The Innate Central Nervous System Immune Response to an Experimental Immune Challenge in People With Fibromyalgia

Protocol

NCT04263454

Version Date: 01/06/2021

Jarred Younger, Professor, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Methods

Design

This study utilized a mixed (group-by-time) design to compare changes in brain metabolites before and after an experimental endotoxin challenge between FM and HC groups. Participants underwent an MRI 1.5 hours before receiving the endotoxin infusion, and 4 hours after. The following were measured with EPSI in 47 brain regions as primary outcomes: brain temperature, CHO, MI, and NAA.

Procedures

Study procedures were approved by the University of Alabama at Birmingham (UAB) Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Participants provided written informed consent prior to any procedures. A payment of $50 was provided following completion of the screening visit, and $600 was provided for the experimental session. Screening and experimental sessions were performed at the Clinical Research Unit (CRU) located at UAB Hospital. Brain imaging was conducted at the UAB Civitan International Imaging Laboratory (CINL). During the experimental session, participants were transported between locations via rideshare transportation.

Participants

Women with FM aged 18-55 and healthy age-matched women were recruited from the Birmingham community via online advertisements on the UAB Clinical Trials website. Our laboratory maintains a database of individuals who have indicated an interest in research, from which additional participants were contacted. Participants in the FM group met the revised diagnostic criteria by the American College of Rheumatology,[1,39,40] endorsed at least eleven out of nineteen positive tender points on a physical exam, and reported an average daily widespread

pain severity of at least 6 on a 0-10 scale. HCs reported average daily pain of 1 out of 10 or less. The following exclusion criteria were applied to both groups: i) MRI contraindications; ii) ECG abnormalities (QTc>450ms, QRS>120ms); iii) fever >99.0 °F; iv) hypotension or hypertension (systolic blood pressure outside of 100-140 range, diastolic blood pressure outside of 60-90 range); v) resting heart rate <55bpm; vi) body mass index (BMI) outside of 19.0-39.9 range; vii) current smoker (within 12 months of study); viii) pregnant, planning to become pregnant, or breastfeeding; ix) high alcohol consumption (>1 drink/day or >4 drinks on a single occasion per week); x) use of illicit substances within six months of participation; xi) vaccination within four weeks of participation; xii) viral or bacterial illness requiring medical attention or antibiotics within three months of participation; xiii) concurrent participation in another research study; xiv) surgical procedure within three months of participating; xv) history of rheumatologic or autoimmune disease (e.g., multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis); xvi) other major medical conditions (e.g., cancer, blood or clotting disorder, HIV, Hepatitis C infection, diabetes); xvii) regular use of anti-inflammatory or immunomodulatory drugs, xviii); current use of opioid analgesics; xix) Hospital Anxiety and Depression Scale (HADS)[41] depression total score ≥13; xx) values outside clinical reference ranges on tests of renal function, tri-iodothyronine, thyroxine, thyroid stimulating hormone, complete blood count with differential, and 25-hydroxy vitamin; xxi) detectable rheumatoid factor or antinuclear antibody, xxii) erythrocyte sedimentation rate >60 mm/h, xxiii) high sensitivity C-reactive protein (hsCRP) >10 mg/L, and xiv) ongoing litigation or worker's compensation claim.

Screening visit

Initial inclusion and exclusion criteria, including medical history, ACR criteria, HADS score, and MRI safety, were established via brief phone calls. Interested individuals presented in person to the CRU to complete the remaining screening procedures. Participants underwent a urine pregnancy test and ECG. A tender point exam was administered by applying up to 4kg pressure at a rate of 1kg per second to the nineteen tender points established by the ACR[39] with an FPK20 manual algometer (1cm diameter; Wagner Instruments, Greenwich, CT). Thirty-three cc blood was collected by research nurses and transported to the UAB Hospital laboratory for processing and confirmation of inclusion/exclusion criteria. Participants also completed the Brief Pain Inventory (BPI)[42] and Fibromyalgia Impact Questionnaire[43] (FIQ, FM participants only).

Experimental Session

Participants presented to the UAB CRU and underwent a repeat ECG for safety and were then transported to the CINL for brain imaging. Participants returned to the CRU, where endotoxin from *E. coli* (0.4ng/kg body weight, N=14, or 0.3ng/kg body weight, N=11) was administered via infusion over 30 minutes. The endotoxin dose was reduced to 0.3ng/kg after several participants experienced adverse events following 0.4ng/kg infusions. Two standardized meals of 834 kcal and 508 kcal were provided to participants prior to the first MRI session and 1 hour after the endotoxin infusion, respectively.

Image Acquisition

MRI data were collected on a Siemens Magnetom Prisma 3-Tesla scanner with 20-channel head coil. Participants laid supine, were provided with hearing protection, and were instructed to keep their eyes closed during the acquisition. A T1-weighted structural brain scan

was collected with a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR: 2000 ms, TE: 2.51 ms, TI: 901ms, flip angle: 8°, field-of-view (FoV): 230 × 230 mm, matrix: 256 × 256, 176 slices, 0.9 mm isotropic voxel resolution. Fast 3-dimensional echoplanar spectroscopic imaging (EPSI) with spin-echo excitation was performed following automatic and manual iterative shimming, with the following parameters: TR: 1550 ms, TE: 17.6 ms, inversion time (TI) for lipid inversion nulling: 198 ms, flip angle: 71°, FoV: 280 × 280 mm, matrix: 50 × 50, 18 slices, 5.6 × 5.6 × 10 mm voxel resolution. The acquisition time for EPSI was 17:48 min. Participants had their body temperature measured in both ears with a Braun Pro 4000 ThermoScan thermometer before and after the MRI.

Image processing

The Metabolite Imaging Data Analysis System (MIDAS)[44,45] was used to process the whole-brain spectroscopy data as previously described.[46-48] Preprocessing is fully automated and includes reconstruction of the spectroscopic images, lipid extrapolation and Gibbs ringing correction, corrections for b0 shifts, Eddy current correction, interpolation to 64×64×32 voxels, smoothing with 5×7mm Gaussian kernel (final voxel size: 5.6×5.6×5 mm), and automated fitting of the CHO, creatine (CR), MI, and NAA peaks with Gaussian line shapes. Apparent brain temperature was calculated with the following formula: $T_{CR} = -102.61(\Delta_{H20-CR}) + 206.1°C$, where Δ_{H20-CR} is the difference in resonance frequencies between the water and CR preaks.[49,50] The metabolite and temperature maps were co-registered with the structural images and the structural images were then non-linearly transformed to Montreal Neurological Institute (MNI) space. Finally, the inverse spatial transform was applied to a modified Automated Anatomical Labeling (AAL) atlas[51] with the PRANA module in MIDAS to obtain atlas regions in subject

space. Mean metabolite levels and temperature were extracted from each ROI for statistical analyses.