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Pilot investigation into the sickness response to influenza vaccination in adults: effect of depression and anxiety

Jessica A. Harper, B.A.¹, Charles South, Ph.D.¹, Madhukar H. Trivedi, M.D.¹, and Marisa S. Toups, M.D.²

¹Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, 75390

²Psychiatry, Dell Medical School, The University of Texas at Austin, Austin, TX, 78712

Abstract

Objective—To determine whether depressed or anxious patients experience greater affective change than mentally healthy individuals following influenza vaccination.

Methods—Participants ($n = 112$) completed the Positive and Negative Affect Schedule (PANAS) before influenza vaccination and 1–2 days post-vaccination ($M = 32.3$ hours). Pre- and post-vaccination PANAS scores were compared using two-tailed, paired-samples t -tests. Change in positive affect between participants with depression or anxiety and those without was compared using two-way ANOVA. Follow up positive affect was further examined using multiple linear regression.

Results—Positive affect decreased following vaccination ($M = 2.18$, 95% CI [1.07, 3.29], $t(111) = 3.89$, $p < .001$) for all participants and was more pronounced for those with anxiety or depression ($F(1, 110) = 7.51$, $p = .009$). Similarly, predicted follow up affect score was higher for those without a mental health conditions ($\beta = 3.67$, 95% CI [1.18, 6.16], $t(103) = 2.92$, $p = .004$).

Conclusions—These data suggest that influenza vaccine has a greater effect on affect in patients with depression and anxiety than in mentally healthy individuals. This effect was focused on positive affect, suggesting that influenza vaccine induced inflammation may be best suited to examine alterations in positive affect and positive valence systems.

Corresponding author: Marisa S. Toups, M.D., Assistant Professor of Psychiatry, University of Texas at Austin Dell Medical School, Health Discovery Building, 1701 Trinity Street, Austin, TX 78712, Phone: 512-495-5672, marisa.toups@austin.utexas.edu.

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Keywords

major depressive disorder; influenza vaccine; positive affect; sickness behavior; inflammation

1. INTRODUCTION

When experiencing immune system activation, individuals exhibit a collection of normal “sickness behaviors” including lethargy, sleep disruption, anhedonia, loss of appetite, social isolation, and cognitive difficulties (1). Sickness is an adaptive response to infection, redirecting energy allocation to rest and allowing healing as well as preventing the spread of disease to others by limiting social contact (2).

In healthy individuals, sickness behavior has been studied using lipopolysaccharide (LPS) and vaccines as immune stimuli. LPS injection triggers increased inflammatory cytokines, which correlate with sickness behaviors and underlying changes in brain activity (3, 4). However, use of LPS evokes a strong immune response and pro-inflammatory cytokine elevations 2–10 times baseline levels even at low doses and causes significant changes in vital signs and physical discomfort in subjects receiving it (5). Vaccines produce milder and more prolonged immune responses with a favorable safety profile; several studies have successfully used typhoid vaccine to elicit and examine sickness behavior, showing increased inflammatory cytokines, sleep disturbances, neurocognitive and psychomotor alterations, and worsened mood (6–8).

Numerous authors have noted the similarity between sickness behaviors and Major Depressive Disorder (MDD) as well as a strong epidemiological association of inflammatory disorders with MDD and presence of increased inflammatory markers in MDD patients even in the absence of diagnosed inflammatory disorders (9–12). This has led to the development of animal models of depression using an immune stimulus to study the effect of an immune response on the brain. Though sickness behaviors typically cease shortly after the resolution of the immune stimulus, they may persist in cases where immune stimulation is more chronic. This may be the case in some instances of depression. Though there is no standard, accepted definition of “inflammatory depression”, previous research has found elevated C-reactive protein, a marker of systemic inflammation, in 46% of MDD patients (13). Further investigation of behavioral component of the immune response is essential to understanding why some individuals with inflammation and sickness behaviors progress to full psychiatric syndromes while others do not. Our current understanding of behavioral immune response and depression in humans comes largely from studying interferon (IFN) therapy, where it is suggested that those with a history of depression are more likely to become depressed upon receiving IFN- γ treatment for Hepatitis C Virus (14).

