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William Yun April 1, 2022

Use of Anti-Inflammatory, Infliximab, may be an Alternative to Antidepressants for Treatment of Major Depressive Disorder Symptoms

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Abstract

Use of Anti-Inflammatory, Infliximab, may be an Alternative to Antidepressants for Treatment of Major Depressive Disorder Symptoms

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Importance: Psychomotor dysfunction is one of the nine diagnostic symptoms of major depressive disorder. Inflammation has demonstrated to potentially be related to Major Depressive Disorder and its symptoms. An anti-inflammatory could treat this inflammation and has the potential to treat other inflammatory-related depressive symptoms.

Objective: To determine the relationship between inflammatory cytokines and psychomotor speed, a diagnostic symptom of major depressive disorder, and to evaluate if Infliximab can treat the inflammation and consequently, the psychomotor speed.

Design/Setting: Clinical study.

Participants: 85 participants (ages 20-65) were recruited, 56 of those finished the entire study and they were considered depressed participants.

Main Outcome and Measures: Inflammatory cytokine marker concentrations and well-validated psychomotor speed tasks at screening and follow-up visits

Results: Infliximab did not significantly improve the psychomotor performance of depressive participants, but it did elicit significant improvements in inflammatory cytokine concentration.

Conclusion and Relevance: Anti-inflammatories such as Infliximab may be a potential anti-depressant treatment through inflammation, a potential correlate with depressive symptoms.

Acknowledgements

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Table of Contents

Introduction

Major depression is a debilitating disorder that impacts an estimated 340 million people worldwide (Chiriţă, Anca Livia, et al, 2015). Despite its widespread prevalence, the pathophysiology of major depressive disorder (MDD) remains poorly understood. Major depressive disorder is characterized by a change in mood and cognitive deficits such as psychomotor retardation or slowing, a phenomenon of moving or talking more slowly than is normal (Schrijvers, Didier, et al, 2008).

Unlike many symptoms of depression, understanding psychomotor dysfunction may be measured objectively and quantitatively using well validated cognitive and reaction-time tasks. One such measure is the Digit Symbol Substitution Task (DSST), a commonly used measure developed by David Wechsler (Jaeger, 2018). The DSST consists of a paper and pen task where participants are asked to draw symbols depending on given different numbers that each have corresponding symbols (Rosano, 2016). The participant is given 90 seconds and the symbols are checked afterwards to be given a score depending on correctness. This task can demonstrate improper cognitive function occurring in the participant as performance on the DSST requires intact motor speed, attention, visuo-perceptual functions, and dexterity (Jaeger, 2018).

For example, in one recent study, the DSST revealed changes in performance for patients with cognitive dysfunction due to major depressive disorder and schizophrenia (Jaeger, 2018). An additional way to assess cognitive function is through reaction time tasks. Another study demonstrated that subjects with MDD performed significantly worse on reaction time tasks compared to the healthy controls (Kertzman, 2010). Another research group surveyed 3,088 UK citizens and found slower reaction times in depressed patients compared to healthy controls in

simple reaction time tasks and choice reaction time tasks (Gale, 2016). Using the DSST and related cognitive, reaction time tasks, a deficit in psychomotor facilities can be assessed.

While the biological mechanisms that contribute to psychomotor slowing are not fully understood, growing work suggests a possible role for chronic, low-grade inflammation (Lucido et al, 2021). Inflammation can occur when the innate immune system attempts to protect an organism from an intruder. It is a defense mechanism that can be triggered from many things from pathogens to other organisms in your body.

Inflammation, while it is meant to protect our body, can sometimes end up harming us when inflammation is not required, and it still occurs resulting in acute or even chronic inflammation. A study conducted observing the relationship between inflammation and depression, found a positive relationship between inflammatory cytokines such as IL-6, IL-IB and cytokines, and depressive symptoms (Liu, 2017). Inflammation impedes the regular neurocircuitry and subcortical brain area function and connections through decreased synthesis and reuptake of dopamine, increased synaptic and extra synaptic glutamate, and activation of the kynurenine pathway (Lucido et al, 2021). More specifically, prior studies have consistently found that the administration of pro-inflammatory cytokines was associated with lower striatal dopamine level, as well as reduced ventral striatal responses to rewards (Felger and Treadway, 2017). Inflammatory cytokines can be evaluated through blood-testing for inflammatory markers, which will indicate inflammation occurring in the body. A different study found that Interleukin-6 (IL-6) and Monocyte Chemoattractant Protein-1 (MCP-1) cytokine markers were found to have an inverse relationship with psychomotor speed in humans with major depressive disorder (Goldsmith, 2016). In addition to associations between circulating cytokines and psychomotor slowing, anti-inflammatory treatments have shown to have anti-depressant effects,

