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Loneliness in monkeys: Neuroimmune mechanisms

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Abstract

Loneliness, or perceived social isolation, may be evident in any group-living species, although its assessment in nonhumans provides some measurement challenges. It is well-known that loneliness in humans confers significant risk for morbidity and mortality, although mechanisms remain unclear. The authors describe a naturally-occurring model of loneliness in adult male rhesus monkeys that shows many parallels with the phenomenon in humans. Lonely monkeys (those that display high frequencies of social initiations but low frequencies of complex interaction) show elevated sympathetic nervous system activity and down regulated Type I interferon responses. Analysis of data from simian immunodeficiency virus-infected monkeys indicates that these physiological changes have functional consequences. Use of this animal model can help identify mechanisms by which loneliness impacts health.

Introduction

Many species of mammals are highly social, with males and females living in continuous proximity to each other. This is especially true of primates, both human and nonhuman; for example, macaque monkeys generally live year-round in multi-male, multi-female groups comprising multiple animals of all ages and both sexes, and with group sizes ranging up into the dozens of animals [1]. To be “social” like this suggests that the benefits of being surrounded by others (e.g., more eyes for predator detection) outweighed the costs of sociality (e.g., increased feeding competition and infectious disease), at least at some point in the species’ evolutionary past [2]. What this suggests is that a species’ sociality is an important part of its basic biology.

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The fact of sociality, however, does not preclude the possibility of individual variation in affiliative tendencies [e.g., 3]. Indeed, studies of nonhuman primate personality nearly always find a dimension that is often referred to as sociability [4,5,6], and variation in this dimension is always evident. We believe that individuals that are low-social (i.e., are at the lower end of the sociability spectrum) are of two types – those that are "satisfied" with that situation, and those that are not. It is the latter group that we believe most closely resembles the condition of loneliness in humans, and can serve as a useful model to understand the mechanisms by which loneliness can affect immunity and health.

Below, we provide important context for our studies of loneliness in rhesus macaques by briefly reviewing literature on the health and immune correlates of loneliness in humans [see also 7]. We next describe our naturally-occurring model of loneliness and the added value that a valid animal model of loneliness can provide for our understanding of immune mechanisms. We conclude with some current and future directions for this work.

Loneliness, mortality, health, and immunity

A recent, comprehensive meta-analysis confirmed prior reviews showing that a) loneliness (a subjective measure of feelings of isolation, as assessed, for example, by the UCLA Loneliness Scale [8]), b) social isolation (an objective measure reflecting a pervasive lack of social contact, assessed by the Social Isolation Scale [9]), and c) living alone (versus living with others, a second objective measure) were all strongly associated with greater risk for mortality [10]. While adjustment for a variety of covariates attenuated the relationships somewhat, the results remained strong, with an increased likelihood of mortality upon follow-up ranging from 26% to 32% for the three measures.

One way that loneliness can impact mortality is via health behaviors: lonely/isolated people tend to smoke more and are less active physically [11,12], for example. Of greater interest to us, however, is what the physiological mechanisms might be that underlie the greater morbidity seen among lonely people. A recent review [7] describes eight potential pathways by which loneliness could exert its adverse effects on health and mortality. These pathways are by no means independent; in fact, two of the pathways, namely altered regulation of the hypothalamic-pituitary-adrenal (HPA) axis [13], and specific alterations in sympathetic nervous system (SNS) tone, are likely the principal biological systems that lead to altered immune function.

Some of the earliest work on loneliness and immunity was conducted by Kiecolt-Glaser and colleagues who studied recently admitted psychiatric patients [14] and medical school students [15,16,17]. Loneliness was assessed using the UCLA Loneliness Scale, and contrasts were made between individuals scoring above and below the median. In general, individuals identified as "high lonely" showed deficiencies in cellular immune function, whether measured using a natural-killer cell cytotoxicity assay [14,16], a lymphocyte proliferation assay [14], a B-cell transformation assay utilizing Epstein-Barr virus (EBV) [15], or via poor control of the latent EBV infection, as assessed by anti-EBV antibody responses, in infected people [17].

