REVIEW ARTICLE

Social isolation and the brain: effects and mechanisms

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An obvious consequence of the coronavirus disease (COVID-19) pandemic is the worldwide reduction in social interaction, which is associated with many adverse effects on health in humans from babies to adults. Although social development under normal or isolated environments has been studied since the 1940s, the mechanism underlying social isolation (SI)-induced brain dysfunction remains poorly understood, possibly due to the complexity of SI in humans and translational gaps in findings from animal models. Herein, we present a systematic review that focused on brain changes at the molecular, cellular, structural and functional levels induced by SI at different ages and in different animal models. SI studies in humans and animal models revealed common socioemotional and cognitive deficits caused by SI in early life and an increased occurrence of depression and anxiety induced by SI during later stages of life. Altered neurotransmission and neural circuitry as well as abnormal development and function of glial cells in specific brain regions may contribute to the abnormal emotions and behaviors induced by SI. We highlight distinct alterations in oligodendrocyte progenitor cell differentiation and oligodendrocyte maturation caused by SI in early life and later stages of life, respectively, which may affect neural circuit formation and function and result in diverse brain dysfunctions. To further bridge animal and human SI studies, we propose alternative animal models with brain structures and complex social behaviors similar to those of humans.

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INTRODUCTION

Social interactions are considered a basic human need, analogous to other fundamental requirements such as nutrition and sleep [1–6]. Since the first report of the novel SARS-CoV-2 in late 2019, public health organizations have advocated for preventative policies to prevent the virus from spreading, including stay-at-home orders that closed businesses, day care centers, schools, and playgrounds, which dramatically reduce the opportunities for face-to-face social interaction outside the household. Mandated measures, including physical distancing, quarantines, and lockdowns during the COVID-19 pandemic, have been associated with increased mental health issues, including anxiety and depression in adults and adolescents, as well as significantly reduced verbal, motor, and overall cognitive performance in children born during the pandemic [7–12]. People experiencing prolonged social isolation (SI), such as orphans and empty nesters, suffer from various neuropsychiatric conditions, including depression and reduced sleep [13–15]. Thus, reduced social interaction at different ages has broad adverse impacts on socioemotional development and mental health. However, our understanding of the effects of SI and the mechanisms by which it affects brain structure and function is far from complete.

Previous reviews have summarized the benefits of social bonds among humans [16] and different aspects of the effects of SI, including social homeostasis (an adaptive function that optimizes behaviors that govern social connection) [17], adolescent development and mental health [18], and endocrine functions [19]. Herein, we review alterations in emotion, behavior, and brain structure and function, together with molecular and cellular changes induced by SI at different ages in different animal models, and summarize the similarities and differences in the effects of SI shown in humans and animal models. We also discuss the limitations of current rodent models and suggest nonhuman primates, marmosets, and domestic dogs as promising animal models for future SI studies. The purpose of this review was to help bridge animal and human studies on SI so that discoveries made using animal models can be better translated to humans.

MAJOR ADVANCES IN SI STUDIES

A PubMed search using the keywords social isolation, social deprivation, and maternal separation revealed that the number of publications on SI has increased substantially in recent years, likely due to preventive measures to halt the spread of SARS-CoV-2 infection (Fig. 1A). The repeated SI experienced by millions due to physical distancing, quarantines or lockdowns during the COVID-19 pandemic has been reported to be related to an increased incidence of anxiety and depression [20] (Fig. 1B).

The effects of orphans' infantile experiences on the development of their physical growth, speech, character, and social relationship were first reported in 1944 [21] (Fig. 1B). To understand the relationship between SI and social behavioral changes, Harry Harlow performed famous experiments on rhesus

