitive demands of maintaining stable social groups become a function of expanding group size. An increasing cognitive cost was incurred as long-term bonded relationships emerged<sup>25</sup>—as evidenced in birds, for example, where species characterized by lifelong pair-bonds have larger brains than species that form new breeding pairs each year and those that mate promiscuously<sup>10</sup>. More importantly, neuroimaging studies of both humans<sup>26–31</sup> and cercopithecine primates<sup>32–34</sup> have shown that inter-individual differences in the number of friends (or living group size) is associated with the volume of the higher associative brain circuits. Such evidence implies that the social brain relationship applies within species as well as between species.

Bonded sociality is enabled by a set of cognitive skills including mentalizing, empathy, self-control, causal reasoning and one-trial rule learning. These mental capacities, especially well developed in humans, allow us to manage several relationships simultaneously<sup>24</sup>. Probably unique to anthropoid primates<sup>35</sup>, these cognitive skills involve specialized neural circuits in the brain, in particular the perspective-taking-related default network<sup>24,36–38</sup>. A proto-form of that macroscopic brain system has been identified in other primates, where it also underpins sociality<sup>39–44</sup>.

In addition to these new requirements on the brain's 'hardware' infrastructure, learning through experience plays a crucial role. Relationships change over time as individuals fall in and out of favour with each other<sup>45</sup>. This makes it impossible to legislate for all possible social contexts with hardwired behavioural responses of the kind that we find in the simpler social systems of many non-primate animals<sup>46</sup>. Equally, conventional associative learning would be too slow and inflexible. Instead, anthropoid primates operate by a set of learned rules (many involving complex social trade-offs in which the values of relationships with different individuals are compared) that can be applied in contexts where the costs and benefits can vary widely over time as social and ecological circumstances change. To provide scope for social learning, primates and especially humans require a prolonged

adolescence during which socialization continuously sharpens the skills instrumental for social interaction. In primates, species that have bigger neocortices tend to have longer maturation periods<sup>47</sup>. Both developmental and neuroimaging studies suggest that, in humans, this critical period of the life cycle can occupy as much as the first two and a half decades of life<sup>48,49</sup>, coinciding with the completion of frontal lobe expansion and neural maturation as indexed by growth patterns<sup>50</sup> and axon myelination<sup>51,52</sup>.

In anthropoid primates (including humans), the process of social bonding is bolstered by the endorphin-mediating parts of the central nervous system<sup>19,21,22,53–58</sup>. The hand actions used in grooming trigger the upregulation of endorphins in the brain<sup>20,59,60</sup>, mediated via the highly specialized afferent C-tactile neural system<sup>61,62</sup>. Aside from the social benefits created by the endorphin system, there is evidence to suggest that endorphins upregulate the immune system for better host defence, in particular by mobilizing natural killer cells<sup>63–65</sup>. Endorphins are also upregulated by exercise, with consequent benefits for the immune system<sup>66,67</sup>. Periods of scarce sociality and/or reduced physical activity may well lead to compensatory behaviours, such as increased use of substitute stimulants (for example, alcohol and nicotine), hinting at mechanistic pathways accompanying health deterioration.

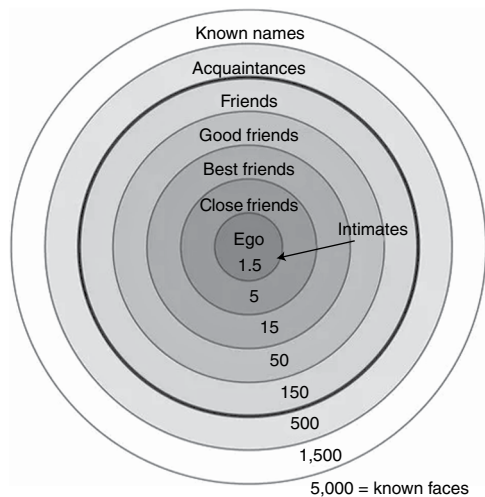
Humans exploit this endorphin mechanism through the many forms of casual 'soft touch', such as hugging, stroking and caressing, that are woven into our modes of social interaction<sup>68,69</sup>. These bonding mechanisms heavily tax our time budgets and involve the investment of a considerable proportion of the waking day. One study of human friendship formation estimated that it takes around 200 hours of face-to-face contact to turn a stranger into a close friend<sup>70</sup>. More importantly, friendships require high frequencies of contact to maintain their emotional quality (for example, a minimum of half an hour per day for intimate friends<sup>71,72</sup>); otherwise, relationship quality decays steeply over time<sup>45,73</sup>. These patterns of investment appear to describe a social fingerprint that is both unique to the individual and stable over time<sup>73,74</sup>. In the absence of opportunity for social exchange, we might expect to see both turnover in social networks and changes in the way individuals think about the social world (as opposed to the non-social environment).

In primates, social grooming is so time-intensive that group size is limited to a maximum of ~50 individuals if stable cohesion is to be maintained<sup>11,75</sup>. Humans have been able to live in larger groups by supplementing the touch-based bonding mechanism of primates with other explicitly social behaviours that also turn out to trigger the endorphin system but are more time-efficient because they allow several individuals to be 'groomed' at the same time. These behaviours include laughter<sup>76,77</sup>, singing<sup>78–80</sup>, dancing<sup>81</sup>, religious rituals<sup>82</sup>, feasting<sup>83,84</sup> and emotional storytelling<sup>85</sup>. Close relationships, however, depend on the more intimate processes of touch and face-to-face contact<sup>68,69,71</sup>. While the behavioural and health-related impacts of social isolation may result from the breakdown of social exchange in the close inner circles, failure to engage in the social activities that we use for the more peripheral relationships in the outer layers of our social networks may nonetheless have measurable consequences.

