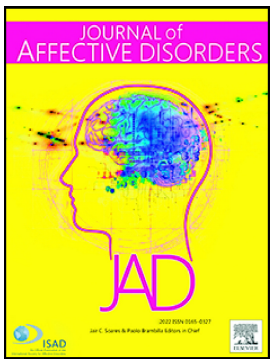

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Inflamed but not Impulsive: Acute Inflammatory Cytokine Response Does Not Impact Prepotent Response Inhibition

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Short Title: Inflammation and Impulsivity

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Introduction

Trait impulsivity is a core facet of many distinct psychiatric diagnoses, such as borderline personality disorder, bipolar disorder, attention deficit disorder, and intermittent explosive disorder (American Psychiatric Association, 2013). The Hierarchical Taxonomy of Psychopathology categorizes psychiatric symptoms on a spectrum, and seeks to match underlying causes to specific symptoms, rather than the traditional disorder classification (Kotov et al., 2017). There is emerging evidence that those who have higher levels of trait impulsivity – both healthy individuals or those with psychiatric disorders –have heightened levels of various basal inflammatory markers in the serum or plasma. For example, cross-sectional studies have found elevated basal peripheral inflammatory markers among those with intermittent explosive disorder (Coccaro et al., 2014), borderline personality disorder (MacDowell et al., 2020), and bipolar disorder (Bai et al., 2014), compared to controls. Even among a non-clinical sample of community-dwellers, those who scored higher on impulsiveness and excitement-seeking facets of the Revised NEO Personality Inventory had higher white blood cell and lymphocyte counts (Sutin et al., 2012). Similarly, two different studies among healthy young adults showed that higher levels of proinflammatory cytokines in the saliva (Gassen et al., 2019a) and in the plasma (Gassen et al., 2019b) predicted more focus on present-moment goals, at the expense of planning ahead for the future. Although other cross-sectional evidence suggests an opposite relationship (e.g., Coryell et al., 2018), generally speaking, mounting correlational evidence points to a positive association between basal peripheral inflammatory markers and impulsivity.

We recently wrote a theoretical article that questioned whether inflammation truly causes or contributes to impulsivity (Madison and Kiecolt-Glaser, 2022). Specifically, we stated that to answer this question, future research would need to (1) examine specific facets of impulsivity(e.g., non-planning or lack of premeditation, motor impulsivity or inability to inhibit responses, cognitive or attentional, urgency, lack of perseverance, sensation seeking); (2) account for reverse causality, given that many impulsive behaviors (e.g., binge eating) may

promote elevated circulating inflammatory markers; (3) activate inflammatory signaling, ideally in a within-subject, randomized, placebo-controlled design. Related to the first point, prior research has shown that there is no single underlying construct of impulsivity, but rather several distinct constructs, including delay discounting, inability to inhibit a prepotent (i.e., dominant, automatic) response, and one's own assessment of self-regulatory capacity (MacKillop et al., 2016). Different biological mediators may underlie each construct. One important aspect of impulsivity is response disinhibition, which may be an underlying cognitive mechanism fueling impulsive behavior (Enticott et al., 2006). In fact, it could be an endophenotype, or a subtle behavior that indicates genetic risk for an impulsive disorder (Congdon and Canli, 2008, 2005). Also, performance on response inhibition tasks can predict impulsive behaviors in real-life (Sharma et al., 2014).

Just as there are different aspects of impulsivity, there are also different ways to measure inflammation. Inflammation is an umbrella term that refers to a host of soluble mediators that respond to wounding, other cellular or tissue damage, or infection to facilitate healing. A time-limited response to a clearly defined provocateur is healthy, but it is problematic when it becomes persistent. Although there are many inflammatory biomarkers, including elevated white blood cell count, another common measure in clinical settings is the acute phase C-reactive protein produced by the liver during an inflammatory state, and in a research setting, inflammatory signaling molecules, called cytokines (e.g., interleukin-6; IL-6, tumor necrosis factor-α; TNF- α), are often measured. It is also necessary to distinguish between the acute, innate inflammatory response and chronic inflammation because they may have distinct psychological and behavioral effects; yet a short-term inflammatory stimulus (like lipopolysaccharide; LPS) is commonly used to model depression (i.e., the sickness behavior model of depression) (Lasselin et al., 2020).

A handful of experimental studies have attempted to provoke or decrease circulating peripheral inflammatory markers and measured facets of impulsivity. For example, an eight

week (three day per week) high-intensity interval training (HIIT) intervention among emotionally-impulsive adults reduced basal levels of serum IL-6, which tracked with a decline in self-reported lack of follow-through, compared to an active stretching control; even so, both HIIT and stretching reduced self-reported emotional impulsivity (Javelle et al., 2021). In contrast, among healthy participants, 18 weeks of anti-inflammatory omega-3 supplementation did not reduce self-reported negative affect or impulsivity nor functionally alter key brain regions associated with mood and impulsivity compared to soybean oil supplementation (Ginty et al., 2017). Studies that provoked an acute cytokine response and specifically measured inhibitory control have not found an effect, but they have had small, young, and healthy samples. For instance, three hours after receiving a LPS injection, which sharply increased inflammation, participants' (*N*=22) reaction time and errors on a simple reaction time task and go/no go task were not different than three hours after they received a placebo injection. This crossover design is a notable strength, as it accounts for individual differences in cognitive function and education. Another randomized crossover trial among 16 young, healthy men used a typhoid vaccine to evoke an inflammatory response and failed to find differences on the Stroop task (Brydon et al., 2008). Even so, participants who had a higher vaccine-induced plasma IL-6 responses had slower Stroop reaction times, which is not indicative of response disinhibition. Randomized controlled trials with a between-subjects design have also reported null effects, though they are also limited by their small, young, and healthy samples (Grigoleit et al., 2010; Van den Boogaard et al., 2010). Also, acute psychosocial stressors promote an acute cytokine response (Marsland et al., 2017) – albeit orders of magnitude lower than LPS – and yet they boost inhibitory control (Chang et al., 2020; Schwabe et al., 2013). In short, the current body of experimental evidence is not large or strong enough to conclude that inflammation causes impulsivity or response disinhibition.

