Impact of Inflammation on Reward Circuits, Motivational Deficits and Negative Symptoms in Schizophrenia

NCT03818516

Date:01/31/2022

IRB00094972

1. Impact of Inflammation on Reward Circuits, Motivational Deficits and Negative Symptoms in Schizophrenia

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The amended protocol includes:

Replacing the M.I.N.I. 6.0 with the updated M.I.N.I. 7.0 version for DSM-V.
Removing optional cortisol collection.

Version Date: 1-31-2022

2. Precis/Abstract

Negative symptoms of schizophrenia, including motivational deficits, are some of the most debilitating aspects of the disorder, being both difficult to treat and representing one of the most significant barriers to functional recovery. Regarding potential mechanisms of these deficits, individuals with schizophrenia reliably show decreased activation of the ventral striatum in reward-based neuroimaging tasks. One pathophysiologic pathway that may contribute to these alterations in reward circuitry in schizophrenia is inflammation. Previous work has demonstrated that inflammatory stimuli decrease neural activity in the ventral striatum and decrease connectivity in reward-relevant neural circuitry. Based on the previous findings that patients with schizophrenia reliably exhibit elevated concentrations of inflammatory markers and that inflammatory cytokines are related to negative symptoms including decreased motivation, I hypothesize that increased inflammation in schizophrenia contributes to negative symptoms by disrupting neural activity in reward circuits leading to motivational deficits. To test this hypothesis, I propose the following Specific Aims: (1) To determine the impact of inflammation on reward circuitry in patients with schizophrenia using both task-based and resting state functional magnetic resonance imaging. (2) To determine the impact of inflammation on objective and clinical measures of motivation and negative symptoms. (3) To explore whether the impact of inflammation on reward circuitry mediates the effects of inflammation on objective measures of reward processing and negative symptoms. Taken together, this work will inform future studies of novel therapeutic strategies to treat negative symptoms in patients with schizophrenia.

3. Introduction and Background

Schizophrenia is a severe mental illness that affects 1% of the population, but accounts for over $60 billion in costs to the national healthcare system.[1,2] Up to 30% of individuals with schizophrenia are considered “treatment-resistant,” adding to even greater morbidity and socioeconomic burden.[3,4] Individuals with schizophrenia suffer from a constellation of symptoms including delusions, hallucinations, trouble expressing their thoughts and a lack of motivation. The disorder is a major public health concern, and many people with schizophrenia suffer chronic debilitating symptoms,[5,6] have high rates of unemployment and homelessness,[7,8] and have a significantly reduced life expectancy (~20 years less than the general population).[9]

The behavioral symptoms of schizophrenia are heterogeneous in nature and have traditionally been categorized as positive and negative symptoms. Positive symptoms reflect the constellation of symptoms that are not usually present and include hallucinations, delusions, and disorganized thinking and speech. Negative symptoms are those symptoms that characterize absent or diminished behavior and include decreased motivation, social withdrawal, as well as poverty of speech, decreased emotional reactivity and psychomotor retardation. Importantly, negative symptoms have consistently been identified as those features of the disorder that are most predictive of functional impairment and poor outcome.[10-13] Moreover, antipsychotic medications are effective in treating positive symptoms, but are less effective in treating negative symptoms.[14-16] Thus, our current armamentarium of medications to treat schizophrenia fails to address some of the most debilitating symptoms of the illness that have been most strongly related to measures of daily function and recovery.

Impaired reward processing and motivational deficits are core components of negative symptoms in

schizophrenia that are most relevant for poor quality of life and impaired functional outcomes.[17-21] For example, patients with schizophrenia may not expend the effort to seek out potentially or previously rewarding activities such as work and social interaction. These deficits can be further delineated into several domains, including decreased reward anticipation, impaired reinforcement learning, reward prediction errors, and reduced effort cost computation,[22] all of which involve subcortical brain regions including the basal ganglia and more specifically the ventral striatum. Reduced neural responses in the ventral striatum have consistently been implicated in studies of patients with schizophrenia, including neuroimaging studies of reward anticipation,[23-26] reinforcement learning,[27,28] and positive prediction errors.[29-32] Importantly, decreased activation in the ventral striatum during motivation tasks has been associated with severity of negative symptoms in a number of studies.[24,26,29,33,34] Patients with schizophrenia also show decreased reward processing as measured by objective assessments of effort expenditure for reward and reinforcement learning,[35-46] such as the Effort Expenditure for Reward Task (EEfRT), which is known to involve ventral striatal circuits.[23,24,26,47-49] Of note, decreased activity in the ventral striatum on a monetary reward based neuroimaging task has been directly related to both objective and clinical assessments of decreased motivation in patients with schizophrenia.[46] In several studies, performance on these objective motivational tasks has also been consistently related to severity of negative symptoms,[35,36,40,41,44-46,50] suggesting that deficits in reward processing are a core component of negative symptoms in schizophrenia.

One pathophysiologic pathway that may contribute to negative symptoms and decreased motivation in schizophrenia is inflammation. Increased inflammation has been reliably linked to deficits in reward processing and decreased motivation via effects of inflammatory cytokines on regions of the basal ganglia, including the ventral striatum.[51] Inflammation has been shown to alter neural activity in ventral striatal regions as assessed by a variety of neuroimaging strategies following administration of several inflammatory stimuli including interferon (IFN)-alpha, typhoid vaccination and endotoxin.[51-54] In addition, increased inflammation has been shown to mediate deficits in objective assessments of motivation as reflected by effort expenditure in laboratory animals including non-human primates.[55-58] Recent work in the Miller lab has demonstrated that one potential mechanism by which inflammation may lead to alterations in reward processing and motivation is through effects on connectivity within brain reward circuitry. Felger and colleagues showed that using functional magnetic resonance imaging (fMRI), increased inflammation (as measured by peripheral blood C-reactive protein; CRP) was associated with decreased functional connectivity between the ventral striatum and ventromedial prefrontal cortex (vmPFC) in patients with major depressive disorder.[59] Decreased connectivity between these regions was, in turn, correlated with decreased motivation as assessed by the Snaith-Hamilton Pleasure Scale (SHAPS).[60] Decreased connectivity in this study was also linked with other inflammatory markers including interleukin (IL)-6 and IL-1 receptor antagonist (IL-1RA). Taken together, these findings suggest that increased inflammation in schizophrenia may disrupt neural activity in reward circuits, leading to motivational deficits and negative symptoms in the disorder. This hypothesis will be tested in Specific Aims 1-3.

Of relevance to the potential role of inflammation in negative symptoms in schizophrenia, in a meta-analytic study, it was recently reported that patients with schizophrenia reproducibly exhibit increased markers of inflammation in both acute and chronic phases of the illness.[61] Preliminary data collected from the patient sample this proposed research will recruit from demonstrates a relationship between inflammatory cytokines and negative symptoms. In a study of 10 patients from Grady Memorial Hospital, there was a positive relationship between IL-1beta and the global rating of avolition on the Scale for the Assessment of Negative Symptoms (SANS), which most closely resembles assessments of reward processing deficits ($r = 0.751$, $p = 0.012$).[35] IL-1beta was also correlated with the avolition-impersistence at work or school ($r = 0.644$, $p = 0.045$) and the attention-social inattentiveness ($r = 0.665$, $p = 0.036$) items of the SANS, in addition to the passive/apathetic social withdrawal ($r = 0.657$, $p = 0.039$) and the disturbance of volition ($r = 0.686$, $p = 0.029$) items on the Positive and Negative Symptom Scale (PANSS). Furthermore, the anti-inflammatory cytokine IL-10 was negatively correlated with the emotional withdrawal ($r = -0.638$, $p = 0.047$) and the passive/apathetic social withdrawal ($r = -0.655$, $p = 0.04$) items of the PANSS as well as the negative symptom total score of the PANSS ($r = -0.792$, $p = 0.006$).[113] Taken together, these preliminary data from patients with schizophrenia indicate that inflammatory cytokines show the predicted relationship with negative symptoms such as avolition. Of note, patients reflected a range of negative symptom severity with the total score on the SANS ranging from 12 to 86 ($M=46.2$, $sd=27.1$).

These findings are consistent with new data that inflammation and the innate immune response may play a fundamental role in the development and progression of schizophrenia.[62] There is also a growing literature showing that increased inflammatory cytokines may be linked to negative symptoms in patients with schizophrenia.[63-69] It should also be noted that inflammation has long been thought to play a role in the

pathogenesis of schizophrenia, as early epidemiological studies demonstrated that exposure to infections in utero as well as in early childhood increased the risk for schizophrenia later in adulthood.[70-72] Autoimmune conditions have also been shown to be increased in children who later develop schizophrenia,[73] adults with the disorder,[74] as well as first-degree relative of patients with schizophrenia.[75] Moreover, the major histocompatibility complex (MHC) region on chromosome 6, in addition to other immune-related genes, have consistently been shown to be associated with schizophrenia in genome wide association studies.[76-79] Neuroimaging (positron emission tomography (PET)) studies in patients with schizophrenia have also demonstrated increased binding of a ligand to translocator protein (TSPO) in individuals considered to: be ultra-high risk for psychosis,[80] have recent onset of the disorder,[81] be in acute exacerbations of the illness,[82] and exhibit persistent symptoms.[83] TSPO is expressed by activated microglia cells, the immune cells in the brain that respond to injury or inflammation by releasing a variety of inflammatory cytokines. Finally, treatment studies using anti-inflammatory agents have been tested in schizophrenia with variable success.[84]

The proposed research represents the first study to address the potential role of the immune system and inflammation in negative symptoms of schizophrenia, specifically by testing the hypothesis that inflammation affects fundamental reward circuitry in the ventral striatum leading to deficits in motivation and reward processing. Negative symptoms are highly resistant to treatment and have a major impact on functional outcomes. Therefore, understanding novel mechanisms by which negative symptoms occur will allow the development of innovative therapeutic strategies to improve quality of life and treatment outcomes in patients with this disorder. Moreover, given that inflammation can be measured in peripheral blood, the opportunity exists to target immune-based therapies to specific subpopulations of schizophrenia patients, thereby allowing a more personalized approach, supporting precision medicine. Indeed, the mixed results of previous studies that have used anti-inflammatory therapies in schizophrenia may be a result of not targeting the appropriate patients or the best outcome measures. There are currently no effective treatments for negative symptoms or motivational deficits in schizophrenia, which as noted above represents a significant obstacle to achieving functional recovery, and as such, the discovery of novel therapies are of paramount importance.[85,86]

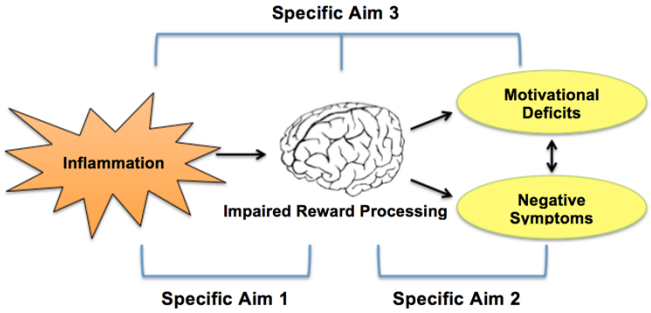

Figure 1: Working Model of Research Proposal

Working Model

Based on these data, the scientific premise and driving hypothesis of the proposed research is that inflammation decreases activation of ventral striatal reward circuits, leading to decreased objective measures of motivation and ultimately negative symptoms in schizophrenia (see Figure 1 for working model).