In sum, social interaction patterns in humans are underpinned by long-standing primate mechanisms, supplemented by novel forms of social interaction that make up a specialized human social toolkit. These are expensive to maintain, both neurophysiologically and in terms of time investment. Failure to invest results in the rapid decline of relationship quality and loss of the associated benefits, leading to increased psychological and physical ill health.

## The structure of our social world

Our friendships and family relationships do not consist of isolated dyads. Rather, these ties form an interwoven network of relationships that spread out around us in a social space that is only partly mapped onto the physical space around us. Understanding the structure and



**Fig. 1 | The structure of the human social world.** Personal social networks have a hierarchically inclusive layered structure, with the layers having distinctive sizes that are determined by the frequency of contact and perceived emotional closeness<sup>86</sup>. The indicated values are robust population averages. In each case, there is interindividual variation due to gender, age, personality and circumstances. These values always have a fractal structure with a scaling ratio of  $\sim 3$ . The darker circle at 150 denotes the normal limit for personal social networks in which relationships are reciprocated, are relatively stable and have a personal history; beyond this, the outer layers consist of individuals with whom relationships are casual, unreciprocated and more fluid. Note that all layers include both friends and extended family, generically referred to as ‘friends’. Most work colleagues would be placed in the ‘Acquaintances’ layer, except for the few that have graduated into being formal friends.

dynamics of this social world provides an important framework that helps explain some of the consequences of social isolation.

We do not treat all the members of our social world equally. Rather, our social networks and communities have a distinctive fractal structure, forming a series of ever-widening layers around us<sup>86</sup> (Fig. 1). These layers are defined both by the frequency with which we contact individual members and by the emotional closeness we feel to them<sup>71</sup>. The social layers in Fig. 1 have very specific sizes, with a scaling ratio close to 3 (refs. <sup>86–88</sup>), such that each layer is three times the size of the layer immediately inside it. Note that each of these layers includes both extended family members and conventional friends, although the outermost layers are largely populated by acquaintances. For convenience, however, we follow the common practice of referring to them collectively as ‘friends’<sup>68</sup> without distinction, unless we specify otherwise. A similar layered structure, with exactly the same numerical values of network layer sizes, is found in both the social networks and the group sizes of other primates<sup>24,89,90</sup>.

This pattern reflects a combination of the choices that we make about investing in individual relationships as a function of the benefits that they provide for us<sup>91,92</sup> when the time available for focused social interaction is inevitably limited<sup>93–95</sup>. In part, this is a direct consequence of the fact that, in both anthropoid primates<sup>71</sup> and humans<sup>72,94</sup>, the strength of a friendship, and hence the expectation that it will provide various essential services, directly reflects the time invested in it<sup>86</sup>. This patterning in how we distribute our effort is responsible for the layered effect, with each layer associated with a characteristic frequency of contact for each member<sup>71</sup>. If we drop below this frequency of contact to an individual, they will, over a period of just a few months, slide out through the circles until they settle into the layer with the new lower frequency of contact<sup>55</sup>. The innermost five layers in Fig. 1 appear to be the ones that have the greatest effect on our health and well-being: they consist of our most reliable family and friend relationships in terms of willingness to provide emotional, social, financial and other forms of help<sup>97</sup>.

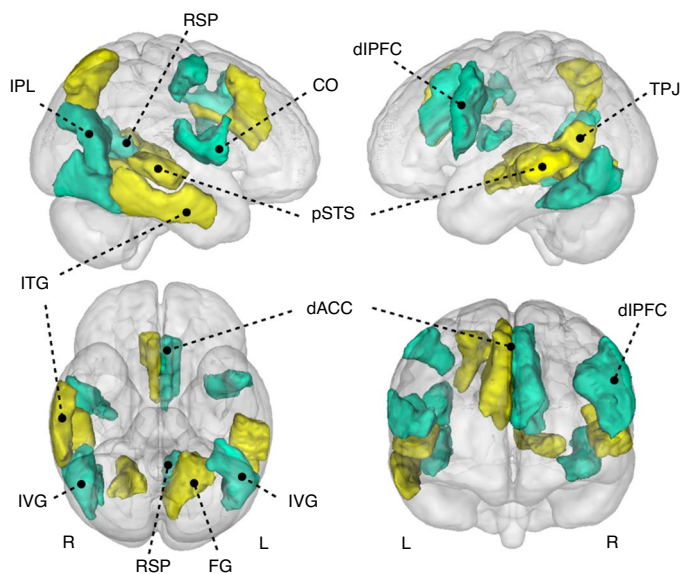
The average size of human personal social networks is 150 individuals<sup>86</sup>. However, there are notable interindividual differences that reflect gender and personality<sup>71</sup>. Women typically have larger inner layers than men do, even though the total network size remains similar. This is commensurate with women’s often better performance on key social cognitive abilities such as putting oneself into others’ shoes<sup>71</sup>. In part, this typical advantage reflects the fact that women’s relationships are more emotionally intense, more focused and thus also more fragile (that is, prone to fracture) than those of men, whose relationships have a more casual, club-like quality<sup>71,98–100</sup>. Similarly, extraverts typically have larger social networks than introverts. Because extraverts distribute their available social time more widely, their average emotional closeness to network members is lower<sup>93,101</sup>. Age also has a dramatic effect on the structure of our social networks. Network size increases with age up to around 250 people in the mid-20s, retrenches to a stable 150 from the later 20s to the late 60s and then declines from the 70s onwards<sup>102</sup>. The increase during adolescence reflects the gradual refinement of perspective-taking and other social cognitive skills that enable us to handle more relationships<sup>103</sup>; the decline into old age largely reflects the failure to replace friendships that have been lost.