including improved psychomotor function (Köhler, 2014). IL-6 is an inflammatory cytokine that responds to different infections to the host, playing an important role in innate immune response. One study found that IL-6 plays a key role in the acute phase response, and with a receptor, it can dictate the transition from acute to chronic inflammation (Gabay, 2006).

Infliximab is an anti-inflammatory drug that is used to treat several autoimmune diseases such as rheumatoid arthritis and Crohn's disease (Siddiqui et al, 2005). Infliximab has also been tested as a potential strategy for treating symptoms of depression, where initial clinical trials have suggested it might be particularly effective for symptoms such as anhedonia, psychomotor retardation, and depressed mood, compared to patients that received a placebo-treatment (Raison, 2013). Importantly, these effects were only present for individuals with high levels of inflammation at baseline, as indexed by C-Reactive Protein (CRP), a standard marker of inflammation. Seeking to extend this work, our lab completed a double-blind, placebo-controlled, randomized clinical trials with Infliximab ins a sample of depressed patients with high inflammation (CRP $\geq$ 3).

Using these data, the goal of the current project was to evaluate the effects of Infliximab on measures of psychomotor slowing. We expected at baseline, higher levels of inflammatory markers will be associated with poorer psychomotor speed and function. We further predicted that following Infliximab administration, psychomotor performance will improve for patients receiving Infliximab as compared to the placebo.

Methods

Study Sample: The study recruited eighty-five participants ages 20-65, 56 of those initial recruitments completed the 14-day visit. Of those 56 that completed the study, 37 of them had high CRP levels and put in a high CRP group (>3 mg/L). Only patients in the high CRP group were randomized to receive Infliximab or placebo (n = 37). Eligibility for participants required them to not take anti-inflammatories for the duration of the study, or any other anti-depressants. The study was registered on clinicaltrials.gov: NCT03006393.

Neuropsychological Testing and Informed Consent: Subjects met with a clinician who conducts clinical assessments to ensure participant eligibility. Subject eligibility included having a primary diagnosis of MDD, bipolar, or depressed type by the DSM-V and a CRP protein concentration greater than 3 mg/L. The subjects also needed to score 16 or high on the QIDS-SR-16 and they must be off all antidepressant therapy for at least 8 weeks prior to baseline visit for eligibility. First, the clinician conducted a chest x-ray on the subject, followed by an electrocardiogram. Then they conducted neurocognitive assessments to determine the previously mentioned eligibility. These assessments include the MMSE, C-SSR, SCID, and a substance abuse questionnaire. At this screening visit the participant is also informed about the study and informed consent is obtained. At the initial intake visit and following visits, blood was drawn from the participants to assess CRP protein concentration and inflammatory cytokine levels.

MRI and Follow-up Visits: Following the screening and determination of eligibility, participants completed an MRI scan. After the scan, infusion of Infliximab as well as the placebo are administered for those randomized into those groups. Then, participants completed several cognitive-based tasks that include the DSST and a reaction time task. After the initial screening and drug administration, participants were asked to return for the 24-hour, 3-day, 7-day, and 14-

day follow-up visits. Due to attrition, the 24-hour, 3-day and 7-day visits were optional for participants. 30 days after the first visit, the participants also received a 30-day follow-up call to complete the visit. At all these follow-ups, excluding the 30-day follow-up call, participants' blood will be tested to assess the inflammatory cytokines and they will be asked to complete the same cognitive-tasks again.