The next generation of studies was more focused on specific mechanisms that might mediate the loneliness - health link. Given the growing recognition that inflammation underlies a variety of poor health outcomes [18,19,20,21], it's no surprise that inflammatory processes were an important focus. In fact, studies demonstrated that in response to acute stress, inflammatory mediators such as tumor necrosis factor-alpha and interleukin-1-beta were increased among lonely, compared to non-lonely, people [22,23]. Larger-scale approaches, involving examination of the transcriptome of leukocytes, brought additional revelations. The first such study [24] examined the transcriptome in 8 low-lonely and 6 high-lonely individuals that had scored consistently on the UCLA Loneliness Scale over a three-year period. 209 genes were differentially expressed, and these genes were associated, among lonely subjects, with over-expression of genes related to immune activation and inflammation, and under-expression of genes related to B-cell function and the Type I interferon response, a pattern consistent with clinical data showing that socially isolated people are at greater risk for inflammation-mediated disease, impaired humoral immunity, and decreased resistance to viral infection. Importantly, bioinformatics analysis applied to the transcriptome data implicated decreased activity of the anti-inflammatory glucocorticoid receptor (GR) signaling pathway, and increased activity of the pro-inflammatory NF-kB and JAK/STAT signaling pathways. Interestingly, salivary cortisol concentrations did not differ between the two groups of people, suggesting that it is not the amount of available cortisol that is important, but rather the reduced ability of that steroid to effect its anti-inflammatory function.

A naturally-occurring model of loneliness in rhesus macaques

Animal models can provide great value in trying to understand the biological mechanisms underlying health and disease [25]. But how might one operationalize loneliness in a nonhuman? One thought might be to simply isolate an animal and quantify biological responses to that manipulation. Such data have, in fact, been very useful [13,26]; but is physical isolation equivalent to loneliness? Most psychologists would agree that loneliness is a subjective experience; one can feel lonely while in a crowd, for example, or when surrounded by family or friends, suggesting that a critical feature of loneliness is a judgement about the quality of, and satisfaction with, one's social relationships [27]. To be sure, there *are* adverse consequences of social isolation in humans, as described above [10]; however, the objective and subjective measures of social disconnection are not always correlated with each other and seem to confer risk independently. One study showed, for example, that high levels of loneliness and a small social network (an objective measure of social isolation) were each associated with a poorer antibody response to an influenza vaccine, and the individuals with the poorest antibody response were those that had both risk factors [28].

One way of addressing this measurement issue in monkeys is to return to one of the earliest formulations of loneliness, namely that it reflects "a discrepancy between one's desired and achieved levels of social relations" [29, p. 32]. We can make a distinction between two classes of social behavior. One class reflects social initiations and comprises approach and walkby, a more tentative initiation. In the case of a walkby, an animal typically starts in one location and ends up in another location. Instead of making a bee-line from points A to B,

however, the animal often briefly passes near another animal, without stopping, before arriving at his destination. The second class of social behavior comprises complex behaviors that reflect social tolerance at a minimum (proximity and contact), and some degree of coordination (social grooming). Here, then, is a possible means of making the distinction between desired and achieved levels of social relations: are animals able to successfully "convert" their initiations into complex interactions? If there are animals that are not successful (i.e., have high levels of initiations, but low rates of complex behavior), then that might suggest a discrepancy between desired and achieved social relations – a hallmark of loneliness. Moreover, because a second hallmark is an elevated sense of social threat [30], we can examine the age/sex class of who our subjects interact with: we would expect putatively lonely animals would be more likely to interact with "safe" targets which, for the adult males that have been our subjects, would include females and juveniles, but not other adult males.

Our subjects are adult male rhesus monkeys living in any of the two dozen half-acre outdoor corrals at the California National Primate Research Center. Each cage contains up to 150 animals with a species-typical age/sex distribution. Trained behavioral observers follow each subject for two weeks recording the frequencies of the behaviors described above, then rate the animals using a rhesus monkey personality inventory (http://psychology.ucdavis.edu/people/fzcapit/rhesus_personality.pdf). Exploratory [31] and confirmatory [32] factor analysis of data from this inventory revealed a four-factor solution, one factor of which is labeled Sociability, and comprises three items: affiliative, warm, and the negatively-loaded trait solitary. The Sociability factor is then z-scored, and animals with a z-score of −0.5 or lower, or +0.5 or higher, are identified as low-Sociable (LS) or high-Sociable (HS), respectively. Next, the approach and walkby data (broken out by the age/sex class of the target of the behavior: adult male, adult female, juvenile, infant) from the LS animals are subjected to a two-group cluster analysis. Along with the HS animals, we now had three groups of monkeys that could be compared on both the social initiation and the complex behaviors. HS animals, as expected, showed high frequencies for both classes of behavior, and one group of LS animals (which we label as putatively introverted) showed low frequencies for both classes. The other LS group, however, which we refer to as lonely, showed frequencies of social initiations that were comparable to those of the HS animals, but frequencies of complex behaviors that were comparable to those of the introverted animals (Figure 1). These lonely animals, then, seemed unable to convert their initiations into complex behavior, reflecting, we believe, "a discrepancy between one's desired and achieved levels of social relations" [29]. Using these classifications, we have performed a variety of behavioral challenge tests to further characterize psychologically the lonely animals, and have found substantial congruence with what is known about lonely humans (described in [33,34]).

