Acute Immune System Activation Exerts Time-Dependent Effects on Inhibitory Control: Results of Both a Randomized Controlled Experiment of Influenza Vaccination and a Systematic Review and Meta-Analysis

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Abstract

Although coming down with an illness or receiving a vaccine are both common experiences, the influence of such acute immune system activations on cognitive processes, such as inhibitory control, has received relatively little attention. We addressed that issue by assessing the effects of acute immune system activation on inhibitory control in a randomized controlled experiment, and by conducting a meta-analysis of similar studies in humans. In our experiment, we found—somewhat surprisingly—that influenza vaccination improved performance on both of our inhibitory control outcomes (i.e., stop-signal reaction times and flanker interference effects). At the meta-analytic level, we found that at a short delay (1.5 to 4 hours post-injection) between immune activation and inhibitory control assessment, such activation impaired multiple forms of inhibitory control, whereas after a longer delay (e.g., > 18 hours post-injection), such activation improved inhibitory control—consistent with our experiment. Moreover, proinflammatory cytokine activity predicted poorer interference control but better response inhibition, even with a long delay between injection and testing. Together, these results highlight nuanced, time-dependent, and—perhaps—multiple-mechanism-driven effects of acute immune system activity on inhibitory control.

1. Introduction

The last time you were sick, were you at your peak cognitive ability? Although there is an intuitive answer to the question of whether heightened immune system activity (e.g., from pathogen exposure) influences cognitive processing, the answer from research is less clear. In particular, relatively little experimental work has examined the effects of immune system activation on cognitive processes, and the work that has been conducted varies widely in methods. The present manuscript addresses these issues 1) by presenting the results of a new experiment that induced immune activity (or not) via flu vaccination (or saline) and subsequently assessed theoretically motivated cognitive processes, and 2) by conducting a meta-analysis of experiments conducted to date that have induced immune system activity and examined its effects on these cognitive processes.

It was not long after discovering that immune system activity influences neural and psychological processes that those in the field began discussing the potential influence of immune system activity on cognition (Maier & Watkins, 1998; McAfoose & Baune, 2009; Pugh et al., 2001). Neither the immune system nor cognition are monolithic, though, and much work has examined the effects of innate (e.g., the rapid-acting, general-purpose arm of our immune system) and adaptive (e.g., the slower, pathogen-specific arm of our immune system) immune system activity on cognitive processes ranging from memory (Cohen et al., 2003; Pugh et al., 1999; Reichenberg et al., 2001; Shields, Dunn, et al., 2019) to decision-making (Gassen, Makhanova, et al., 2019; Shields, Moons, et al., 2017). For example, excessively high levels of cytokines—signaling proteins that upregulate both innate and adaptive immune system activity—can, via binding to their receptors on neurons (de Pablos et al., 2006; Friedman, 2001; Ringheim et al., 1995), impair memory encoding processes (Goshen et al., 2007; Yirmiya & Goshen, 2011). This work has generally found that various forms of excessively heightened immune system activity produce a cognitive phenotype that would facilitate rest and recovery (McAfoose & Baune, 2009; Shields, Moons, et al., 2017).

Drawing on the above work, theories of the role of the immune system in cognitive functioning have begun to emerge, positing that immune system activity related to injury or infection (e.g.,

inflammatory cytokine activity) may exert particularly strong effects on cognitive processes that result in a reduction of exploration or movement. For example, the immunologic theory of self-regulation (Shields, Moons, et al., 2017) posits that heightened immune system activity should increase rest and recovery via reducing reward sensitivity and motivation, increasing negative affective responses to adverse events (e.g., pain), and impairing executive control of cognition. Similarly, the theory of inflammation and present focus (Gassen, Makhanova, et al., 2019; Gassen, Prokosch, et al., 2019) posits that heightened immune system activity should increase rest and recovery via increasing impulsivity, present focus, and temporal discounting.

Common to both of the above theories is the idea that heightened immune system activity should impair the function of cognitive processes that help to prevent impulsivity. These impulsivity-reducing processes are collectively referred to using the umbrella term, "inhibitory control," which includes inhibitory control of thoughts and distractions (i.e., *cognitive inhibition*) and inhibitory control of motor actions (i.e., *response inhibition*) (Shields & Hunter, 2024; Shields & Yonelinas, 2024). To date, however, work examining experimental inductions of immune system activity has provided mixed support for the idea that immune system activity impairs inhibitory control, which has led some to challenge the idea that excess immune system activity contributes to impulsivity (Madison & Kiecolt-Glaser, 2022). Therefore, the extent to which each of these theories find support in empirical work is unclear.

However, the aforementioned mixed findings in relevant empirical work may be driven by at least three methodological issues. First, there is a critical task design issue: Inhibitory control tasks in fact only reliably require inhibitory control processes for performance under very specific conditions (Wessel, 2018). To date, however, few studies have examined the influence of immune system activation on inhibitory control tasks with designs shown by cognitive work to elicit or require the inhibition processes of interest. Second, innate and adaptive immune system activity may elicit distinct cognitive effects, but the timing of immune activation to inhibitory control tasks across many of these studies varies considerably (e.g., Madison et al., 2023; Nicoletti et al., 2004); notably, early adaptive-initiating immune

responses to antigens are present much earlier than the full adaptive response (e.g., within hours of antigen exposure; Hayes et al., 2019; Lee et al., 2009). Third, as could be inferred from the above, there is a high degree of heterogeneity among the extant work on immune system activation and inhibitory control task performance, including heterogeneity from sources not yet described (e.g., magnitude of immune activation, endotoxin vs. vaccination, etc.), which makes summarizing the general results of this work difficult without a comprehensive review and analysis.

1.1. Current Research

In this manuscript, we attempt to clarify the effects of immune system activation on inhibitory control task performance using two rigorous approaches. First, we present the results of a new experiment examining inhibitory control task performance in participants who were first randomly assigned to receive an influenza vaccination or a saline (placebo) injection. Second, we present the results of a meta-analysis of all studies examining inhibitory control task performance following experimental induction of immune system activity.

Drawing on the theories described above, we hypothesized that inductions of immune system activity would impair inhibitory control task performance. We further expected to find heterogeneity among prior studies and study design factors that explained that heterogeneity.