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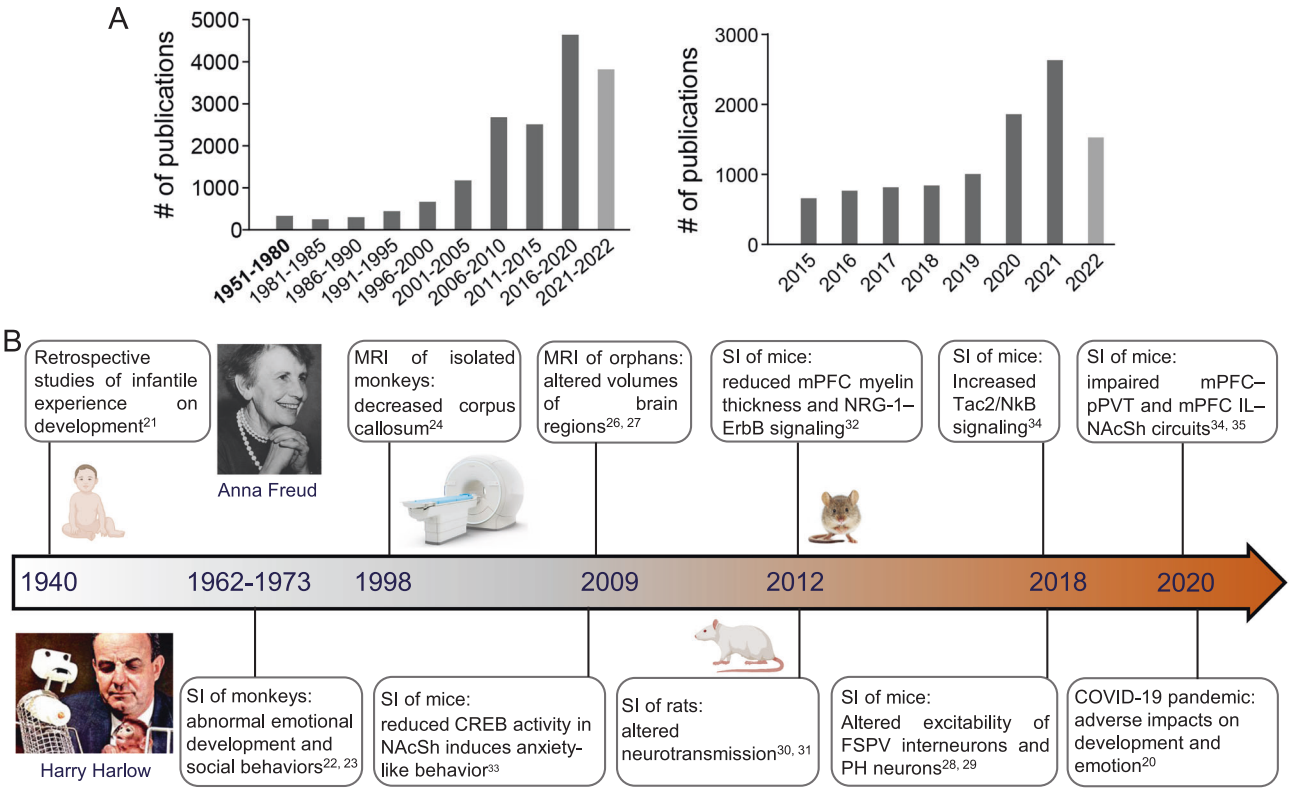


Fig. 1 Overview of studies on social isolation. A As of the end of July 2022, the number of publications on social isolation has increased substantially in the last few years based on a PubMed search using the keywords social isolation, social deprivation, and maternal separation. **B** Landmarks in SI studies in human and animal models. CREB cAMP response element–binding protein, FSPV fast-spiking parvalbumin-expressing, IL infralimbic, PH prominent h-current, pPVT posterior paraventricular thalamus, mPFC medial prefrontal cortex, MRI magnetic resonance imaging, NAcSh nucleus accumbens shell, NRG-1–ErbB neuregulin-1–Erb-b2 receptor tyrosine kinase 2, Tac2/NkB tachykinin 2/neurokinin B.

monkeys and demonstrated that animals raised in partial or total isolation from birth were hostile and could not form adequate social attachments to others when such opportunities were provided in adolescence or adulthood [22, 23]; the degree of social damage is related to the duration of SI [23]. Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) neuroimaging analysis revealed structural alterations in specific brain regions, including the prefrontal cortex (PFC) and amygdala, in humans and monkeys after SI [24–27]. The potential molecular and cellular mechanisms underlying SI-induced brain structural and behavioral changes have been mostly explored using rodent models in recent decades (Fig. 1B), including SI-induced alterations in neuronal activity [28, 29], neurotransmission [30, 31], oligodendrocyte development [32], and signaling pathways [33, 34]. Moreover, various neural circuits that are impaired by SI in mice have been recently characterized [35, 36]. Despite significant progress, the mechanisms underlying distinct phenotypes caused by SI across different ages and species and to what extent SI-induced brain changes in animal models mimic those in humans remain unclear.

BEHAVIORAL, EMOTIONAL, AND COGNITIVE ABNORMALITIES INDUCED BY SI IN HUMANS

There are two well-described critical periods for social development in childhood, when environmental inputs result in irreversible changes in brain development and function with permanent effects on social behavior. The first critical period, which is called “primary socialization”, occurs between 6 weeks and 6 months of age, beginning with the onset of learning abilities, continuing with the smiling response, and ending with the fear of strangers [37–40]. Thus, early positive interactions with a primary caregiver are very important for the development of social capacities. From ~27 months of age, the use and understanding of sentences mark the beginning of the second critical period, ‘verbal socialization’, in which the process of socialization begins all over again through a different form of communication [40]. Thus, during the first few years of life, the developing brain is particularly vulnerable to environmental stresses [41]. The disruption of social interaction during early critical periods will negatively impact cognitive, social, and verbal performance, resulting in a predisposition to mental health issues [42–44].

The adverse effects of early-life SI have been studied mostly in orphans in institutions. Early life social deprivation in orphans has life-long impacts on their brain development and socioemotional functioning, based on studies from cohorts of Romanian orphans who entered institutions in the first few weeks after birth and spent different lengths of time there before being adopted [42–44] (Fig. 2 and Table 1). In these institutions, the children experienced minimal social contact, received insufficient care, and had a lack of toys for cognitive stimulation, which resulted in a devastating and pervasive effect on their cognitive and social development [45]. Children who spent more than 6 months in the institutions displayed increased symptoms of neurodevelopmental disorders, including attention deficit/hyperactivity disorder, autism spectrum disorder, and disinhibited social engagement disorder [45]. These disorders persisted in many of the orphans from infancy through young adulthood [42, 43, 46]. Thus, SI during early life has profound effects on socioemotional development and cognitive abilities (Fig. 2 and Table 1), although the effects of other confounding factors such as malnutrition and negligence of orphans cannot be excluded [47–49].