Despite a lack of compelling experimental evidence in humans, it is plausible that higher levels of circulating peripheral inflammatory markers can set the stage for more impulsive

behavior. Peripheral inflammatory markers are closely related to inflammatory markers in the cerebrospinal fluid (i.e., neuroinflammation) (Felger et al., 2020), but the peripheral markers are less invasive and less costly to obtain. A murine model showed that chronic overexpression of TNF-α in the periphery led to microglial activation and heightened inflammatory activity in the cortex, striatum, and thalamus but not the hippocampus or cerebellum, and postmortem brain tissue from rheumatoid arthritis patients showed evidence of microglial activation in the cortex (Süß et al., 2020), but more work is needed to identify how chronic, low-grade inflammation in the periphery differentially relates to inflammatory activity in various brain regions. Acute inflammatory responses may affect distinct parts of the brain (e.g., insula)(Harrison et al., 2015). In terms of neurotransmission, proinflammatory cytokines activate indoleamine 2,3-dioxegenase, an enzyme that shunts tryptophan to the kynurenine pathway, resulting in neurotoxic and neuro-excitatory products such as quinolinic acid, at the expense of serotonin synthesis. Meta-analytic evidence has uncovered functional abnormalities in this pathway in people with bipolar disorder (Bartoli et al., 2021). Another possible pathway involves dopamine, as inflammatory cytokines can play a major role in its synthesis and binding. Individuals with impulsivity-related disorders have low tonic mesolimbic dopaminergic activity and blunted dopamine responses to reward (Zisner and Beauchaine, 2016).

Here we add to this nascent experimental literature by testing response inhibition after an experimental manipulation of i the acute cytokine response in a larger and older sample of women. In a randomized, placebo-controlled crossover trial, we hypothesized that women would struggle to inhibit responses on cognitive tests after a mild inflammatory stimulus (typhoid vaccine), compared to placebo (saline injection). We also expected that those who had a steeper inflammatory cytokine rises would have poorer response inhibition, compared to those who had milder inflammatory responses. We opted to use the typhoid vaccine to stimulate an acute inflammatory cytokine response because the magnitude of this cytokine response is more

similar to that observed in chronic diseases and some psychiatric disorders, compared to other stimuli that promote responses that are on par with acute infection (e.g., LPS) (Lindsay, 2022). Because the inflammatory response is milder, participants do not experience as many sickness symptoms; thus, such symptoms did not confound cognitive testing performance. The data for these secondary analyses came from a parent study that tested predictors of breast cancer survivors' inflammatory responses (Kiecolt-Glaser et al., 2022). Although there is relatively little research investigating the prevalence of impulsivity-related disorders (e.g., bipolar disorder, binge eating disorder) in breast cancer survivors, they are at an increased risk for neurocognitive dysfunction (Carreira et al., 2018), including lower blood-oxygen levels in several frontal regions involved in prepotent response inhibition during a relevant task (Kam et al., 2016; Scherling et al., 2012). Even so, prior work has not found differences between breast cancer survivors and controls, either before or after chemotherapy, on response inhibition task performance (Kam et al., 2016; Scherling et al., 2012)

Methods

Participants

For the parent study, we recruited 172 postmenopausal women with a history of Stage I-IIIA breast cancer, one to nine years after their primary cancer treatment. We primarily recruited them from the James Cancer Hospital, with supplemental recruitment through the Army of Women website. Women were excluded if they had a history of any other malignancy except for basal or squamous cell skins cancers, autoimmune and/or inflammatory diseases, liver disease, heart disease or uncontrolled hypertension, stroke, diabetes, anemia, alcohol/drug abuse, smoking, or any other medical condition that would hinder participation. Other exclusions included a prior typhoid vaccine, or current steroid, statin, or other anti-inflammatory prescription medication use.

Procedure

A screening visit determined eligibility, and eligible women were randomized to either the vaccine/placebo sequence or the placebo/vaccine sequence. A trained experimenter administered the Structured Clinical Interview for DSM-V to assess lifetime history of mood and anxiety disorders (First, 2014). Blinding indices, reported elsewhere (Kiecolt-Glaser et al., 2022), showed that experimenters and nurses were blind to condition, but participants were not completely blind likely due to differences in arm pain between the two injection types. The two 9.5 hour visits occurred an average of 46.9 days (SD=47.5) apart. At each visit, participants completed a 20-30 minute adaptation period, and afterwards, a nurse inserted an intravenous catheter and took a baseline blood draw. Around 8:30 am, the nurse injected saline (the placebo) or Typhoid capsular polysaccharide vaccine (Typhim-Vi, Sanofi Pasteur) into the non-dominant deltoid muscle. Blood draws occurred approximately every 90 minutes for the next eight hours. Within five minutes after the injection, women ate a standardized breakfast. Five and a half hours after the vaccine, women completed the computerized Stroop and N-Back tasks (see below). They then completed other tasks relevant to the parent study (thought listing, resting metabolic period, blood draw, hot/cold plate task, questionnaires). About seven hours after the vaccine, they completed a continuous performance task on the computer. The timing of cognitive testing aligned with the typhoid vaccine's peak inflammatory response (6-8 hours post-vaccine; Paine et al., 2015). Prior to the injection and then approximately every 1.5 hours thereafter, women reported their current fatigue. The Ohio State University Institutional Review Board approved this study, and participants provided written informed consent.

Inflammatory Cytokines

We measured both IL-6 and interleukin-1 receptor antagonist (IL-1Ra) because prior literature showed that they both increased in response to the typhoid vaccine (Hingorani et al., 2000; Kharbanda et al., 2002). Serum IL-6 was assayed with the Quantikine HS ELISA kit (R & D Systems, Minneapolis, MN), and serum IL-1Ra was assayed using

an electrochemiluminescence method with Meso Scale Discovery kits (Rockville, MD). Sensitivity for IL-1Ra was 6.3 pg/mL and for IL-6 was 0.03 pg/mL. Intra-assay coefficients of variation were 4.1 % for both inflammatory markers. Intra-assay coefficients of variation were 8.6 % for IL-1Ra and 6.5% for IL-6.