Some of these differences between people can be traced to brain substrates. Attachment style, for example, is closely linked to endorphin receptor density, notably in the frontal part of the higher association cortex<sup>57</sup>. This is reflected in the fact that those individuals with a cooler attachment style tend to have fewer friends than those with a warmer style<sup>104</sup>. Similarly, analysis of the topology of immigrants’ social networks provides clear evidence that the limited access to a pool of potential friends limits the size of personal networks and thus alters network topology<sup>94</sup>.

On the basis of these earlier findings, we anticipate that prolonged social isolation will lead to an elevated sense of social disconnection as the felt distance to one’s contacts widens with time. Those whom we normally see the most often (the members of the innermost circles in Fig. 1) will incur the greatest sense of loss. In addition, the known sources of interindividual variation in social style predict that sex/gender as well as other identity and diversity factors will influence the impact that social isolation has on different strata of society. For example, given the findings we summarize above, we expect more acute consequences of the recent COVID-19 lockdown in women (with their typically more intense relationships) than in men (with their often more casual social ties). Similarly, and perhaps more obviously, we would expect extraverts to find social isolation more frustrating than individuals with more introverted personalities. With regard to age, we might identify two periods of vulnerability: adolescence (when social skills are being honed and relationships developed) and old age (when social networks are naturally prone to contraction).

## The emerging neurobiology of social isolation

At the brain level, the experience of social isolation has been found to exhibit manifestations (Fig. 2) especially in the prefrontal cortex and other parts of the higher association cortex in the wider human population<sup>37,105</sup>. Among all macroscopic brain circuits, the default network—known to represent information content about oneself as well as other people’s thoughts and likely intentions<sup>106,107</sup>—exhibits by far the strongest grey matter volume associations with perceived social isolation (that is, loneliness)<sup>37</sup>. With regard to intrinsic connectivity measures, functional coupling inside this major brain network was upregulated in lonely individuals. By contrast, the default network was functionally decoupled from the visual system in perceived social isolation. These findings were interpreted as reflecting the known tendency for internally generated thoughts to increase in individuals who feel socially isolated, including anthropomorphizing their pets, developing intense relationships with TV characters and being overly reminiscent about past social exchanges with others.



**Fig. 2 | Experienced social isolation shows a brain signature implicating especially the higher-order association circuits.** A Bayesian hierarchical model was applied to ~40,000 UK Biobank participants to distinguish lonely (target group, encoded as 1) from non-lonely participants (control group, encoded as 0), by quantifying the degree of structural differences in brain region volume measurements in 100 cortical regions (Schaefer–Yeo atlas; for the details, see ref.<sup>37</sup>). Yellow and green show positive and negative volume associations, respectively, indicating (for example) bigger volume effects in yellow areas in lonely participants. CO, central operculum; ITG, inferior temporal gyrus; pSTS, posterior superior temporal sulcus; TPJ, temporoparietal junction; IPL, inferior parietal lobule; dACC, dorsal anterior cingulate cortex; dIPFC, dorsolateral prefrontal cortex; RSP, retrosplenial cortex; FG, fusiform gyrus; IVG, inferior visual gyrus; L/R, left/right hemisphere. Figure reproduced with permission from ref.<sup>37</sup>.

In support of shifts in brain correlates commonly related to thinking about other individuals, an analysis of 48 white matter tracts revealed a unique association between loneliness and the fornix<sup>37</sup>. This core fibre tract transports neural signals via axonal connections from the hippocampus towards the medial default network. The microstructure of this unidirectional hippocampus output pathway is known to vary between individuals as a function of episodic memory traits, such as vividness of recall, which would be needed to recall past social events or imagine future ones. In a targeted co-analysis of 38 microanatomically defined hippocampal subfields of these allocortical and neocortical regions<sup>108</sup>, it was especially the hippocampal CA1 and the stress-susceptible molecular layer that showed differences in structural covariation with specific medial prefrontal and posteromedial partner regions of the default network midline in the subjective perception of social isolation (that is, loneliness; Fig. 3). In the monkey brain, hippocampal CA1 neurons have direct neuron-to-neuron axon connections to the medial prefrontal cortex through the fornix white matter pathway—pyramidal CA1 neurons being the only hippocampal sites sending axons directly to cortical partners<sup>109,110</sup>. Notably, these same neural circuits have been implicated in the primary biology of Alzheimer's disease as well as the retrieval and richness of episodic memory—linked to clinical hallmarks of that major neurodegenerative condition. The neurobiology of loneliness therefore appears to bear a close relation to the alteration of internally generated dimensions of cognition, including mental simulation of others' thoughts and reactions of the kind that would be needed when we communicate with others, such as when texting people (for example, on Facebook or WhatsApp-type messengers) or when calling them on the phone. This

offers a likely explanation for the associated differences in covariation between the hippocampus and the default network.