2. Experiment Method

2.1. Participants

Participants (N=91, which represents all participants without technical issues [e.g., who were able to open the task and hear the stop signal] that provided usable inhibitory control data, see below; M_{age}=24.92, SD_{age}=5.73, 77.1% female) were recruited from the community around a large public university for a study on influenza vaccination (Makhanova et al., 2024). Participants were randomly assigned to receive either the influenza vaccine (“vaccine condition”) or saline injection (“placebo condition”). Inclusion criteria were those which are standard for similar studies (Shields, 2020) as well as influenza-vaccine-specific criteria. In particular, participants were eligible if they (a) were between 18 and 40 years old, (b) had a BMI between 18.5 and 30, (c) have not received the annual influenza vaccine

that season, (d) have never had an allergic reaction to the influenza vaccine or other vaccines, (e) were not pregnant, (f) did not have any illnesses known to affect cytokine levels (e.g., auto-immune disorders, hypothyroidism, sleep disorders), (g) were not taking medication known to affect cytokine levels (e.g., SSRIs, steroids), and (h) did not smoke or use tobacco products. Of this sample, 75.8% identified as non-Hispanic White, 6.6% as Asian or Pacific Islander, 6.6% as Hispanic or Latino/a/x, 2.2% as Black or African American, 1.1% as Native American, and 6.6% as more than one race/ethnicity; 1.1% declined to state.

2.2. Materials

2.2.1. Experimental Manipulation. Participants in the vaccine condition received Flucelvax Quadrivalent egg-free influenza vaccines, manufactured by Seqirus. Participants in the placebo injection condition were injected with 0.5 mL of saline solution.

2.2.2. Salivary Cytokine Assays. Saliva samples provided via passive drool were assayed in duplicate for interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) using commercially available multiplexing assay kits (Miso Scale Delivery [MSD], Rockville, MD, United States). Inter- and intra-assay coefficients of variation were all less than 5%.

2.2.3. Inhibitory Control Assessment. A hybrid stop-signal/flanker task was used to assess inhibitory control processes. Participants were told to indicate the direction of the center arrow using the "d" key for left and the "k" key for right, and to ignore any flanking arrows. In 2/3 of trials, flanking arrows occurred to the left and right of the center arrow, pointing either in the same direction (congruent trials; 1/3 of trials) or the opposite direction as the center arrow (incongruent trials; 1/3 of trials); 1/3 of trials (neutral trials) had no flankers. In 1/3 of each trial type (congruent, incongruent, and neutral), a stop signal (i.e., a tone) occurred after a delay. Participants were told to withhold their response if they heard the stop signal. The stop signal was initialized at 0.25 s from arrow onset and subsequently followed the standard stairstep procedure: The delay was extended by 0.05 s if the participant withheld their response to a stop-signal trial but reduced by 0.05 s if the participant responded to a stop-signal trial. Participants were told that the stairstep procedure results in 50% stop failures on average, and that waiting would not

change this—that waiting would only make the task longer for them. Stimuli were displayed for the lesser of 1.75 s or response. The intertrial interval was 0.45 s. Participants first completed 24 practice trials with feedback; they then completed three test blocks of 72 trials each (216 total test trials) with 8 s of rest between each block.

As is typical in the stop-signal task, we assessed response inhibition via stop-signal reaction time (SSRT), calculated using the recommended integration method (Verbruggen et al., 2013, 2019). Stop-signal reaction time represents the time required for a participant to inhibit an activated response; higher values represent poorer response inhibition.

As is typical in the flanker task (Shields, Rivers, et al., 2019), we assessed cognitive inhibition via the flanker interference effect on reaction time, which is the difference between mean reaction time on trials with incongruent flankers and mean reaction time on trials with congruent flankers (i.e., mean $RT_{incongruent/correct}$ − mean $RT_{congruent/correct}$). Flanker interference represents the influence of perceptual distractors on task performance; higher values represent poorer ability to suppress attention to perceptual distractors.

2.3. Procedure

Participants completed this experiment during the influenza seasons of 2020-2021 and 2021-2022. Therefore, all procedures occurred remotely, via video call. Inquisit Web was used to administer the inhibitory control task. Participants first came to campus to obtain their study materials, which included all instructions, the saliva collection vials, and a paper stating their participant ID, which was presented to the health care provider at the vaccination clinic. The vaccine administration log kept by the nurses had the random assignment information and participant condition by ID. Immediately prior to their appointment, participants provided their baseline saliva sample as instructed and subsequently recorded the time of sample provision. Participants then received either the vaccine or the placebo injection. The nurses who administered the vaccines were not blinded to participant condition, but they were blinded to study hypotheses, and all other study procedures were conducted by research assistants who were blind to both participant condition and study hypotheses.

One day after the experimental manipulation (*M*=24.56 hours, range=17.24-33.83 hours)—at the time of the peak cytokine response to influenza vaccination (Talaat et al., 2018) and after the beginnings of the adaptive immune system response (Hayes et al., 2019; Lee et al., 2009)—participants provided their second saliva sample, and they began their Zoom session within two hours of sample provision. Following completion of measures described elsewhere (Makhanova et al., 2024), participants completed the inhibitory control task described above. Finally, after completing measures unrelated to the current study (Makhanova et al., 2024), participants and research assistants were unblinded. Participants were debriefed and dismissed; during debriefing, placebo-injection participants were instructed to return to the clinic to receive their vaccine. All participants were compensated with a $40 gift card.

2.4. Data Reduction and Analysis

Data analyses were conducted by the first author, who was blind to participant conditions until the analyses examining condition differences in inhibitory control performance were completed.

Cytokines were log transformed to correct their strong positive skew. We then calculated residualized change scores (Shields, McCullough, et al., 2019), as these scores are more reliable than simple change scores (Cronbach & Furby, 1970). Finally, given the overlap in cytokines in binding to cytokine receptors (Donzis & Tronson, 2014), we did not have *a priori* hypotheses about particular cytokines in relation to study variables. Therefore, we constructed a single cytokine change score via extracting factor scores from a single cytokine change factor calculated via exploratory factor analysis.

A priori exclusion criteria for the inhibitory control task (Shields & Hunter, 2024) were making five or more responses under 150 ms (indicating intentional premature responding), having ten or more failures to respond on "go" trials (indicating waiting, violating SSRT model assumptions), having less than 80% target accuracy on "go" trials, and having less than 35% or greater than 65% accuracy on stop-signal trials (indicating responses violating SSRT model assumptions). Participants excluded for task-related reasons did not differ by vaccine/placebo condition, $\chi^2(1)<.001$, $p>.999$, and analyses including all participants produced similar results.

We manually inspected for outliers in each variable. Analyses with and without excluding outliers are presented below.

3. Experiment Results

Effect of the Manipulation on Cytokines

We first examined whether participants in the vaccine condition differed in salivary cytokine change from participants in the placebo injection condition. In this analysis, we found that participants in the vaccine condition showed marginally greater increases in salivary cytokines from pre- to post-manipulation than participants in the placebo-injection condition, $t(87)=1.86$, $p=.066$, $d=0.40$. Restricting analyses to include only participants whose condition-blind independent ratings indicated that they following study instructions ($n=76$), this difference was significant, $t(74)=2.05$, $p=.043$, $d=0.48$ (see Figure 1). In short, participants in the vaccine condition showed greater increases in salivary cytokines from pre- to post-manipulation than participants in the placebo-control condition.