There is also evidence that the relationship between the immune system and brain is bidirectional – that is, that presence of depression affects the immune response. For example, psychological state impacts cytokine response to influenza vaccine. Baseline depressive symptoms have been shown to predict exaggerated and prolonged immune responses in response to vaccination (15, 16). This is in line with evidence that psychosocial variables such as chronic stress, often a precursor to depression, are associated with immune

function and, more specifically, dysregulation of normal immune and inflammatory processes. Individuals with chronic stress have poorer immune responses to vaccination as measured by antibody response (17). Conversely, individuals with greater social support in concert with lower stress have been shown to have higher antibody responses to Hepatitis B vaccination (18). Sickness literature using other stimuli, such as LPS, is limited, because of concerns about the safety of giving LPS to patients who are not fully healthy. Despite evidence of altered immune response to vaccination in individuals with depression and stress, there is no literature that demonstrates a greater behavioral sickness response to influenza vaccine in those with mental illness. However, subclinical depression scores in healthy participants have been shown to predict physical sickness symptoms following LPS administration (19), warranting further examination of behavioral immune response in the context of mental illness. The primary purpose of this project was to interrogate behavioral immune response in participants with depression or anxiety compared to healthy participants.

Individual perception of bodily changes associated with immune activation (as in vaccination) may influence changes in affect and behavior. The neural circuits underlying interoception, or the perception and awareness of internal bodily states and processes (20), are dysregulated in depression; it is hypothesized that this contributes to negative cognitive distortions about the self that are both a key component of and risk factor for depression (21). Metacognitive processing of interoceptive feedback is suggested to contribute to understanding, representation, and formation of affective states (22–24). Interoceptive sensitivity is also suggested to underlie emotional style; emotions and their intensity differ based on individual sensitivity to internal cues (25). High attendance to those internal cues can influence the interpretation of somatic information (26), and high perception, worry about, and attendance to physical symptoms has been associated with poorer prognosis and more complicated recovery in medical illness (27–29). Therefore, we considered interoceptive awareness as another factor that may contribute to inter-individual variation in behavioral immune response.

This project sought to demonstrate that depressed or anxious patients experience greater sickness behavior, as measured by change in affect, following immune stimulation using influenza vaccine. Influenza vaccine is recommended by the CDC and safely evokes a temporary immune response; side effects are typically mild and brief, resolving within 2–3 days (30–32). Proinflammatory cytokines peak at 1–2 days after injection (33), followed by an adaptive immune response in which T-cells specific to vaccine antigen develop over about two weeks (34). While the majority of people report no systemic symptoms following vaccination, subjective symptoms correspond with proinflammatory cytokine response (33). We hypothesized that there would be a decrease in positive affect and increase in negative affect following vaccination, that individuals with anxiety or depression would have more pronounced changes in affect, and that increased attendance to bodily sensations would moderate affective change.

2. METHODS

2.1. Participants

Participants were adult employees of [institution redacted for double-blind review]. 163 participants, ages 18–65 were recruited during the annual influenza vaccine drive. Participants were approached by research staff as they approached the vaccination area and asked if they were interested in participating and then completed a brief verbal screening and verbal consent process approved by the [institution redacted for double-blind review] Institutional Review Board. Eligibility for influenza vaccine required being free of most infectious disease (other than mild upper respiratory infection, for example). Participants were excluded if they reported being on immunosuppressive therapy (e.g. corticosteroids, chemotherapy, anti-rejection medications).

2.2. Self-Report Assessments

Participants provided demographic information, mental health information, physical health information, and self-reports electronically using REDCap electronic data capture tools hosted at [institution redacted for double-blind review] (35). Presence of mental and physical health diagnoses were determined using a checklist which asked participants to endorse having major depressive disorder, bipolar disorder, anxiety, eating disorder, substance use, other mental health conditions, hypertension, cardiovascular disease, history of cardiovascular event, diabetes, chronic kidney disease, history of cancer, autoimmune disease, thyroid disease, or a chronic painful condition.

2.2.1. Positive and Negative Affect Schedule (PANAS)—This 20-item standardized instrument assesses current affective states, with two 10 item subscales for positive and negative affect. Each subscale score represents increase affect in that category; participants with depression therefore typically have higher negative affect and lower positive affect scores than healthy participants. Participants rate words describing current positive and negative affective states on a scale from 1 (not at all) to 5 (extremely) (36). Participants completed the PANAS both before and after vaccination.

2.2.2. Body Awareness Questionnaire (BAQ)—This 18-item scale assesses attentiveness to normal body processes that are not typically associated with strong emotions or physical complaints (e.g. the ability to detect and predict small changes in body state). It uses a Likert scale of 1–7 ranging from “not true of me at all” to “very true of me” (37) for a score range of 0–126 where a higher score indicates more body awareness.