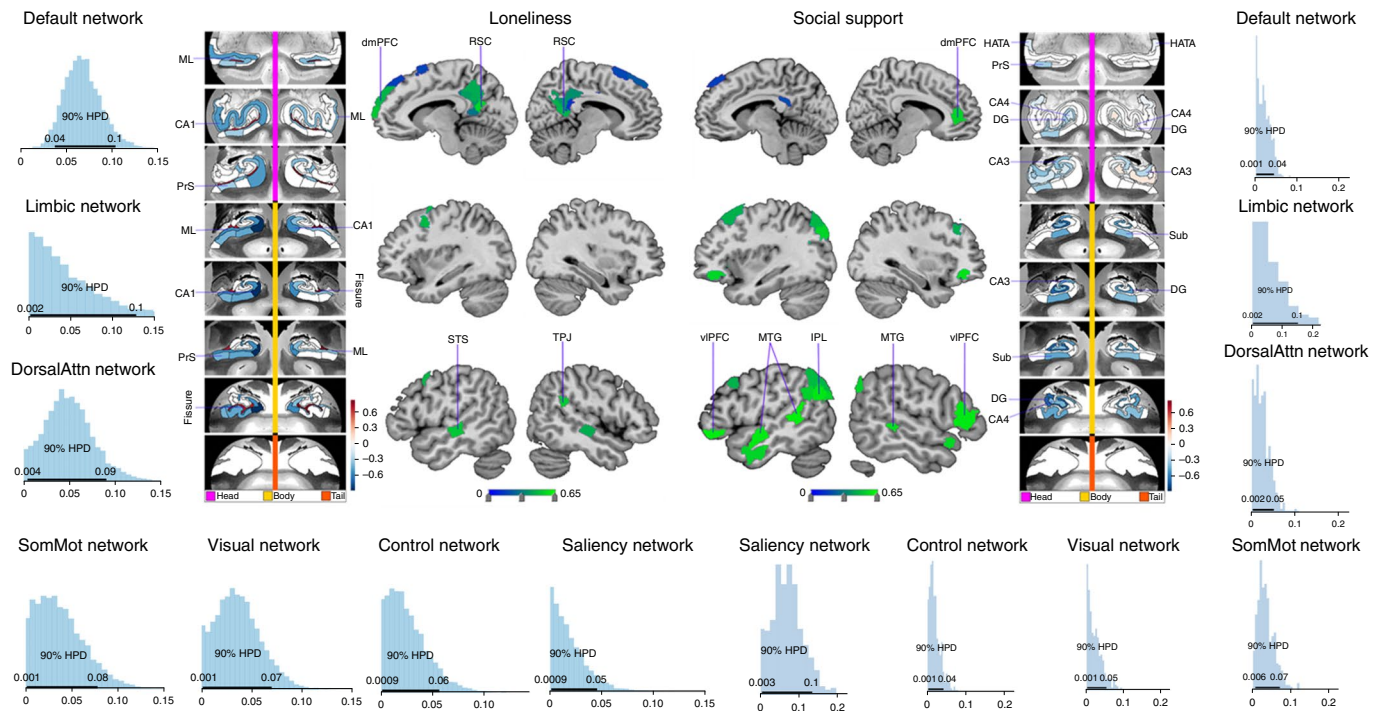
Loneliness is increasingly distinguished from more objective measures of social isolation, especially social support, which we here defined as the frequency of social contact (as directly measurable as days per week). Individuals may not subjectively feel isolated (that is, loneliness) but may still report a lack of regular social contact with other people (that is, weak social support), and vice versa. People typically invest as much as ~40% of their social effort in their 'support network'—the innermost circle of about five family members and close friends from whom they receive the most social, emotional and economic help<sup>71</sup>. In contrast to the neural signature of loneliness, interindividual differences in (objective) social support are related to characteristic volume signatures in the salience and limbic networks<sup>26–28</sup>.

Regions of other higher neural circuits, especially the salience network, have repeatedly been shown to be closely involved in processing others' emotions and monitoring one's own interoceptive states<sup>107</sup>. Implemented shared representations thus underlie empathy—our ability to 'click in' emotionally with other people and mimic their emotional states, especially when engaged in similar or identical processes during direct face-to-face contact of an affective state and when witnessing someone else in that state<sup>88</sup>. According to demographic profiling and genome-wide analyses, these neural circuits, related to the social interaction frequency with close others, were implicated in factors associated with poor health and substance misuse, including smoking and alcohol consumption, as well as overall sadness and vulnerability to stress<sup>108,111</sup>. Reinforcing a difference in scarce social isolation with close versus more casual acquaintances, previous brain-imaging experiments have reported neural activity responses in these regions when humans think about familiar members of their social circle, such as friends as opposed to strangers<sup>112</sup>.

Of potential relevance for public health decision-making and intervention, these same neural circuits were highlighted in a seminal longitudinal study on the social brain that administered daily exercises of emotional sharing with others to several hundred participants<sup>113</sup>. This regular empathic engagement mediated adaptive increases in grey matter structure, which included the insula and the mid and posterior cingulate cortex. Neural plasticity changes induced by day-to-day social engagements coincided with improvements in behavioural assessments of social and emotional skills<sup>113</sup>. Thus, across-species (see above) and within-species (this paragraph) evidence speaks to the flexible changes of brain architecture as a function of regular face-to-face social exchange.