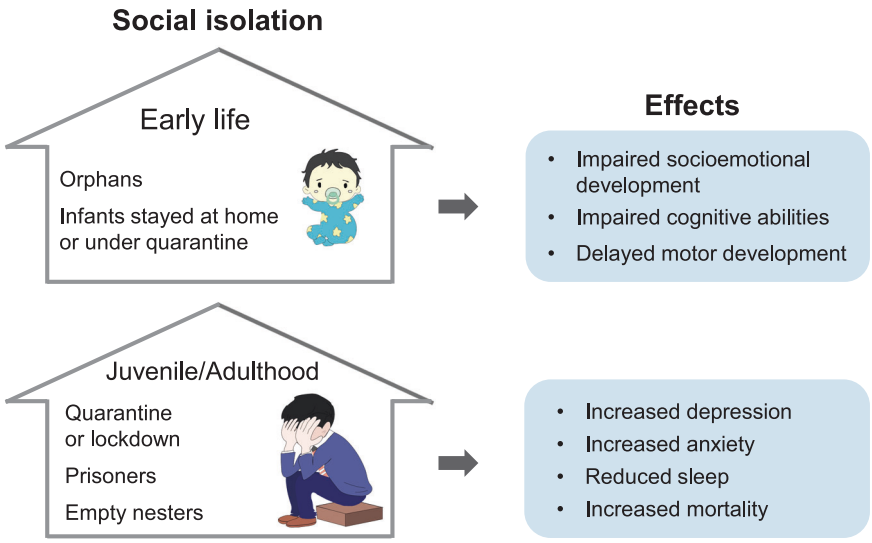


Fig. 2 Social isolation at different ages has distinct impacts on human health.

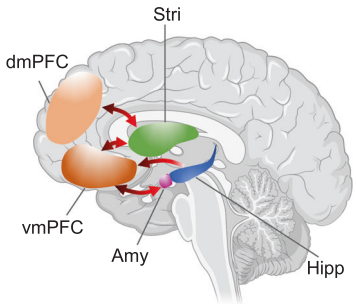
Table 1. Summary of changes induced by SI in humans and nonhuman primates.

	Early life*		Juvenile		Adult		Ref	
	H	NHP	H	NHP	H	NHP	H	NHP
Brain structure and function								
Altered brain region volume[#]	PFC, Amy, Hipp	Visual cortex	na	na	Amy	na	26, 27, 61–64, 79	24, 81
Altered inter-regional functional connectivity[#]	Amy–PFC, Hipp–PFC, Stri–PFC	na	na	na	na	na	73, 75, 76	
Altered WM volume or structural connectivity[#]	Limbic and frontostriatal circuits	pSTS	na	na	na	na	25, 64, 66–69	81
Activation of neurons	na	na	na	na	Midbrain	na	77	
Behavior and cognition								
Impaired socioemotional development	Yes	Yes	na	na	na	na	11, 12, 42, 43, 46	22, 23, 80, 81, 109
Impaired cognitive ability	Yes	Yes	na	na	na	na	42, 45	24
Increased depression and anxiety	na	na	Yes	Yes	Yes	Yes	7, 8, 53–55, 58, 59	83, 140

Amy amygdala, *H* humans, *Hipp* hippocampus, *NHP* non-human primates, *pSTS* posterior superior temporal sulcus, *PFC* prefrontal cortex, *Stri* striatum, *WM* white matter. *Early life means 0–5 years old for humans and 0–1 year old for primates.
[#]decreased or increased; na, data not available.

Infants born during the COVID-19 pandemic were forced to stay at home during their first year with limited social interaction outside the household due to physical distancing, quarantines, or lockdowns. Studies of these babies showed that they had significantly lower scores for gross and fine motor control and communication skills than those born before the pandemic at the age of 6 months, regardless of whether their parents had been infected with the virus [11] (Fig. 2). Another study showed that children born during the pandemic had significantly reduced verbal, motor, and overall cognitive performance compared with children born in the prepandemic period [12]. Reduced human-to-human interactions during the pandemic, including reduced peer interactions, are considered major factors inhibiting the development of children born during this period [50]. In addition, prenatal and postnatal maternal distress during the COVID-19 pandemic have been associated with slower infant socioemotional development [51]. Whether other factors, such as mask wearing (obstructed face recognition) during the pandemic, affect the brain development of infants remains unclear. Longitudinal studies are required to determine whether the socioemotional and cognitive delays are transient or long lasting.