The psychoneuroimmunology of loneliness in monkeys

Our physiological studies of lonely monkeys have been greatly enhanced by the inclusion of data from humans in our report [34]. Comparison of the human and monkey data show many parallels, providing further evidence in support of our model. First, lonely members of both species show a leukocyte transcriptome profile consistent with an upregulation of pro-

inflammatory responses and a down-regulation of Type I anti-viral interferon responses (Figure 2A). Second, lonely individuals of both species show elevated monocyte numbers, with analyses of the monkey data confirming the suggestion from the human data that it is the immature CD14++/CD16− classical monocyte subset that appears responsible for the transcriptome differences (Figure 2B & C). Third, lonely individuals demonstrate evidence of increased SNS activity, as suggested by elevated levels of urinary norepinephrine metabolites. Finally, the monkey data also demonstrate reduced glucocorticoid receptor sensitivity, as indicated by an examination of leukocyte numbers relative to diurnal variation in cortisol levels (Figure 2D), confirming results seen in lonely humans. Bioinformatic analysis of the monkey data also showed, consistent with this picture, a down-regulation of glucocorticoid receptor transcriptional activity, and an upregulation of the activity of the pro-inflammatory NF-κB pathway in the promoter sequences of the differentially expressed genes (Figure 2E).

Together, the human and monkey data show evidence of altered immune function among lonely individuals. But do these differences have functional consequences? Work done with HIV-infected men suggests they might [35,36]. We explored this question by re-examining data from a completed study of simian immunodeficiency virus (SIV) infection in a separate cohort of adult male rhesus monkeys [37]. Because we begin all of our monkey studies by collecting quantitative behavioral data in the corral environment, we were able to identify, post-hoc, animals that satisfied the behavioral definition of loneliness as described above. We then compared them to introvert animals and high-social animals prior to SIV inoculation (i.e., at baseline), and at 2 weeks post-inoculation (p.i.; the time of peak plasma SIV viremia) and at 10 weeks p.i. (the time of establishment of viral replication set-point).

At baseline, the lonely monkeys showed increased numbers of monocytes, particularly the CD14++/CD16− classical monocytes, and reduced expression of Type I and Type II interferons in PBMCs, consistent with our earlier data. At Week 2 p.i., gene expression was upregulated for all animals and groups did not differ. At Week 10 p.i., however, the group differences in interferon gene expression returned, with lonely animals showing reduced expression (Figure 3A). Presumably, this impaired anti-viral response was instrumental in this group's showing poorer control of SIV gene expression (Figure 3B), elevated SIV viral load in plasma and cerebrospinal fluid (Figure 3C), and impaired SIV-specific IgG responses (Figure 3D).

Conclusions and future directions

Together, the data from our monkey studies suggest that loneliness – reflecting a discrepancy between desired and achieved levels of social relations – can occur in nonhumans, and that its neuroimmune consequences parallel those seen among lonely humans. It's quite possible, for example, that in the wild, lonely animals might be those most at risk in the event that a pathogen spreads in a population. Indeed, recent evidence indicates that rhesus monkeys that are most embedded in their social networks in well-established social groups are at *decreased* risk of infection for a bacterial enteric pathogen, a result that is contrary to what one might expect for a pathogen that is spread via social contact [38]. Similarly, in humans,

having diverse ties is associated with decreased risk of infection following challenge with a rhinovirus [39; see also 40].

The establishment of a naturally-occurring monkey model permits us to take full advantage of what an animal model can provide [25]. For example, based on the data described above, our current working model of the effects of loneliness on health proposes that the chronic perception of social threat experienced by lonely individuals (whether human or monkey) results in elevated SNS activity, including in the bone marrow where blood cells develop and differentiate. We believe that the effect of SNS activity on myelopoiesis results in the development and release of immature monocytes that are inflammation-primed, glucocorticoid resistant, and interferon-impaired. The most direct test of this proposed mechanism would involve obtaining bone marrow tissue to look for differences between lonely and non-lonely people; while this would be nearly impossible to do in healthy humans, bone marrow aspiration is a relatively routine procedure in monkeys, and we are collecting such tissue in our current study of lonely monkeys. And because there is plasticity in these systems, one might expect that remediation of a lonely condition should be followed by reversal of these neuroimmune effects, another line of inquiry in our present studies.