As an amendment to the original protocol, this research also includes computational analysis of language. Recent developments in the automated analyses of language have shown promising findings in identifying computational measures of language to characterize thought disorder in schizophrenia. However, most of the research to date has focused on measure of incoherence and little attention has been paid to other central features of language in schizophrenia such as poverty of content. This additional research protocol aims to measure “semantic density” through the use of machine learning and Natural Language Processing. It also aims to detect latent semantic content reflective of the psychopathology of thought disorder in schizophrenia. The resulting linguistic findings can be potentially analyzed in conjunction with other biomarkers and future findings of the original study.

4. Objectives

Objective 1. Determine the impact of inflammation on reward processing in patients with schizophrenia using functional magnetic resonance imaging (fMRI).

Hypothesis 1*:* Increased peripheral blood markers of inflammation will be associated with decreased activation of reward-related ventral striatal regions and decreased connectivity between the ventral striatum and medial prefrontal cortex using whole brain analysis.

Dependent variables:

Immune Markers: Peripheral inflammatory markers: plasma CRP, IFN-alpha, IL-6, sIL-6R, IL-10, TNF-alpha, sTNFR 1 and 2, IL-1 beta, IL-1ra, sIL-2R, and MCP-1

Neuroimaging Tasks: Degree of functional connectivity between the striatum and other brain regions on resting state scan (Z scores); performance on fMRI tasks (see below)

Objective 2. Determine the impact of inflammation on objective and clinical measures of motivation and negative symptoms in patients with schizophrenia.

Hypothesis 2: Increased inflammation will be associated with increased impairment in objective and clinical measures of motivation and negative symptoms.

Dependent variables:

Immune Markers: Peripheral inflammatory markers: plasma CRP, IFN-alpha, IL-6, sIL-6R, IL-10, TNF-alpha, sTNFR 1 and 2, IL-1 beta, IL-1ra, sIL-2R, and MCP-1

Behavior: Scores on the: Positive and Negative Symptom Scale (PANSS); Brief Negative Symptom Scale (BNSS); Snaith Hamilton Pleasure Scale (SHAPS); Inventory of Depressive Symptomatology (IDS-SR), Childhood Trauma Questionnaire (CTQ); Motivation and Pleasure Scale (MAPS-SR)

Neuropsychology: Performance on the Effort Expenditure for Rewards Task (EEfRT), and neurocognitive tasks (see below)

Objective 3. Explore the interrelationship among inflammation, altered reward processing as measured by fMRI, and objective and clinical measures of motivation and negative symptoms in patients with schizophrenia.

Hypothesis 3: Decreased neural activation in reward-related regions will mediate the relationship between inflammatory markers, impaired motivation and negative symptoms.

Immune Markers: Peripheral inflammatory markers: plasma CRP, IFN-alpha, IL-6, sIL-6R, IL-10, TNF-alpha, sTNFR 1 and 2, IL-1 beta, IL-1ra, sIL-2R, and MCP-1

Neuroimaging Tasks: resting state scan; fMRI tasks

Behavior: Positive and Negative Symptom Scale (PANSS); Brief Negative Symptom Scale (BNSS); Snaith Hamilton Pleasure Scale (SHAPS); Inventory of Depressive Symptomatology (IDS-SR); Calgary Depression Scale for Schizophrenia (CDSS), Childhood Trauma Questionnaire (CTQ); Motivation and Pleasure Scale (MAPS-SR)

Neuropsychology: Effort Expenditure for Rewards Task (EEfRT), and neurocognitive tasks (see below)

5. Study Design and Methods

Figure 2: Overview of Proposed Study Visits

Screening Visit Between 9:00 am – 12:00pm	Subject arrives at Grady BHC for consenting and MINI diagnostic interview. They will also complete a physical and psychiatric exam, blood sampling for routine labs, CRP, urine drug screen and pregnancy test. All subjects will be eligible to also complete the MMSE, BNSS, WRAT, and MRI safety screen.
Visit 1	Subjects will be eligible to complete the PANSS, behavioral EEfRT, IDS-SR or SHAPS, and other assessments the PI and study staff may choose from other study visits.
Visit 2 9:00 am	Subject arrives at Emory University Hospital ACTSI suite
9:30 am	Blood Sampling
10:00 am	Behavioral Testing
12:00 pm	Lunch
13:00 pm	MRI Scan
14:30 pm	Complete Study
Visit 3	Complete Behavioral Testing

Figure 2 gives an overview of the proposed study visits. **Study Overview:** The proposed experiments will evaluate the impact of inflammation on reward processing, motivation, and negative symptoms in 100 male and female patients with schizophrenia or schizoaffective disorder. The Screening Visit will take place virtually or at one of the following sites; Grady Behavioral Health Clinic (Grady BHC), Emory University Hospital Georgia Clinical & Translational Science Alliance Clinical Research Center (EUH GCRC), Woodruff Memorial Research Building (WMRB-PI Office Space) or at the Facility for Education and Research in Neuroscience (FERN) at Emory, where subjects will be recruited. During the **Screening visit**, subjects will be approached for inclusion in the study and will provide informed consent. The MINI International

Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders (MINI) will be administered. Subjects will also be requested to provide detailed information on past medical and psychiatric history and treatment, as well as current symptom status. A physical exam will be completed, and vital signs will be recorded. Routine labs will be obtained to rule out chronic illness or acute infectious process and a urine toxicology screen will be obtained. A blood draw to measure CRP will be obtained at this visit to ensure a range of inflammation from low (CRP≤3 mg/L, n=30) to high (CRP>3mg/L, n=30) based on guidelines from the American Heart Association.[87] Subjects will also complete the Mini Mental State Exam (MMSE), the Wide Reading Achievement Task (WRAT), the Brief Negative Symptom Scale (BNSS) and the MRI Safety Screening form. Subjects who meet the inclusion criteria will be asked to schedule **Visit 1**. All subjects who sign consent on the screening visit will be included in the following additional assessments at **Visit 1:** (1) Positive and Negative Symptom Scale (PANSS) (2) the behavioral EEfRT task, the Snaith Hamilton Pleasure Scale (SHAPS) or the Inventory of Depressive Symptomatology (IDS-SR) and any other behavioral assessments that the PI and designated study staff decide to include from the other study visits. Visit 1 will be take place at Grady BHC, EUH GCRC, WMRB or FERN. **Visit 2** will be scheduled within two weeks of Visit 1. Subjects will be brought by taxi to Emory University Hospital at the ACTSI Research Site. During this visit, patients will undergo: (1) fasting blood sampling for plasma inflammatory markers and isolation of peripheral blood mononuclear cells (PBMCs) (collected between 9:00AM and 10:00AM to control for circadian variations), optional blood for induced pluripotent stem cells (iPSCs), optional blood for immune repertoire sequencing, and mRNA gene expression analyses, (2) behavioral testing with the objective, self-report and clinician-rated described below, and (3) MRI scan with imaging tasks described below. See below for breakdown of each study visit. The PI and designated study staff will have the discretion to decide which tasks are to be completed at each study visit. Furthermore, the PI and designated study staff may decide that a subject may go through behavioral testing only at Visit 2 and not undergo the neuroimaging protocol. **Visit 3** will be scheduled within 72 hours of Visit 2 (may be extended up to 1 week per the PI's discretion). Visit 3 will be conducted virtually or in-person at one of the following sites; Grady BHC, EUH GCRC, WMRB or FERN. The remainder of the behavioral assessments will be completed at this visit.

Part A
Study Sample:
Enrollment: One hundred patients between the ages of 18 to 59 with diagnoses of schizophrenia or schizoaffective disorder will be recruited. Both diagnoses will be included in this study as there is a high degree of overlap between these disorders and both are often included in similar studies.[88,89] The upper age of 59 was chosen to limit the impact of cortical atrophy and age-related white matter changes in the basal ganglia on MRI. Given our previous experience working with this patient population, we plan to screen 200 individuals, assuming that at least half will decline or drop out. All patients will be recruited from the Grady Outpatient Behavioral Health Clinic (BHC), where the PI currently serves as co-director of the PSTAR Clinic (Persistent Symptoms: Treatment, Assessment and Recovery). The PI has an excellent working relationship with Dr. [redacted], the medical director of the BHC. Approximately 30% of patients in the BHC have a primary psychotic disorder and approximately 1000 individuals have a diagnosis of schizophrenia or schizoaffective disorder. We anticipate recruiting 2-3 patients per month (20-30 patients per year) who will consent to enter the study, though should more patients express interest, we would recruit more patients then 2-3 a month. Our estimate of the number of patients able to provide informed consent is based on another study being conducted at the BHC, where the majority (16 out of 17) of patients with schizophrenia recruited were able to provide informed consent. In the preliminary data described above, the 10 patients in the cytokine study were equally split between two groups with CRP ≤3mg/L and >3mg/L. While the sample was not recruited to ensure this split, it is consistent with clinical data from a random sample of 50 patients from the PSTAR Clinic, 21 of whom have CRP ≤3mg/L and 29 with a CRP >3mg/L. This suggests that we should be able to recruit the CRP range proposed herein.

Figure 3 shows all proposed assessments and the study visits at which they will be collected. The PI reserves the right to waive any of these assessments or change the visit in which they are administered, should he feel they would not benefit the patient or the study procedures.

Screening visit/consent signing: Screening Visit will take virtually or in-person at one of the following sites; Grady BHC, EUH GCRC, WMRB or FERN. Subjects will be approached for inclusion in the study and will provide informed consent. After providing informed consent, subjects will undergo the Mini International

Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders (MINI) to determine diagnostic eligibility for the study. Subjects who sign consent and meet the diagnostic criteria to be eligible for the study will undergo the remainder of the screening visit, which will include the following assessments:

(1) Mini-Mental State Exam
(2) Wide Reading Achievement Test (WRAT-3)
(3) Psychiatric History Form
(4) Medical history and physical exam performed by a physician
(5) Brief Negative Symptom Scale (BNSS)
(6) Behavioral EEfRT
(7) Blood draw for CRP
(8) Laboratory testing including
    a) Complete blood count with automated differential
    b) Comprehensive metabolic panel (with renal and hepatic function tests)
    c) Glycosylated hemoglobin test (HbA1C)
    d) Urinalysis with microscopic
    e) Serum quantitative pregnancy test (if female)
    f) Urine toxicology for drugs of abuse
    g) Anti-nuclear antibodies (ANA)
    h) Rheumatoid Factor (qualitative) (RF)
    i) Thyroid Stimulating Hormone (TSH)
    j) HIV-1/HIV-2
    k) Hepatitis C Antibody
    l) Hepatitis B Surface Antigen

Inclusion and Exclusion Criteria:

Inclusion: a. willing and able to give written informed consent; b. men or women, 18-59 years of age; c. a primary diagnosis of DSM-V schizophrenia or schizoaffective disorder as diagnosed by the MINI 7.0; d. Mini Mental Status Examination Score ≥24; e. Brief Negative Symptom Scale Score ≥25; f. no psychotropic medication changes for one month prior to study enrollment; may be taking other psychotropic non-antipsychotic medications (i.e., antidepressants, mood stabilizers, benzodiazepines).