Cognitive Assessments

For all cognitive tasks below, our primary outcomes of interest were errors or accuracy rates. Inflammatory stimuli like the typhoid vaccine reliably slow psychomotor function (Brydon et al., 2008), so examining inflammation's effect on response times would not be a valid test of the hypothesis that inflammation causes response disinhibition. Although our goal was to index inhibitory control, all cognitive tests involve more than one cognitive domain; for example, CPT commission errors also measures attention and 2-back accuracy also indexes working memory (Fernández-Quirós et al., 2023; Meule, 2017).

Stroop Task

We created and administered the Stroop on Empirisoft software DirectRT v2016. Participants were instructed to decide as quickly as possible the color of the word on the screen, and to ignore what the word said, by pressing keys on the keyboard that were color-coded red, yellow, blue, or green. They completed one practice block of 28 trials, followed by three blocks of 28 trials each, and the stimuli appeared in a random order within each block. Twelve trials were color-congruent (a color word with the same color type), 24 trials featured non-color words like chair and lamp that were color-coded (neutral trials), and 48 trials were color-discrepant (a color word with different colored type). Response times and errors were recorded. Trails with response times that were less than 200 milliseconds or greater than 3000 milliseconds were excluded (<.01% of all trials). To assess inhibitory control, we were interested in the number of errors on the color-discrepant trials, in that a higher number of errors indicate lower inhibition of interfering stimuli features (Wöstmann et al., 2013). That is, those who had fewer errors on the

color-discrepant trials were better able to override their dominant, automatic impulse to respond based on the word itself, rather than its color.

N-Back

The N-back was also created and administered on DirectRT software. Participants were instructed to press the 'yes' and 'no' keys with their left and right pointer fingers to indicate whether the letter matches the letter presented on the previous trial (1-back) or two trials ago (2-back). They completed 20 practice trials prior to beginning the task, and then there were 64 1-back trials and 64 2-back trials. At both visits, around 0.2% of all trials had a low response time (<200 milliseconds), and these trials were eliminated. The outcome of interest was accuracy on the 2-back, given its relevance to inhibitory control; to answer correctly, participants must not let the previous stimulus interfere (Gajewski et al., 2018). Thus, it is generally correlated with performance on the color-discrepant Stroop (Gajewski et al., 2018).

Conners Continuous Performance Test

For the 15-minute Conners Continuous Performance Test (CPT) 3, women were instructed as follows: "During the task, letters will flash up on the screen. Your job is to hit the spacebar as quickly as possible when you see any letter that is not an "X". It may seem a little frustrating or difficult at some points but do your best to stay focused." We were interested commission errors, or the number of times a participant pressed the space bar for a non-target stimuli, because they are strongly related to inhibitory control and can predict attention-deficit/hyperactivity disorder and oppositional defiant disorder symptoms (Avila et al., 2004) better than other impulsivity-related tests. In the CPT 3, scores are computed based on the age and gender of the respondent. T-scores of 45-54 considered average. Higher T scores (especially > 60) indicate a more impulsive response style and less inhibitory control. Conversely, those who had fewer commission errors were better able to inhibit their responses to non-target stimuli.

Covariates

Cancer staging and treatment information was obtained from medical records. Women reported their medical comorbidities on the Charlson Comorbidity Index (De Groot et al., 2003), and we used the index that is adjusted specifically for breast cancer populations (Klabunde et al., 2007). Periodically throughout the day, women reported their fatigue on a 10-point Likert scale bounded by 0 'No Fatigue' to 9 'Fatigue as bad as you can imagine' by answering the following prompt: "Please rate your fatigue (weariness-tiredness) on a scale of 0-9 by selecting the one number that best describes your level of fatigue RIGHT NOW." We opted to include fatigue as a covariate because inflammatory challenges commonly fatigue participants, and we wanted to ensure that any changes in cognitive testing performance after the typhoid vaccine were over and above its fatiguing effect.

Analytic Method

Of primary interest was the effects of injection type on impulsivity-related outcomes from the CPT (commissions), Stroop (errors on color-discrepant trials), and N-back (accuracy on 2-back) at both visits. We used generalized estimating equations (GEE) with an independent working correlation matrix and robust standard error estimates (Ballinger, 2004; Zeger and Liang, 1986) to test whether injection type influenced each of these cognitive outcomes, in separate models. Below, covariate significance is reported from these models. In a second round of analyses, we used the same modeling strategy but substituted cytokine increases for injection type to model the cognitive outcomes of interest. Because the Stroop and N-back were completed prior to the fifth blood draw, only the first four timepoints were used to calculate IL-6 area under the curve with respect to increase (AUCi) for these models. However, five timepoints were used to calculate IL-6 AUCi when modeling CPT commissions. Due to cost, IL-1Ra was only assayed for the first and fifth blood draws. We calculated the IL-1Ra change score, but this score could only be used when modeling CPT commissions because the other two tests were completed prior to the fifth blood draw.

GEE models are appropriate for these repeated measures analyses because the outcome variables were not normally distributed, and therefore the residuals in hierarchical linear models were heteroskedastic. GEE models can handle such outcomes, as they model participants' average responses, thereby providing efficient, unbiased estimates of how much the average response changes for every one-unit increase in a predictor variable (Ballinger, 2004; Zeger and Liang, 1986). In GEE models, all available data are used, and therefore, a participant was not excluded if she only had one data point, for example.

All models controlled for age, cancer stage (Stage I versus II or III), cancer treatment (surgery only, surgery plus chemotherapy, surgery plus radiation, or surgery plus chemotherapy and radiation), current hormone treatment, current fatigue, education (high school or some college, college graduate, graduate or professional training), comorbidities, and visit (first versus second). The fatigue rating at five hours post-injection was used when modeling Stroop and N-back outcomes, and the fatigue rating at 6.5 hours post-injection was used when modeling CPT commission errors. In models with inflammatory change as the primary predictor, we additionally controlled for baseline levels of the inflammatory marker to guard against regression to the mean. To reduce the impact of large values due to the highly skewed nature of the observed IL-1Ra values, the IL-1Ra change score was calculated on the natural-log scale, and baseline IL-1Ra (as a covariate) was also log-transformed.