That loneliness confers greater risk for poor health outcomes and mortality is no longer disputed. Moreover, studies have shown that the relationship between loneliness and health remains, even after controlling for health behaviors. A valid animal model of loneliness can help us understand the biological mechanisms that are likely involved in this relationship, and whether treatments for loneliness – whether pharmacological or social – can reverse the physiological changes.

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Highlights

- Loneliness reflects a discrepancy between social desire and social attainment.
- It is likely that members of any social species can display evidence of loneliness.
- Lonely monkeys show elevated norepinephrine levels and immune compromise.
- A valid animal model can reveal mechanisms associated with morbidity in humans.

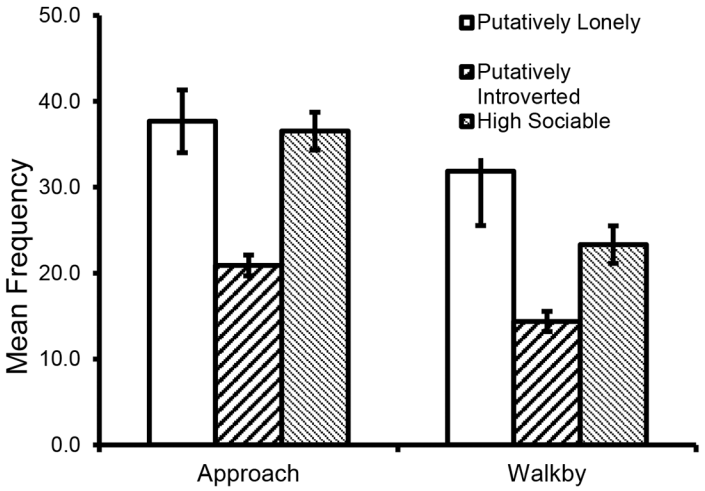
MEANS

	approach	walkby
MLS	37.6660	31.8573
TLS	20.8914	14.3665
High Sociable	36.5286	23.3141

Ses

	approach	walkby	
ALS	3.64425	6.33124	
TLS	1.20460	1.16201	
HS	2.20755	2.17160	

approach mean walkby mean appraoch SE walkby SE



Contact	Groom Initiate
120.4000	22.0000
95.5204	25.3462
218.7239	51.5172

Contact SE	tgri SE
21.10829	11.71751
11.67435	4.45661
12.54582	5.83531

"Lonely"
TLS
HS

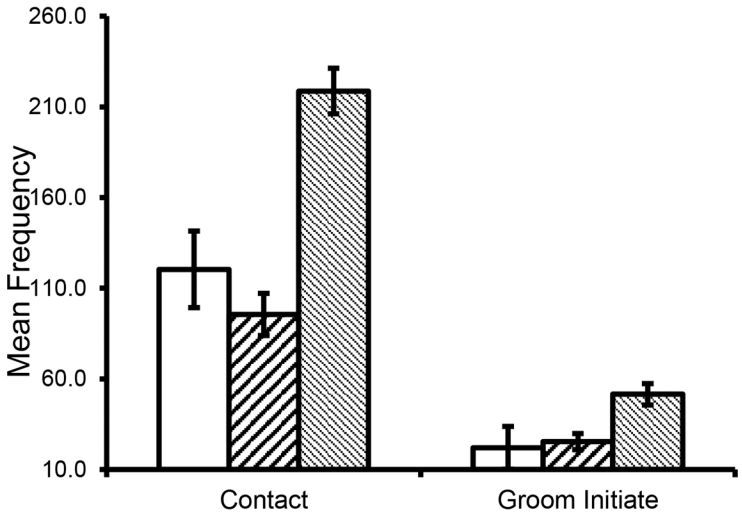


Figure 1:

Frequencies of social behaviors for putatively lonely, putatively introverted, and high-sociable adult male rhesus monkeys. (A) Social initiation behaviors. (B) Complex social behaviors. Reprinted with permission from ILAR Journal (58(2)), Institute for Laboratory Animal Research, The Keck Center of the National Academies, 500 Fifth Street NW, Washington DC 20001.