2.2.3. Body Vigilance Scale (BVS)—This 4-item scale assesses sensitivity to and focus on perceived bodily stimuli, including sensations related to physical symptoms of panic attacks, using an 11-point scale ranging from 0–10 for a total score range of 0–44 where a higher score reflects increased body vigilance (38).

All measures collected for this study have been reported herein.

2.3. Intervention

Participants received the trivalent Afluria influenza vaccine (Seqirus, Parkville, Australia) as part of the [institution redacted for double-blind review] employee influenza vaccine program during October 2016. Vaccines were administered via intramuscular injection into the deltoid within 60 minutes of self-report assessment completion. Each 0.5mL dose contained 45 mcg hemagglutinin (HA), with 15 mcg HA each of A/California/7/2009 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 influenza strains.

2.4. Statistical Analysis

Statistical analyses were conducted using SAS software (v.9.4, SAS Institute Inc., Cary, NC, USA). Self-reported physical conditions were collapsed into the dichotomous variable “history of chronic medical condition” for analysis. Pre- and post-vaccination scores of positive and negative affect on the PANAS were compared using two-tailed, paired-samples t-tests. Demographic and self-report comparisons of those with anxiety or depression and those with no mental health conditions were done using two-tailed, independent-samples t-tests (PANAS, BVS, BAQ, age, follow up time), chi-square tests (sex, history of chronic medical condition), and Fisher’s exact test (ethnicity). Based on paired t-test results, follow up positive affect score was further examined using multiple linear regression with baseline positive affect score, history of chronic medical condition, age, gender, presence of anxiety or depression, BVS, BAQ, and all two-way interactions of either BAQ or BVS and the other covariates included in the model. Two-way interactions that were not significant were removed from the model, and the final model included baseline positive affect score, history of chronic medical condition, age, gender, presence of anxiety or depression, BVS, BAQ, and the two-way interaction of BVS and presence of physical health condition. Finally, change in positive affect between participants with depression or anxiety and those without was compared using two-way ANOVA.

3. RESULTS

Of the 163 recruited participants, 113 completed the study. One participant was excluded from analysis due to mental illness that was neither anxiety nor depression. Demographic and clinical characteristics of the sample are shown in Table 1. Participants who did not complete the study had higher baseline positive affect than those who did ($t(160) = 2.20$, $p = .029$, $d = 0.39$, 95% CI [0.32, 5.89]) but did not differ in BVS, BAQ, or in mental or physical health. There was a relationship between race and follow up completion ($X^2(2, N = 162) = 10.02$, $p = .007$, $V = 0.25$); African American individuals were less likely to complete follow up (42%) than individuals identifying as white (74%) or multiple/other (76%). The remaining 112 participants completed follow up surveys at an average of 32.3 hours after the initial assessment ($SD = 17.0$, minimum: 21, maximum: 120), with the majority (93%) responding within 3 standard deviations of the mean response time. There was a statistically significant difference between baseline and follow up positive affect ($t(111) = 3.89$, $p < .001$, $d = 0.37$, 95% CI [1.07, 3.29]), but no difference between baseline and follow up negative affect ($t(111) = 0.03$, $p = .97$, $d = 0.004$, 95% CI [-0.51, 0.53]) (Figure 1).

Positive affect at both time-points was lower in those with depression/anxiety ($t(110) = 2.08$, $p = .040$, $d = 0.45$, 95% CI [0.17, 7.43]; $t(110) = 3.98$, $p < .001$, $d = 0.88$, 95% CI [3.66, 10.91]). There were no differences between groups in baseline negative affect, but those with anxiety or depression had higher negative affect at follow up ($t(36) = 2.56$, $p = .015$, $d = 0.63$, 95% CI [0.53, 4.58]). Additionally, those with anxiety or depression took longer to respond to follow up surveys than those without mental illness ($t(31) = 2.10$, $p = .045$, $d = 0.59$, 95% CI [0.26, 21.85]). There was no significant correlation, however, between follow up response time and change in affect. Those with anxiety or depression had higher BVS scores than those without ($t(110) = 2.49$, $p = .014$, $d = 0.53$, 95% CI [0.88, 7.75]) (Table 1). Change in positive affect was significantly larger in those with depression/anxiety ($F(1, 110) = 7.51$, $p = .009$, $\eta^2 = 0.42$) (Figure 2).