Cognitive Tasks: The three neurocognitive assessments that were conducted at the visit includes the digit symbol substitution task, the Cantab RTT task, and a simple finger-tapping task. The DSST that our lab group employs, follows the same procedure as used in Rosano et al. 2016 (Rosano, 2016). The digit symbol task is a written task with pen and paper. The participant is presented rows of numbers (0-9). Each number corresponds to a symbol that the participant is asked to draw under the respective number. The participant is given 60 seconds to write as many of the 100 symbols as they can, with correct and incorrect number of symbols being tracked. The key variables on this task include the number of right symbols because that should demonstrate proper psychomotor function. The reaction time task that was used, is known as the Cantab RTT and follows the same procedure used in Bento-Torres et al. 2017 (Bento-Torres, 2017). This task consists of measuring the participants reaction time on a computer-based task. The participant is presented with different color dots and as soon as a certain color is shown, the participant is asked to hit the button quickly. The key variables are how the reaction time of the depressed patients performed compared to their previous trials and to the healthy controls. The last neurocognitive assessment used was a simple finger-tapping task. Participants were asked to tap a button with their dominant hand for 60 seconds, followed by their non-dominant hand. This task assesses effort and cognitive function. These results will be compared to the inflammation, assessed by the inflammatory cytokine markers.

Data Analysis: The objective of this study is to compare the inflammatory cytokine marker levels of the participants to their performances on these well-validated psychomotor tasks. Due to their skewed distribution, cytokines values and neurocognitive task scores were log-transformed. The psychomotor speed of these subjects after being administered Infliximab, compared to the psychomotor speed prior to Infliximab administration will also be analyzed. Linear regressions and ANOVAs were conducted using SPSS software (IBM, Armonk, NY). Participant age and sex were included as covariates for all statistical analysis.

Results

To assess the association between IL-6 and simple movement times, we conducted linear regressions at baseline comparing the two variables. At baseline (Fig. 1), a linear regression model including log-transformed IL-6, age and sex was not significant ($R^2 = 0.085$ and a p-value of 0.108 and 0.873 respectively) and the coefficient for IL-6 was B = 0.063 (a p-value of 0.258). Next, we assessed the association between IL-6 and five-choice movement time on the RTT task. The participants' IL-6 inflammatory marker concentrations compared to the five-choice movement times (Fig. 2) reported a $R^2 = 0.133$ and a p-value of 0.848 for sex and 0.011 for age. The coefficient for IL-6 was B = 0.004 (p-value of 0.930). To show the relationship between the participants' TNF-alpha inflammatory marker concentrations compared to the five-choice reaction time during the Cantab RTT task, we ran another linear regression. This regression (Fig. 3) elicited a $R^2 = 0.085$ and neither sex nor age was significant (p-value of 0.874 and 0.888 respectively) The coefficient for TNF-alpha was B= 0.096 (p-value of 0.048). This was significant, suggesting that higher TNF-alpha values were associated with slower (longer) reaction times during the RTT task.

Next, we analyzed the participants' CRP concentrations compared to the dominant hand mean score recorded during the FTT task at the baseline visit. At baseline (Fig. 4), the regression performed, elicited a $R^2 = 0.013$ and a p-value of 0.412 and 0.891 for sex and age respectively. The coefficient of CRP produced a value of B = 0.009 (p-value = 0.715).

To test the effect of Infliximab on the participant's inflammation levels, we used a repeated ANOVA of the inflammatory CRP protein concentrations at baseline visit compared to the 14-day visit, based in which treatment group the participants were placed in. This statistical test (Fig. 5) compared the treatment groups and their change in CRP from baseline to the 14-day

visit, an found a group X time interaction of p = 0.877, such that CRP was significantly lower at 14 days for the Infliximab group relative to the placebo group (p-value =0.005). This was statistically significant, suggesting that the Infliximab treatment group had significant decreases in their CRP protein concentrations compared to those who only received a placebo, as expected.

We then compared the average dominant hand taps during the FTT task at baseline and at the 14-day visit, based on the treatment group. A repeated-measures ANOVA (Fig. 6) was ran comparing these averages. This produced a p-value of 0.108. Sex and age were also factored in, producing a p-value of 0.731 and 0.044 respectively. Next, we conducted a similar ANOVA (Fig. 7) where we analyzed the average non-dominant hand taps during the FTT task at baseline and at the 14-day visit. The group X time interaction produced a p-value of 0.551 based upon the treatment groups. As with the previous ANOVA, sex and age were included in analysis, producing a p-value of 0.326 and 0.847.