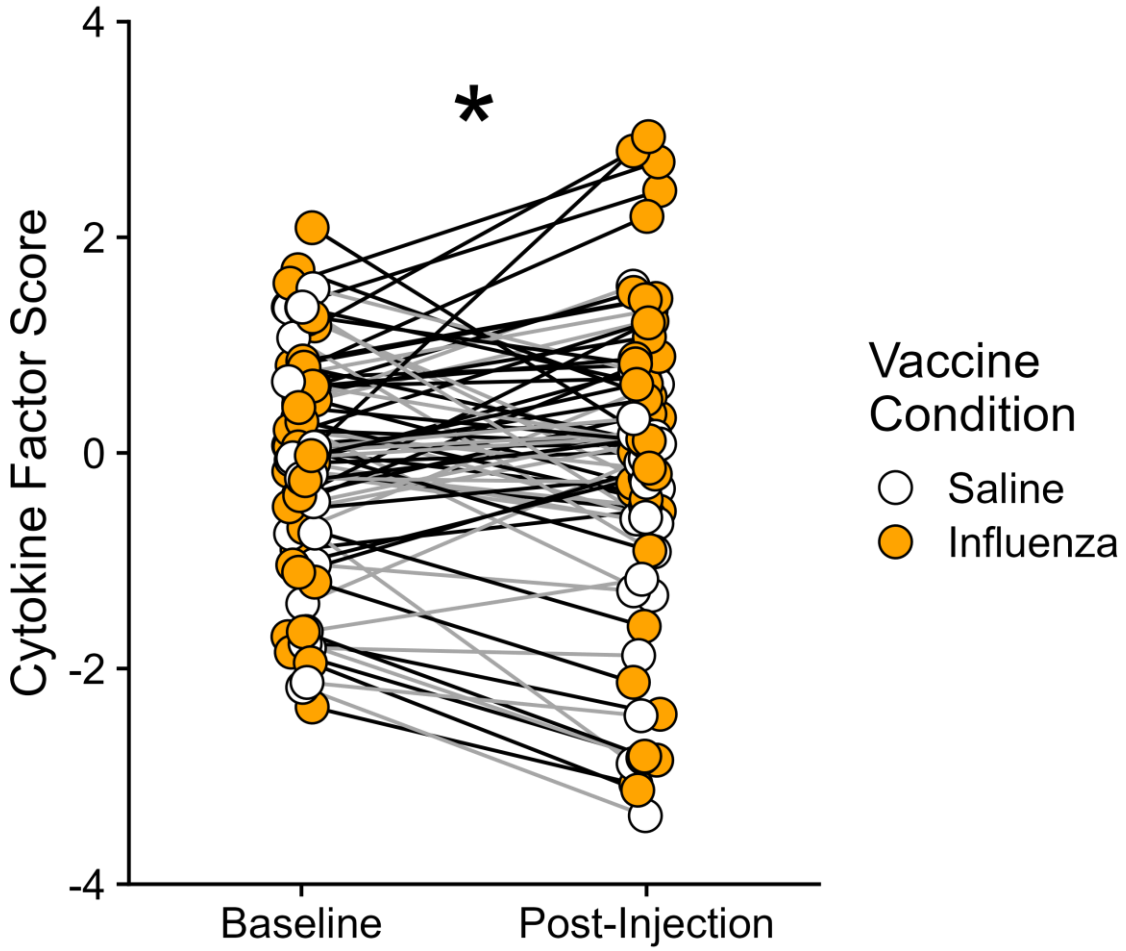

Figure 1. Changes in cytokine levels from pre- to post-manipulation by condition. Participants in the influenza vaccine condition increased in cytokine levels from baseline to 24 hours post-injection relative to participants in the saline injection condition.

Effect of the Manipulation on Inhibitory Control

For our primary analyses, we examined whether participants in the vaccine condition differed in inhibitory control task outcomes from participants in the control condition using a mixed ANOVA (Type III SSs) with Condition (vaccine, placebo) as a between-subjects factor and Outcome (SSRT, flanker interference) as a within-subjects factor. In this analysis, we found a main effect of Condition, $F(1, 89)=6.05$, $p=.016$, and a main effect of Outcome, $F(1, 89)=476.09$, $p<.001$, but no Condition × Outcome interaction, $F(1, 89)=0.44$, $p=.510$. Contrary to our hypotheses, however, the Condition effect we observed was such that vaccine-condition participants showed better inhibitory control—across both

outcomes—than placebo-injection-condition participants, $t(89)=2.46$, $p=.016$, $d=0.52$ (see Figure 2). Put simply, influenza vaccination improves inhibitory control task outcome performance at a delay of approximately 24 hours from receiving the vaccine.