## Consequences of mass social isolation in COVID-19

Various emerging studies carried out under COVID-19 lockdown suggest that social distancing has had considerable psychological and behavioural consequences. These include elevated levels of anxiety and depression, deterioration of mental health, changes in diet and increased suicidal ideation, in addition to less physical activity and higher levels of experienced loneliness. Importantly, there have been considerable interindividual differences, with some people experiencing limited effects, but others experiencing more serious consequences. The prevalence of reported loneliness was higher, for example, among those who were self-isolating alone and unemployed, and lower in people who were married or living with a partner<sup>114</sup>. Rates of loneliness were twice as high among people who met clinical criteria for depression, anxiety and post-traumatic stress disorder than they were in the rest of the population. Greater difficulties with emotion regulation and poorer sleep quality were also commonly associated with loneliness. On average, older people were found to show greater satisfaction with life, higher levels of social cohesion, less concern about family members contracting COVID-19 and lower levels of self-reported panic, depression, emotional disturbances and risk perception<sup>115</sup>.



**Fig. 3 | Objective and subjective social isolation show different brain signatures implicating the higher-order association cortex versus limbic/saliency brain circuits.** In ~40,000 UK Biobank participants, we quantified the degree to which population variation in grey matter volume can be better explained by loneliness (left half) or social support (right half)<sup>37</sup>. The outer histograms show the contribution of each of seven examined canonical networks (brain volume measures); the black horizontal line shows the 5–95% highest posterior density [HPD] to disambiguate lonely individuals (left) and those with social support (right). The x-axis denotes the magnitude of each variance parameter value, while the y-axis denotes the relative plausibility of these possible parameter values (that is, a higher histogram bar means higher certainty), given the model posterior parameter distributions inferred from the brain data. As shown in the inner brain slices, we examined the structural covariation between the 38 subregions of the hippocampus and

91 subregions of the default network<sup>105,133</sup>, by achieving a co-decomposition using a canonical correlation analysis<sup>108</sup>. We conducted a rigorous test of how the ensuing subregion patterns diverged in people who reported feeling lonely (left) or having social support (right). Red and blue show positive and negative volume associations, respectively. In recent cross-phenome analyses, loneliness was especially associated with depression, anxiety and drug use outcomes<sup>37</sup>, while social support was mostly linked to overall happiness and satisfaction with family, friends and health<sup>111</sup>. PCC, posterior cingulate cortex; RSC, retrosplenial cortex; dmPFC, dorsomedial prefrontal cortex; STS, superior temporal sulcus; ML, molecular layer; PrS, presubiculum; Sub, subiculum; DG, dentate gyrus; MTG, middle temporal gyrus; vIPFC, ventrolateral prefrontal cortex; HATA, hippocampal–amygdala transition area. Figure reproduced with permission from refs. <sup>37,105,111,133</sup>.

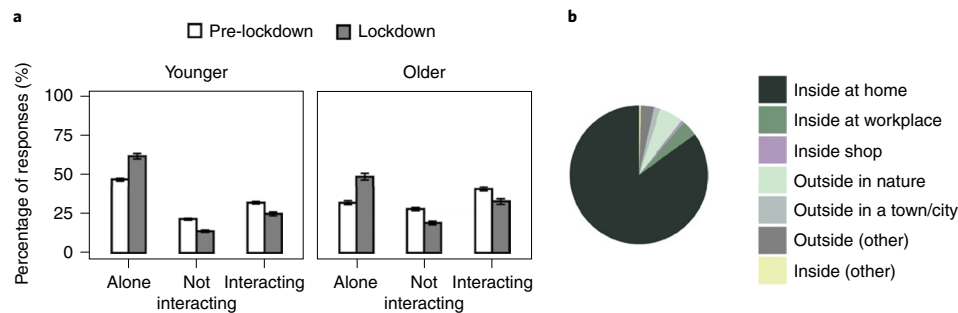
Best and colleagues<sup>115</sup> also showed evidence that, compared with men, women experienced more overall distress and higher levels of panic, depression, emotional disturbances and concerns about contracting COVID-19 and about the safety of their family—a finding in line with the generally greater intimacy of women’s friendships (see above). Individuals who relied on credible sources of information, such as mainstream news, employer-based information and public health announcements, reported less overall COVID-19 distress, panic, depression and emotional disturbance, as well as greater satisfaction with life and social cohesion<sup>115</sup>. Various physical factors were also identified. These effects might be exacerbated by confinement-induced decreases in physical activity levels and increases in sedentary behaviour, for example<sup>116</sup>. Such a lifestyle has been shown to precipitate rapid deterioration of cardiovascular health and premature death, especially through transitory ischemic attacks and strokes<sup>117</sup>.

One seminal study<sup>118</sup> used an innovative experience-sampling approach to investigate the naturally occurring changes in everyday cognition before and during the first COVID-19 lockdown in the UK (Fig. 4). This naturalistic experiment is based on the notion of ‘mind-wandering’, a form of daydreamed, spontaneous thought that is typically unrelated to the ambient environment and known to vary along several dimensions such as vividness, content and time direction to past/present/future. These sometimes random, sometimes purposeful internally paced episodic mental scenes tend to occur especially

commonly when people are not actively focused on a mental task—which makes experience sampling at random time points during the day a particularly attractive research tool.