SI during juvenile and adult stages has substantial emotional impacts (Fig. 2). For example, school closures during COVID-19 lockdowns have been associated with mental health problems among students due to a prolonged state of physical isolation from their peers, teachers, extended family, and community networks [52, 53]. Depressive symptoms increased from 18.5% before school closures to 24.9% after school reopenings [54]. Similarly, physical distancing measures leading to reduced social interactions during the pandemic have been associated with substantial increases in anxiety and depression, substance use and domestic violence in adults [7, 8, 55–57]. Approximately 10.9% of 1,450 English-speaking adult participants in the USA met the criteria for generalized anxiety disorder between March and April 2020, which was significantly higher than the 3.1% estimated prior to the pandemic [55]. Other stressors that occur during the pandemic, such as economic loss and caregiving burden, may also contribute to mental abnormalities in adults. Another example of



SI-affected brain regions are involved in multiple functional circuits				
	PFC	Amy	Hipp	Stri
Fear	+	+	na	na
Reward	+	na	na	+
Anxiety	+	+	+	na
Cognitive	+	+	+	na
Social	+	+	+	na

Fig. 3 Major brain regions and connectivities affected by early-life SI in humans and functional circuits in which these regions are involved. dmPFC dorsal medial prefrontal cortex, vmPFC ventral medial prefrontal cortex, Amy amygdala, Hipp hippocampus, Stri striatum. Arrows indicate interregional connections. na data not available or no changes. The illustration of the brain is from BioRender.com.

SI in adults includes prisoners under solitary confinement, who experience more severe SI than those experiencing social distancing, and they exhibit increased distress, depression, and aggression as well as an increased prevalence of self-harm [58]. In addition, empty nesters were reported to be more vulnerable to depressive symptoms than nonempty nesters [59]. It was hypothesized that SI in adulthood induces a reduction in the social homeostatic set-point, which may make a social stimulus that was previously perceived as optimal now be interpreted as a surplus, thus leading to depression, aggression, or social anxiety [17].

In summary, the apparently different effects of SI during early life and later stages of life suggest the importance of the timing of SI when studying the underlying neural mechanisms.

BRAIN REGIONS AND INTERREGIONAL CONNECTIVITIES AFFECTED BY SI IN HUMANS

Human social and cognitive functions are regulated by information that is processed through neural circuit hierarchies connecting different brain regions [17, 60]. Studies on adopted children exposed to SI in institutions during early childhood offer opportunities to disentangle the effects of early life SI on brain structure and function using MRI (Fig. 3 and Table 1). In general, neuroimaging studies of individuals with early life institutional experiences showed brain structure abnormalities in the PFC, amygdala, and hippocampus. These abnormalities include consistently reduced total gray and white matter volumes in the PFC and hippocampus [61–64]. The effects of SI on amygdala volume are inconsistent, probably due to different methods of brain volume analysis [26, 27, 61]. With brain volume correction, the relative amygdala volume was larger in the institutionalized group than in the control group, which has been associated with profound emotional problems [27]. Moreover, electroencephalography analysis revealed abnormal patterns of brain activity in the frontal, temporal, and occipital regions among children reared in institutions, which reflects a delay in cortical maturation [65].

Children under institutional care also exhibit altered structural connections between brain regions. The DTI-based structural connectome of children reared in institutions showed significant reductions in global connectivity strength and local connectivity, especially in the ventral medial PFC, compared with matched controls [66]. Children who experienced early social deprivation in Romanian orphanages showed decreased white matter integrity in the left uncinate fasciculus connecting the orbitofrontal and temporal lobes [25, 67]. Compromised integrity of the white matter tracts involved in limbic and frontostriatal circuitry was also observed in children under institutional care [68], while another study of previously institutionalized children using DTI identified increased frontostriatal connectivity, which was associated with increased externalizing behavioral problems [69].

Altered functional connectivities between brain regions of children under institutional care were examined by functional MRI (fMRI). The amygdala and its connections with the medial PFC (mPFC), which are critical for emotion regulation and fear learning, are markedly immature in children [70–72]. However, children reared in institutions showed mature amygdala-mPFC connectivity by fMRI [73]. Moreover, previously institutionalized children showed elevated amygdala activity in response to emotional faces [74]. Children and adolescents who experienced prior institutionalization also showed increased connectivity between the hippocampus and PFC by fMRI during fear learning [75]. In addition, resting-state fMRI showed that early institutional care enhanced ventral striatal-mPFC connectivity, which is associated with social problems [76]. While other factors may impact the brain development of institutionalized children, the brain regions most affected by early life SI include the PFC, amygdala, hippocampus and striatum, which are involved in fear, reward, anxiety, cognitive, and social brain circuitries (Fig. 3).

Only a few studies have examined brain structural and functional changes after SI during adulthood. For example, in adults, the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) in the midbrain were selectively activated for social cues such as images of social activities after acute SI for 10 h, similar to the way fasting causes midbrain activation in response to food cues [77]. Activation of the neural circuit that induces hunger is also observed in adult *Drosophila* after chronic SI [78]. In addition, long-term reduced social interaction during the COVID-19 outbreak and lockdown resulted in volumetric increases in the bilateral amygdala, putamen, and anterior temporal cortices [79]. Changes in the amygdala diminished as time elapsed following lockdown relief, suggesting that the intense experience associated with the lockdown induced reversible brain changes that are commonly associated with stress and anxiety [79]. Whether the volume increase in specific brain regions is primarily due to SI or other stresses during lockdowns remains unclear.

SI AFFECTS NEURAL CIRCUITS AND BEHAVIORS IN ANIMAL MODELS

Studies of SI in animal models are an important complement to human studies because randomization and experimental manipulations of isolation in humans are limited in intensity and duration by ethical restrictions. SI-induced effects at different ages in nonhuman primates and rodents are summarized in Table 1 and Table 2, respectively. SI studies in monkeys were performed mostly during early life, similar to those in humans, while those in rodents were mostly performed at juvenile stages.