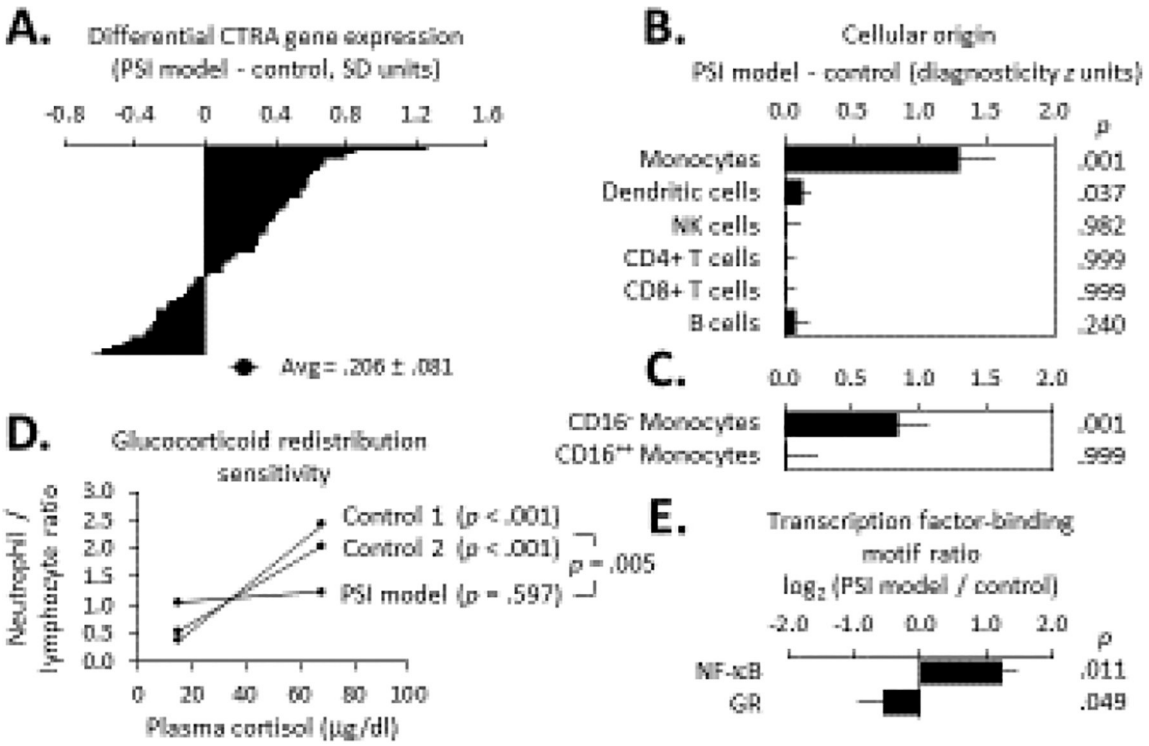


Figure 2:

Leukocyte-related differences between lonely (i.e., perceived social isolation [PSI] model) versus introverted and high-Sociable rhesus monkeys. (A) Differential expression of 53 transcripts from lonely vs. non-lonely rhesus macaques. (B) Transcript origin analyses [41] identifying monocytes and dendritic cells as origins of the 229 gene transcripts that showed ≥1.2-fold differential expression in lonely vs. non-lonely animals. (C) Transcript origin analyses showing that it is the CD14++/CD16− classical monocyte subset contributing to differential gene expression. (D) Correlation of circulating neutrophil numbers (normalized to lymphocyte counts) with cortisol concentrations, showing glucocorticoid desensitization in lonely animals. (E) *In vivo* transcriptional activity of glucocorticoid receptor (GR) and NF-κB transcription factors as assessed by TELiS bioinformatic analysis [42] of transcription factor-binding motif prevalence in promoter DNA sequences of genes showing ≥1.2-fold differential gene expression in lonely vs. non-lonely animals.