The participants’ ongoing thoughts and the contexts in which they occurred (for example, social environment, activity and location) were randomly sampled in real time over five days. Future-directed problem-solving was lower during lockdown, especially in older individuals (55+ years old) and in those who engaged in regular real-world interaction with others. Yet, this was less prominent when participants were interacting physically as opposed to virtually. Before the first lockdown was imposed, younger participants (18–35 years old) reported engaging in less vivid imagery during introspection when they were alone than when they were interacting with others. But during lockdown, the younger participants reported more vivid imagery when they were alone than when they were interacting with others. However, the kinds of episodic social cognition normally observed in interactive environments were greater during lockdown, this being more apparent across all forms of interaction when compared with not interacting at all. Detailed task focus was more apparent when interacting virtually than in other contexts.

Taken together, this behavioural comparison of moment-to-moment spontaneous thoughts before versus during COVID-19 suggests that the lockdown led to notable changes in ongoing thought patterns in daily life and that these changes were associated



**Fig. 4 | Lockdown entails changes in ongoing random thoughts using multidimensional experience sampling. a, b.** In separate time points before and during the first lockdown during the COVID-19 pandemic in the UK, participants were queried by experience sampling at various moments, five random times per day for a whole week<sup>118</sup>. The participants were prompted at random times in their everyday lives to obtain multiple reports describing features of their ongoing thoughts and the context in which they occurred (for example, social environment, activity and location). The aim was to illuminate how specific features of the stay-at-home order impacted people's thinking in daily life. Multidimensional experience sampling assessed people's thoughts across 22

assessment dimensions, including aspects of social thinking and future-directed problem-solving. Panel **a** shows a comparison of the overall responses to the experience-sampling queries. During the lockdown, both groups of 59 younger (18–35 years old) and 23 older adults (55+ years old) reported feeling more alone. Panel **b** shows where the participants were when being queried during the lockdown (most were at home). The collective findings show that the lockdown led to significant changes in ongoing thought patterns in daily life. These changes were associated with changes to daily routines that occurred during lockdown. Figure reproduced with permission from ref. <sup>118</sup>.

with changes to daily routines before versus after the public health restrictions were in place, to which individuals may have conformed to varying degrees. In particular, the naturalistic thought probes have characterized how social encounters are an important influence on our day-to-day thinking. Shifting opportunities for regular social contact following the stay-at-home orders are likely to have changed the expression of people's ongoing in-the-moment thought tendencies.

It is clear that COVID-19 has also taken a heavy toll in terms of mental health, especially for some strata in the wider population. Robb and colleagues<sup>119</sup> investigated the psychological effects of COVID-19 lockdown on 7,127 cognitively healthy older adults (mean age, 70.7; s.d., 7.4) from the UK. The authors found an association between subjective loneliness and increased indicators of depression and anxiety following lockdown. More than half of the respondents reported feeling lonely, and a quarter lived alone. These proportions were higher in women than in men. Around 12.3% and 12.8% of the respondents reported increased symptoms of anxiety and depression, respectively, during lockdown. Again, these proportions were higher for women than for men. Compared with those who never felt lonely, individuals reporting that they often felt lonely had 11- and 17-times-higher odds of feeling more anxiety and depression, respectively, during lockdown. Compared with men, lonely women were twice as likely to report worse symptoms of depression, whereas lonely men were around 5% more likely to report greater anxiety than females. Those who lived alone were more likely to report feeling worse on components of anxiety and depression than those living with others. Compared with individuals who reported daily contact, those reporting two to six occasions of online social contact per week had a 19% lower risk of feeling greater anxiety. These outcomes are broadly in line with what our review of the dynamics of human social networks (see above) would lead us to expect.

Interestingly, remote contact with friends or family via technology did not significantly alter the risk of reporting feeling worse on components of depression. Robb and colleagues<sup>119</sup> reasoned that “Wider access to technology may help buffer loneliness and isolation that lead to worsened mental health. Older people, however, are more likely to have limited ability to access technology, most likely representing the more vulnerable of this demographic ... As in-person intervention strategies during pandemics may be limited or impossible, the use of technologies, such as apps, may remain an important tool, albeit limited by the digital divide, thus potentially excluding significant numbers of particularly vulnerable older people.”

Adding further detail to the reported effects of social isolation from social distancing during COVID-19 in a pre-existing, longitudinal UK cohort<sup>119</sup>, in males, smokers were more likely to report greater depression than non-smokers, with no association observed among females. In women, a three-unit increase in alcohol consumption per week (approximately one large glass of wine) was associated with a 22% lower probability of reporting an improvement in components of depression. Additionally, as many as 40% of the cohort reported sleep disturbances, possibly because worry and ruminating thoughts provoke cognitive arousal and may disturb stress-related cortisol homeostasis, resulting in poorer sleep. However, as an important caveat, Robb and colleagues did not have pre-pandemic anxiety or depression measures to compare against the ones acquired during physical distancing mandates, which weakens causal attribution. Those reporting poor sleep at least three times per week had eight- and seven-times-higher odds of reporting worse symptoms of anxiety and depression, respectively. Robb and colleagues<sup>119</sup> also found that those who were single/widowed/divorced and/or who lived alone were also at increased risk of reporting worse symptoms of depression and anxiety following COVID-19 lockdown, especially men. Indeed, being widowed or divorced as a risk factor for worse mental health has been reported in COVID-19 cohort studies in Spain ( $n = 3,055$ )<sup>120</sup> and China ( $n = 1,060$ )<sup>121</sup>, although these were younger cohorts. Overall, women were more likely to report worse components of anxiety and depression than men, with this observation replicated in different age groups and in different countries, including Denmark, Spain, Italy, Turkey and Iran<sup>119</sup>.