Exclusion: Exclusion criteria will be split between those related to data quality and those related to subject safety. Data quality exclusion criteria may be waived at the discretion of the PI, though those exclusion criteria for subject safety may not be waived under any circumstances.

Data Quality Exclusion Criteria: a. evidence of untreated or poorly controlled endocrine, thyroid, cardiovascular, hematological, renal, neurological disease, hepatitis B or C or HIV; b. current HbA1C ≥ 8.5%; c. prior treatment with antiviral or immunomodulatory drugs, including corticosteroids within six months of study entry; d. current treatment with antibiotics; e. primary diagnosis of major depressive disorder or bipolar disorder; f. active abuse of alcohol or illicit/prescription drugs within the past 6 months including a urine toxicology screen positive for drugs of abuse (patients may still be included with a positive THC result at the discretion of the PI); g. predominant left-handedness excluded for portions of the MRI scan; h. WRAT-3 score indicating less than 8th grade reading level, unless otherwise approved by the PI or PI's designee; i. any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with participating in or completing the protocol.

Subject Safety Exclusion Criteria: a. history of CNS trauma or active seizure disorder requiring medication; b. positive pregnancy test; c. presence of metal in the body (excludes from MRI scan only); d. active suicidal ideation as determined by the PI and/or study staff.

Visit 1: Visit 1 will be scheduled between the screening visit and visit 2 and will either occur at Grady BHC, EUH GCRC, WMRB or FERN. The following assessments may include (scales and tasks may not be administered at the discretion of the PI and the study team):

(1) Positive and Negative Symptom Scale (PANSS)
(2) Snaith-Hamilton Pleasure Scale (SHAPS-C)
(3) Inventory of Depressive Symptomatology (IDS-SR)
(4) Quality of Life Enjoyment and Satisfaction Scale (QLES-Q)
(5) World Health Organization Disability Assessment Scale (WHODAS)
(6) Childhood Trauma Questionnaire (CTQ)

If the PANSS and EEfRT are not completed at Visit 1, they may be completed at either Visit 2 or Visit 3 at the discretion of the PI or designated study team. Additionally, if the subject is not fatigued, the CANTAB and Neurocognitive battery may be administered at Visit 1 or Visit 2 in lieu of coming in for Visit 3. Should this occur, compensation for Visit 3 in the amount of $20.00 will be added to Visit 1 or Visit 3.

Visit 2: Visit 2 will be scheduled within 2 weeks (may be extended by 1 week at the discretion of the PI) of Visit 1. Subjects will be brought by taxi, arranged by study staff, to Emory University where they will undergo behavioral assessments, fasting blood sampling, and MRI scan. These assessments will be conducted at one of two sites to be determined by the PI and the study team: either the ACTSI Emory University Hospital Clinical Research Site and complete the MRI scan at the Emory University Hospital BITC Research Scanner, or the Emory University Department of Psychology and their Facility for Education and Research in Neuroscience (FERN). Transportation will be arranged for patients to be picked up at their home or designated location and brought safely to the Emory University campus. During this visit, patients will undergo the following assessments: (1) fasting blood sampling for plasma inflammatory markers (collected between 9:00am and 10:00am to control for circadian variations), PBMCs, induced pluripotent stem cells (iPSCs), immune repertoire sequencing, and optional mRNA gene expression analyses, (2) Urine Drug Screen (THC quantitative test if required) (3) Urine pregnancy test, (4) Optional saliva collection for microbiome analysis, (5) behavioral testing with objective, self-report and clinician-rated assessments, (6) Optional saliva collection for cortisol testing, (7) MRI scan with imaging tasks described below. Patients will not be allowed to smoke or eat at least 1 hour before the scan. Breaks will be allowed throughout the day, and snacks and a standardized lunch will be provided. Taxi service will be arranged to safely transport the patients back to their home. The Calgary Depression Scale for Schizophrenia (CDSS) and the Motivation and Pleasure Scale (MAPS-SR) will also be administered (scales and tasks may not be administered at the discretion of the PI and the study team).

Visit 3: Visit 3 will be scheduled within 72 hours (up to a week per the PI's discretion) of Visit 2. Visit 3 will take place virtually or at one of the following sites; Grady BHC, EUH GCRC, WMRB or FERN. All assessments that have not been completed will be completed at this visit. Alternatively, these assessments can be administered at Visit 1 or 2 at the study staff's discretion, depending on scheduling and the patient's preference. Assessments include the following:

(1) CANTAB
(2) Neurocognitive Battery (described below)

Figure 3: Schedule of Assessments

Procedures	Screening Visit	Visit 1	Visit 2	Visit 3
Medical Assessments				
Physical Exam	X	X^		
Concomitant Medications	X	X	X	X
Adverse Events	X	X	X	X
Medical History	X	X^		
CRP	X		X	
Safety Labs*	X		X	
Additional Blood (immune)			X	
Optional blood for mRNA			X	
Optional Urine Collection for iPSC's			X	
Optional blood samples for iPSC's and immune cell repertoire analyses			X	
Optional saliva collection for Cortisol Testing			X	
Optional Saliva Collection for Microbiome Testing			X	
MRI Scan**			X	
Neuropsychiatric Assessments				
Mini International Neuropsychiatric Interview (MINI)	X			
Mini-Mental State Exam (MMSE)	X			
Wide Reading Achievement Test 3 (WRAT-3)	X			
Positive and Negative Symptom Scale (PANSS)		X	X^	
Brief Negative Symptom Scale (BNSS)	X			
Effort-Expenditure for Reward Task (EEfRT)	X	X^	X^	
Neurocognitive Battery (described below)		X^	X^	X
Self-Reports/Questionnaires				
MRI Scan Form	X	X^		
Psychiatric History Form	X			

Calgary Depression Scale for Schizophrenia (CDSS)			X	
Motivation and Pleasure Scale (MAPS-SR)			X	
Snaith-Hamilton Pleasure Scale (SHAPS-C)		X		
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q_SF)		X		
Inventory of Depressive Symptomatology (IDS-SR)		X		
Childhood Trauma Questionnaire (CTQ)		X		
WHO Disability Assessment Scale 2.0 (WHODAS 2.0)		X		
MRI Scan Food, Drink and Cigarette Intake Form			X	

*Safety labs may include Comprehensive Metabolic Panel, Complete Blood Count with differential, Glycosylated, Pregnancy Test (females), Urinalysis with microscopic, Urine Drug Screen, TSH, HIV-1/HIV-2, ANA, RF, HbA1C, Hepatitis B Surface Antigen, Hepatitis C Antibody
**MRI scan may include structural scan, resting state scan, diffusion tensor imaging (DTI) scan, task-based scans
^may be completed at this visit at the study staff's discretion

Urine drug screening: A urine drug test (DrugCheck: NxScan Onsite Testcup/THC quantitative test) may be performed for each patient at screening and upon arrival at EUH for Visit 2. The urine test will allow for the qualitative detection of drug or drug metabolites in urine, including benzodiazepines, methamphetamine, cocaine, THC, and morphine. Identification of a urine test positive for substance use will exclude the subject from participation, unless substance is a prescribed medication, or otherwise approved by the PI or PI designee. The THC quantitative test will be performed to assess the varying levels of THC if the results for THC are positive from the UDS.

Blood Collection for iPSCs: At Visit 2, an optional, additional blood sample (~15mL) may be collected and sent to a collaborating laboratory led by Dr. [redacted]. The collaborator will use cells from this sample to create induced pluripotent stem cells (iPSC). Over the past decade, researchers – including Dr. [redacted] (Wen et al., 2014; Tang et al., 2016; Wen et al., 2016) – have harnessed the power of cellular-reprogramming technologies to turn differentiated cells in the adult, like those found in urine, blood or skin, into induced pluripotent stem cells (iPSCs). Importantly, patient-derived iPSCs feature the same mutations as those found in the donor individual (Wen et al., 2016). Thus, researchers can use these cells to model a condition or disease in the context of an individual person. A description of how the cells will be used is laid out in detail in the consent form.

Blood Collection for Immune Repertoire Sequencing: At Visit 2, an additional optional blood sample (up to 32 mL) may be collected and sent to a collaborating laboratory led by Dr. [redacted]. His team will isolate cells from this blood sample to study different subpopulations of lymphocytes using adaptive immune repertoire sequencing to understand how lymphocytes may help mediate the neuroinflammation that can occur in schizophrenia. (Yaari and Kleinstein, 2015; Cashman et al., 2019).

Gender and Minorities: Based on the composition of the patients treated for psychosis at the Grady BHC, we anticipate that an equal number of men and women will be included in the study. Given the demographic makeup of the PSTAR Clinic at the BHC, we should not have any difficulty recruiting from minority populations as this represents the majority of individuals seen at the Grady BHC.

Drop-outs: The schizophrenia patient population can at times be difficult to recruit as their negative symptoms, in addition to cognitive deficits, often lead to refusal to participate and high no-show rates. We plan to address this by screening more than double the number of patients proposed to enroll in the study (approach 400 to screen 200 to enroll 100) to account for this challenge. We also plan to continue recruiting patients until we reach a total of 100 individuals who complete the study, even if individuals drop out between study visits.

Compensation: Patients will be compensated $15 for their participation in the screening visit irrespective of whether or not they meet eligibility requirements for the remainder of the study; however, following the informed consent process, a clean urine drug screen will be required to proceed with the screening visit. If the urine drug screen is positive for any drugs of abuse, the screening visit will not continue, and the participant will not be compensated, with the exception of a positive THC result which may be included at the discretion of the PI. In addition to the $15, patients will also get winnings from 2 random trials of the behavioral EEfRT task (up to $25 total). Patients will be compensated $15 for their participation in Visit 1. Patients will be compensated $50 for their participation in Visit 2 in addition to compensation for their performance on the two imaging tasks.

Per convention in the literature, patients will be given their total earnings in the MID task in addition to the amount of two random selections of "win" trials in the EEfRT task (up to $100 total compensation for Visit 2). Patients will be compensated $20 for their participation in Visit 3. The optional collection of blood samples at Visit 2 to generate induced pluripotent stem cells and/or perform immune repertoire sequencing will be compensated an additional $25. In total, patients will be compensated up to $185 for completing all study visits.

