The Type I interferon antiviral gene program is impaired by lockdown and preserved by caregiving

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Previous research has linked perceived social isolation (loneliness) to reduced antiviral immunity, but the immunologic effects of the objective social isolation imposed by pandemic “shelter in place” (SIP) policies is unknown. We assessed the immunologic impact of SIP by relocating 21 adult male rhesus macaques from 2,000-m² field cage communities of 70 to 132 other macaques to 2 wk of individual housing in indoor shelters. SIP was associated with 30% to 50% reductions in all circulating immune cell populations (lymphocytes, monocytes, and granulocytes), down-regulation of Type I interferon (IFN) antiviral gene expression, and a relative up-regulation of CD16$^+$ classical monocytes. These effects emerged within the first 48 h of SIP, persisted for at least 2 wk, and abated within 4 wk of return to social housing. A subsequent round of SIP in the presence of a novel juvenile macaque showed comparable reductions in circulating immune cell populations but reversal of Type I IFN reductions and classical monocyte increases observed during individual SIP. Analyses of lymph node tissues showed parallel up-regulation of Type I IFN genes and enhanced control of viral gene expression during juvenile-partnered SIP compared to isolated SIP. These results identify a significant adverse effect of SIP social isolation on antiviral immune regulation in both circulating immune cells and lymphoid tissues, and they suggest a potential behavioral strategy for ameliorating gene regulatory impacts (but not immune cell declines) by promoting prosocial engagement during SIP.

Significance

“Shelter in place” (SIP) orders have been deployed to slow the spread of SARS-CoV-2, but they induce social isolation that may paradoxically weaken antiviral immunity. We examined the impact of 2-wk SIP on immune cell population dynamics and gene regulation in 21 adult rhesus macaques, finding 30 to 50% declines in circulating immune cells, decreases in antiviral gene expression, and increased inflammatory cells in blood and inflammatory gene expression in lymph nodes. Declines in antiviral gene expression (but not circulating immune cells) were blocked by the presence of a novel juvenile partner during SIP, suggesting a potential strategy for maintaining antiviral immunity during SIP by enhancing prosocial engagement.

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raises the possibility that adverse immunological effects of extended SIP might potentially be reduced by promoting prosocial engagement during SIP.

Results

To assess the immunologic impact of SIP, we relocated 21 adult male rhesus macaques from 2,000-m² (half-acre) field cages containing 70 to 132 other macaques to 2 wk of individual housing in 2.0 × 0.8 × 0.7 m indoor shelters and examined changes in circulating immune cell (white blood cell; WBC) subpopulations, Type I IFN innate antiviral gene regulation, and viral gene transcription. Individual shelters met all Institutional Animal Use and Care Committee, US Department of Agriculture, and US NIH guidelines for humane macaque husbandry, including the presence of enrichment objects, daily foraging enrichment, and auditory and olfactory access to conspecifics in the same room.

As shown in Fig. 1, total immune cell (WBC) counts declined by an average 32% within the first 48 h of SIP (Fig. 1A; F(3, 20) = 37.13, P < 0.0001), whereas red blood cell counts, hematocrit, hemoglobin, platelet counts, and fibrinogen concentration remained stable (Fig. 1B). All major WBC subpopulations declined by 35 to 49% (Fig. 1A), including neutrophils (F(3, 20) = 6.34, P = 0.0034), lymphocytes (F(3, 20) = 14.29, P < 0.0001), and monocytes (F(3, 20) = 5.88, P = 0.0048). WBC reductions (leukopenia) persisted throughout the 2-wk SIP period with minimal abatement. Within the declining monocyte subpopulation, however, we observed multiple CTRA-characteristic immunoregulatory alterations, including relative up-regulation of CD16+ classical monocytes (Fig. 1C; F(3, 20) = 5.24, P = 0.0079) and up-regulation of the CTRA gene expression profile (per-cell ratio of inflammatory versus Type I IFN response gene messenger RNA (mRNA): F(3, 3.546) = 3.01, P = 0.0291), the latter of which stemmed primarily from down-regulated expression of Type I IFN response genes (Fig. 1D; F(3, 1,969) = 6.92, P < 0.0001). Consistent with these alterations, promoter-sequence-based bioinformatics analysis of the 1,804 gene transcripts that showed consistent change in average expression within the first 48 h of SIP (genes listed in Dataset S1) indicated reduced activity of transcription control pathways mediating expression of Type I IFNs (Fig. 1E; Interferon Response Factor/IRF: mean log2 ratio of transcription factor–binding motifs (TFBMs) in promoters of up- versus down-regulated genes: −0.607 ± 0.094, z = −6.45, P < 0.0001), IFN receptor signaling (STAT: −0.801 ± 0.113, P = 0.00010), and development of the plasmacytoid dendritic cells (pDC) that constitute the primary source of Type I IFNs in circulating blood (GFI: −0.700 ± 0.029, z = −23.98, P < 0.0001). Flow cytometry confirmed an average 19% reduction in circulating pDCs (Fig. 1F; F(3, 20) = 5.35, P = 0.0072) and 35% reduction in classical dendritic cells (cDCs; F(3, 20) = 8.43, P = 0.0008).