In a comparison of outcomes before and during the pandemic at the psychological and behavioural levels, Niedzwiedz and colleagues<sup>122</sup> analysed data from almost 10,000 adults in the longitudinal arm of a nationally representative sample (the UK Household Longitudinal Study). In addition to increased regular and binge alcohol consumption, psychological distress rose, especially in women and young adults generally, as well as in the Asian community and among individuals with a degree education. Robinson and colleagues<sup>123</sup> conducted a systematic meta-analysis of 65 longitudinal studies and documented an increase in mental health burden, particularly in the months after lockdown, especially in depressive symptoms, anxiety and mood disorder symptoms in American, European and other samples. Several of these changes during COVID-19 were especially pronounced in individuals with pre-existing physical conditions, which the authors interpreted as likely to reflect an elevated risk of infection. Moreover, Zaninotto

and colleagues<sup>124</sup>, who examined the profiles of >5,000 adults from the English Longitudinal Study of Aging, reported that depression, anxiety, loneliness and poor quality of life increased in the months after the pandemic started. The manifestations were stronger in certain population strata: women, older individuals, and those who live alone or are less affluent. The collective findings from these longitudinal population investigations converged on a major breakdown in mental health and health-related behaviours throughout the COVID-19 pandemic in 2020. Targeted monitoring and psychological interventions are suggested by these authors, especially for more vulnerable parts of the community, including more socially isolated individuals (such as single, widowed and divorced people), who suffered disproportionately.

Only very few longitudinal brain-imaging studies relevant to COVID-19 have been published so far. Douaud and colleagues sampled 782 UK Biobank participants who had been brain-scanned before the pandemic and have been re-scanned during the pandemic<sup>125</sup>. Of these, 394 had been infected by COVID-19, and 388 acted as matched controls. Brain changes due to the infection itself were linked to a loss of grey matter (with cortical thickness and mean diffusivity measures as proxies to capture tissue changes) in the left parahippocampal gyrus, the left lateral orbitofrontal cortex and the left insula. When looking over the entire cortical surface, these results extended to a set of brain circuits including several nodes of the prefrontal, parietal and temporal default network, in addition to the anterior cingulate cortex and olfactory circuits. These differences in brain correlates of infection were associated with increased cognitive decline, as evidenced by significantly more time required to complete the numeric (A) and alphanumeric (B) version of the Trail Making Test. In addition, a decrease in whole brain volume suggests a diffuse loss of grey matter superimposed onto the more regional effects. In addition to the study's unique pre- and post-COVID-19 data and careful matching of the patients and controls for age, sex, scan interval and ethnicity, rigorous diagnosis of infection made it possible to test for brain correlates of the disease in a way that was statistically more precise than would have been the case for cross-sectional post-infection differences alone. Although the social consequences of COVID-19 infection were not followed up, the reduced grey matter volume, especially in units of the default network, suggests that a loss of social skills and social network size is a likely outcome, although inferring causal directionality is challenging.

The rare evidence on brain changes in medial-temporal limbic, insula and orbitofrontal cortex seems to bear similarities to longitudinal studies in non-human primates. One brain-imaging study of dopaminergic function compared macaque monkeys housed in social isolation for 1.5 years and during later social housing with other monkeys<sup>126</sup>. The repercussions of diminished frequency and intensity of social interaction may be traced to dopaminergic neurotransmitter pathways implicated in reward processing, such as in the orbitofrontal cortex. Indeed, after social rehabilitation, less socially interactive males with fewer grooming opportunities displayed hyperactive dopamine responses not present before the isolation condition. The authors concluded that experimentally altering the social richness in the environment led to reward-related neural plasticity effects. The medial-temporal limbic system in turn has been related to plasticity changes in social network sizes in non-human primates, based on regularity of social contact in longitudinal research<sup>33</sup>. The authors also flagged changes in the prefrontal cortex structure, which may relate to social hierarchy organization that breaks down in times of scarce social interaction or changing social order with lower predictability. Finally, the insula was emphasized in longitudinal research in free-ranging monkeys, and its changes were interpreted to relate to affiliative behaviour and forms of empathy towards others<sup>34</sup>, instrumental for maintaining the regular grooming social network.

As reflections for future research on social isolation, among the elderly whose social circles are already contracting, we might expect isolation to hasten the rate at which friendships decay and are

ultimately lost, resulting in increased susceptibility to mental (for example, cognitive decline, depression and anxiety) and physical (for example, stress, diminished cardiovascular health and impaired immune defence) deterioration over the following decade. Given that most of the social skills needed for the adult world are acquired through peer interaction rather than interactions with adults, we might anticipate some slowdown in the rate of social development in adolescents, possibly resulting in long-term loss in social skills. However, an alternative interpretation might be that the elderly tend to have smaller, more tightly knit, more family-oriented social networks that buffer them against the worst effects of isolation, whereas young adults usually have wider social networks in which peripheral friendships play an important casual role. Viewed from this angle, younger adults would be expected to experience more loss of social capital during the pandemic, with higher costs for mental and physical health. Follow-up studies will be needed to determine which causal sequence is correct. Either way, the population stratum that may be the least likely to be affected by lockdown is young adults: this age group's strong natural desire to be social whenever possible is likely to result in a rapid re-establishment of normal social interaction patterns.