Part C
Optional Oral Glucose Tolerance Test (OGTT) Arm:

Individuals who completed Part A will be invited to participate in an optional study (Part C), which will use an oral glucose tolerance test to test the hypothesis that insulin resistance drives inflammation. We will recruit subjects with a range of insulin resistance, as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) to ensure a range of IL from low to high (~50% <2.5 and ~50% >2.5). This will allow us to investigate the contributions of metabolic dysfunction and inflammation on inflammatory/metabolic markers, brain reward circuitry, motivational deficits, and negative symptoms. Relevant to the impact of inflammation on insulin signaling, measures of insulin sensitivity are significantly worse in patients with schizophrenia, including at illness onset.[143, 144] Moreover, antipsychotic medications lead to metabolic syndrome, contributing to risk for insulin resistance and ultimately diabetes.[145] Insulin resistance (IR) is believed to be caused by increased inflammation, and in turn can contribute to inflammation through alterations in glucose metabolism.[146-150] The following specific aims are proposed in this optional study:

Specific Aim 1) To determine the impact of IR on inflammatory markers in patients with schizophrenia before and after a glucose challenge. Medically stable, male and female (n=20) subjects with metabolic syndrome and a range of insulin resistance (HOMA-IR; ~50% <2.5 and ~50% >2.5), who complete part A of the protocol will be enrolled. Baseline fasting blood glucose, insulin, leptin, adiponectin, resistin and lipids will be measured, and insulin and glucose will be assessed at 1, 2 and 3 hours post-OGTT. CRP, cytokines and their soluble receptors in plasma will also be measured before and after OGTT. Blood will also be drawn before and after OGTT for mRNA gene expression analyses. *Hypothesis 1*: Evidence of IR will be associated with enhanced inflammatory responses to OGTT and altered metabolic related signaling pathways in gene expression analyses.

Specific Aim 2) To determine the impact of IR and inflammation on reward circuits and negative symptoms in patients with schizophrenia, before and after glucose challenge. Participants described in Aim 1 will undergo the following assessments before and after OGTT: 1) Resting-state and task-based fMRI to assess changes in activation of functional connectivity between the ventral striatum and other reward relevant brain regions using targeted and network-based analyses in relation to inflammatory and metabolic markers. 2) clinical and objective assessments of motivation and negative symptoms. Inflammatory verses metabolic responses to OGTT will be examined as predictors and controlled for in the analyses. *Hypothesis 2a*: Peripheral IR will be associated with decreased functional connectivity within reward circuits, decreased ventral striatum activation, and greater motivational deficits/negative symptoms post-OGTT. *Hypothesis 2b*: Inflammation will mediate the effects of IR on reward circuit functional connectivity, as well as changes in motivational deficits/negative symptoms before and after OGTT.

Study design and methods: Participants from Part A will be approached to enroll in this optional study. A new written informed consent will be obtained from all patients before protocol-specified procedures are conducted. The schedule of assessments for the optional OGTT study can be found in Table 5.

Figure 5: Part C OGTT Schedule of Assessments

Procedures	Screening Visit (Grady BHC)*	Visit 1 Pre-OGTT (Emory GCRC/FERN)	Visit 1 Post-OGTT (Emory GCRC/FERN)
Medical Assessments			
Physical Exam	X*		
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Safety Labs**	X	X	
Vital Signs including waist circumference	X	X	X
CRP	X		
Additional Research Blood (immune and metabolic markers)		X	X
MRI Scan		X***	X
Neuropsychiatric Assessments			
Positive and Negative Symptom Scale (PANSS)	X^		
Brief Negative Symptom Scale (BNSS)	X^		
Calgary Depression Scale for Schizophrenia (CDSS)	X^		
Effort-Expenditure for Reward Task (EEfRT)		X	X
Neurocognitive Battery		X	X
Self-Reports/Questionnaires			
Profile of Mood States (POMS)		X	X

*If >6 months
**Safety labs may include complete blood count, urinalysis, urine drug screen, chemistry
***If Part C is completed within 2 weeks of Visit 2 from Part A of the protocol (or at the discretion of the PI), MRI data may be used from part A as pre-OGTT scan and the pre-OGTT MRI may be omitted.
^ If Part C is completed within 2 weeks of Visit 2 from Part A of the protocol (or at the discretion of the PI), data from these assessments may be used from part A and these may be omitted

Choice of OGTT as a metabolic challenge: We will use the OGTT because 1) responses to OGTT have been shown to be altered in patients with schizophrenia,[144] 2) it is a clinical diagnostic test, not an intervention, that can pull out differences in IR in non-diabetic but at-risk patients with schizophrenia, 2) IR is associated with dyslipidemia and changes in cholesteral,[151] and altered OGTT response should be seen in patients with evidence of altered lipid/cholesterol metabolism in these panels, 3) it has been shown to cause changes in measures of brain functional connectivity, due to either leptin signaling or glucose uptake, that is altered in patients with evidence of IR,[152-155] 4) it stimulates inflammatory responses,[158,159] allowing us to further probe immune and metabolic interactions, and 5) OGTT has been used to assess psychiatric/behavioral symptoms as they relate to IR in the Grady population through work in the Grady Trauma Project.[156]

Participant Selection

Inclusion Criteria: The same inclusion criteria from Part A will be used.

Exclusion Criteria: The same exclusion criteria from Part A will be used with the added criteria of a) diagnosis of diabetes mellitus.

Description of Study Procedures

Optional Study Screening: Subjects who potentially qualify for enrollment in Part C will be approached at the end of Part A. The exclusion of a diagnosis of diabetes will be made by medical history or HbA1C >6.5, both of which are assessed/measured in Part A. Of note, some individuals may qualify for both Parts B and C. If this is the case, subjects will first be offered Part B and then informed about Part C. This visit will occur at Grady BHC, EUH GCRC, WMRB or FERN. Fasting insulin and glucose will be measured to calculate HOMA-IR. CRP, CBC, urinalysis, vital signs, urine drug screen and pregnancy test (for women) will be collected as well to ensure that there are no active infections, active drug use, and/or pregnancy. If it has been >6 months since Part A, HbA1C will also be measured to ensure that the subject does not have diabetes. If >6 months, a physical exam will be repeated as well. If Part C is completed >2 weeks after Part A, the BNSS, PANSS, and

CDSS will be repeated at this visit. In addition, subjects will also complete the MRI safety screening form again in case anything has changed since Part A. The total burden of the prescreening visit includes approximately ~1-2 hours of informed consent and blood draw (if symptom measurements need to be completed at this visit, the visit will likely be closer to 2-3 hours). Subjects will be compensated $25 for the prescreening visit.

OGTT Visit 1: Subjects will be invited to participate in Visit 1 after signing informed consent at screening and meeting all inclusion/exclusion criteria. Visit 1 will be scheduled within 10 days (>10 days can be approved at the discretion of the PI) of Screening to ensure stability of CRP measurement (of note, the CRP at screening will not be used in analyses). Subjects will be brought by taxi/ride share (i.e, Uber) to Emory University Hospital at the Georgia CTSA Clinical Research Center (GCRC). All procedures during this visit will occur prior to and following a 75gm oral glucose tolerance test (OGTT).

Subjects enrolled and previously approved by the PI, with a positive UDS for THC will undergo a THC quantitative test. Subjects will undergo blood draw (fasting) for inflammatory and metabolic markers once before OGTT and at 15 min, 30 min, and 1, 2 and 3 hours post-OGTT. Whole blood will also be collected in Tempus Tubes for gene expression analyses at each time point. The following behavioral assessments will be administered pre and post OGTT administration: 1) Effort Expenditure for Reward Task, 2) Profile of Mood States, and 3) Neurocognitive Assessments described below. An MRI scan will be performed at the Emory Department of Psychology Facility for Education and Research in Neurosciences (FERN), where subjects were previously scanned during Part A. Subjects may undergo 1) Resting State fMRI, 2) Task Based MRI using the fMRI EEfRT and MID tasks, 3) DTI. Which of these MRI procedures will be made at the discretion of the PI. Post-OGTT MRI scan will be performed 3 hours after OGTT administration in order to measure reward circuitry at the peak of the inflammatory response. If Visit 1 is scheduled within 2 weeks of Part A from Visit 2, the pre-OGTT MRI scan may be omitted at the discretion of the PI.

Given the pre-post design with blood draws, behavioral assessments, and MRI that will all be performed twice, Visit 1 will last approximately ~6 hours and the timeline can be found in Figure 2. Subjects will be compensated up to $150 for this visit based on their performance on the fMRI tasks.

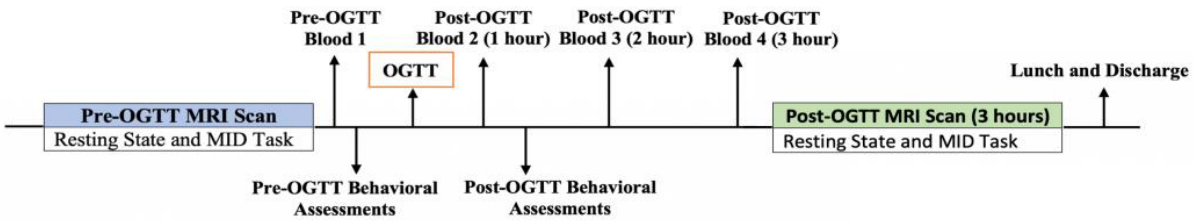

Figure 2. Visit 1 timeline for fMRI, blood, and behavior pre and post-OGTT.

Part D: Optional Antinuclear Antibodies (ANA) Study:

Individuals who completed Part A will be invited to participate in an optional study (Part D), which will use immune repertoire sequencing to understand the relationship between antinuclear antibody test positivity and schizophrenia. Though individuals that had a positive ANA screening result were excluded from Part A, this is still an important subpopulation to study as ANA positivity is three-fold more likely in individuals with schizophrenia than in healthy controls.[166,167] Some antinuclear antibodies have the ability to bind to the GluN2A and GluN2B subunits of the NMDA receptor, which contributes to psychosis through glutamatergic dysfunction in systemic lupus erythematosus.[168,169] We hypothesize that antinuclear antibodies contribute to schizophrenia pathogenesis in a similar manner. We propose to use B cell receptor sequencing to study how immune tolerance can breakdown in schizophrenia in order to explain the increased prevalence of antinuclear antibodies in schizophrenia. All individuals who previously tested positive for ANA and were therefore excluded from part A will be asked to participate in this study, up to a total of 20 male and female participants.

Study design and methods:

Adaptive immune repertoire sequencing will be performed with the collaboration of Dr. [redacted] at

Emory University. B cell receptor sequencing will provide data about clonality, somatic hypermutation, and antibody selection. Data from ANA-positive individuals will be compared with ANA-negative participants (collected in Part A), as well as previously characterized datasets of healthy controls and individuals with systemic lupus erythematosus. These data will be combined with the PANSS to identify possible phenotypes of schizophrenia based on B cell repertoire fingerprints. We hypothesize that ANA-positive individuals with schizophrenia will show similar B cell repertoire fingerprints as individuals with lupus.