The multiple linear regression model to predict follow up positive affect was significant ($F(8, 103) = 30.60$, $p < .001$), with an adjusted R^2 of 0.681. The strongest predictor of follow up positive affect score was baseline positive affect score ($\beta = 0.76$, 95% CI [0.64, 0.88], $t(103) = 12.92$, $p < .001$). Presence of anxiety or depression impacted follow up positive affect, with a predicted score 3.67 points higher for those without a mental health condition ($\beta = 3.67$, 95% CI [1.18, 6.16], $t(103) = 2.92$, $p = .004$). Sex, BVS, and BAQ did not affect predicted positive affect score ($p = .41$; $p = .63$; $p = .20$). Additionally, neither measure of interoception (BVS, BAQ) interacted with baseline positive affect to predict follow up positive affect. BVS did interact with history of physical health conditions to predict follow up positive affect ($\beta = -0.45$, 95% CI [-0.73, -0.18], $t(103) = -3.25$, $p = .002$). As BVS increases, the discrepancy in positive affect scores between those with and without mental health conditions widens, showing that people with physical health conditions have the lower positive affect scores (Figure 3).

4. DISCUSSION

The major finding of this report is that, while there was overall drop in positive affect following influenza vaccination, the presence of depression or anxiety predicted a significantly larger response. This suggests that people with these conditions are more affectively sensitive to immune stimulation.

Additionally, those with anxiety or depression had lower baseline positive affect than those without mental health conditions. This is in line with previous work that indicates that positive valence is relevant to depression pathology and treatment (39). Sickness behavior includes anhedonia, a loss of positive affect, as a prominent symptom. This suggests that the observed affect change is part of the sickness response. It is also hypothesized that inflammatory cytokine effects on dopamine function contribute to motivational deficits via changes in reward neurocircuitry, further supporting the relevance of positive valence systems in behavioral changes in depression driven by inflammation (40). Interestingly, while there was no corresponding increase in negative affect or baseline group difference in negative affect, individuals with anxiety or depression had higher negative affect than healthy individuals at follow up. Changes in negative affect may be smaller (and therefore the current pilot was underpowered to detect them), and may be a unique feature of sickness behavior in depression that has not previously been identified. In either case, it appears that

influenza vaccine induced inflammation is best suited to examine alterations in positive affect and positive valence systems.

Body vigilance was not directly associated with inflammatory affective change despite being associated with anxiety and depression at baseline. However, medical comorbidity with high body vigilance did predict a greater drop in positive affect. Consistent with BVS utility in measuring panic and other negative mental health symptoms, individuals with depression and anxiety had higher BVS scores. However, neither the BVS nor BAQ alone moderated change in positive affect, indicating that, while awareness of and attendance to internal sensations may be intensified in mental illness, they do not increase changes in affect. This can be explained by the idea that only interoceptive signals corresponding to an actual medical illness contribute to sickness behavior. Vigilance without symptoms to attend to may not be sufficient. Interoceptive sensitivity may, therefore, only be important in determining depression in those with medical comorbidity.

The observed affective change in this study indicates that influenza vaccine is an effective stimulus for inducing inflammation and affective change in an experimental setting. Influenza vaccine can be given both to healthy and depressed study subjects safely, minimizing concerns about generalizability in IFN- γ models which enroll only subjects whose immune systems are affected by chronic infection. Similarly, the acute behavioral immune response observed in LPS may not be generalizable to long term inflammation found in chronic depression associated illnesses; peak cytokines in LPS studies (41) may be two or more orders of magnitude above those in, for example, cardiovascular disease (42) or diabetes (43). Therefore, researchers are in need of new models with which to study the effects of the immune response on behavior that address these limitations. The influenza vaccine produces an immune response that is less acute than that of LPS and more immediate than that of IFN, improving feasibility to cause peak increases in cytokines similar to that of chronic disease. We show here that it has selective behavioral effects in subjects with depression and anxiety, so that it has potential to parse normal from abnormal behavioral immunity.

4.1. Limitations

This study was conducted as a pilot and has the attendant limitations. Generalizability is limited because this was an observational study of a convenience sample. Participants were employed at an academic medical center, and may not be representative of the general population. Additionally, being employed by the organization where the study was completed may have affected participant willingness to disclose some physical or mental health conditions. The study relied solely on self-reports and did not verify diagnoses; actual rates of mental illness may be higher or lower than reported here. We did not collect comprehensive mental or physical health histories or medication lists, leaving possible confounders from any of these categories. Additionally, other underlying cognitive biases due to preconceptions about vaccines may have influenced the observed change in affect. If participants anticipated that the vaccine would affect them negatively, they may have been more attentive to and likely to report altered affect at follow up. However, this seems unlikely given that only positive affect showed significant change.