### Social isolation effects linked to social inequality

A final possibility to consider is that social inequality significantly modulates the effects of lockdown. In a data-driven machine-learning study of >17,000 variables describing ~10,000 families in >20 cities across the USA<sup>127</sup>, social determinants of inequity were found to explain most differences in how children and parents experienced the COVID-19 pandemic, above and beyond other candidate predictors such as pre-existing medical or psychiatric conditions. Sociological factors such as household income, socio-economic status and the experience of racism emerged as the primary correlates of negative pandemic experiences. These effects included increased difficulties with schoolwork among children and concerns over racism among parents. Non-White and Hispanic families faced reduced income and resources and higher likelihoods of financial worry and food insecurity. Yet, these families were the most likely to abide by safe practices such as social distancing and hand washing. By contrast, White families, who typically enjoyed higher pre-pandemic income and presence of a parent with a post-graduate degree, experienced less harsh impacts from COVID-19. These families' children reported longer nighttime sleep, less difficulty with remote learning for school and less worry about the impact of the pandemic on their family's stability.

These findings may be analogous to observations from non-human primates, which report that social-isolation-induced plasticity effects in dopaminergic brain function depend on a monkey's position in the social hierarchy<sup>126</sup>, with pronounced differences in social rehabilitation in higher- versus lower-ranking individuals. Additionally, lower dominance rank typically reduces the availability of social outlets, which are especially crucial in times of stress and disruption<sup>128</sup>. Sapolsky argued that lower resilience to encountered stressors escalates the glucocorticoid stress hormone levels and certain disease vulnerabilities<sup>128</sup>, with declining effectiveness of the immune response and other physiological impacts.

In sum, societal determinants of inequity have emerged as an important driver of negative pandemic experiences, regardless of pre-pandemic functionality. Yip and colleagues<sup>127</sup> concluded that community-level, transgenerational intervention strategies may be needed to combat the disproportionate burden of pandemics on racial/ethnic minoritized and marginalized populations. Taken together, these findings have significant implications for child education and society, as well as the relevant public health decisions, in the future.

### Conclusion

The human social world is deeply rooted in our primate ancestry. This social world is, however, extremely sensitive to the time we invest in it.

Enforced social isolation can easily destabilize its delicate equilibrium. Many of the psychological sequelae of COVID-19 lockdowns are readily understood as resulting from the dislocation of these deeply rooted social processes. Indeed, many of these findings could have been anticipated long before the COVID-19 pandemic. For example, almost one in ten Europeans admitted never meeting friends or family outside of their own household in the course of an entire year, with direct consequences for their psychological and physical health<sup>129</sup>. Solitary living made up >50% of households in a growing number of metropolitan cities worldwide and has long been thought to be the cause of increasing levels of depression and psychological dystopia<sup>130,131</sup>. Indeed, aversive feelings of social isolation probably serve as a biological warning signal that alerts individuals to improve their social relationships<sup>132</sup>.

Three key points emerge from our present assessment. One is that COVID-19 and associated public health restrictions to curb the spread of the virus are likely to have demonstrable mental health and psychosocial ramifications for years to come. This will inevitably place a significant burden on our health systems and societies. The impact may, however, be largely restricted to specific population strata. Older people, for example, are likely to face disproportionately adverse consequences. Worryingly, prolonged social isolation seems to invoke changes in the capacity to visualize internally centred thoughts, especially in younger sub-population. This may presage a switch from an outward to an inward focus that may exacerbate the experience of social isolation in susceptible individuals. The longer-term implications of this are, however, yet to be determined. Second, the experience of undergoing social isolation is known to have significant effects on the structure and function of the hippocampus and default network, long recognized as a primary neural pathway implicated in the pathophysiology of dementia and other major neurodegenerative diseases as well as in effective social function. The fact that these same brain regions turn up in the neuroanatomical consequences of COVID-19 infection is concerning. Our third key point is that social determinants that condition inequality in our societies have strong impacts on lived day-to-day pandemic experiences. This is highlighted by the negative outcomes from COVID-19 for families of lower socio-economic status, single-parent households, and those with racial and ethnic minority backgrounds.

As a note of caution, in our judgement, few datasets or methodological tools exist today to definitively establish causal directionality in many of the population effects we have surveyed in this review. For example, many of the correlative links do not allow us to infer whether loneliness directly causes depression and anxiety, as opposed to already depressed, anxious individuals being more prone to developing loneliness in times of adversity. Similarly, none of the reviewed findings can be used to tease apart whether changes in psychopathology during periods of mass social isolation are the chicken or the egg of the many biological manifestations. To fill knowledge gaps on mediating mechanisms for theoretical models, future research requires carefully designed and controlled longitudinal before-versus-after COVID-19 population investigations.

### Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

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## Author contributions

R.I.M.D. and D.B. conceived and wrote the work.

## Competing interests

The authors declare no competing interests.

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