Participant Selection

Medically stable, male and female (n=20) subjects with ANA positivity who were screened out of part A of the protocol will be enrolled:

Inclusion Criteria: In addition to ANA positivity, the same inclusion criteria from Part A will be used.

Exclusion Criteria: The same exclusion criteria from Part A will be used with exception of ANA positivity. Additionally, a clean urine drug screen will be required for study participation and screening compensation.

Description of Study Procedures

Participants from Part A who were not eligible to participate due to ANA test positivity will be approached to enroll in this optional study. A new written informed consent will be obtained from all patients before protocol-specified procedures are conducted. This visit will occur at Grady BHC. Following completion of informed consent, the PANSS will be administered. Up to 60 mL of blood will then be drawn for analysis. Lab draws will be timed to occur around 10 AM for consistency with Part A. A urine drug screen will be administered and a urine pregnancy test if you are a woman. CBC performed for screening in Part A will be repeated if indicated (e.g. if >6 months have passed since the screening visit). Blood will then be transported to Emory University using appropriate containment methods for use in immune repertoire sequencing. Additionally, CRP, cytokines and their soluble receptors in plasma will be measured at the discretion of the PI.

The total burden of all study procedures is estimated to by 120 to 150 minutes, including approximately 60 minutes of informed consent, and an additional 60 to 90 minutes for lab collection and assessment administration. Subjects will be compensated $25 for the study visit provided their urine drug screen is unremarkable.

Figure 6: Part D ANA Schedule of Assessments

Procedures	Screening Visit
Safety Labs**	X
CRP	X
Additional Blood for immune repertoire sequencing (up to 60mL)	X
Neuropsychiatric Assessments	
Positive and Negative Symptom Scale (PANSS)	X

*If >6 months
**Safety labs may include complete blood count and urine drug screen

Part E Optional Study: Musical Preferences Assessment

Individuals who participate in Part A of this study will be invited to take part in this optional study that explores musical preferences and how music may impact symptoms associated with schizophrenia. The Part A informed consent will be modified to include this as an optional study to which patients may agree to participate. Patients who previously consented to Part A will be re-contacted and if interested, will sign a new informed consent in person or electronically.

Specific Aim 1) To determine how patients with auditory hallucinations experience music and how music impacts their symptoms.

Study design and methods

Twenty participants from Part A will be invited to participate in this optional study. If the participant is interested, a separate informed consent, either written or electronic, will be obtained from all patients before protocol-specified procedures are conducted. Following the informed consent process, an interview will commence. The interview, which lasts approximately 30-35 minutes, will include questions about musical preferences, whether or not the participant plays a musical instrument, and how music impacts one's ability to deal with symptoms of schizophrenia.

Participant Selection

Inclusion Criteria: The same inclusion criteria for Part A will be used.

Exclusion Criteria: The same exclusion criteria for Part A will be used, with the added criteria of lack of self-reported auditory hallucinations.

Description of Study Procedures

Following the informed consent process, a study team member will initiate the survey and take notes based on the participant's responses. The participant may or may not consent to having the session recorded. All audio recordings will be de-identified and used to ensure internal reliability.

The total burden of all study procedures is estimated to be approximately 50 minutes, including approximately 20 minutes for the informed consent process. Participants will not be compensated for their time.

Part E Musical Preferences Assessment:

The Musical Preferences Questionnaire is a 19-item interview created by study team members that explores listening to and actively creating music as well as playing a musical instrument.

The Involuntary Musical Imagery Scale (IMIS)[170]: This scale assesses the positive or negative experience of music coming into the mind and repeating itself over and over without conscious effort.

Part A and C Study Procedures

Neuropsychiatric Assessments:

Observer-rated assessments

Demographic Data Form: Will be used to collect demographic data for the study.

Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders (MINI): The MINI is a semi-structured interview conducted by trained interviewers aimed at establishing the presence of disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[90]

Mini-Mental State Exam (MMSE): The MMSE is a 27-item interviewer-administered questionnaire widely used for the evaluation of general cognitive functioning and identification of altered mental status.[91] Previous work in patients with schizophrenia from community-based outpatient samples similar to the cohort we plan to recruit from demonstrates that a 24/30 on the MMSE represents having less than a 9th grade education.[92]

Positive and Negative Symptom Scale (PANSS): The PANSS is the most commonly used measure for assessing the symptoms of schizophrenia.[93] Seven items measure positive symptoms, 7 measure negative symptoms, and 16 measure general psychopathology symptoms.

Brief Negative Symptom Scale (BNSS): The BNSS is a 13-item scale designed for research studies in response to the 2005 NIMH consensus development conference on negative symptoms of schizophrenia.[94] Based on findings from the meeting, the BNSS measures the five commonly accepted domains of negative symptoms: blunted affect, alogia, asociality, anhedonia and avolition.[95] A BNSS cutoff of 25 is based on mean scores from various international validation studies of the BNSS.[137-141] This cutoff will ensure that we enrich our sample with individuals who have negative symptoms, while still ensuring an adequate range for analyses.

Wide Range Achievement Test-3 Reading Scale (WRAT-3): The WRAT-3 is a very brief screening measure for reading level, which has been shown to estimate premorbid intelligence in individuals with schizophrenia.[96-98]

Calgary Depression Scale for Schizophrenia (CDSS): The CDSS is a clinician-administered, 9-item rating scale designed for the assessment of depressive symptoms in schizophrenia. Depressive symptoms are highly

prevalent in patients with schizophrenia and may lead to a higher burden of disease. It is reliable, valid, and able to distinguish depressive symptoms from negative symptoms and extrapyramidal symptoms.

Collecting Speech Data: The protocol aims to audio record the interview of patients during either the Brief Negative Symptom Scale (BNSS) assessment or the Positive and Negative Symptom Scale (PANSS). Additionally, patients will be presented with an abstract piece of art and asked to describe their impressions of the art to elicit free and more abstract speech. Patients will be audio recorded for up to 10 minutes for the latter question. Audio recording will only be performed if patients consent to the audio recording section of the informed consent form. Audio recordings will be transcribed, and all protected health information will be removed from the text and replaced by a token denoting this type of content. The transcribed text will be used for computational analyses of speech. The analyses involve the use of machine learning and distributional semantics to represent sentences as vectors in a high-dimensional space. The number of core semantic units in each sentence vector will be measured as an index of poverty of content.

For Optional Study Part E, participants will have the option of consenting to the audio recording of The Musical Preferences Questionnaire and the IMIS.

Video-recording Clinical Interviews: Subjects will be offered the additional option to consent to the video-recording of clinical interviews, including the PANSS, BNSS, and/or MINI. Video recordings will only be used for training purposes and to ensure internal reliability and validity of subjective measures.

Self-report questionnaires:

Motivation and Pleasure Scale (MAPS-SR)[55]: The Motivation and Pleasure Scale – Self Report (MAPS-SR) is an 18 item self-report measure based on the Clinical Assessment Interview for Negative Symptoms (CAINS). The scale has been validated in patients with schizophrenia, shown to be associated with clinician-rated negative symptom severity, and has thus been shown to be a reliable self-report measure of negative symptom severity.[160]

Snaith-Hamilton Pleasure Scale (SHAPS-C): This clinician administered scale is a reliable, valid and unidimensional instrument to assess hedonic capacity in adults with psychiatric disorders, including studies of effort-based motivation in schizophrenia. [36, 39, 60]

Inventory of Depressive Symptomatology (IDS-SR): This 30-item self-report reliably assesses depressive symptom severity for the past 7 days.[60]

Childhood Trauma Questionnaire (CTQ): The CTQ is a self-report inventory assessing 3 types of childhood abuse: sexual, physical, and emotional. Studies have established the internal consistency, stability over time, and criterion validity of both the original 70-item CTQ and the current brief version.[121] The CTQ yields a total score and subscale scores for each of the types of child abuse. The data from the CTQ will be used to classify subjects into 2 categories for each type of abuse (physical, sexual, and emotional): (1) those with CTQ scale scores in the none to mild range, and (2) those with CTQ scores in the moderate to severe range. We will then create a composite variable across all of the 3 types of abuse. Using this composite, we can divide participants into 2 groups with respect to the numbers of types of abuse that fall into the moderate to severe range: (1) those with no type of abuse in the moderate to severe range, and (2) those with at least 1 type of abuse in the moderate to severe range.[122]

World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0): The WHODAS 2.0 is a 36-item interviewer administered assessment which provides a score for global disability as well as six domain scores in cognition, mobility, self-care, getting along with others, participation in society, and life activities. It is included in the DSM-5 as a measure of further study.[103]

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF): The Q-LES-Q-SF is a 16 item self-report scale assessing the participant's quality of life in various domains, including physical health, mood, social relationships, and overall sense of well-being. [127]

Profile of Mood States (POMS): The POMS is a 30-item rating scale designed to measure mood states across short periods of time.[161,162] The POMS has been widely used in studies with patients with schizophrenia.

Neurocognitive Assessments:

Though the driving aim of this proposal is to investigate the effects of inflammation on reward relevant circuitry in the brain leading to motivational deficits and negative symptoms of schizophrenia, previous data has also demonstrated that inflammation leads to altered basal ganglia function, specifically impacting the dorsal striatum, and has been associated with reduced psychomotor speed. Inflammation has been shown to alter

neural activity and dopamine metabolism in basal ganglia regions including the dorsal striatum as assessed by a variety of neuroimaging strategies following several inflammatory stimuli including Interferon-alpha, typhoid vaccination and endotoxin[51-53, 59, 123] Administration of inflammatory stimuli have also been shown to lead to depressive symptoms, including psychomotor retardation as well as objective measures of psychomotor slowing.[52,124, 125] In a recent study of the role of inflammation in patients with depression, IL-6, IL-10, and MCP-1 were all shown to be associated with objective measures of psychomotor slowing[126]. These inflammatory markers have all been demonstrated to be aberrant in patients with schizophrenia[61]. Psychomotor retardation has been described in patients with schizophrenia and is considered to be a negative symptom of the disorder. As such, we will plan to test the hypothesis that inflammation also decreases activation of the dorsal striatum and its associated circuitry, leading to decreased objective measures of psychomotor speed and negative symptoms in schizophrenia.

A range of neuropsychological assessments will be used to probe basal ganglia function and will be associated with inflammation status as noted above. Assessments will lie along a continuum, progressing from more purely motor tasks (such as finger tapping) which assess circuitry within the basal ganglia to those that involve motor speed with increasing cognitive demand and cortical participation (e.g. the Digit Symbol Task). In addition, we will administer a test of procedural memory, with minimal processing speed or reaction time demands, that has been shown to be sensitive to dysfunction in the basal ganglia, without the executive demands associated with tests of frontal lobe function. Every effort will be made to match groups on the basis of demographic factors affecting test performance, such as age, education level, gender and ethnicity. These factors can significantly influence neuropsychological test results and while relatively small variations between groups can be handled through addition of covariates to statistical analyses, more significant differences in-group composition will threaten the integrity and interpretation of the results.