Lastly, we followed up on the results from Figures 6 and 7, conducting ANCOVAs with the co-variate as the baseline visit scores recorded. The first ANCOVA (Fig. 8) conducted was comparing the average dominant hand taps during the FTT task based on the treatment group the subject was in. This statistical test produced a p-value of 0.261 when comparing which treatment, the participants received. As with the prior statistical tests, sex and age were used as co-factors (p-value 0.627 and 0.025 respectively). The last ANCOVA (Fig. 9) conducted was compared the average non-dominant hand taps during the FTT task based on the treatment group. This was similar to the previous figure and a follow-up test to the original ANOVA. The non-dominant hand ANCOVA produced a p-value of 0.056 when looking at which treatment group the participants were from. As usual, sex and age were used as co-factors, eliciting p-values of 0.228 and 0.354 respectively.

Discussion

Psychomotor slowing is a diagnostic symptom of Major Depressive Disorder. This deficit can be objectively demonstrated through well-validated psychomotor tasks. Inflammation in the brain has shown to be associated with depressive symptoms. The objective of this study was to analyze the association between inflammation and psychomotor dysfunction, and to observe if Infliximab, a potent anti-inflammatory drug, could reverse the inflammation and consequently restore psychomotor speed. Many of the results elicited by the inflammatory cytokines and cognitive tasks were inconsistent with previous literature. In Figure 1 the participants' IL-6 inflammatory marker concentrations were compared to the simple movement times recorded during the Cantab RTT task. There was no significance in the association between the participants' IL-6 inflammatory marker concentrations and SMMT ($R^2 = 0.085$). Figure 2 was similar as it compared the participants' IL-6 inflammatory marker concentrations to the five-choice movement time. Again, the baseline correlation ($R^2 = 0.133$) between the two variables was not statistically significant. Our results were inconsistent with those from Goldsmith et al. 2016, which found that an increased IL-6 concentration was associated with decreased performance on simple and choice movement time tasks. One explanation for why these results might be different is due to our sample range compared to the sample of people used in Goldsmith et al. 2016. They used a sample of low-inflammatory to high inflammatory subjects while our study primarily used high inflammatory subjects, hence why we might not have seen the same association from IL-6 and performance on simple and choice movement time tasks.

Next, we looked at a linear regression with a different inflammatory cytokine. Figure 3 was a linear regression of participants' TNF inflammatory marker concentrations compared to the five-choice reaction time during the Cantab RTT task at the baseline. The correlation at

baseline between the two variables reported was statically significant. This was consistent with the results from Goldsmith et al. 2019, which found higher baseline TNF levels were associated with a greater increase in negative symptoms at the screening visit. Figure 4 was the last linear regression conducted, contrasting the participants' inflammatory CRP protein concentrations to the dominant hand mean score recorded during the FTT task at the screening visit. This analysis was not statistically significant, which was inconsistent with previous literature as a study found baseline CRP levels to be significantly correlated with initial performance in the FTT task (Chang et al. 2012). These results were surprising considering related literature. A potential larger sample comparison with a larger and more diverse range of low to high inflammatory subjects should be conducted between these variables to further understand this discrepancy.

The rest of the data analysis conducted were ANOVA statistical tests. These ANOVAs compared arms 1 and 2 of the study, which were the placebo treatment group, and the Infliximab treatment groups respectively, at baseline contrasted to the follow-up 14-day visit. Figure 5 was a repeated ANOVA of the participants' inflammatory CRP protein concentrations at the baseline visit. This statistical analysis produced a p-value of 0.005 when comparing the Infliximab treatment group to the placebo control group. This was statistically significant and provided strong support that Infliximab did lower the inflammatory CRP protein concentrations of depressed patients when compared to the placebo treatment. Figure 6 examined the average dominant hand taps during the FTT task at baseline and at the 14-day visit. While the Infliximab showed greater improvement in task performance from baseline to follow-up visit, it was not statically significant. This was different than what we expected because the psychomotor performance by the Infliximab treatment group was not significantly improved despite CRP protein concentrations having decreased. These results were similar to Figure 7, which looked at