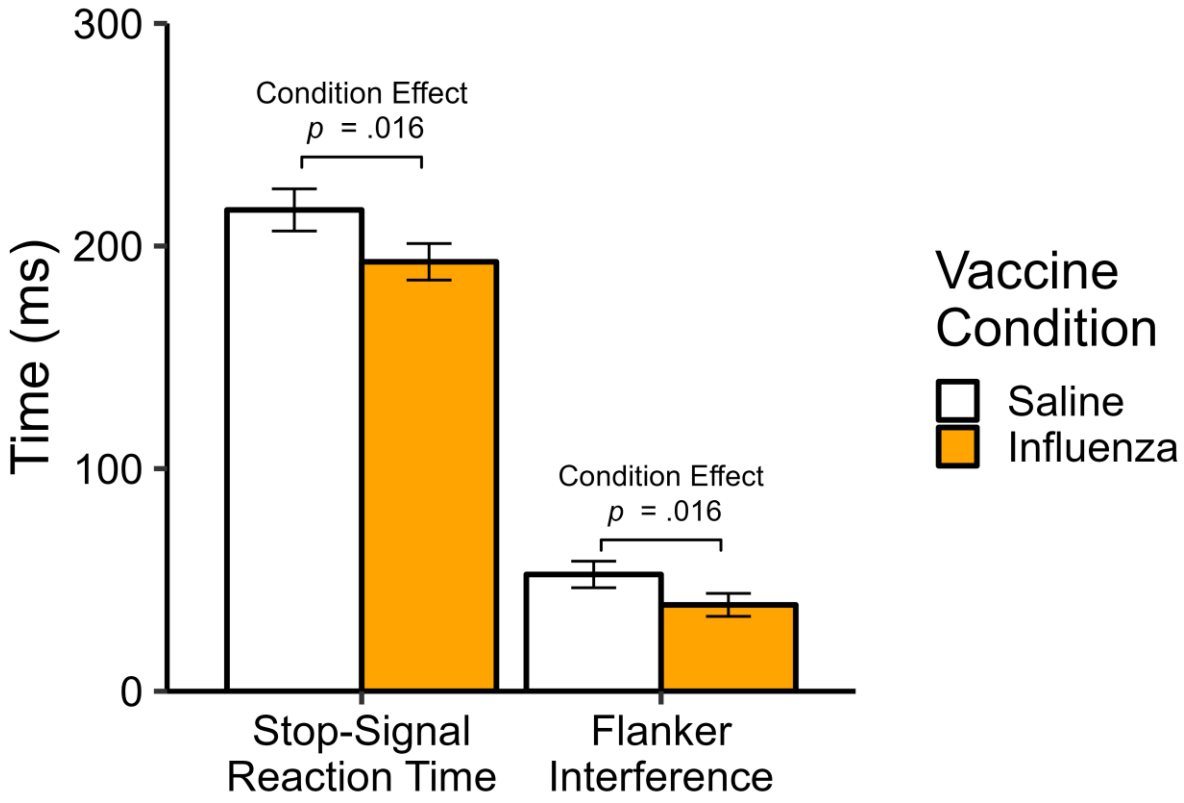

Figure 2. Effects of influenza vaccination on inhibitory control task performance. Relative to a saline (i.e., placebo) injection, participants who received influenza vaccination performed better on both response inhibition and cognitive inhibition outcomes. In particular, participants randomized to receive the influenza vaccine showed faster stop-signal reaction time (i.e., better response inhibition) and less flanker interference effects (i.e., better cognitive inhibition) than participants in the saline condition.

Association Between Cytokine Changes and Inhibitory Control

We next examined whether cytokine changes were associated with inhibitory control task performance, and whether this association differed by condition. In this analysis, we found a main effect of Condition, $F(1, 85)=5.89$, $p=.017$, and an interaction between Cytokine Change and Outcome, $F(1, 85)=6.05$, $p=.016$, but no Condition × Outcome interaction, $F(1, 85)=0.51$, $p=.477$, nor any three-way Condition × Cytokine Change × Outcome interaction, $F(1, 85)=0.76$, $p=.386$. Probing these results, the main effect of Condition was the same as in the above analysis: Vaccine-condition participants showed

better performance across outcomes than placebo-condition participants. Intriguingly, however, greater increases in cytokines were associated with better response inhibition (i.e., lower SSRT) but worse cognitive inhibition (i.e., greater flanker interference) (see Figure 3). Exploratory analyses confirmed that this cytokine change association was not a suppression effect: In a model with only Cytokine Change and Outcome, we again observed a significant interaction between Cytokine Change and Outcome, $F(1, 87)=5.39$, $p=.023$ (see Figure 3). Together, these results point to a beneficial effect of influenza vaccination on inhibitory control at 24 hours post-vaccination that is not accounted for by cytokine changes, and independent associations of cytokine changes with distinct inhibitory control processes that are not accounted for by additional immunological effects of the vaccine.

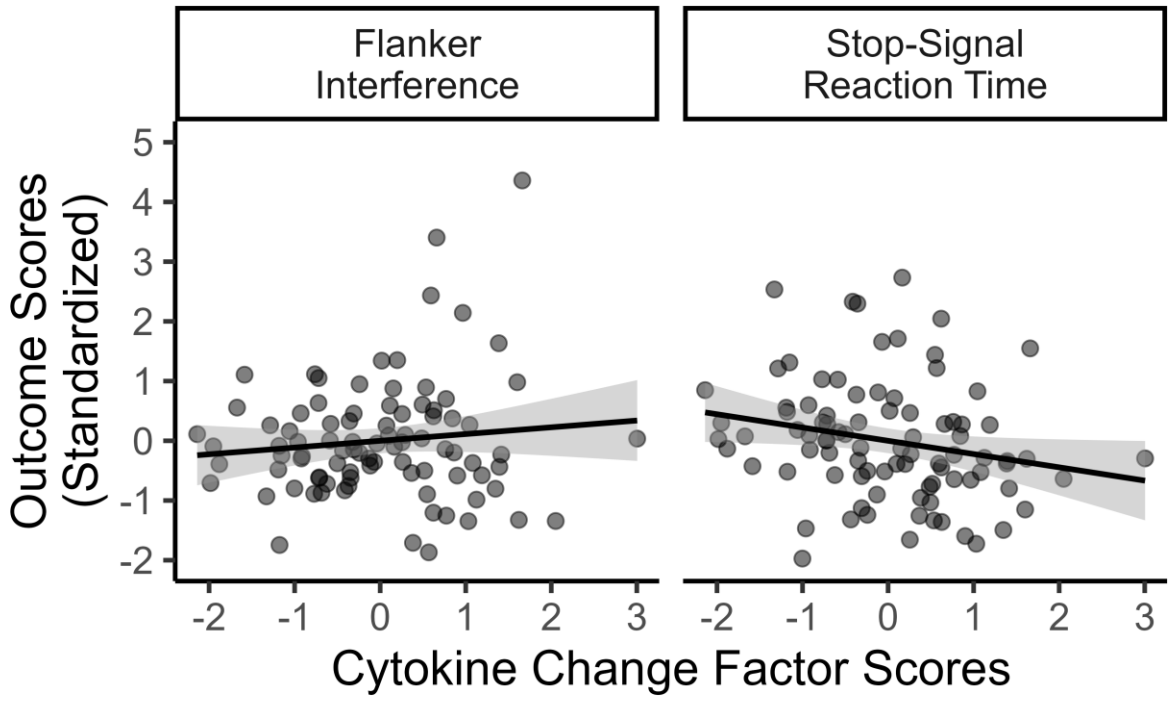

Figure 3. Associations of cytokine increases with inhibitory control task performance. Greater increases in cytokines were differentially associated with cognitive inhibition and response inhibition. Specifically, greater increases in cytokines predicted faster stop-signal reaction time (i.e., better response inhibition) but numerically greater flanker interference effects (i.e., worse cognitive inhibition).

4. Experiment Discussion

In this experiment, we examined the effects of influenza vaccination on inhibitory control outcomes within a hybrid stop-signal flanker task. Consistent with our hypotheses, we found a significant effect of vaccine condition on inhibitory control outcomes. Contrary to our hypotheses, participants in the flu vaccine condition performed better on both inhibitory control outcomes. However, we found that greater increases in cytokines were differentially associated with outcomes, such that—consistent with our hypotheses—greater increases in cytokines predicted poorer interference control. Moreover, consistent with the hypothesis that cytokine activity would facilitate inhibition of motor activity, greater cytokine activity predicted faster stop-signal reaction time (i.e., better inhibitory control). Because this experiment prompted our follow-up with a systematic review that informed our results, we save the majority of our discussion of this experiment for the General Discussion, below.