Early life SI-induced brain structural alterations and abnormal behaviors are studied the earliest and the most in monkeys [22–24, 80–82]. Specifically, baby rhesus monkeys raised individually from 2 to 12 months of age exhibited a significantly decreased size of corpus callosum, fewer interhemispheric projections, and

Table 2. Summary of brain structural and functional alterations induced by SI in rodents.

Animal models	Age of SI	Onset of SI; SI period	Structural and functional changes	Ref
Mouse	Postnatal	Birth; 2 w	Increased level of myelin-related genes and depleted OPC pool	[112]
		P10; 1.5/8 h	Activated Agrp neurons modulating ultrasonic vocalization	[95]
		P14; 7d + 12 w	Activated astrocytes in the locus coeruleus	[113]
	Juvenile	P21; 2 or 8 w	Reduced myelination and NRG-1–ErbB signaling	[32, 116]
		P21; 2 w	Increased firing property of FSPC interneurons and reduced excitatory synaptic inputs and intrinsic excitability in PH neurons in mPFC	[28, 29, 96]
		P21; 2 w	Reduced excitability of parvalbumin interneurons in dmPFC and impaired active social approach	[97]
		P21; 2 w	Reduced excitability of mPFC–pPVT neurons and social deficits	[35]
		P21; 4 w	Reduced serotonergic fiber density in the inferior colliculus	[106]
		P21; 5 w	Sex-specific behavioral abnormalities and altered neuronal activity in PFC, BLA, and VTA	[90]
		P21; 8 w	Decreased excitability of mPFC IL–NAcSh neurons and impaired social recognition	[36]
		P28; 1 w	Activated putative dopamine neurons in VTA which can be regulated by PVN oxytocin neurons	[89]
	Adult	P35; 4 w	Abnormal connections with the dorsolateral orbitofrontal cortex	[88]
		2 m; 4 w	Decreased number and overactivation of microglia	[115]
		2 m; 10–12 w	Anxiety-like symptoms and decreased CREB activity in NAcSh	[33]
		2–4 m; 2 w	Brain-wide upregulation of the neuropeptide Tac2/NkB	[34]
		3 m; 4 w	Accelerated necroptosis in BLA and behavioral inflexibility	[101]
Rat	Postnatal	Birth; 7 d	Elevated expression of neural proteins such as BDNF and reduced apoptosis and neuronal pruning	[108]
		P2; 18 d	Reduced synaptogenesis and mature spine density in Hipp	[100]
		P7-P11; 6 h/d	Inactivated cofilin and decreased AMPA receptors and LTP	[30, 98]
		P14; 7 d	Fewer hippocampal microglia	[114]
	Juvenile	P20; 26 d	Changed expression patterns of IEGs regulating cell differentiation and apoptosis in mPFC	[110]
		P21; 3 w	Enhanced LTP of NMDAR-mediated glutamatergic transmission	[31]
		P21; 15 w	Decreased volume of Hipp and dentate gyrus; decreased activity of the Wnt–beta-catenin pathway in PFC	[85, 86]
		P21; 8 w	Decreased dendritic spine density on pyramidal neurons in PFC and Hipp	[105]
		P25–28; 30 d	Altered microtubule stability by decreased MAP-2 in Hipp	[104]
		P28; 8 w	Reduced mPFC volume	[87]
	Adult	2 m; 7 d	Social memory deficit	[84]
		3 m; 21 d	Increased mitochondrial glucocorticoid receptor in PFC and Hipp	[107]
		Adult; 12 d	Delayed positive influence of running on adult neurogenesis in Hipp	[99]

m month(s), *w* week(s), *d* day(s), *Agrp* Agouti-related peptide, *AMPA* amino-3-hydroxy-5-methylisoxazole-4-propionic acid, *BDNF* brain derived neurotrophic factor, *BLA* basolateral amygdala, *CREB* cAMP response element-binding protein, *dmPFC* dorsal medial prefrontal cortex, *Hipp* hippocampus, *IEGs* immediate early genes, *IL* infralimbic, *LTP* long-term potentiation, *NAcSh* nucleus accumbens shell, *NMDAR* N-methyl-D-aspartate receptor, *NRG-1–ErbB* neuregulin-1–Erb-b2 receptor tyrosine kinase 2, *OPC* oligodendrocyte progenitor cell, *pPVT* posterior paraventricular thalamus, *PVN* paraventricular nucleus, *Tac2/NkB* tachykinin 2/neurokinin B, *VTA* ventral tegmental area.

cognitive deficits [24], while the separation of rhesus monkeys from their mothers from birth resulted in structural abnormalities in the visual cortex and premature myelination in the posterior superior temporal sulcus together with abnormal emotional and social behaviors [80, 81]. SI during adulthood in macaques (*Macaca fascicularis*) induced depression-like behaviors with significantly reduced aggressive, communicative, sexual, and parental behaviors [83]. The SI of adult mice decreased cAMP response element–binding protein (CREB) activity in the shell regions of the nucleus accumbens (NAcSh) and induced anxiety-like symptoms, which were reversed by chronic antidepressant treatment [33]. The SI of adult rats for 7 days induced social memory loss, which is associated with molecular changes in the medial amygdala [84].