Based on the SCID-V, no woman had a current or past diagnosis of cyclothymia; three had a history of bipolar disorder. In sensitivity analyses, we excluded these three women, but results were unchanged. In terms of missing data, nine women (*n*=2 allocated to vaccine at Visit 1, *n*=7 allocated to placebo at Visit 1) did not return for Visit 2, primarily because they were not interested and/or canceled the visit. One woman did not have Stroop data at Visit 1, and 12 did not have complete data for the N-back (*n*=10 due to program error, *n*=2 women did not understand instructions). We had CPT data for all who returned for Visit 2, but we did not have Stroop data for one person at Visit 2 due to time constraints during the visit. We were missing

N-back data for nine women at Visit 2 (*n*=8 due to program error, *n*=1 woman did not understand instructions). However, all women had at least one cognitive testing outcome, so all were included in at least one model. One woman did not have a comorbidity score, and because it was included as a covariate in every model, this individual was excluded, yielding a sample size ranging from 162-171 for each model. Models were run in SAS version 9.4 (Cary, NC). We set alpha levels at .05 and did not make p-value adjustments made for multiple testing.

Results

Preliminary Analyses

Women were middle-aged (*M*=56.7, *SD*=8.4), relatively healthy except for their history of cancer (87% reported no comorbidities), mostly White (92%), and most had a college degree (71%) (Table 1). We previously reported that self-reported depressive symptoms, as measured by the Center for Epidemiological Studies Depression Scale, were mild on average at each visit (Visit 1: M=7.5, *SD*=6.8, Visit 2: *M*=7.7, *SD*=6.9) with a wide range (Visit 1: 0 – 37, Visit 2: 0 – 41) (Kiecolt-Glaser et al., 2022). At Visit 1, mean CPT commission T-scores were average (*M*=47.8(7.8)), with substantial range (36.0 – 70.0). Fifteen women had abnormally elevated Commission T scores (> 60). Women averaged 84% of trials correct on the 2-back (*SD*=14.0%; range: 28% - 100%). The average number of errors on the color-discrepant Stroop trials was 0.7 (*SD*=1.3; range 0.0 – 5.0), and 124 women (73%) did not commit any errors on the color-discrepant Stroop trials.

The saline visit was used to assess baseline cognitive functioning, and Table 2 depicts descriptive information by visit. Based on norms or test performance in non-cancer samples of a similar age, mean performance was not indicative of widespread cancer-related cognitive impairment (Conners, 2014; Gajewski et al., 2018). Also, when comparing performance at the placebo visit between those who received chemotherapy and those who did not, there was no evidence of chemotherapy-related effects (ps>.19; Table 3).

In terms of a manipulation check, we previously reported that the typhoid vaccine provoked increases in interleukin-6 (IL-6) and interleukin-1 receptor antagonist (IL-1RA), compared to placebo. The inflammatory response peaked between 6.5 – 8 hours post-vaccine (Kiecolt-Glaser et al., 2022). We previously reported that after receiving the vaccine, women reported more pain, aches, and headache, but did not have a higher oral temperature nor higher self-reported negative emotions (i.e., anger, anxiety, sadness, submissiveness) (Madison et al., 2023).

Primary Analyses

On the Stroop, women committed marginally fewer errors on the Stroop color-discrepant trials after the typhoid vaccine (*M*=0.36, *SE*=0.08), compared to placebo (*M*=0.54, *SE*=0.09, $\chi^2(1)=3.16$, *p*=.076). Injection type did not predict 2-back accuracy (*p*=.80) or CPT commissions (*p*=.47). See Figures 1-3 for raw values of the outcomes by injection type. Neither IL-1Ra nor IL-6 rises predicted any outcome of interest (*p*s> .16). In these same models, baseline inflammatory cytokines were also unrelated to the outcomes of interest (*p*s>.41), except that those with higher levels of IL-6 at baseline committed fewer commission errors (*B*= -0.12, *SE*=0.4, *z*= -3.47, *p*=.0005). Results from our primary models are depicted in Supplemental Tables 1 and 2.

In terms of covariates, at Visit 1 women had fewer errors on the color-discrepant trials of the Stroop ($\chi^2(1)=8.28$, *p*=.004), were less accurate on the 2-back ($\chi^2(1)=19.24$, *p*=.001), and had more commissions on the CPT ($\chi^2(1)=19.58$, *p*<.0001) than at Visit 2. Women with more comorbidities committed more errors on the Stroop color-discrepant trials ($\chi^2(1)=3.88$, *p*=.049), Also, women who had lower levels of education (high school or some college) ($\chi^2(2)=8.71$, *p*=.013) and older women ($\chi2(1)=7.45$, p=.006) were less accurate on the 2-back. Cancer treatment type predicted CPT commission errors ($\chi^2(3)=8.21$, *p*=.042) and 2-back accuracy ($\chi^2(3)=9.56$, *p*<.023) but not Stroop errors on color-discrepant trials (p=.055). Specifically, those who received surgery and chemotherapy had the highest mean for commissions and the

highest CPT commission errors as well as for 2-back accuracy. . No other covariates significantly predicted the outcomes of interest.

Discussion

Results from this randomized, placebo-controlled trial comparing an acute inflammatory stimulus to placebo did not support the notion that short-term cytokine rises cause response disinhibition. We used three distinct cognitive tasks that each included an element of response inhibition to compare women's performance after they received a typhoid vaccine versus after they received a saline placebo. In our study, inflammatory cytokine levels peaked when women completed these cognitive tests, and other work showed that the typhoid vaccine can induce neuroinflammation within three hours post-injection (Plank et al., 2022) – indicating that the timing of our cognitive measures was appropriate. Even so, women's cognitive performance generally did not differ after the vaccine versus placebo. That is, our results were null, but there was one marginally non-significant trend worth mentioning. The trend was not in the direction that would be expected if inflammation promoted response disinhibition: Women committed marginally *fewer* errors on the Stroop color-discrepant trials after receiving the typhoid vaccine, implying *greater* response inhibition, compared to placebo. Also, we did not find evidence that inflammatory cytokine rises themselves predicted response disinhibition. Therefore, taken together with prior null findings from smaller experiments among young and healthy participants (Brydon et al., 2008; Grigoleit et al., 2010; Handke et al., 2020; Van den Boogaard et al., 2010), acute inflammatory responses do not appear to provoke response disinhibition.