5. Meta-Analysis Introduction

The experiment described above returned unexpected results, which we felt might be better understood with a systematic review of the literature. In particular, we hoped that by conducting a meta-analysis of this literature, we might be able to understand the main effect of acute immune system activation on inhibitory control, and to elicit moderators that could explain the effects we observed in the experiment above. For that reason, we conducted a systematic review and meta-analysis of studies that experimentally manipulated acute immune system activity via a manipulation specifically targeting the immune system itself (e.g., vaccine, endotoxin) that then assessed the effects of that manipulation on inhibitory control. Drawing on theories described above (Gassen, Makhanova, et al., 2019; Shields, Moons, et al., 2017), we expected to find a weak but significant impairment in inhibitory control overall following acute immune system activation, and to find moderators that might explain our results obtained above.

6. Meta-Analysis Method

6.1. Search String and Inclusion Criteria

6.1.1 Literature review. To obtain studies for use in the meta-analysis, we performed an

exhaustive search of the databases PubMed, PsycArticles, and Web of Science for all papers published until November 26, 2023, using the following search string:

> ("endotoxin" OR "lipopolysaccharide" OR "vaccine" OR "typhoid" OR "influenza")
> AND ("Stroop task" OR "flanker" OR "go/no-go" OR "stop-signal task" OR "Simon task" OR "inhibitory control" OR "response inhibition" OR "interference control" OR "cognitive inhibition" OR "impulsivity")

In this search, PubMed returned 80 results, PsycArticles returned 122 results, and Web of Science returned 82 results. References from relevant articles (e.g., Bollen et al., 2017) were reviewed, and studies that were potentially relevant were examined from those references. Nonexhaustive searches using other strings and other databases (e.g., Google Scholar) were conducted to ensure that no relevant articles were missed. For all articles considered, we followed prior work in reviewing abstracts and examining full texts whenever an article had the potential to include a relevant effect (e.g., if a study incorporated or could have incorporated an acute induction of immune system activity, the full article was examined).

6.1.2 Inclusion criteria. Our seven inclusion criteria for this meta-analysis were as follows: Studies had to (1) experimentally manipulate—using an appropriate control (e.g., saline injection)—(2) the immune system, via endotoxin or vaccine, (3) within human participants, (4) and (5) assess the effects of that manipulation on one or more task outcomes known or shown to primarily index inhibitory control. More will be said on inhibitory control outcomes below. (6) The effect of that manipulation had to be assessed within three days of the induction. (7) Because vaccines activate the immune system for days (e.g., our experiment), participants in the control condition could not have been subjected to an immune system activity induction within the days preceding inhibitory control assessment. This entails that if a study used a counterbalanced, within-subjects, crossover design, the counterbalance of immune system activation and control had to be separated by at least one week. We chose these inclusion criteria to best isolate the effects of acute immune system activation on inhibitory control.

6.1.3 Selected studies. Our search and study inclusion criteria, after removal of multiple publications from the same dataset (e.g., Brydon et al., 2008; Harrison et al., 2009), led to the

incorporation of eight studies, all of which besides the experiment reported in this manuscript were already published in peer-reviewed papers. There were 14 relevant effect sizes across these eight studies.

6.2. Moderator Coding

At the effect-size level, outcome type (i.e., accuracy/error vs. response-time-based), whether the task required inhibition of motor responses on some trials (i.e., if the task included no-go or stop trials; coded as motor inhibition vs. nonmotor inhibition), and whether excessively high and low response times were excluded (RTs cleaned vs. not cleaned) were coded categorically. The task's proportion of trials requiring inhibition (e.g., incongruent, no-go, etc.; proportion ranging from zero to one) was coded continuously, as was the delay between injection and the inhibitory control task.

At the study level, percent female participants and mean participant age were coded continuously, whereas injection type (vaccination vs. endotoxin), study design (within- vs. between-subjects), and sample clinical status (healthy vs. clinical sample) were coded categorically.

Other variables, such as participants' BMI and the percent nonminority participants, were coded, but missing data prohibited analyses with these moderators.

6.3. Analytic Method

When data were presented as incongruent and congruent in isolation, because the difference between those trial types is considered the appropriate inhibition outcome, the difference was computed. The mean difference was calculated as a difference between means, and the standard deviation of the difference was calculated via:

$$\sigma_{V1-V2} = \sqrt{\sigma_{V1}^2 + \sigma_{V2}^2 - 2\rho_{V1V2}\sigma_{V1}\sigma_{V2}}$$

Similarly, baseline-corrected differences were computed when participants completed the same task both before and after both the placebo/saline injection and the immune-inducing injection, and the standard deviation of this difference score was computed using the same formula as above. When the correlation between measurements was unknown, we imputed the average from studies that had provided it.

The effect size measure of interest was the standardized mean difference in inhibitory control outcomes between immune induction and control conditions. We used Hedges' *g* rather than Cohen's *d* as the effect size for analysis, given that the former is a relatively unbiased estimate of the population standardized mean difference effect size while the latter is a biased estimate. Whenever possible, we calculated Hedges' *g* from the means, standard deviations, and sample sizes presented in the article. If means and standard deviations were not reported and the design was between-studies, we used *t* or one-way *F* statistics—or *p* values resulting from tests of those two statistics—to calculate the effect size. If none of these statistics were reported, we emailed corresponding authors for these statistics.

Given the multifaceted nature of inhibitory control, most studies often report more than one inhibitory control outcome (e.g., the Stroop interference effect on reaction time, the Stroop interference effect on error rates, etc.). Multiple outcomes are a problem for conventional meta-analytic methods, as averaging effect sizes within studies without accounting for their correlations can alter or obscure true effect size estimates (Borenstein et al., 2009; Scammacca et al., 2014). Thus, we employed the meta-analytic technique of robust variance estimation, a random-effects meta-regression that can account for dependence between effect size estimates (Hedges et al., 2010; Tanner-Smith & Tipton, 2014). This technique robustly estimates effect size weights and standard errors for the given effects, allowing for multiple outcomes within studies (Hedges et al., 2010). We employed the `robu()` function of the `robumeta` package in **R**, version 4.4.0, to conduct these analyses using the correlated weights given by Hedges et al. (2010), with our primary analyses using the small sample corrections suggested by Tipton (2014). To account for dependency, ρ was set to the recommended .80 (Tanner-Smith & Tipton, 2014).

Degrees of freedom for all primary analyses were estimated using the Satterthwaite approximation, as simulation studies have indicated that this method of estimating degrees of freedom is most analytically valid with study set sizes under 40 using the RVE meta-analytic technique (Tipton, 2014). Because of how the degrees of freedom are estimated, if the degrees of freedom are less than four, then there is a heightened risk of a Type I error and the analysis results cannot be trusted to represent population values (Tipton, 2014). However, because this estimation of degrees of freedom is extremely

sensitive to outliers given a study set size such as in this meta-analysis (since degrees of freedom are divided by the coefficient of variation), one can be relatively confident that when degrees of freedom are greater than four, outlying studies are not driving observed significant effects.