Stress-induced glucocorticoid release can reduce circulating WBC counts by shunting leukocytes out of blood and into other tissue compartments (44–47). Such effects do not appear to mediate the effects of SIP, however, because plasma cortisol concentrations did not increase during SIP but rather decreased progressively over 2 wk (Fig. 1G; F(3, 20) = 40.55, P < 0.0001). Stress can also alter circulating WBC numbers and CTRA gene expression via SNS catecholamine activation of β-adrenergic receptors that alter cell trafficking (48–50) and transcriptional regulation (31–35). Consistent with SNS activation, promoter-based bioinformatics analyses indicated increased activity of the CREB family of transcription factors that mediate β-adrenergic signaling (Figs. SI Appendix and Table S1). To determine whether prosocial engagement might buffer the immunoregulatory impact of SIP isolation, the same adult male macaques were subject to a second 2-wk SIP accompanied by a novel (unrelated) juvenile companion macaque (following an established conspecific caregiving protocol for abating effects of prolonged social isolation) (51). The 0.5- to 1.0-y-old male macaques were transferred to an individual shelter adjacent to each adult male, and a divider between the two shelters was subsequently removed to allow continuous interaction throughout the 2-wk SIP period. In all other respects the sheltering protocol was identical to the previous 2-wk isolated SIP. During juvenile-partnered SIP, adult macaques spent 23% of their time directly interacting with juveniles (e.g., grooming, contact, play), 51% of their time in the same cage, and 26% apart from the juvenile. The adults also showed a 54% reduction in abnormal behavior relative to isolated SIP (e.g., huddling, lying on floor, hanging on shelter walls; mean 186 ± 45 s per 1,200-s observation period versus 403 ± 68 during isolated SIP; F(1,20) = 27.05, P < 0.0001) and complementary increases in species-typical patterns of physical locomotion (+37%; 89 ± 22 versus 65 ± 22; F(1,20) = 21.76, P < 0.0001), sitting at rest (+29%; 879 ± 44 versus 680 ± 57; F(1,20) = 10.57, P = 0.0040), and ongoing exploratory behavior despite the arrival of a novel human intruder (a commonly employed measure of threat sensitivity; +267%; 2.64 ± 1.08 exploration events per 60-s observation period versus 0.72 ± 0.52; F(1,20) = 6.78, P = 0.0170).

As shown in Fig. 2, SIP with a juvenile conspecific (solid symbol/solid lines) did not significantly abate either WBC declines in general (Fig. 2A) or declines in monocytes and dendritic cells (Figs. 2 B and C). However, juvenile partnering did abate SIP effects on CTRA-characteristic immunoregulatory parameters including, 1) up-regulation of the classical monocyte subset (which now decreased from pre-SIP baseline, rather than increasing as observed in isolated SIP; Fig. 2E; SIP day × SIP mode interaction:
F(3, 20) = 8.81, P = 0.0006); 2) down-regulation of Type I IFN gene expression (which now showed no significant decline from pre-SIP baseline; Fig. 2F; SIP day × SIP mode interaction contrast: F(3, 3981) = 2.99, P = 0.0296); 3) down-regulation in bioinformatic indications of IFN-related transcription control pathways (which were all either quantitatively abated or fully reversed in analyses of 2,189 gene transcripts that showed consistent change in average expression from baseline to day 2 of juvenile-partnered SIP; Dataset S2; Fig. 2G; IRF: -0.156 ± 0.075, z = -2.09, P = 0.0382; STAT: 0.262 ± 0.029, z = 8.97, P < 0.0001; GFI: 0.312 ± 0.028, z = 11.35, P < 0.0001); and 4) bioinformatic indications of CREB activation (which now declined from pre-SIP baseline; Fig. 2G; -0.465 ± 0.064, z = -7.78, P < 0.0001). Parallel analyses indicated increased GR activity (0.225 ± 0.015, z = 15.65, P < 0.0001).