Even though our acute inflammatory challenge did not cause response disinhibition, there are multiple biological mechanisms via which inflammation could impact other aspects of impulsivity. Inflammatory cytokines affect the availability and function of neurotransmitters implicated in impulsivity-related disorders, like reduced availability of serotonin via the kynurenine pathway. Although this pathway's involvement in neurodegenerative disease is well-established (Tan et al., 2012), there is little research investigating its connection with impulsivity.

One study found that an eight-week high-intensity exercise program reduced IL-6 levels, as well as kynurenine pathway activity, which itself tracked with lower emotion-related impulsivity (Javelle et al., 2021). However, in another study, cancer patients who had the greatest declines in tryptophan during cytokine therapy had the highest depressive symptoms, especially anorexia, pessimistic thoughts, suicidal ideation, and concentration difficulties – but impulsivity was not measured or reported (Capuron et al., 2002b). Inflammation also affects dopamine synthesis and binding. Low tonic mesolimbic dopaminergic activity and blunted dopamine responses to reward are features of impulsivity-related disorders (Zisner and Beauchaine, 2016). In this respect, chronic inflammation may be a better model than an acute inflammatory stimulus because lower dopamine levels accompany chronic inflammation, whereas dopamine rises during acute inflammation (Felger et al., 2013). It is not ethical to promote chronically elevated levels of inflammation in healthy individuals; however, results from observational studies among cancer patients or HIV patients undergoing cytokine therapy are instructive. Neurovegetative and somatic symptoms peak within two weeks of treatment initiation, while depressive, anxiety and cognitive symptoms appear six to ten weeks later, but impulsivity is not commonly noted (Capuron et al., 2002a). In fact, there was no change in Stroop performance after cytokine treatment among hepatitis C patients (Amodio et al., 2005). Therefore, naturalistic experiments with persistent proinflammatory cytokine increases do not bear out the plausible inflammation-impulsivity relationship. Even so, there are plausible biological pathways leading from heightened inflammatory markers to the availability and function of neurotransmitters implicated in impulsivity-related disorders. Therefore, although we did not find a causal effect for response inhibition, it is possible that future studies could find an effect on other facets of impulsivity.

Strengths and Limitations

This study has several strengths, including (1) the experimental manipulation of inflammation with an inflammatory challenge (i.e., a typhoid vaccine), which is the only way to

test the behavioral effects of acute inflammation in humans; (2) the typhoid vaccine paradigm, which does not induce the range or severity of sickness symptoms observed with stronger inflammatory stimuli; (3) statistical adjustment for pre-task self-reported fatigue, which could otherwise confound the relationship between inflammation and cognitive performance; and (4) the randomized crossover design, which addressed the potential confounds of practice effects on cognitive testing, as well as inter-individual differences in education, baseline cognitive function, and basal levels of inflammation. Concerning the second point, the typhoid vaccine is a relatively mild inflammatory stimulus, so it is possible that a stronger inflammatory stimulus would have yielded different results. For example, the typhoid vaccine is not as strong as other pro-inflammatory stimuli (e.g., lipopolysaccharide; LPS), and we have previously reported that the typhoid vaccine does not affect social behavior or feelings of social connection (Madison et al., 2023), even though other labs have shown that LPS does (Eisenberger et al., 2010). Despite this fact, the typhoid vaccine may be more clinically relevant than LPS, at least when it comes to modeling the lower levels of inflammation that may fuel psychiatric disorder symptoms (Lindsay, 2022).

In terms of limitations, we did not specifically recruit people with impulsivity-related clinical disorders or people with high levels of trait impulsivity because our goal was to investigate response disinhibition as a behavioral construct. Therefore, results should not be generalized to that population, and further research is needed to explore inflammation as an etiological factor in these disorders. However, even in a non-clinical sample, less response inhibition on a cognitive test may align with higher scores on self-report measures of impulsivity (Jauregi et al., 2018). Also, our sample was female, had a history of breast cancer, and was primarily White and highly educated, all of which may impacted our results; future research should investigate inflammation's relationship with impulsivity in more diverse samples. Even so, it is not unprecedented to investigate inflammation's psychological or behavioral effect in cancer survivors; in fact, the initial causal relationship between inflammation and depression

was first observed among cancer patients undergoing interferon-α treatment (e.g., Meyers, 1999). As another limitation, there are many facets of impulsivity, and we only measured response inhibition. Future research should explore whether inflammation causally affects other aspects of impulsivity. Lastly, people use multiple cognitive abilities for even relatively simple tasks, so none of our cognitive tasks (nor any task) measures only response inhibition.

Clinical Implications

Although computerized cognitive tasks are somewhat removed from behavior in daily life, test performance has practical implications. Meta-analytic evidence suggests that correlations between lab tasks and self-report measures of impulsivity are low to very low, but both independently predict impulsive behavior in daily life like substance use and gambling – with moderate effect sizes (Sharma et al., 2014). Therefore, our null results may suggest that acute inflammatory cytokine increases do not underlie response disinhibition in daily life. It is possible that non-experimental reports of higher levels of basal inflammatory markers among those with impulsivity-related psychiatric disorders could result from impulsive behaviors (e.g., a low-quality diet) fueling heightened levels of basal inflammatory markers, rather than the reverse. On the other hand, it is possible that factors unique to our study design, such as the cancer sample that may have lasting effects from cancer treatment on their immune response, the limited battery of cognitive tests, and the typhoid vaccine as an acute inflammatory stimulus, overshadowed a true causal relationship. Further experiments manipulating inflammation and testing other aspects of impulsivity, particularly among clinical populations or those with genetic risk, would provide additional insight into whether acute inflammatory rises can contribute to impulsive behavior. Also, including self-report and behavioral measures of impulsivity in naturalistic experience in which a pro- or anti-inflammatory treatment is administered over a longer time course (e.g., proinflammatory cytokine antagonists for autoimmune disease) would provide greater insight into whether chronic low-grade inflammation might be an etiological factor in psychiatric disorders with impulsivity as a core feature. There is compelling evidence

that heightened inflammation is an etiological factor in some cases of clinical depression – especially those characterized by anhedonia (Haroon et al., 2018), but evidence that it underlies impulsivity-related disorders is not as convincing. Moreover, impulsivity or impulsive-like behaviors (such as aggression) are not commonly observed among humans or rodents injected with an inflammatory stimulus (Shattuck and Muehlenbein, 2016). Our null findings help to delineate the bounds of an acute inflammatory stimulus's effects in humans.