For all of the following analyses, a positive effect size indicates that the acute immune system activity induction *improved* performance on the inhibitory control outcome relative to the control condition, whereas a negative effect size indicates the acute immune system activity induction *impaired* performance on the inhibitory control outcome relative to the control condition. In addition, because the outcome in these analyses is the standardized mean difference between groups (the effect size), a significant continuous moderator means that the effect size estimate depends upon levels of that continuous variable. In other words, if the coefficient for a continuous moderator is significant, it means that as the continuous variable increases or decreases, the effect of immune activation on inhibitory control relative to the control condition increases or decreases.

7. Meta-Analysis Results

We first examined the overall effect of all of the manipulations we examined. Across all studies, we observed a nonsignificant overall effect of vaccination or endotoxin injection on inhibitory control, g^{+}=0.074, t(5.9)=0.55, p=.600 (Figure 4), with no significant evidence of publication bias, p=.491 (Figure 5). However, a fair amount of heterogeneity existed in these data, I^2=54.4, τ^2=0.08. As can be seen in Figure 4, studies with multiple outcomes each showed relatively strong within-study conceptual replication (e.g., clustering together) despite similar tasks. This suggests that study design factors may have moderated the influence of these manipulations on outcomes.

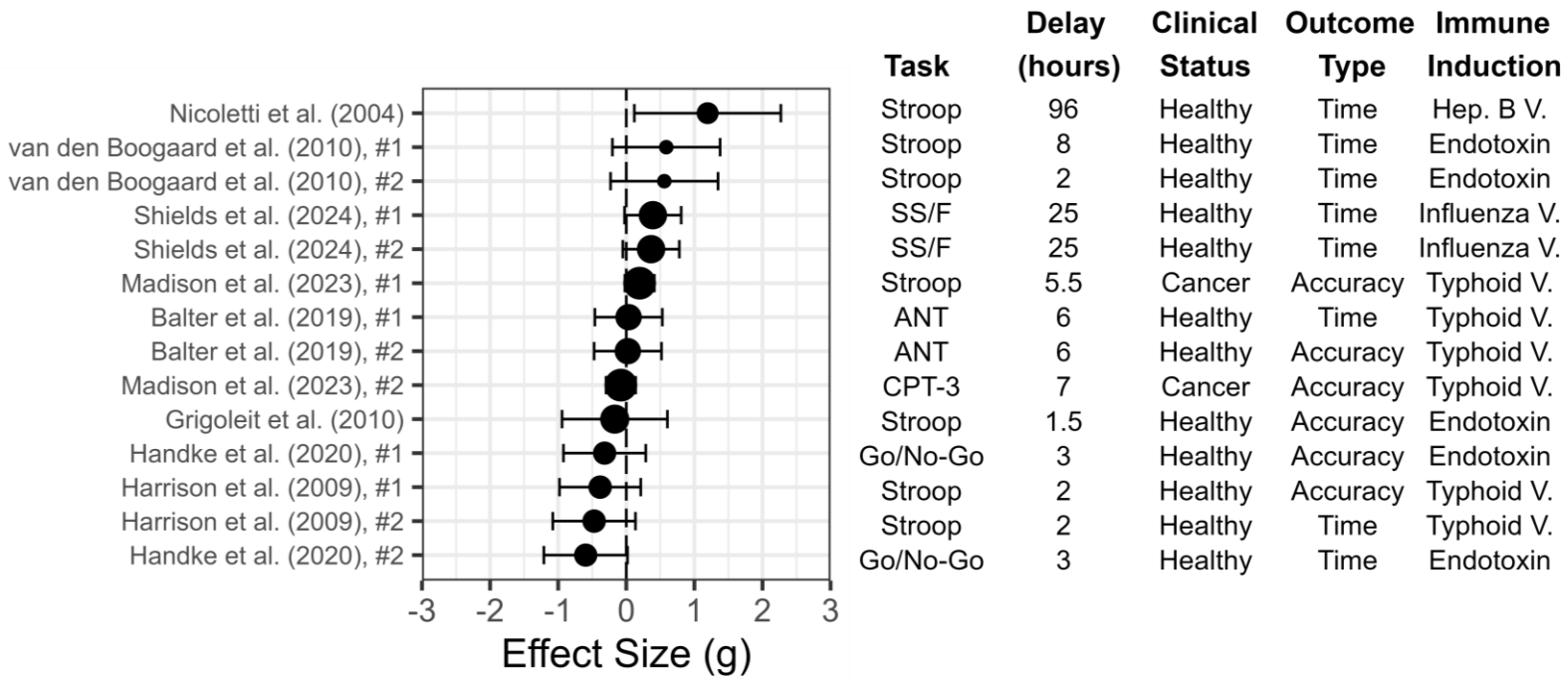

Figure 4. Effects of endotoxin or vaccination on inhibitory control outcomes. SS/F = Stop-Signal/Flanker; ANT = Attentional Network Test; CPT-3 = Connor's Continuous Performance Test, Third Edition; Hep. = Hepatitis; V. = Vaccination.

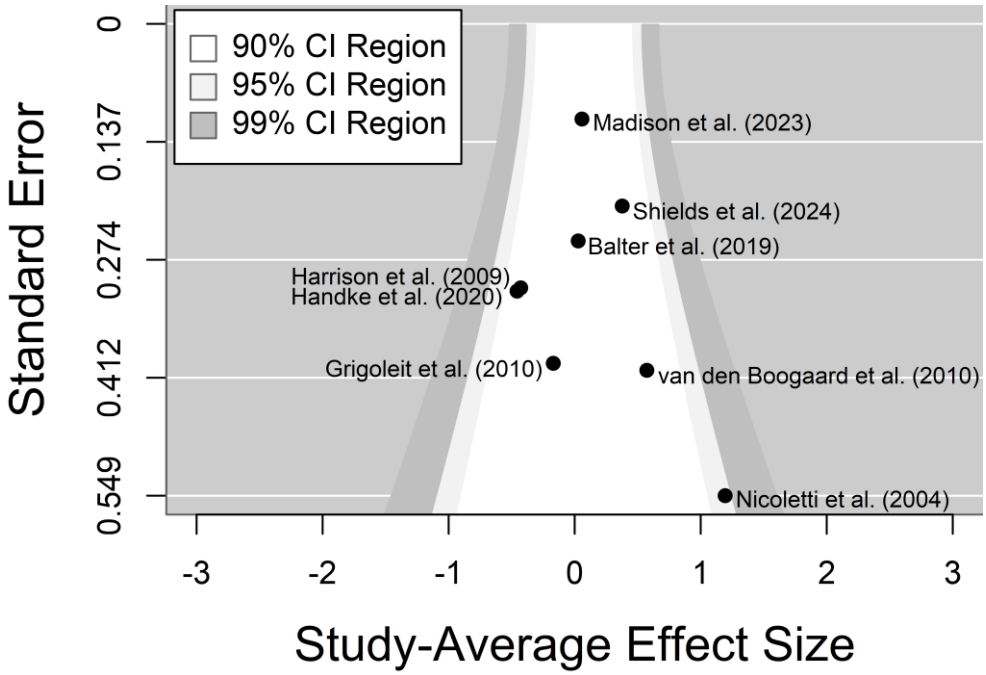

Figure 5. Funnel plot of study-average effects. There was no significant evidence of publication bias among these effects.