Finger Tapping Task (FTT): This task uses a specially adapted tapper that the subject is asked to tap as fast as possible. The subject is given 5 consecutive 10-second trials for the preferred and non-preferred hands. The FTT is designed to assess subtle motor impairment and found to be altered in subjects with basal ganglia disorders and lesions.[104]

Reaction Time Task (CANTAB): This reaction time test includes simple and choice reaction time tasks and is divided into 5 stages requiring increasingly complex chains of responses and providing distinction between reaction (or decision) time and movement latencies. Movement times on the CANTAB reaction time task have been slowed during IFN-α treatment and correlated with IFN-alpha-induced depression and fatigue.[105]

Trail Making Test Part A (TMT-A): The Trail Making Test-A is a timed task that provides information on motor function and speed of processing.[106] Previous studies have indicated that performance of TMT-A significantly correlates with reduced caudate volumes in older persons with depression.[107]

Digit Symbol Substitution Task (DSST): The DSST is a subtest of the Wechsler Adult Intelligence Scale and involves graphimotor speed, visual scanning and memory, with about half of the variance being accounted for by graphimotor speed, a third by visual scanning and 4-5% by memory.[108] Performance on the Digit Symbol Test has been found to correlate with subcortical (caudate) atrophy in disorders involving the basal ganglia.[105]

Effort-Expenditure for Rewards Task (EEfRT): The EEfRT task is a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards.[109] For all trials, participants make repeated manual button presses within a short period of time. Each button press raises the level of a virtual ‘‘bar’’ viewed onscreen by the participant. Participants are eligible to win the money allotted for each trial if they raise the bar to the ‘‘top’’ within the prescribed time period. Each trial presents subjects with a choice between two levels of task difficulty, a ‘high effort’ and ‘low effort’ task that require different amounts of speeded button pressing. Reward magnitudes for the high effort task will vary between $1 and $10, while reward magnitudes for the low effort task remain constant (between $0.50 and $1.00). The reward magnitudes will be decided at the discretion of the PI. Trials will also vary in terms of 3 levels of probability of winning the amount associated with the choice selected. Subjects participate in the task for approximately 20 minutes and the first 50 trials are used for analysis. Because of the requirement for rapid button presses for a long period of time, we will exclude participants who report chronic pain in their wrists/hands and or those who have wrist/hand injuries, such as Carpal Tunnel Syndrome. At the discretion of the PI, the EEfRT may be repeated after the neuroimaging scan.

Neuroimaging Tasks:

The PI will choose which of these fMRI tasks will be performed at the fMRI study visits.

Monetary Incentive Delay (MID) Task*:* Assessment of reward anticipation will be achieved using the MID task.[26,110-112] Briefly, during this task participants have the opportunity to win or lose money by making a rapid button press in response to a target visual stimulus. The primary epoch of interest is the "anticipatory delay" – a period of ~2000ms that occurs after participants have been informed how much money they can win or lose on a given trial, but prior to the presentation of the target. This epoch has repeatedly been associated with robust ventral striatal activity.[26,110,113-114] Participants will complete 2 functional runs of between 50 and 200 trials each (the number of trials will be decided at the discretion of the PI), with evenly distributed reward magnitudes between $0.20 and $10.00, to be decided by the PI.
fMRI-adapted version of the EEfRT task*:* Assessment of effort-based decision making will be assessed using the EEfRT task.[109] During each trial, subjects are presented with a choice between two levels of task difficulty, a High Effort option and a Low Effort option. Unlike in the behavioral version of the task, subjects will not be required to make button presses during the scan. The reward magnitude for a No Effort option remains constant, while the reward magnitude for the High Effort option varies from $1.00 to $10.00. Additionally, the amount of effort required for the High Effort option will vary between 20%, 50%, 80% and 100% of the subject's maximum effort (set for each individual prior to scan).
Reinforcement Learning (RL) Task: Trials for this task involve a 3s cue presentation during which subjects choose between two abstract stimuli, followed by an exponentially jittered delay, and then a 3s feedback presentation with positive (monetary win), negative (monetary loss) or neutral outcomes. This task has been shown to robustly activate the ventral striatum in response to prediction errors.

Safety and Tolerability
Adverse Event Recording: All adverse events will be coded in standard MeDRA terms (Version 14.1), and whether events are expected and study-related will be determined by the study PI. In addition, severity and start and end dates will be recorded as well as any evidence of unanticipated problems. This information will be provided to the Department of Psychiatry and Behavioral Sciences DSMB and IRB annually as described in the Human Subjects Section.

Laboratory Variables
Blood Collection*:* At screening, blood will be collected by venipuncture for measurement of CRP (for high versus low inflammatory screening only; this CRP will not be used for data analysis) and screening labs including Full Chemistry Panel (Chem14), Complete Blood Cell Count (CBC), and Hemoglobin A1C (HbA1C). At Visit 2, a fasting blood sample will be collected by venipuncture into EDTA-containing vacutainer tubes using standard sterile technique. Plasma for the evaluation of plasma cytokines and their receptors as well as CRP will be obtained by centrifugation of whole blood at 1000x g for 10 minutes at 4°C. Plasma and buffy coat will be removed and aliquoted into siliconized polypropylene tubes and stored at -80°C until batch assay. Additional blood samples (up to 55mL of blood) may also be collected for 1) the isolation of PBMCs, 2) induced pluripotent stem cell creation (optional; in collaboration with Dr. [redacted]) and 3) immune repertoire analysis (optional; in collaboration with Dr. [redacted]).
Plasma cytokines and soluble cytokine receptors: Fluorokine MAP Multiplex Human Biomarker Panels (R&D Systems, Minneapolis, MN) will be used to measure plasma TNA-alpha, sTNFR2, IL-1ra, IL-1beta, IL-6, sIL-6R, IL-10, and monocyte chemoattractant protein (MCP-1). These inflammatory markers have all been found to be altered in schizophrenia.[61] Each determination requires 50-100 µl, and all samples will be assayed in duplicate according to manufacturer's instructions. Quality control plasma of both low and high cytokine concentrations will be included with every assay. The mean inter- and intra-assay coefficients of variation for control samples are reliably 10% or less.
C-reactive protein (CRP): Plasma CRP for screening will be assessed by a high sensitivity turbidimetric assay using the CLIA-certified lab at Grady Memorial Hospital. For study purposes, an immunoturbidometric method will be used to measure high sensitivity CRP concentrations with a Beckman AU480 chemistry analyzer and Ultra WR CRP kit (Sekisui Diagnostics).
Optional mRNA collection: Subjects will be asked to collect peripheral blood at Part A Visit 2 for messenger RNA (mRNA) for gene expression analyses. If enrolled in Part B, subjects will be asked to collect peripheral

blood at the Infusion Visit and Post-Infusion Visit 1. No DNA will be collected for analyses. One 9ml Tempus tube of blood will be collected and the tube will be inverted to mix for 10-15 seconds and immediately placed on wet ice. This tube will be stored overnight at 4°C. The next day, these Tempus tubes will be transferred to a -20°C freezer for storage. Patients may decline to provide blood for mRNA gene expression analyses, which will not affect their participation in the rest of the study.

Optional Blood for iPSCs: Optional blood samples (~15mL) collected at Part A Visit 2 and Part B Post Infusion Visit 1 may be sent to a collaborating research group at Emory (the laboratory of Dr. [redacted]). From these samples, Dr. [redacted] will reprogram adult somatic cells into induced pluripotent stem cells (iPSCs). From that point, Dr. [redacted] can use these cells (which can be differentiated into cells like neurons) in controlled experiments to study microglial cells, the immune cells found in the brain, for example (Wen et al., 2016). This further study would serve as a complement to the objective of the main study: examining the effects of inflammation on brain circuitry and negative symptoms in patients with schizophrenia. Blood samples may be stored for future research with Dr. [redacted]. Blood samples collected for further research will be stored in the laboratory space of Dr. [redacted]. It will be explained to participants in the consent form that their samples and data will be available for any research question, such as research to understand what causes certain diseases (for example heart disease, cancer, or psychiatric disorders), development of new scientific methods, or the study of where different groups of people may have come from. The PI will determine how samples and data collected through this study are used. Any use of the samples of data for other studies of the PI's would be submitted to the IRB through a separate submission. Dr. [redacted] will receive no other information with the samples other than the study record ID and sex. The link between a participant's study record ID and name or other information that could be used to identify him or her will not be shared with other researchers. This information will be kept in a password-protected computer file located stored on Emory Box or Microsoft One Drive. Only core research personnel will have access to this information.

Blood for immune repertoire sequencing: A blood sample (up to 32 mL) may be sent to a collaborating research group at Emory (the laboratory of Dr. [redacted]). Blood samples collected for further research will be stored in the laboratory space of Dr. [redacted]. These blood samples will be sorted into lymphocyte subpopulations and the B cell receptor will be sequenced to generate information about B cell somatic hypermutation and B cell clonal dynamics. It will be explained to participants in the consent form that their samples and data will be available for any research question, such as research to understand what causes certain diseases (for example heart disease, cancer, or psychiatric disorders), development of new scientific methods, or the study of where different groups of people may have come from. The PI will determine how samples and data collected through this study are used. Any use of the samples of data for other studies of the PI's would be submitted to the IRB through a separate submission. Dr. [redacted] will receive no other information with the samples other than the study record ID. The link between a participant's study record ID and name or other information that could be used to identify him or her will not be shared with other researchers. This information will be kept in a password-protected computer file located stored on Emory Box or Microsoft One Drive. Only core research personnel will have access to this information.

Reliability of ratings: All clinicians performing the MINI in this study will be trained to conduct the assessments according to standardized guidelines for the administration of the instrument and will conduct interim training sessions to maintain standardization. In addition, training on all other clinician rated scales will be provided for the relevant study personnel, and interrater reliability will be established. Trained staff will conduct the neurocognitive assessments. New staff joining the study team will go through an apprenticeship for the ratings and training for reliability prior to performing independent ratings.