Other brain changes, including volume changes in different brain regions [85–87], abnormal regional connections [88], and altered neural circuits [35, 36, 89, 90], have been reported in rodents after SI at the juvenile stage. For example, the SI of juvenile mice led to reduced excitability of mPFC neurons projecting to the posterior paraventricular thalamus (pPVT) and increased inhibitory input from somatostatin interneurons to mPFC neurons projecting to the pPVT; the sociability deficits in adulthood can be rescued by chemogenetic or optogenetic stimulation of mPFC neurons projecting to the pPVT [35]. The SI of mice at the juvenile stage also reduced the excitability of prefrontal infralimbic neurons (mPFC IL) projecting to the NAcSh, which was activated when group-housed mice encountered a

familiar conspecific; the resulting social recognition deficit can be reversed by activation of these neurons [36]. Moreover, the SI of mice during the juvenile stage resulted in acute hyperexcitability of putative dopamine neurons in the VTA and long-lasting expression of GluA-lacking AMPARs at excitatory inputs onto putative dopamine neurons that project to the PFC [89]. The SI-induced changes in neural activity and synaptic plasticity in the VTA and behavioral deficits can be reversed by the chemogenetic inhibition of paraventricular nucleus (PVN)-VTA projection neurons [89]. DAergic neurons of the VTA contribute to both social and reward-seeking behaviors [91, 92]. Moreover, PVT neurons project to various reward-associated areas, including the VTA and NAc, which are key nodes of reward circuitry [93, 94]. In summary, SI during juvenile stages interferes with the functions of multiple neural circuits, including the reward circuit.

Social abilities are shaped by the interactions of multiple neural circuits during different critical periods of development. If we can further identify social behavior-related neural circuits that develop during early life and adulthood, it may be possible to manipulate key factors regulating circuit plasticity at specific stages and restore normal function to the affected circuits of individuals who experience SI.

NEURONAL ABNORMALITIES IN ANIMAL MODELS INDUCED BY SI

The SI of individuals at different ages exerts adverse impacts and causes different symptoms, suggesting distinct molecular and cellular mechanisms underlying the abnormalities, including neuronal dysfunction. Indeed, previous studies of SI at different developmental stages in animal models have reported distinct changes in neuronal excitability and synaptic transmission.

Alterations in neuronal excitability have been observed in rodents that were socially isolated at both neonatal and juvenile stages [28, 29, 95–97]. Isolating neonatal mice from the nest activated hypothalamic agouti-related protein (Agrp) neurons, which modulate isolation-induced ultrasonic vocalizations. The increased activity of Agrp neurons and ultrasonic vocalizations were ameliorated by care and warmth, suggesting that Agrp neurons play a role in offspring-to-caregiver bonding [95]. The SI of mice at the juvenile stage acutely increased the excitatory inputs to fast-spiking parvalbumin-expressing (FSPV) interneurons and thus increased the firing of FSPV interneurons [29]. The increased intrinsic excitability of FSPV interneurons was still observed in the mPFC of mice in the adult stage after SI in the juvenile stage [96], together with increased inhibitory synaptic inputs onto a subtype of layer 5 pyramidal cells (prominent h-current (PH) cells) [28]. These results suggest that juvenile SI primarily disturbs circuits involving FSPV interneurons and eventually affects circuits involving PH pyramidal cells in adulthood. In addition, SI in the juvenile stage caused altered maturation of parvalbumin-positive interneurons (PVIs) in the dorsal medial PFC, which are activated preceding an active social approach toward a novel animal, and thus led to reduced excitability of dorsal medial PFC PVIs and decreased social interaction [97].

In addition, the isolation of neonatal rats inhibited α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor trafficking by increasing corticosterone, and disrupted long-term potentiation (LTP) in the barrel cortex [30], while the SI of juvenile rats enhanced LTP of N-methyl-D-aspartate (NMDA) receptor-mediated glutamatergic transmission in the VTA [31]. The synaptic trafficking of AMPA receptors in rats was affected by an increased level of actin filament through the inactivation of actin-depolymerizing factor cofilin after SI [98].

The SI of animals also resulted in other neuronal changes, including decreased adult neurogenesis [99], reduced synaptogenesis [100], increased neuronal necroptosis [101], altered levels of transmitters or receptors [102, 103], cytoskeletal changes [104], decreased dendritic spines and fiber density [105, 106], disturbed signaling pathways [84, 86, 107], and altered expression of specific genes [34, 108–110] (Table 2). For example, SI in adult mice broadly induced an upregulated expression of neuropeptide neurokinin B (NkB) encoded by *tachykinin 2 (Tac2)*, which is involved in fear memory consolidation [111], in neurons of multiple brain regions [34]. The systemic administration of an antagonist of the NkB receptor Nk3R prevented virtually all behavioral abnormalities caused by chronic SI; conversely, enhancing NkB expression and release phenocopied SI in group-housed mice [34].