To determine whether any significant moderators existed that could explain this heterogeneity, we conducted a reverse stepwise regression with all moderators we considered (i.e., injection type [endotoxin, vaccine], outcome type [accuracy, time], inhibition trial proportion, whether the sample was a clinical one [clinical, nonclinical], whether the task is a response inhibition task [no, yes], and the log-transformed delay between injection and the inhibitory control task). We removed the least significant at each iteration until only significant coefficients remained—if any. In this, we found that the effect of acute immune induction on inhibitory control task outcomes was moderated by both the task being a response inhibition task, $B = -.345$, $t(2.2) = -6.18$, $p = .020$, and the delay between injection and inhibitory control task performance, $B = .359$, $t(3.3) = 9.53$, $p = .002$; effect size at moderator reference values (i.e., 1.5-hour delay, not a response inhibition task), $g^{+} = -0.299$, $t(4.8) = -2.96$, $p = .033$. See Figure 6.

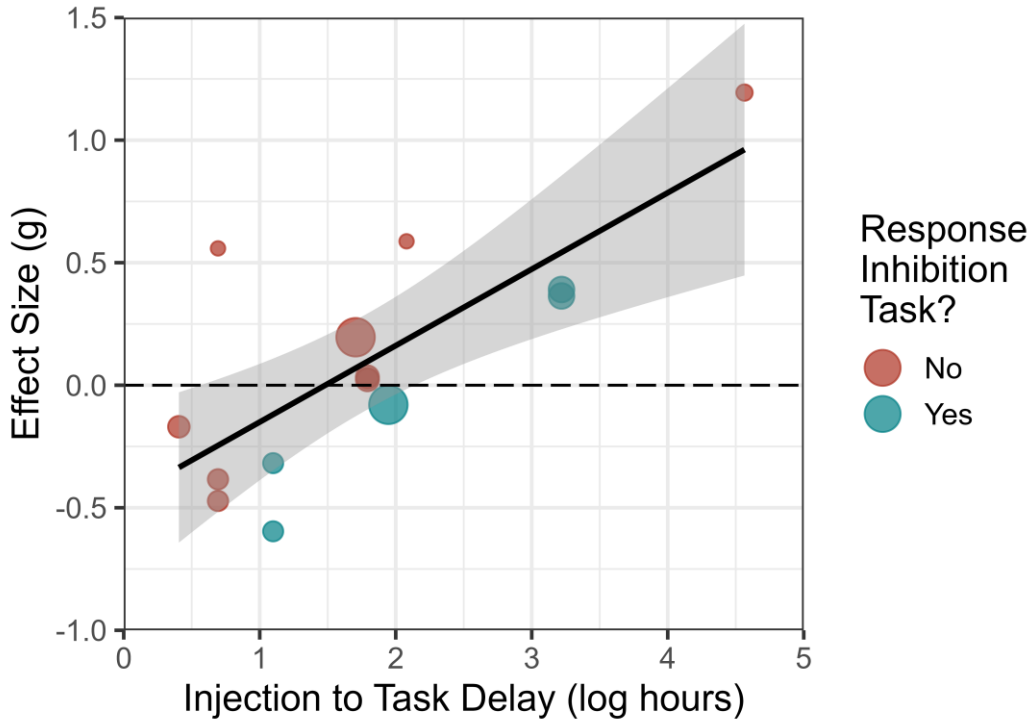

Figure 6. Effects of acute immune activation on inhibitory control by study timing and task type. A shorter delay with a response inhibition task component was associated with an impairing effect of immune induction on inhibitory control, and a longer delay coupled with a nonresponse inhibition task was associated with an enhancing effect of immune induction.

Importantly, these effects were still present in the five studies (k=9) that remained when studies that manipulated immune activity via endotoxin were excluded [response inhibition moderation, B= −.303, t(1.4)= −5.30, p=.072; delay between injection and inhibitory control task moderation, B=.396, t(1.7)=10.90, p=.014]—albeit with few degrees of freedom, indicating inferential caution. These results thus suggest that the moderations described above were not driven by endotoxin studies, which can increase cortisol and body temperature in ways not typical for acute immune inductions outside of illness. In the three endotoxin studies (k=5), the moderators showed the same patterns [inhibition trial proportion moderation, B= −.736, t(1)= −4.48, p=.140; delay between injection and inhibitory control task performance, B=.392, t(1)=1.85, p=.315], but there were too few effect sizes to support inferences. In short, the pattern of moderator effects replicated across immune system induction types.

Exploring the moderation effects in greater detail, immune system induction exerted an estimated overall impairing effect on inhibitory control task performance between the minimum observation of 1.50 hours post-injection, g^{+}= −0.471, p=.004, and 3.55 hours post-injection, g^{+}= −0.162, p=.049, whereas it exerted an estimated overall enhancing effect between 7.80 hours post-injection, g^{+}=0.121, p=.050, and the maximum observed 96 hours post-injection, g^{+}= 1.023, p=.002.

At every delay, the effect of immune system induction on response inhibition task performance is over one-third of a standard deviation more impairing than it is on cognitive inhibition task performance, g^{+}= −.345, p=.020.

In short, an inhibitory control task, and especially a response inhibition task, is completed approximately 1.5–4 hours post-induction, such immune induction impairs performance relative to a saline injection. In contrast, such an induction enhances performance on inhibitory control outcomes at a delay of ∼10 or more hours post-induction.

8. Meta-Analysis Discussion

In this meta-analysis, we examined the effects of experimental manipulations of acute immune system activation via endotoxin or vaccination vs. saline/placebo control injection. In these analyses, we found two significant moderators: inhibitory control task trial design and delay between injection and

inhibitory control task performance. Put simply, acute immune activation impaired performance on inhibitory control tasks, and especially response inhibition tasks, when those tasks were administered between 1.5 and approximately 4 hours post-induction. Immune activation is complex, though, and it appeared to exert a beneficial effect when more than an estimated 10 or more hours had elapsed post-vaccination. In short, these results suggest that acute immune system activity can influence inhibitory control outcomes, and they clarify conditions in which those influences might differ.

Our results also speak to the importance of the inhibition task type in the effects of immune system activation on inhibitory control. In particular, we found that acute immune system activation impaired performance to a greater extent when the task required response inhibition, regardless of the delay. This is consistent with our expectation that immune system activity might particularly influence motor-based inhibitory control.