Magnetic Resonance Imaging: At Part A Visit 2 and Part B Post Infusion Visit 1, MRI experiments will be performed on a 3T MRI scanner (either at the BITC Research Scanner at the Emory University Hospital, the Department of Psychology Facility for Education and Research in Neuroscience (FERN) or the Center for Systems Imaging (CSI) at Wesley Woods, to be decided by the PI prior to the start of the study. Only one scanner will be used throughout the course of study to maintain consistency). The subject will be pre-screened with the "MRI Screening form" to confirm that he/she is eligible to participate in the scan. Because MRI scanning can affect metallic and other implants, all subjects will be careful screening for metallic implants and other contra-indications to MRI prior to the procedure, using the standard Emory University Biomedical Information Technology Center MRI screening form. Subjects with contra-indications will not receive a MRI

scan. The MRI scanner is an enclosed space and subjects may experience claustrophobia while being scanned. Should a subject develop claustrophobia during the procedure, the scan will be terminated. All subjects will be required to limit caffeine intake for two hours prior to the scan. Any food or drink intake during this time frame will be recorded using a MRI Scan Food, Drink and Cigarette Intake Form immediately prior to the scan. Subjects will be offered an opportunity to be scanned with one of two scanning protocols. Depending on which protocol they choose, the scan may take between 60 to 90 minutes in length, though will not exceed one and a half hours. The patients will be informed of the time requirements prior to participation in the study. Protocol one would include the following scans: Structural Scan (~6 minutes), Resting State Scan (~ 8 minutes), Diffusion Tensor Imaging Scan (~6 minutes), Task-Based Scans (~24 minutes). Protocol two would be similar though would allow for a break between the Diffusion Tensor Imaging Scan and the Task-Based Scans where the subject would be allowed to exit the scanner, rest, go to the bathroom, and drink water, should they choose. This second protocol will be longer in total time given the break. Figure 4 details the two proposed scanning protocols.

Figure 7: Scanning Protocol Options

	Scanning Protocol One		Scanning Protocol Two
0:00*	Enter Scanner	0:00*	Enter Scanner
5:00	Symptom Check	5:00	Symptom Check
6:00	Start Scan	6:00	Start Scan
11:00	Structural Scan	11:00	Structural Scan
17:00	Symptom Check	17:00	Symptom Check
18:00	Resting State Scan	18:00	Resting State Scan
26:00	DTI Scan**	26:00	DTI Scan**
32:00	Symptom Check	32:00	Exit Scanner for Break
33:00	MID Task***	47:00	Symptom Check
45:00	fMRI EEfRT****	48:00	MID Task***
57:00	Exit Scanner	60:00	fMRI EEfRT****
58:00	Symptom Check	72:00	Exit Scanner
		73:00	Symptom Check

*All Times are Approximate
** Diffusion Tensor Imaging
*** Monetary Incentive Delay Task (may be substituted for another of the tasks at the PI's discretion)
**** fMRI adapted Effort Expenditure For Reward Task (may be substituted for another of the tasks at the PI's discretion)

Collection of structural and functional data includes: a 13-s localizer scan; an "auto-align scout" scan that uses a reference database to ensure consistent slice positioning across subjects; a rapidly acquired, T1-weighted, multi-echo MPRAGE volume for structural analysis and localization of fMRI data and multiband echo planar imaging for task related fMRI. This last sequence is re-used to acquire task-evoked fMRI data. During resting-state scan, participants will lie passively and refrain from thinking about anything specific. The Task Based Scans would consist of 1-2 of the following tasks chosen at the discretion of the PI or designee: fMRI-based Effort Expenditure for Reward task, Monetary Incentive Delay task, or the Reinforcement Learning Task. During the course of the imaging protocol, brief periodic checks of mood and psychosis ("Symptom Check") will be conducted to ensure the safety/comfort of the patient and to ensure that fluctuations in symptoms do not interfere with the interpretation of the scanning data during analysis.

Confidentiality: All participant data will be de-identified. All paper copies of data will be kept in a locked file cabinet in a locked office, accessible only by the PI and study staff. Audio and video recordings and the transcribed speech will be input into the Box system, a secure data management system. An identifier will be assigned to each data file and no data will contain the participant's name or any other identifying information. Neuroimaging data will be stored on Emory's secure network. A password-protected master enrollment log, also stored on Emory's secure network, will be the only key between participants' identifying information and the participant ID numbers. All data will be input into the Redcap system, a secure data management system.

6. Participant selection

One hundred males and females between the ages of 18 and 59 will be recruited for this study. All subjects (50% males and 50% females) will meet criteria for schizophrenia or schizoaffective disorder. 50 of these subjects will have plasma CRP concentrations >3 mg/L and 50 will have plasma CRP concentrations ≤3 mg/L. We plan to prescreen 400 subjects in order to consent 200 medically stable individuals. Of these, we anticipate that 100 subjects will be eligible and complete the protocol for the study. There will be no exclusions for race/ethnicity, and we expect that >50% of participants will be of minority race/ethnicity given the demographic make-up of the Grady Behavioral Health Clinic. Women will be actively recruited to ensure that 50% of the subjects will be female. No patients will be enrolled from vulnerable populations, including neonates, children, prisoners, or institutionalized individuals. Patients will largely be recruited from the Grady BHC, though we will also plan to recruit from the Emory Psychopharmacology Clinic as a secondary site to ensure we are successful at recruitment. We anticipate consenting 2-3 patients per month (20-30 patients per year). This estimate is based on ongoing projects that have recruited similar subjects for research studies.

Patients enrolled in the study will meet DSM-V criteria for schizophrenia or schizoaffective disorder as

determined by the MINI 7.0. To be included, subjects must not demonstrate active suicidal intent or plan and must have no suicide attempts within six months of screening. Subjects will not be enrolled if they have a primary diagnosis of a mood disorder (i.e; major depressive disorder or bipolar disorder), intellectual disability, delirium, or dementia or MMSE <24 (indicating cognitive impairment), unless otherwise approved by the PI or PI's designee. Subjects may be taking psychotropic medications at the time of the study (including antipsychotics, antidepressants, mood stabilizers, benzodiazepines) but may have no psychotropic medication changes for one month prior to study enrollment. At the PI's clinical discretion, subjects who screen positive for antinuclear antibodies (ANA) may be included as long as there is no evidence of an autoimmune disorder by history or on physical examination. Subjects will be at risk for exclusion for a urine toxicology screen positive for alcohol or drugs of abuse. The presence of post-traumatic stress disorder, obsessive compulsive disorder, panic disorder or social phobia will not disqualify subjects from enrollment, though cannot be the subject's primary diagnosis. Additionally, subjects may have a secondary diagnosis of major depressive disorder. Enrolled subjects may have a comorbid personality disorder; however, subjects who meet criteria in clinical interview for antisocial personality disorder will be disqualified, as will subjects with a history of hospitalization and/or recurrent suicidal behavior judged to be directly due to a personality disorder.

Potential subjects may be excluded for a number of medical conditions that might confound relationships between psychiatric diagnoses and inflammation, including uncontrolled cardiovascular disease, autoimmune condition (i.e. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, lupus), chronic infection (i.e. HIV, hepatitis B or C, herpes), abnormal lab results deemed by study physicians as contraindicated for study participation, or pregnancy. Similarly, patients may be excluded for evidence of medical or neurological abnormality on physical examination. Subjects will also be excluded for the following: a) history of CNS trauma or active seizure disorder requiring medications; b) prior treatment with antiviral or immunomodulatory drugs, including corticosteroids within six months of entry into the protocol; c) current treatment with antibiotics. Subjects who develop signs of an infection between screening and commencing the protocol assessments will be rescheduled when symptoms have resolved, if agreeable to the subject.

Risks in Participation

Behavioral Component: Participant risks are minimal. Participants may find the computer tasks to be boring, and associated with mild fatigue. Additionally, some tasks may require some rapid key pressing, which could induce mild discomfort in the hands. Consequently, individuals with medical conditions that limit the use of their hands are ineligible for the study.

Questionnaires: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning and/or the subject's past of present emotional state.

Confidentiality: This study has a Certificate of Confidentiality and as detailed, multiple procedures are in place to reduce the likelihood of a breach of confidentiality. However, there is a small risk that information about subjects could become known to people outside the study, and this risk is identified in the informed consent form. A number of procedures will be in place to prevent a breach of confidentiality from taking place. All potential subjects will be fully informed of their rights pertaining to disclosure of PHI in accordance with HIPAA regulations. Confidentiality will be maintained by assigning participants a study number and numerically coding all data. One hard copy file linking the code number with identifying information will be kept in a separate locked file with direct access available to the PI only. All records and research data will be kept in locked filing cabinets or computers. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. These precautions should serve to minimize legal risks to participants.

Additional Risks in Participation

MRI Component: In addition to the risks described for the behavioral component, the MRI component involves several additional risks. MRI is non-invasive but due to the strong externally generated magnetic field, the participant's safety in ensured by excluding participants that are not compatible with this environment using the standard MRI screening form. MRI studies will use radiofrequency power deposition and gradient switching, which have been approved by the FDA. The magnetic fields are within the limits recommended by the FCC. The 3.0T field strength itself has been deemed a non-significant risk by the FDA. The scanner is loud, and participants will be given earplugs and headphones to reduce the noise of the MRI machine, while they are in the scanner. Participants may additionally experience some muscle discomfort or feel too hot or cold. In these cases, participants may ask for an adjustment of room temperature or a blanket. Participants who become

nervous or claustrophobic or feel a sense of dizziness while in the scanner may ask to be withdrawn immediately.
Blood Draw: Blood drawing may cause some pain and has a small risk of bleeding, bruising, infection at the puncture site, or dizziness. There is also a small risk of fainting. Standard sterile procedures for blood draw will be used. Blood draws will be conducted by clinicians with significant experience in the technique. Should any of these occur during blood draw, the PI and/or designee will be contacted to assess the situation and offer medical intervention if deemed necessary.
mRNA Collection: All stored specimens will be labeled with subject's unique study identification without any other identifying information. The master list linking the study identifying code will be kept in a separate location from the storage of these samples and will be kept safely locked. Only the PI and Co-Is will have access to this master list. Specimens will be stored in freezers until all data has been collected and the study team is ready to conduct analyses (not greater than one year from study collection). Only the PI and Co-I's will have access to these samples. There are no currently known potential consequences of the genetic information to insurability, employability, or social esteem of the subject. Subjects will be informed that there could be future unknown consequences which could affect their insurability, employability, or social esteem and, as such, all efforts will be made to ensure there is no linked identifying information. The mRNA/gene expression data collected will only be used for the purposes of research and subjects, nor their families, will not be informed of the results of these tests. Subjects will have the right to withdraw from research, withdraw data, and/or withdraw their genetic information either before or after the research has begun or has been completed. We will not transfer this data to other researchers. If a subject wishes to withdraw any and/or all data from the study, they will be instructed to contact the PI. Subjects may participate in the other portions of the study while refusing to undergo genetic testing.

Part C OGTT (optional study): There are no additional risks to subjects beyond what has been described above for Part A regarding risks to MRI, blood draw, mRNA collection, and psychiatric assessments. The OGTT is a safe diagnostic procedure to determine insulin resistance frequently used in clinical practice and as such poses no additional risks to the subject.

7. Statistical Analysis

Power Analysis: For all three specific aims, analyses will be performed on data collected from 100 patients. Given that the primary statistical analyses will be correlational in nature, an N of 100 will be sufficiently powered (>80%) for moderate effect size (~r=0.5) at an alpha = 0.05, two-tailed.[116] All analyses will correlate inflammatory markers with both neuroimaging and behavioral task performance.