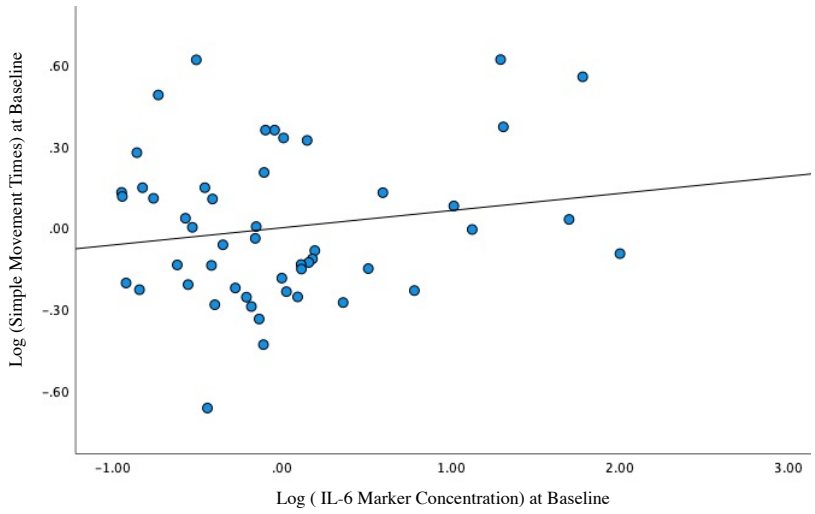
the average non-dominant hand taps during the FTT task at baseline compared to the follow-up visit. Again, arm 2 or the Infliximab treatment group showed improvement on the task from baseline to the follow-up visit, especially when compared to the placebo treatment group. This ANOVA was not statistically significant either (P-value = 0.551). Since neither of these ANOVAs produced significant results but demonstrated slight improvements in arm 2 compared to arm 1, another statistical test was conducted.

Following up from the results from Figures 6 and 7, ANCOVAs were conducted for the average dominant hand taps and non-dominant hand taps to account for the measured baseline performances on those tasks. Figure 8 was an ANCOVA of the average dominant hand taps during the FTT task at the 14-day visit, that accounts for the baseline average dominant hand taps as the co-variate. This statistical test produced a p-value of 0.261 when comparing which treatment, the participants received and using the baseline performances as a co-variate. Figure 9 was the same follow-up test as Figure 8 but instead analyzing the average non-dominant hand taps during the FTT task. This elicited a p-value of 0.056 when comparing the treatment groups and accounting for the baseline measures as a co-variate. This trend-level result suggests a potentially mild effect of Infliximab on psychomotor slowing and may warrant further investigation in future studies.

In summary, Infliximab did not significantly improve the psychomotor performance of depressed participants as we had expected. Infliximab did manage to significantly decrease inflammatory CRP protein concentrations following treatment, and consequently inflammation when compared to a placebo treatment group. While the decrease in the inflammatory cytokines did not elicit a significant improvement in psychomotor performance, there were slight improvements in psychomotor performance which may an area of interest in a future study.

Despite the results demonstrating that participants' TNF-alpha inflammatory marker concentrations compared to their five-choice reaction time was statistically significant at baseline, the administration of Infliximab did not significantly improve their reaction time. An alternative explanation as to why Infliximab lowered inflammatory cytokine levels but not significantly improve psychomotor performance, could be due to an aspect of time needed to reverse depressive symptoms. Given that inflammation can impede the regular neurocircuitry and subcortical brain area function, the reversal of that inflammation might not cause an immediate change or restoration of regular neurocircuitry function. In the Raison et al. 2012 procedure, they administered 3 infusions of Infliximab over a 12-week study, much longer than the 14-day study we conducted. In a follow-up study, researchers should record psychomotor improvement over a longer period of time after Infliximab administration, which should further clarify the treatment effects on Major Depressive Disorder's symptoms.

Tables and Figures



Coefficients	p-value	B
Log (IL6) Baseline	.258	.63
Sex	.873	-.018
Age	.108	.007

a. Dependent Variable: Log (SMMT) @ screening

Figure 1: Log of IL-6 Marker Concentration compared to Log of Simple Movement Time on RTT task at Baseline Visit.