It should be noted that, except for one study (Madison et al., 2023) that used a sample of older cancer survivors, every study included in this meta-analysis used a sample of healthy young adults. Aging, cancer, and other conditions can induce long-lasting changes in the immune system at rest, as well as how the immune system responds to challenges (Shields, Moons, et al., 2017). We do not claim that our moderator analyses would necessarily come out exactly as they did with a larger sample of clinical or older adult studies. Indeed, we believe that clinical and/or older participants would show a distinct effect of acute immune system activation on inhibitory control. We believe that it may be a fruitful line for future research to directly compare effects in such a sample against those obtained using the same paradigm within a healthy young-adult sample. Such a study would provide insight into the extent to which immunosenesence or similar dynamics modulates the effects of acute immune systems activation, which would provide valuable clinical insights for populations wherein inhibitory control deficits and immunosenesence are both common (O'Donovan et al., 2009; Sebastian et al., 2013; Trollor et al., 2012).

The delay between acute immune system activation and inhibitory control outcomes producing a positive effect was unexpected, but it dovetails nicely with the results of our experiment, described above. Given this, we discuss this delayed enhancement effect to a greater extent in the general discussion below.

9. General Discussion

Although the effects of acute immune system activation on cognition may feel intuitive, relative to other contextual factors (e.g., stress; Shields et al., 2016, 2024; Shields, Sazma, et al., 2017), little work has examined the effects of acute immune system activation on cognition. Across a large experiment and a meta-analysis, we examined the effects of acute immune system activation on multiple forms of inhibitory control. In this, we found that acute immune system activation exerted time-dependent effects on inhibitory control: At a very short delay between activation and cognitive assessment (e.g., 1.5 to 4 hours), acute immune system activation broadly impaired inhibitory control, whereas at a longer delay between activation and cognitive assessment, immune system activation improved inhibitory control performance. However, cytokine activity—which exists early in immune activation in isolation, but in tandem with adaptive immune system activity later following pathogen challenge—predicted poorer inhibitory control fairly consistently, no matter the timescale. Together, these results highlight the complexity and nuances of the effects of acute immune system activation on inhibitory control and begin to potentially clarify mechanisms.

Our results partially support and partially oppose the predictions of the immunologic theory of self-regulation (Shields, Moons, et al., 2017) and the immune-induced present-focus theory (Gassen, Makhanova, et al., 2019). In particular, neither of these theories make predictions about time-dependent effects of immune system activity on inhibitory control, but an enhancement of inhibitory control one day after vaccination was found both in our experiment and within the meta-analysis. These results therefore suggest that theories of acute immune system activation and cognition may need to be revised to account for differential short- and medium-term effects of immune activation on cognition.

Our results suggested that extended effects of acute immune system activation may exert a positive effect on inhibitory control. Although speculative, these results could be interpreted to fit well with the idea that greater overall inhibition may reduce exploration and facilitate rest. It should be noted, though, that only vaccine studies assessed inhibitory control more than eight hours after injection, entailing that it is unclear whether the delayed effects are due to simple genomic effects of prior immune

system activation (e.g., as might be expected if endotoxin produced a benefit after 24 hours) or if they are due to persistent or prolonged combat with a potential pathogen (e.g., as might be expected if only vaccine or illness, not endotoxin, improved inhibitory control at a delay). Testing these possibilities may be a fruitful avenue for future research.

In contrast to the delayed condition effect of vaccination, at a delay greater than 12 hours, changes in cytokines showed an inverse correlation with some, but not all, inhibition outcomes. This pattern could be taken to suggest that cytokine activity, in isolation, exerts the same effects on inhibitory control until the immune system activation has subsided, but other immune system processes (e.g., adaptive immune system function) exert other, potentially opposite, effects on inhibitory control as the delay between injection and inhibition assessment increases.

These results do not imply that the link between immune activity and cognition always starts with the immune system. Indeed, as we have described previously (Shields et al., 2021; Yang et al., 2018), poor inhibitory control or executive functioning is likely to lead to impulsive decisions and poor health behaviors that increase inflammatory activity, such as nicotine consumption, excessive alcohol consumption, saturated fat consumption, poor sleep, and more (Hostinar et al., 2015; Yang et al., 2019). Nonetheless, these results do highlight pathways through which the immune system can influence inhibitory control, perhaps in a way that initiates a positive feedback loop that may exacerbate inequity (Hunter & Shields, 2022; Shields, Moons, et al., 2017).

Our results also do not imply that acutely elevated and chronically elevated immune system activity exert the same cognitive effects. Indeed, a vast number of studies have documented impairments in inhibitory control in the context of sustained immune system activity (reviewed in Shields, Moons, et al., 2017), which is likely due to the neurotoxic effects of sustained systemic and neuroinflammatory activity (Cibelli et al., 2010; Hu et al., 1997; Meyers et al., 1994; Sobesky et al., 2014). Our results should be considered only in light of acute immune system activation, such as occurs following vaccination—or, perhaps, a short-duration illness.

Despite its strengths, our experiment has some limitations that should be noted. First, our experiment used one type of vaccine, which primarily elicits antiviral immune activity. It is possible that antibacterial, antifungal, or other forms of immune activation may exert different effects on inhibitory control. Second, our experiment was conducted from August 2020 to May 2022, and it is possible that the COVID-19 pandemic influenced basal or responsive immune function—directly via recent viral infection, or indirectly via stress. Third, our meta-analysis included only eight studies. Although the observed moderators were robust to subsets of studies and manipulations, it is likely that we lacked sufficient studies to uncover all moderators of the effects of acute immune system activation on inhibitory control. Fourth, our experiment and all included in the meta-analysis were samples from Western, Educated, Industrialized, Rich, and Democratic (WEIRD) societies, and most people are not WEIRD (Henrich et al., 2010). Well-known psychological effects do not replicate in non-WEIRD societies, and it is possible that our results would not generalize in the same way. Finally, even within WEIRD samples, it is unknown whether our results would generalize to older or clinical samples. Future work should attempt to address these limitations.

9.1. Conclusion

Although coming down with an illness or receiving a vaccine are both common experiences, the influence of such acute immune system activations on cognitive processes, such as inhibitory control, has received relatively little attention. We addressed that issue by assessing the effects of acute immune system activation on inhibitory control in a randomized controlled experiment, and by conducting a meta-analysis of similar studies in humans. We found that at a short delay (1.5 to 4 hours post-injection) between immune activation and inhibitory control assessment, such activation impaired multiple forms of inhibitory control. At a long delay, such activation improved inhibitory control, but proinflammatory cytokine activity nonetheless predicted poorer inhibitory control even at a long delay between injection and testing. Together, these results highlight nuanced, time-dependent, and multiple-mechanism-driven effects of acute immune system activity on inhibitory control. If you received a vaccine today, perhaps wait a day or so to do anything that might require a fair amount of self-control—if you can wait, that is.

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