For the optional OGTT, to investigate the correlational relationships between inflammatory markers and metabolic markers, a sample size of 19 would be required to find a correlation of 0.7 at an alpha of 0.05 with Power of 0.95 (calculated in G*Power), which suggests that we have adequate power to investigate these primary relationships both before and after OGTT challenge. However, we are underpowered to identify relationships between changes in inflammatory and metabolic markers pre- and post-OGTT with reward circuitry or motivational deficits. These analyses are thus exploratory and will serve as preliminary data for future research proposals.

Interim Monitoring and Early Stopping:

Subjects will receive a physical examination at Part A Screening or Visit 1. Subjects will also receive safety laboratory testing as well as pregnancy (if female) and substance abuse testing at the Part A Screening or Visit 1, in addition to at Part A Visit 2.

The following events are considered sufficient reasons for discontinuing a subject from the study:
- An adverse event (AE) that, in the judgment of the investigator, may cause severe or permanent harm
- A clinical finding, such as an untreated medical condition, from safety labs or the history and physical examination
- Subject withdraws consent

- Subject lost to follow-up
- Pregnancy
- Protocol violation
- Substance abuse
- Death

Study:
If more than two individuals experience a reportable serious adverse event related to study procedures within a six-month period, the study will be stopped and reviewed by the DSMB.

Analysis Plan and Statistical Methods:

Objective 1: The first-level individualized design matrices for each participant will be estimated using a general linear model. Effects of task (see above contrasts) will be computed on a voxelwise basis for each participant in the form of statistical parametric maps of discrete contrasts. Subsequent second level paired t test analyses will be performed on the SPM contrast images. Between-subject effects of task and individual inflammatory marker concentrations (beginning with CRP) will be determined using regression analysis. For the resting state and task based functional connectivity analysis, whole brain, subject-level correlation maps indicating regional similarity with the striatal seed region time series will be generated and Fisher transformed to Z-score maps. In addition, data reduction strategies will be employed to address inflammatory marker collinearity in analyses combining relevant inflammatory markers. To assess significance of correlated activity with each bilateral seed region, paired t-tests will be conducted on participants' Z-score maps, adjusted for multiple comparisons. For significant brain regions, descriptive statistics will be used to characterize the mean, standard deviation, and standard error of the Z scores. Relevant covariates, which may be associated with alterations in functional connectivity or task performance, include body mass index (BMI), age, sex, education, nicotine use, antipsychotic dose (as measured by chlorpromazine equivalents), use of other medications, as well as depression, and will be included in the analyses as appropriate.
Region of Interest (ROI) seed placement and connectivity analysis: 8 basal ganglia seeds (4 per hemisphere) will be used representing regions of the ventral and dorsal striatum as defined in Montreal Neurological Institute (MNI) space. In each hemisphere, seeds will be comprised of a spherical mask with a 6 mm radius centered on the ROI. The ventral striatum will be defined by coordinates (±14, 5, -4) from a previous fMRI study in IFN-alpha-treated subjects demonstrating maximal decreases in response to a hedonic reward task. The other 3 regions, ventral rostral putamen (± 20,12, -3), dorsal caudate putamen (± 28, 1, 3), and dorsal caudate (±13, 15, 9), will be defined according to Di Martino et al. 2008 and other studies assessing functional connectivity with the striatum,[117-119] and consistent with identified subdivisions of the striatum. Whole brain, subject-level correlation maps indicating regional similarity with the seed region time series will be generated and Fisher transformed to Z-score maps. To assess significance of correlated activity with each bilateral seed region, I will conduct paired t-tests on participants' Z-score maps. To correct for multiple comparisons, resulting maps will be cluster corrected ($p<0.05$ whole-brain correction, with a height threshold of $p<0.001$, uncorrected), using SPM12.

Objective 2: Descriptive statistics will be used to characterize the mean, standard deviation, and standard error for each of these clinical and behavioral measures. For the EEfRT, proportion of hard-task choices across each level of probability as well as the difference between the proportions of hard task choices in low and high reward probabilities (effort allocation) will be calculated. Lower proportions of hard task choices indicate decreased motivation for monetary rewards. A larger difference in the proportion of hard task choices reflects more effort allocation. Regression analyses will be conducted to examine the relationship between task performance and concentrations of inflammatory markers (beginning with CRP). Regression analyses examining the relationship between changes in functional connectivity (Z scores) obtained using fMRI and changes in behavior and neuropsychological performance will also be conducted. In cases where data are not normally distributed, we will use standard transformation procedures to achieve normality, and/or use non-parametric tests of significance. The same covariates and data reduction strategies described above will be used in these analyses.

Objective 3: Formal mediation analysis will be conducted to assess whether functional connectivity mediates

the relationship between inflammation (as measured by inflammatory marker concentrations – beginning with CRP) and behavior (clinical ratings and objective measures, as described above). Bootstrapping will be used to provide an empirical estimate of the sampling distribution for indirect effects and will be used to generate confidence intervals for the purpose of inferential testing. A model of moderated-mediation will also be tested to assess whether mediation pathways are influenced by the presence of high vs. low baseline inflammation. Path analysis will be implemented using macros developed by Preacher and Hayes (http://quantpsy.org/medn.htm), which enable inclusion of covariates as well as possible moderators.

Optional Study C Aim 1: Relationships between inflammatory and metabolic markers will be examined by linear regression at baseline and pre and post-OGTT. Change in these markers pre and post-OGTT will also be calculated and compared. Cytokines and their soluble receptors, as well as glucose-related markers at baseline, will be combined into a composite score based on the sum of Z-scores for initial analyses, then assessed individually by linear regression models with selection including clinical covariates. Covariates such as sex, age, race and BMI will be explored as potential confounders or mediators in all analyses.

Optional Study C Aim 2: Targeted FC for each subject and condition will be calculated as the degree of correlation in activity between 3mm3 radius spheres placed in four regions of striatum,[57, 163 142]) that subserve reward processing and other goal-directed behaviors such as motor control,[117,164] and the vmPFC ROI identified as being reward-sensitive in neuroimaging meta-analyses and as used to define vmPFC in our previous work (MNI coordinates x=0, y=44, z=-8, cluster size=1408 mm3 and encompassing parts of BA11 and ventral BA32 of ACC).[57,163,165] Z-scores will be extracted for FC values at baseline and pre and post-OGTT. FC will be assessed between bilateral striatal seeds and the vmPFC ROI separately based on our previous work in MDD and IFN-a-induced depression,[51,57] indicating that effects of inflammation are more pronounced on the left side. Linear regression models will be used to independently examine relationships between inflammation or metabolic dysfunction (Part C, Aim 1) and reward motor pathways. In our previously published work and Preliminary Data, use of inflammatory or metabolic measures as continuous rather than categorical variables were more sensitive for detecting associations with corticostriatal connectivity,[57] and will be the primary method for assessing relationships between inflammation or metabolism (as independent variables) and motivation and motor pathways (as dependent variables, including FC and behaviors). Covariates such as sex, age, race and BMI will be explored as potential confounders or mediators of relationships between biomarkers, brain and behavior.

8. Adverse Event Reporting

Enrolled participants will be monitored closely by study clinicians for any adverse events. If any overt study-related adverse events occur, a decision will be made about study continuation. Additionally, a record of adverse events for study participants will be reported to the DSMB on a regular basis (see below). Subjects will be closely monitored during the course of the study for development of any serious or unexpected adverse reactions. Those events meeting Emory IRB criteria for a reportable event will be reported to the IRB or DSMB according to standard regulations and procedures. The Emory IRB defines a serious adverse event as: “any adverse experiences occurring that result in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. For the purposes of this policy, death is never expected.”

9. Data and Safety Monitoring Plan (DSMP)

Adverse events are a normal part of participation in human subjects research and thus will be assessed at each study visit. For this reason, we have elected to utilize the Data Safety Monitoring Board (DSMB) of the Department of Psychiatry and Behavioral Sciences as a third-party oversight committee. The DSMB is described in detail below. In addition, study clinicians will be available 24 hrs/7 days a week during the period between screening and study completion. Should a subject’s psychiatric symptoms appreciably worsen or should active suicidal ideation develop, either Dr. [redacted] will be immediately notified. Drs. [redacted] are board certified psychiatrists with extensive experience in the treatment of psychiatric emergencies. If the assessment in question was done by a clinician other than either of them, one of them will

immediately contact the subject and will evaluate the need for further psychiatric treatment and will arrange psychiatric follow-up. They will evaluate each case individually to make a determination regarding whether the subject can remain in the study or whether the subject should be terminated in addition to receiving a mental health referral. All adverse events, serious adverse events and unanticipated problems will be captured for severity and relatedness to study participation, evaluated by a study physician or designee, and reported to the IRB, the DSMB, and the NIH if appropriate.

Of note, in regards to the Part B optional infliximab study, based on a random internal audit (not for cause) of a previous infliximab trial in Dr. [redacted] lab, accolades were given for regulatory compliance and documentation of all adverse events as well as timely reporting and processing with the Emory DSMB and IRB.

Composition of the Data Safety Monitoring Board (DSMB)

Frequency of DSMB review for this protocol will follow recommendations from the IRB based on the assessed risk status of the study. The DSMB for this study will consist of the Clinical Research Oversight Committee with members including [redacted] M.S.W. They have agreed to serve as the external DSMB for investigator initiated clinical trials conducted by Emory researchers in the Department of Psychiatry & Behavioral Sciences. If the DSMB requires additional specialized expertise to evaluate safety issues related to the performance of this study, a relevant specialist will be consulted by the DSMB.

Procedures and Responsibilities of the DSMB

The DSMB will meet quarterly. This protocol will be submitted to the DSMB simultaneously with the initial submission to the Emory IRB. The DSMB will review the research protocol and plans for data and safety monitoring. Once per year (or after 6 months if the protocol is considered 'high risk' by the IRB), the DSMB will review a report from the study's data manager that includes: the number of participants who signed consent for the study, the number of dropouts, reasons for these dropouts, and any safety concerns, adverse events, an up-to-date consent form, and measures taken to protect confidentiality (e.g., data storage, use of coded ID numbers, etc.). The DSMB will also review the Principal Investigator's summary of any new data or evidence that might alter the risk/benefit ratio for participating in the study (e.g., newly published studies, etc.). After reviewing this information, the DSMB will issue its own report summarizing any serious and unexpected adverse events or other unanticipated problems that involve risk to study participants, and whether these appear related to the study-based interventions or research assessment protocols.

There will be regular, ongoing communication between the PI, Emory's IRB, and the DSMB. The PI will take responsibility for submitting reportable serious and unexpected adverse events or other unanticipated study problems to Emory's IRB according to standard regulations. A copy will be sent to the DSMB. Actions taken by the IRB in response to adverse event reports will be immediately reported to the DSMB.

The study will not involve a waiver of informed consent in an emergency room setting.

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