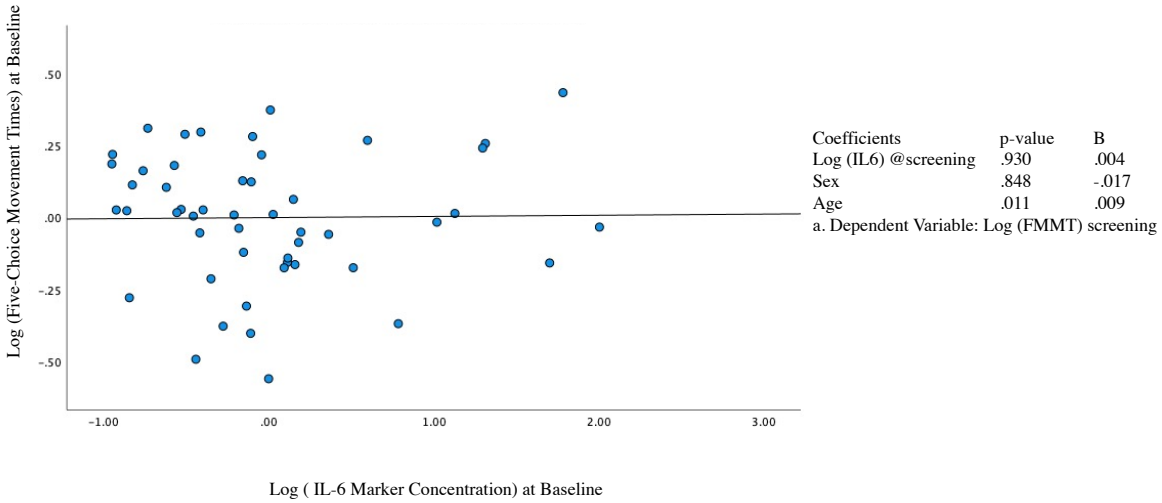
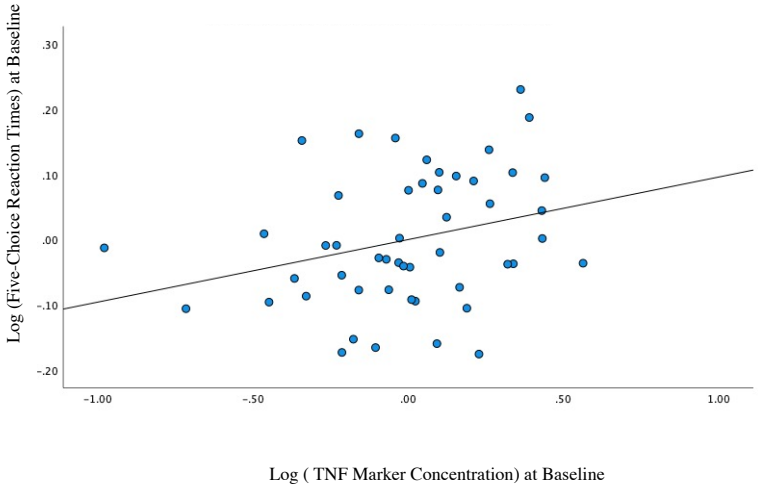


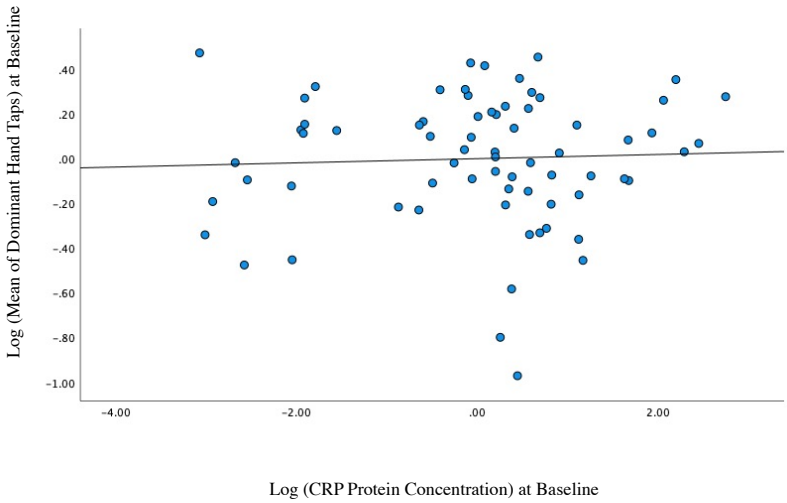
Figure 2: Log of IL-6 Marker Concentration compared to Log of Five-Choice Movement Time on RTT task at Baseline Visit.