**Lymphoid Tissue Impact.** To assess the relevance of SIP-related changes in circulating WBC gene regulation for the lymphoid tissue environments in which leukocytes initiate adaptive antiviral immune responses (52), we biopsied axillary lymph nodes from each macaque at the end of each 2-wk shelter period. (Lymph nodes were not collected at pre-SIP baselines to avoid any immunologic impact of surgery during the SIP period.) Compared to lymph nodes collected after isolated SIP, those collected after juvenile-partnered SIP showed an 18% reduction in inflammatory gene expression (Fig. 3A; F(1, 18) = 13.54, P = 0.0017) and a 22% increase in Type I IFN response gene expression (Fig. 3A; F(1, 18) = 9.87, P = 0.0056). Promoter-based bioinformatic analysis of 884 gene transcripts showing consistent difference in expression following juvenile-partnered versus isolated SIP (Dataset S3) indicated increased activity of IFN-related transcription factors (Fig. 3B; IRF: 0.724 ± 0.144, z = 5.04, P < 0.0001; STAT: 0.332 ± 0.092, z = 3.63, P = 0.0004; and nonsignificant increase in GFI: 0.724 ± 0.144, z = 1.64, P = 0.1025) accompanied by reduced activity of CREB (−0.929 ± 0.235, z = −3.95, P = 0.0001) and increased activity of the GR (0.149 ± 0.072, z = 2.08, P = 0.0388).

**Antiviral Impact.** To determine how the immunoregulatory alterations associated with SIP might impact host response to viral infection, we conducted metagenomic RNA sequencing of lymph node tissues to quantify the relative abundance of host-derived (metazoan) and viral-derived gene transcripts (53). Compared to lymph nodes collected after isolated SIP, those collected after juvenile-partnered SIP showed a 45% reduction in viral gene transcripts as a fraction of total lymph node RNA abundance (Fig. 3C; -0.264 ± 0.026 log₁₀ viral RNA reads per million total RNA reads, F(1, 18) = 99.40, P < 0.0001). To determine whether similar effects occur specifically for lymphotropic viruses, we conducted parallel metagenomic analyses of WBC RNA sequences collected at pre-SIP baseline and SIP day 2. Viral transcript abundance was 29-fold lower in circulating WBCs relative to lymph nodes, but results continued to show a 9.8% reduction in virus-derived gene transcripts during juvenile-partnered SIP (Fig. 3D; −0.046 ± 0.018, F(1, 20) = 6.45, P = 0.0196) whereas no significant reduction occurred during isolated SIP (−0.022 ± 0.020, F(1, 20) = 1.23, P = 0.2801).

**Discussion**

Pandemic-style SIP induced rapid and persistent immunoregulatory alterations in rhesus macaques, including 30% to 50% reductions in circulating immune cell populations and CTRA-characteristic down-regulation of innate antiviral activity (Type I IFN response genes) and relative up-regulation of classical monocytes. These effects emerged within 48 h of “lockdown,” persisted for at least 2 wk, and abated within 4 wk of return to baseline social conditions. Provision of a novel juvenile partner during a subsequent round of SIP blunted CTRA-characteristic immunoregulatory dynamics (but not leukopenia), resulting in down-regulation of classical monocytes, increased Type I IFN gene expression, and preservation of antiviral gene regulation (IRF, STAT, GFI). Analyses of lymph nodes collected at the end of each SIP period showed parallel up-regulation of Type I IFN response genes and transcription control pathways following “lockdown with caregiving” compared to “lockdown alone.” Metagenomic sequencing confirmed the functional significance of changes in host antiviral gene transcription, documenting reduced viral gene expression during juvenile-partnered SIP relative to isolated SIP in both lymph nodes and circulating immune cells. These results identify significant reductions in host antiviral activity in both the circulating leukocyte pool available for recruitment into infected tissues and the lymphoid tissue leukocyte pool available to initiate adaptive immune responses (e.g., antibody and cytotoxic T cell...
trafficking patterns representing key targets for future research. Defined, with changes in leukocyte development, cell death, and if such responses are more frequent or pronounced in females (69), and a relatively simple partnering protocol (different effects may occur with different partner numbers or characteristics, or with greater competing demands). SIP also affects nonsocial processes (e.g., mobility, natural environment exposure), and the immunologic effects observed here cannot be attributed purely to social deprivation. Partnered SIP always followed isolated SIP in this study, which might confound partner status with habituation (although recent leukopenia shows any habituation to be partial at best). This study does not contain any direct measures of viral disease (tissue pathology, illness symptoms) or host resistance to de novo infection, and the health significance of the observed effects remains to be defined in future research.