Baseline assessment and vaccination were not constrained to a consistent time of day. As such, results may be affected by circadian changes (44). Operationally, there was also significant variability in response time for the follow up affect assessment. However, we do not know when the best window is for assessing affective and behavioral changes after vaccination. This study was not designed to examine the time course of inflammatory response. Current literature suggests that physical side effects may last up to 72 hours; nearly all participants completed follow up within that window. However, full vaccine response takes up to two weeks (45, 46). We did not find any association between time of response and change in affect in our sample, but our range of response times may have been insufficient to detect the temporal course of the behavioral immune response. Therefore, additional studies evaluating affective state and immune response in individuals over longer periods of time are needed.

We have shown that influenza vaccine has a greater effect on affective state in patients with depression and anxiety than in mentally healthy individuals. This effect was focused on drop in positive affect, consistent with prior studies of sickness behavior. Physical health diagnoses interacted with interoceptive sensitivity for a more limited effect of inflammation on change in affect. Because the affect change due to influenza vaccine was pronounced for patients with anxiety and depression, further study of the immune and behavioral responses to influenza vaccine could shed light on the entire brain-immune axis in depression.

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Figure 1. Change in affect scores on the Positive and Negative Affect Schedule (PANAS) following Influenza vaccination. Data presented are shown as mean $\pm$ SEM. $n = 112$. $*p < .001$

Figure 2.

Positive affect scores on the Positive and Negative Affect Schedule (PANAS) before and after Influenza vaccination in individuals with preexisting mental illness ($n = 29$) and without ($n = 83$). Data presented are shown as mean $\pm$ SEM. $*p < .05$, $**p < .001$

Figure 3.

Body Vigilance Scale (BVS) scores and presence of physical health condition interact to predict mean positive affect score on the Positive and Negative Affect Schedule (PANAS) ($\beta = -0.45$, 95% CI $[-0.73, -0.18]$, $t(103) = -3.25$, $p = .002$).

Table 1

Participant characteristics

	Without Mental Health Conditions mean (SD) or n(%) (n = 83)	With Depression and/or Anxiety mean (SD) or n(%) (n = 29)	p-value
Age (years)	37.2(10.2)	40.6(12.8)	.20
Follow-up Time (hours)	29.4(9.8)	40.5(27.9)	.045
Sex			.70
Male	29(34.9)	9(31.0)	
Female	54(65.1)	20(69.0)	
Race			*
White	59(71.1)	27(93.1)	
African American	10(12.0)	0(0.0)	
Multiple/Other	14(16.9)	2(6.9)	
Ethnicity			.68
Hispanic	7(8.4)	1(3.4)	
Non-Hispanic	76(91.6)	28(96.6)	
Mental Illness			NA
Depression	NA	16(55.2)	
Anxiety	NA	23(79.3)	
Both Depression and Anxiety	NA	11(37.9)	
Eating Disorder	NA	1(3.4)	
Substance Use	NA	1(3.4)	
Physical Health Condition	18(21.7)	14(48.3)	.006
Diabetes	1(1.2)	2(6.9)	
Chronic Kidney Disease	1(1.2)	0(0.0)	
Cancer	2(2.4)	3(10.3)	
Autoimmune	4(4.8)	1(3.4)	
High Blood Pressure	7(8.4)	7(24.1)	
Thyroid Disease	6(7.2)	3(10.3)	
Chronic Pain	3(3.6)	2(6.9)	
PANAS			
Baseline Positive Affect	30.5(8.5)	26.7(8.4)	.040
Follow Up Positive Affect	29.2(8.7)	21.9(8.0)	<.001
Baseline Negative Affect	12.4(3.4)	13.0(3.3)	.45
Follow Up Negative Affect	11.9(3.1)	14.5(5.1)	.015
Body Vigilance Scale	16.25(7.91)	20.57(8.39)	.014
Body Awareness Questionnaire	81.1(16.8)	76.0(13.5)	.14

PANAS = Positive and Negative Affect Schedule. Categorical variables were compared with chi-square tests (Fisher's exact test for ethnicity variable); continuous variables were compared with two-tailed independent samples t-tests.

* Insufficient sample for statistical comparison