Coefficients	p-value	B
Log (TNF) @screening	.048	.096
Sex	.874	-.006
Age	.888	.000

a. Dependent Variable: Log (FMRT) screening

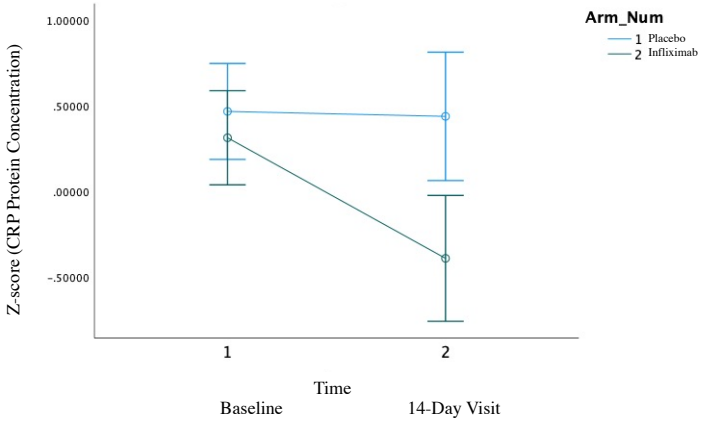
Figure 3: Log of TNF Marker Concentration compared to Log of Five-Choice Reaction Time on RTT task at Baseline Visit.



Coefficients	p-value	B
Log (CRP) @screening	.715	.009
Sex	.412	-.087
Age	.891	.000

a. Dependent Variable: Log (Dominant hand taps) screening

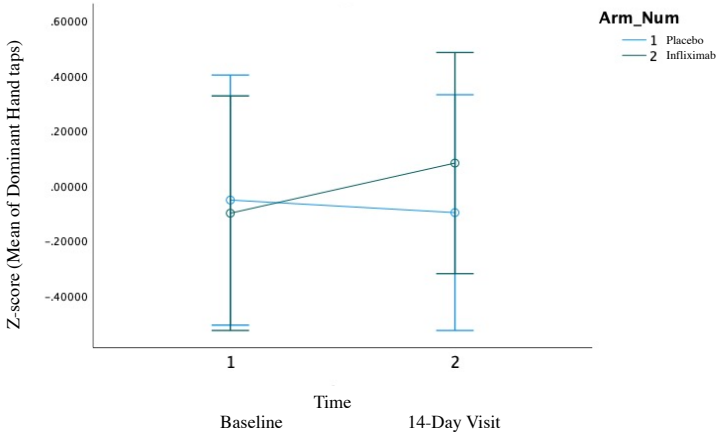
Figure 4: Log of CRP Protein concentration compared to Dominant Hand During FTT Task at Baseline Visit.



Multivariate Tests	p-value
Time	.877
Time * Sex	.079
Time * Age	.201
Time * Arm_Number	.005

a. Log (CRP Protein Concentration) ANOVA

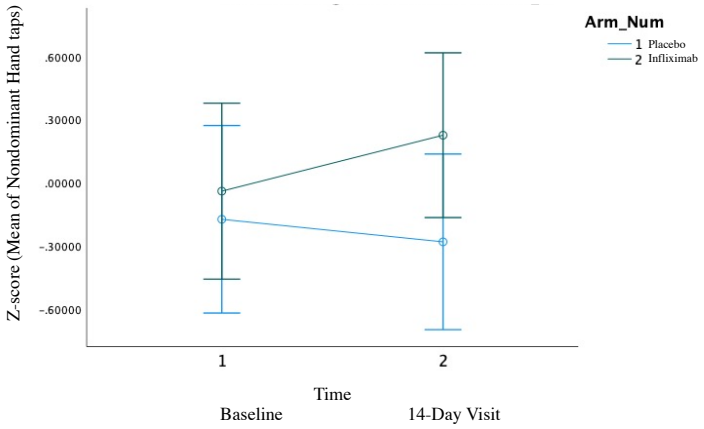
Figure 5: ANOVA of the Log of CRP Protein Concentration Recorded at the Baseline Visit Compared to the Concentration Recorded at the 14-day Visit Split into Treatment Groups.