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Abstract

Background: Prior evidence has linked inflammation with impulsivity, but most of this evidence is cross-sectional. In this study, we provoked an acute inflammatory cytokine response to see whether it lowered prepotent response inhibition on three cognitive tasks.

Method: This study features secondary analyses from a randomized crossover trial in which 171 postmenopausal breast cancer survivors (Stage I-IIIA) each received a typhoid capsular polysaccharide vaccination and a saline placebo injection in a random sequence at two separate visits at least one month apart. Participants completed the Stroop Color-Discrepant Task, the 2-back, and the Conners Continuous Performance Test (CPT) on the computer between five and seven hours after the injections.

Results: Women committed marginally fewer errors on the Stroop color-discrepant trials after the typhoid vaccine (M=0.36, SE=0.08), compared to placebo (M=0.54, SE=0.09, p=.076). Injection type did not predict 2-back accuracy (p=.80) or CPT commission errors (p=.47).

Conclusion: We found no evidence that an acute inflammatory cytokine response provokes response disinhibition – an important facet of impulsivity. In fact, our only marginally non-significant result suggested that women were better able to inhibit their prepotent responses on the Stroop after receiving the typhoid vaccine, compared to placebo. Further experimental tests of the acute inflammatory cytokine response's effect on other aspects of impulsivity are warranted.

Limitations: The sample was female, primarily White, highly educated, and recruitment was not premised on impulsive traits or diagnosis with an impulsive-related disorder. Also, there are many facets of impulsivity, and this study only measured response inhibition.

Keywords: inflammation, impulsivity, response inhibition, CPT, Stroop, N-back

Table 1. Visit 1 Sample Demographic Information.

	N	Mean (SD) or N (%)	Range
Age	171	56.67 (8.4)	36-78
Race	171		
White		158 (92.4%)	
Black		10 (5.9%)	
Asian		1 (.6%)	
Multiracial		2 (1.2%)	
Education	171		
High school or some college		50(29.2%)	
College degree		62(36.3%)	
Grad/prof training		59(34.5%)	
Years since treatment	171	3.6 (2.3)	0.8-9.9
Chemotherapy treatment	171	116 (67.8%)	
Radiation treatment	171	104 (60.8%)	
Current hormone therapy	171	137 (80.1%)	
Cancer stage	171		
Stage I		80 (46.8%)	
Stage II or III		91 (53.2%)	
Any comorbidities	171	22 (12.9%)	

Table 2. Outcome descriptive information for the saline placebo and vaccine visits

Variable		N	Mean (SD)	Median (IQR)	Range
CPT Commissions	Saline	169	46.8 (7.7)	45 (41, 51)	33 to 68
	Vaccine	162	47.1 (8.2)	45 (41,51)	35 to 77
2-back Accuracy	Saline	156	0.85 (0.12)	0.88 (0.81, 0.92)	0.28 to 1
	Vaccine	154	0.85 (0.13)	0.89 (0.83, 0.92)	0.36 to 1
Stroop Errors	Saline	168	0.60 (1.15)	0 (0, 1)	0 to 5
	Vaccine	164	0.41 (1.01)	0 (0, 0)	0 to 5

SD = Standard deviation; IQR = Interquartile range = (25^{th}, 75^{th} percentiles)

Table 3. Outcome descriptive information based on chemotherapy exposure at the placebo visit only

Variable	Chemotherapy	N	Mean (SD)	P-value*
CPT Commissions	No	55	46.75 (8.14)	
	Yes	114	46.81 (7.45)	
	Diff (No - Yes)		-0.06 (7.68)	0.96
2-back Accuracy	No	54	0.84 (0.12)	
	Yes	102	0.85 (0.12)	
	Diff (No - Yes)		-0.01 (0.12)	0.60
Stroop Errors	No	54	0.44 (0.96)	
	Yes	114	0.68 (1.23)	

Diff (No - Yes)	-0.23 (1.15)	0.19

*Two-sample t-test with unequal variances
SD = Standard deviation

Figure 1. Figure 1. Raw Continuous Performance Test (CPT) Commission Errors by Injection Type. The typhoid vaccine did not impact CPT commission errors, compared to placebo (*p*s>.47).

Figure 2. Figure 2. Raw 2-Back Accuracy by Injection Type. Women's 2-back accuracy did not differ after they received the typhoid vaccine, compared to after they received the placebo injection (*p*=.80).

Figure 3. Raw Stroop Errors by Injection Type. Women committed marginally fewer errors on the color-discrepant Stroop trials after the typhoid vaccine, compared to placebo (*p*=.076) – suggesting greater response inhibition even during the peak inflammatory response.

Author Contribution Statement

Conceptualization: A.A.M; Methodology: J.K.K., A.A.M., R.A.; Software: R.A.; Validation: R.A.; Formal Analysis: R.A.; Investigation: M.R., J.KK.; Resources: J.S., M.L., B.R., R.W., N.O.W., S.D.S, A.M.N., R.E.R., M.A.C., W.B.M., J.K.K.; Data Curation: R.A.; Writing – Original Draft: A.A.M.; Writing – Review & Editing: A.A.M., R.A., M.R., J.S., M.L., B.R., R.W., N.O.W., S.D.S., A.M.N., R.E.R., M.A.C., W.B.M., J.K.K.; Visualization: R.A.; Supervision: A.A.M., M.R., J.K.K.; Project Administration: A.A.M., M.R., J.K.K.; Funding Acquisition: J.K.K.