GLIAL ALTERATIONS INDUCED BY SI IN ANIMAL MODELS

In addition to neuronal changes, altered glial development and functions also play an important role in SI-induced brain dysfunction. For example, maternal separation or early-life SI of mice decreased the pool of oligodendrocyte progenitor cells (OPCs) and promoted the premature differentiation of OPCs to oligodendrocytes (OLs) [112]. Early-life SI also induced astrocyte activation in the locus coeruleus of female mice [113]. Maternal separation or early-life SI in rats led to fewer hippocampal microglia and depressive-like behavior, which can be reversed by promoting microglial proliferation in the hippocampus [114]. Moreover, studies of chronic SI during adulthood in mice also showed a decreased number and overactivation of microglia in the hippocampus, together with increased anxiety levels, which were ameliorated by anxiolytic dihydromyricetin [115]. Thus, the SI of animals at different stages affects the development and function of different glial cell types.

Specifically, the SI of mice during juvenile and adult stages resulted in reduced OL gene expression and myelin thickness, and simpler morphology with shorter processes and fewer branches of OLs in the mPFC (Fig. 4) [32, 116]. Socially isolated mice showed a significant decrease in the expression of NRG1 [32]. The NRG1–ErbB signaling pathway, which is important for OL maturation, is linked to reduced mPFC myelination in response to SI in juvenile mice [32]. Unlike the effects of SI during the juvenile stage, maternal separation in the form of repeated daily separation of dams from their litters leads to depletion of the OPC pool and premature differentiation of OPCs to OLs in the mPFC and hippocampus [112, 117]. These results indicate that maternal separation in mice results in earlier differentiation of OPCs into OLs and thus fewer OPCs, while SI during juvenile or adult stages inhibits OL maturation. In the postnatal developing mouse brain, the critical period of OPC differentiation in the corpus callosum is 3–8 days after birth [118], while the critical period of OL maturation in the mPFC is from P21 to P35 [32]. Thus, these different effects of SI on oligodendrocytes may reflect whether the period of SI overlaps with the critical periods of oligodendrogenesis (the formation of myelinating OLs from OPCs), OL maturation or both (Fig. 4).

Notably, alterations in mPFC myelination and function caused by the SI of juvenile mice for 2 weeks after weaning (P21−P35) could not be reversed by social reintegration, demonstrating that P21−P35 is a critical period of OL maturation for mPFC myelination [32]. In contrast, the reduced white matter volume in the PFC of orphans could be ameliorated significantly many years after adoption [64]. This recovery may be due to the adoption of orphans in early life (<5 years of age) before the completion of oligodendrogenesis (Fig. 4) [119]. Moreover, prolonged myelin growth and maturation extends at least through the first 20 years of human life [120], allowing long-term neural plasticity. As the developmental trajectory of neocortical myelination in rodents is distinct from that in humans [118, 119], we must be cautious when translating results from mice to humans.

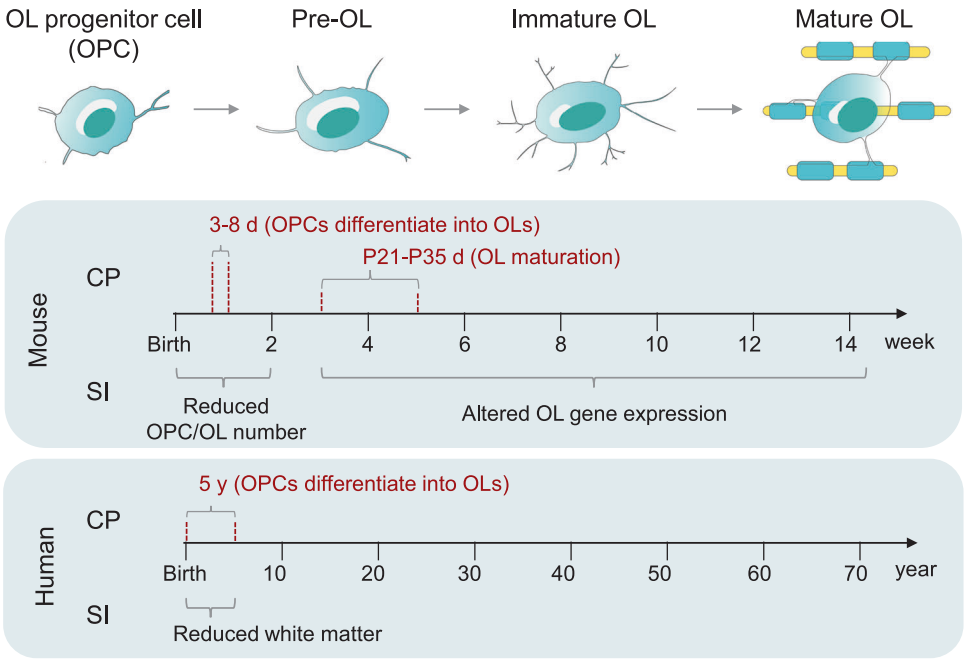


Fig. 4 Effects of SI on oligodendrocyte progenitor cell (OPC) differentiation and oligodendrocyte (OL) maturation. Oligodendrocytes are myelinating cells of the central nervous system that are generated from OPCs, and they follow a tightly orchestrated process of migration, proliferation and differentiation [159]. In the postnatal developing mouse brain, most divided OPCs differentiate into oligodendrocytes during a critical time window of 3–8 days after birth. The critical period (CP) of OL maturation in the mouse mPFC is from P21 to P35. Consistently, SI after weaning at P21 affects only OL gene expression and not the number of OPCs/OLs, while SI for 2 weeks after birth reduces the number of OPCs and promotes earlier maturation of OLs. In the human corpus callosum, most OPCs are differentiated into OLs at 5 years of age, and the number of OLs begins to plateau. Early-life SI results in reduced white matter in several brain regions in orphans. Thus, five years of age might be a turning point when SI causes different effects on myelination (the number of OPCs/OLs versus OL maturation) in the human brain.