Multivariate Tests	p-value
Time	.108
Time * Sex	.731
Time * Age	.044
Time * Arm_Number	.271

a. Log (Dominant hand taps – FTT task) ANOVA

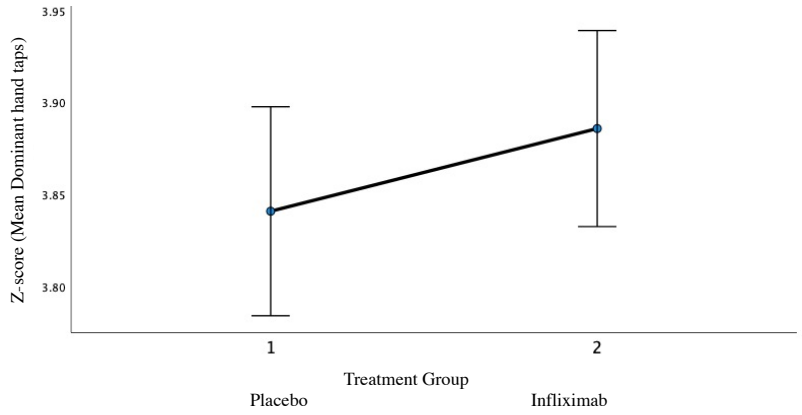
Figure 6: ANOVA of the Log of Average Taps from Dominant Hand During FTT Task at Baseline Compared to the 14-day Follow-up Visit Split into Treatment Groups.



Multivariate Tests	p-value
Time	.551
Time * Sex	.326
Time * Age	.847
Time * Arm_Number	.126

a. Log (Nondominant hand taps – FTT task)
ANOVA

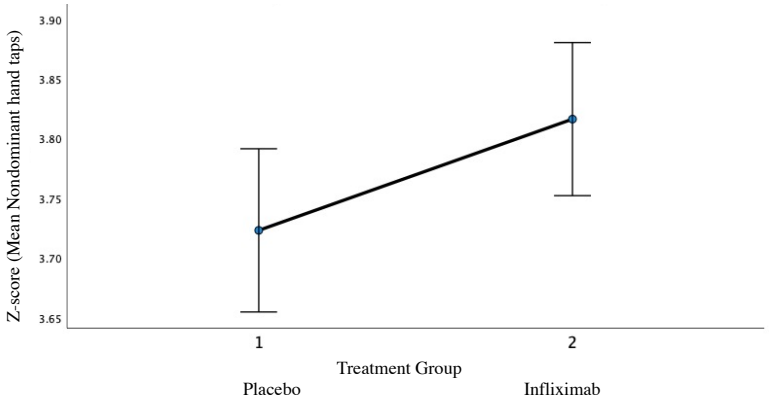
Figure 7: ANOVA of the Log of Average Taps from Nondominant Hand During FTT Task at Baseline Compared to the 14-day Follow-up Visit Split into Treatment Groups.



Test of Between-Subjects Effect	p-value
Sex	.627
Age	.025
Arm Number	.261

a. Co-Variate: Dominant hand taps (FTT task)

Figure 8: ANCOVA (Co-variate: Log of FTT Dominant hand mean at baseline) of the Log of Average Taps from Dominant Hand During FTT Task at 14-day Visit Split into Treatment Groups.



Test of Between-Subjects Effect	p-value
Sex	.228
Age	.354
Arm Number	.056

a. Co-Variate: Nondominant hand taps (FTT task)

Figure 9: ANCOVA (Co-variate: Log of FTT Nondominant hand mean at baseline) of the Log of Average Taps from Nondominant Hand During FTT Task at 14-day Visit Split into Treatment Groups.

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