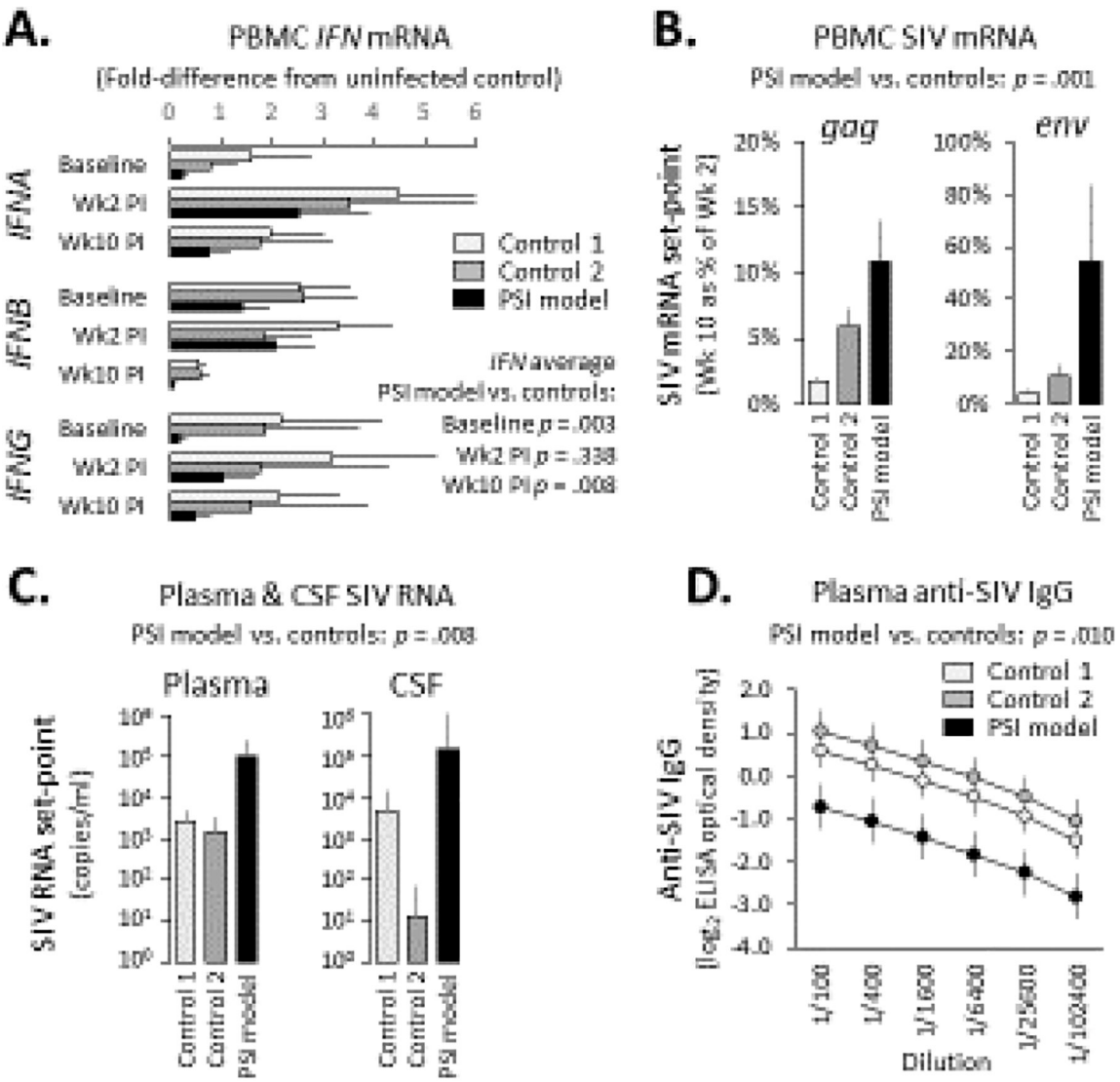


Figure 3:

Immune and viral measures in lonely (PSI model), high-Sociable (Control 1) and introverted (Control 2) SIV-inoculated rhesus monkeys. (A) mRNA encoding type I (IFNA, IFNB) and type II (IFNG) interferons assessed in peripheral blood PBMCs from adult male macaques experimentally infected with SIV at preinfection baseline, 2 wk postinfection, and 10 wk postinfection. Data represent mean ± SE fold-difference from SIV-uninfected controls. (B) Immunologic response to SIV was assessed by quantifying suppression of SIV gag and env mRNA levels in PBMC from wk 2 to wk 10 postinfection). Data represent mean ± SE % reduction from wk 2 to wk 10. Long-term control of viral replication was assessed by plasma SIV viral load (C) and anti-SIV IgG titers (D) at wk 10. Data represent mean ± SE log10 SIV RNA copies per milliliter of plasma or log2 optical density of IgG ELISA over fourfold plasma dilutions. IFNA: interferon alpha; IFNB: interferon beta; IFNG: interferon gamma; PBMC: peripheral blood mononuclear cells; SIV: simian immunodeficiency virus.