These molecular and cellular changes in OPCs and OLs induced by SI demonstrate an important role of myelination in SI-induced brain dysfunctions. Myelin enables the rapid transmission of action potentials through salutatory conduction [121, 122] and provides trophic support to maintain axon integrity [123–125]. Genetic manipulations of oligodendrogenesis and myelination result in profound alterations in neural circuit structure and function [126, 127] and brain dysfunction [128]. The apparent abnormalities in OPC differentiation and OL maturation induced by SI at different developmental stages may explain the more profound phenotypes induced by SI in early life than by SI in adulthood.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Humans are social creatures, and social interaction and cooperation have promoted the rapid development of human culture and civilization. The reduced social interaction outside the household in the last few years imposed by ongoing measures in response to the COVID-19 pandemic has caused apparent public health consequences, including increased anxiety, depression, self-harm, and suicide attempts [7, 8]. However, the mechanisms underlying SI-induced behavioral and emotional alterations remain unclear. This review helps bridge previous animal and human studies of SI. Although the exact timing of SI in most studies on animals and humans is different, animal research provides valuable insights into the effects of SI in humans at both the molecular and neural circuit levels, which are important for understanding the underlying mechanisms and developing potential interventions.

Despite substantial progress, there are still important aspects of SI to be further investigated. For example, human social performance relies on social touch and posture, affective visual cues such as social gazing and facial expressions, and verbal communication [129, 130]. Whether structural and functional alterations occur in the somatosensory and visual cortices of humans following SI during early life requires further investigation. In addition, virtual social methods combined with advanced brain imaging techniques can be applied to determine which forms of virtual social interactions best mimic the neural circuit activation that underlies real-life social interaction [131]. The identification of neural circuits affected by virtual social interactions may guide the development of interventions to mitigate the detrimental effects of SI.

Human social behaviors are probably the most complex among any species. In addition to the duration and frequency, the quality of social interactions, which is affected by relationships with family members and engagement with broader communities, is also important. While rodent models have contributed substantially to our current understanding of the molecular mechanisms underlying SI-induced brain dysfunction, the translational value of rodent models may be limited to certain aspects due to anatomical, behavioral and cognitive properties of rodents that diverge from those of humans [132, 133]. For example, in the rodent brain, the white matter (WM) underneath the cerebral neocortex is poorly developed and occupies a much smaller volume than humans [134]. The brains of nonhuman primates, such as those of macaques, closely resemble human brains in terms of structure and function [135]. However, extremely high costs and slow reproduction rates (5 years to reach adulthood) render macaques hardly practical and not readily accessible for most researchers.

Recently, another species of nonhuman primates, the common marmosets (*Callithrix jacchus*), has emerged as a promising animal model for social neuroscience research, including studies on social isolation [136–141]. Marmosets share many similarities in behavior and social structure with humans, including social monogamy and cooperative breeding [139]. Moreover, marmosets have a much smaller body size and faster reproduction rates (1.5 years to reach

adulthood) than macaques, with 2−3 offspring per pregnancy [142]. When three offspring are born, one is typically abandoned by the parents due to limited nursing capabilities, resulting in a natural model for SI studies.

In addition to nonhuman primate models, domestic dogs (*Canis familiaris*), with a long history of coevolution and coadaptation with humans, have developed exquisite and complex heterospecific dog-human social and cognitive capabilities that are not apparent in other animal models [143, 144]. The behavior of dogs as long-standing favorite pets worldwide has been well documented in the literature [145]. Moreover, some of the complex and cross-species social behaviors, such as tail wagging in dogs, can be analyzed quantitatively by artificial intelligence-based methods [146]. The critical periods of social development in dogs have been extensively studied since the 1960s [39, 40, 147], which provides an accurate time window for SI studies. Furthermore, dogs not only have similar brain structures (gyrification with expanded white matter) but also have similar postnatal development, illustrated by the more conserved spatiotemporal protein expression patterns with humans than those of mice in our recent study [148]. Last but not least, MRI, which is particularly suited for comparative studies across species, has been readily used for structural and functional analysis of both laboratory and pet dogs [149–151].

Thus, marmosets and domestic dogs, combined with advanced functional MRI techniques to image awake animals [152, 153], artificial intelligence for objective and quantitative behavioral and emotional analysis [154–156], integrative multiomics including proteomics and metabolomics to elucidate molecular changes at different levels, and genome-editing techniques [151, 157, 158], offer a unique opportunity for a deeper understanding of the neural mechanisms operating in response to SI.

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YX: conceptualization, visualization, writing—original draft, writing—review and editing; HH: visualization, writing—original draft; CL: writing—review and editing; YQZ: conceptualization, writing—review and editing, supervision.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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