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Conflicts of Interest: The authors report no potential conflicts of interest.

Highlights

- Whether inflammation drives impulsivity or impulsive-related disorders is unclear.
- We manipulated inflammation and measured response inhibition among 171 women.
- They had a typhoid vaccine and placebo injection in a random order at two visits.
- We found no evidence that acute inflammation provoked response disinhibition.
- Further research should see if inflammation affects other aspects of impulsivity.

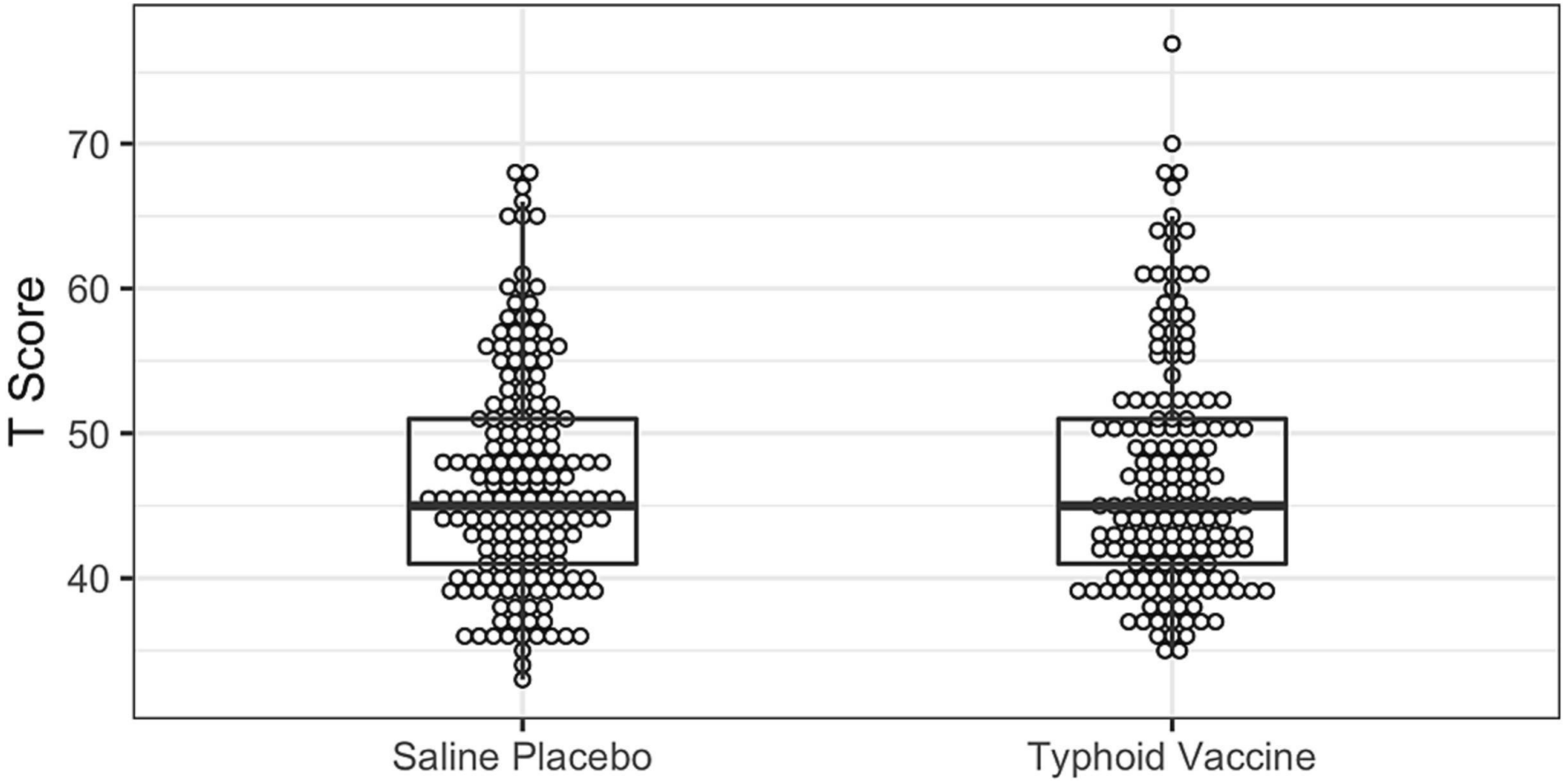

Figure 1

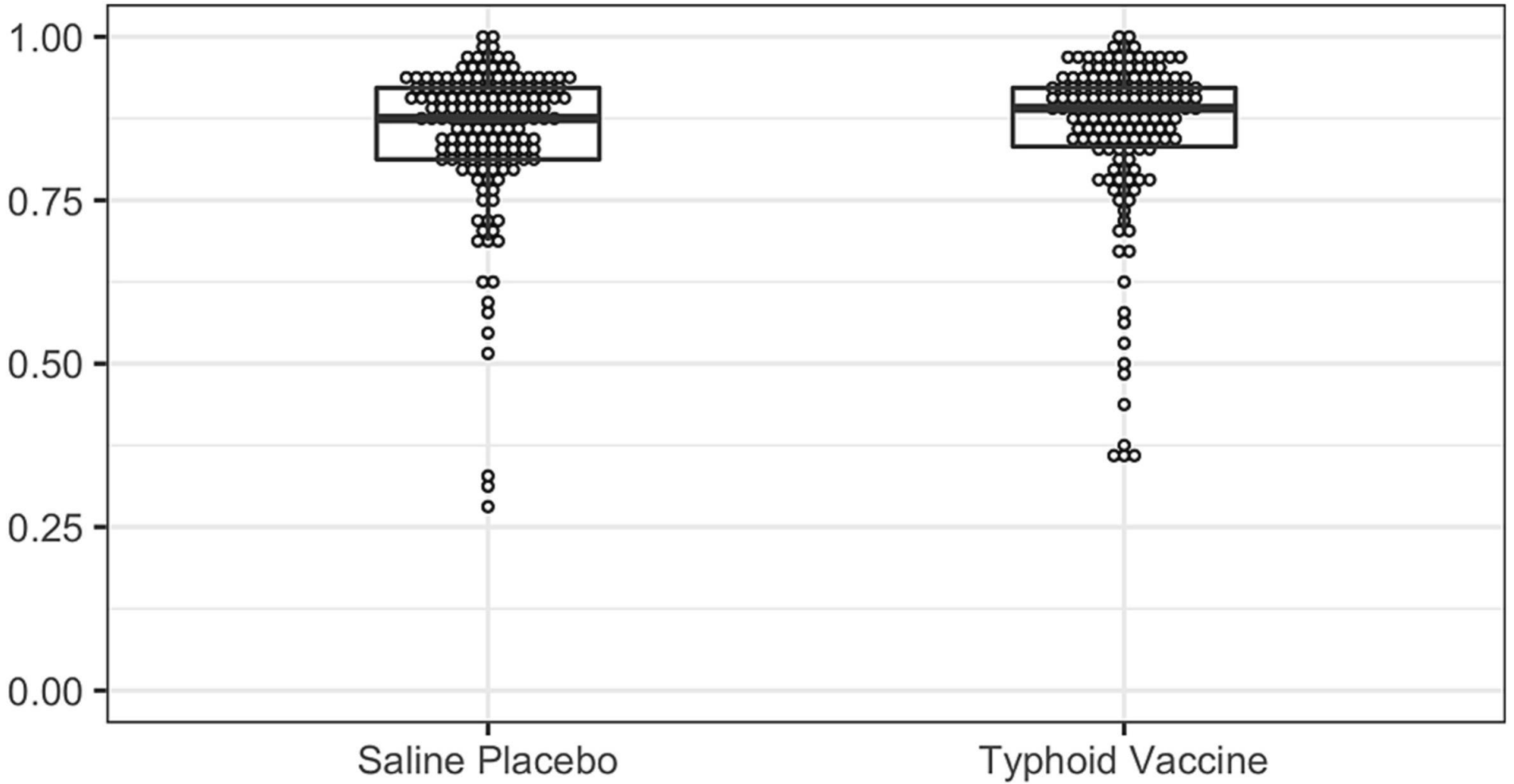

Figure 2

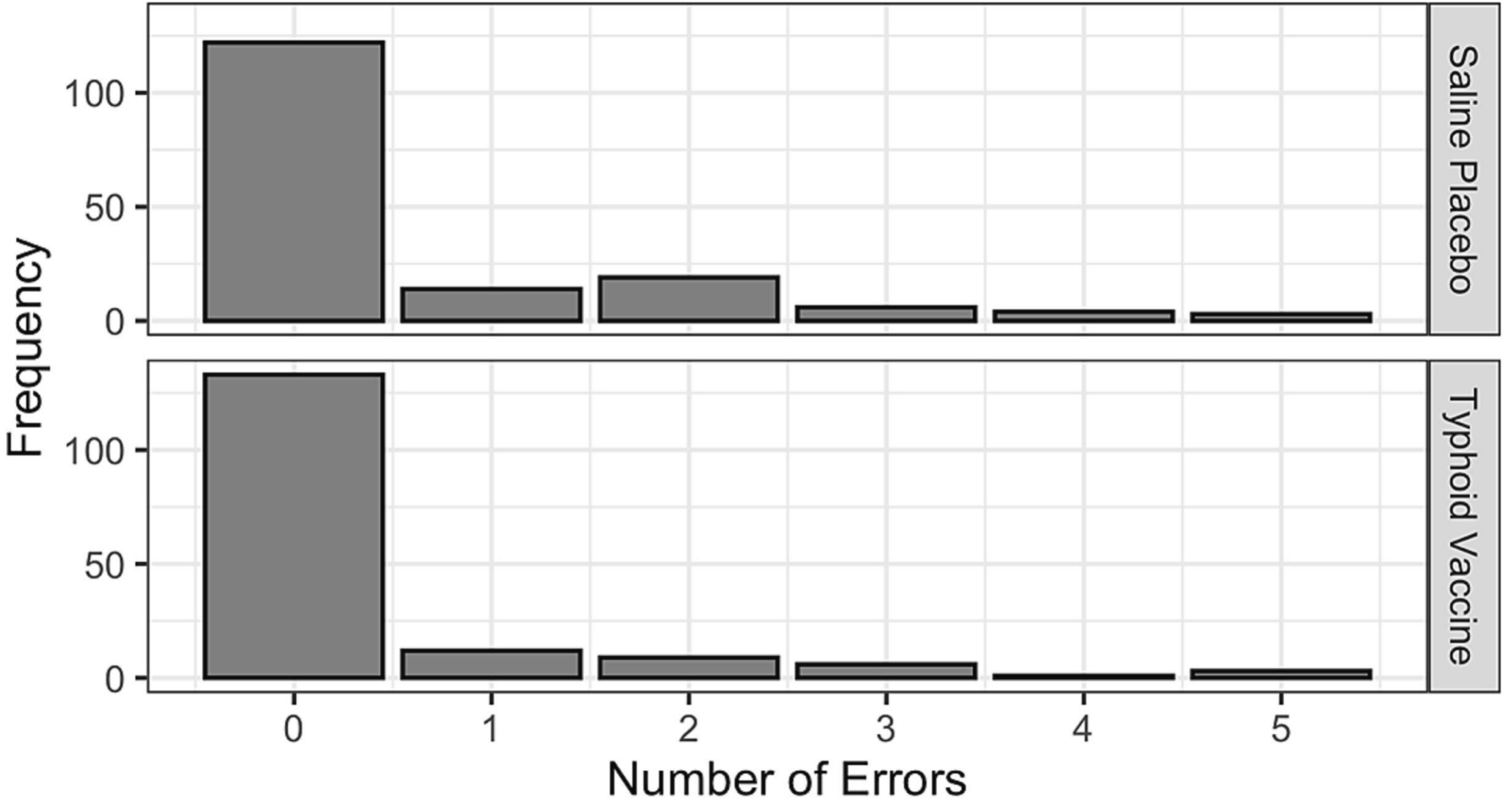
Saline Placebo
Typhoid Vaccine
Frequency
100
50
0
0
1
2
3
4
5
Number of Errors

Figure 3