SIP impaired host control of viral infections in this study, but these results do not imply that the costs of SIP outweigh its benefits. Policy analyses of disease prevalence capture the net effect of host resistance costs and viral exposure benefits, and substantial observational data have linked social distancing policies in general to reduced viral disease rates per unit time (9, 10). However, among all distancing policies examined, SIP and extended “stay at home” orders appear to have the weakest net benefit (i.e., above and beyond more targeted business closures, school closures, and restrictions on large gatherings) (9, 11–14). The present results suggest that the relatively modest epidemiologic benefits of SIP
policies may stem in part from their unrecognized costs in undermining host resistance to viral infection even as they reduce the probability of viral exposure. To the extent that SIP is retained as a policy response (e.g., due to political demand), it may be possible to enhance SIP’s epidemiologic benefit by altering the mode and conditions of sheltering to maximize caregiving opportunities and other prosocial engagements. Mapping the psychological and biological mechanisms involved may also suggest new policy, behavioral, or pharmacologic strategies for controlling the immunological impacts of protracted social isolation and thus help evolve more sustainable and effective disease mitigation strategies for social control of pandemic infectious diseases.

Methods

A total of 21 adult male rhesus macaques were relocated from their home 2,000-m² field cages containing 70 to 132 other macaques to 2 wk of individual housing in 2.0 × 0.8 × 0.7 m indoor quarters for adult male rhesus macaques at the California National Primate Research Center. Individual quarters comprised two standard individual housing cages (1.0 m W × 0.8 H × 0.7 m D) connected by an opened door and met all Institutional Animal Care and Use Committee, US Department of Agriculture, and US NIH guidelines for humane macaque husbandry, including the presence of enrichment objects, daily foraging enrichment, and auditory and olfactory access to conspecifics in the same room. Relocation to individual quarters occurred between 8:00 and 8:45 AM. A 7.5 ml venous blood sample was obtained at 3:00 PM 1 wk prior to and 2, 8, and 13 d after relocation. Distress-related and species-typical (non-distressed) behaviors were quantified by ethogram scoring of 5-min videotaped behavioral samples collected four times per day between 9:00 and 11:00 AM from each animal at day 1, 2, 7, 8, 12, and 13 and separate observations during a “human intruder” behavioral challenge at 3:00 PM on day 9 (see details in SI Appendix). On day 14, each animal underwent an axillary lymph node biopsy and subsequently recovered in the hospital for ≥3 d before return to their home field cage. Approximately 1 mo after return to their home field cage, each macaque was again relocated to the same individual shelter, which now contained a 0.5- to 1.0-y-old novel (unrelated) male macaque (following previous “therapy monkey” protocols for socially isolated macaques) (S1). With the exception of juvenile partner pairing, all other aspects of the sheltering protocol were identical to those of the previous round of isolated sheltering.

All procedures were approved by the Institutional Animal Care and Use Committee of the University of California, Davis.

Hematology, Immune Cell, and Hormone Analysis. Detailed analytic methods are presented in SI Appendix, Detailed Methods. Briefly, each blood sample was assayed by automated complete blood count with differential; flow cytometric enumeration of major leukocyte subsets, classical (CD16+), and nonclassical (CD16-) monocytes, and CD3+CD20+/HLA-DR+/CD123+ pDC and CD3+CD20+/HLA-DR+/CD1c+ cDC; chemiluminescent immunoassay of plasma cortisol; and mRNA sequencing of peripheral blood mononuclear cells (PBMCs) to generate genome-wide transcriptional profiles (70). Transcriptional profiles were analyzed to quantify expression of prespecified sets of genes involved in Type I IFN, proinflammatory, and CRTA gene regulation (71). Activity of Type I IFN- and pDC-related transcription control pathways (IRF, STAT1, GFI) and SNS- and GR-related transcription control pathways (CREB, GR) was also assessed using promoter-based bioinformatics analyses of all gene transcripts (genome-wide) found to show consistent up-regulation versus down-regulation from baseline to SIP day 2 (blood cells) or from isolated to juvenile-partnered SIP (lymph nodes). Viral and metazoan gene expression were quantified by metagenomic RNA profiling (S3).

Data Analysis. Hematology, flow cytometry, cortisol, and leukocyte RNA data were analyzed by mixed effect linear models (SAS 9.4 PROC MIXED) specifying fixed effects of SIP day (baseline, day 2, 8, and 13), SIP mode (isolated versus juvenile-partnered), a SIP day × SIP mode interaction, and a random effect of subject (animal) with a fully saturated (unstructured) variance-covariance matrix to account for heteroscedasticity and correlation among residuals. For parameters assessed once per SIP cycle (behavior, lymph node RNA), parallel mixed effect linear models analyzed fixed effects of SIP mode (isolated versus juvenile partnered).

Data Availability. Anonymized RNA profiling data have been deposited in Gene Expression Omnibus (GSE174065) (70).

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