Food Additives Effects on EEG Profiles in College Students With ADHD

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Protocol

Participants with ADHD and controls without ADHD will be recruited from a mid-Atlantic University through on-campus advertisements and word of mouth. Inclusion criteria are 1) currently enrolled at the university, 2) 18-24 years old, 3) following a stable medication dose and frequency (ADHD medication or otherwise) for at least 3 months. If in the ADHD group, additional inclusion criteria are 1) diagnosed with ADHD by a primary care doctor, psychiatrist, or psychologist and 2) willingness to suspend ADHD medication for 24-48 hours before testing days. Exclusion criteria are 1) seizure disorder, 2) past hospitalization for asthma, or 3) any comorbid disorder requiring an anti-psychotic medication.

The research study was approved by the University's IRB (IRB-2017-151) and written informed consent will be provided by each participant. Baseline assessments for ADHD and control participants included collection of demographic and anthropometric data, completion of cognitive testing using CNS Vital Signs ® (CNSVS) software, completion of the Adult ADHD Self-Report Scale (ASRS), and 4 minutes of eyes closed resting-state EEG recording. To avoid medication effects, ADHD medication use will be suspended for 24-48 hours before testing, as appropriate for the half-life of the medication.

After baseline testing, ADHD participants and a small subset of control participants will complete in-person dietary training to learn how to identify and avoid AFC in the diet. Dietary training will include reviewing the FDA approved AFC names, identifying such names on food labels, reviewing common foods containing AFC and their AFC-free alternatives, and talking through their average diet to identify foods containing AFC. Participants will be given a paper copy of the dietary training and emailed a PDF version.

Participants will avoid AFC in the diet for the remaining 4 weeks of the study: participants followed the diet for 2 weeks before beginning the 2-week crossover challenge. After 2 weeks on the diet, participants will complete an AFC specific Food Frequency Questionnaire (FFQ) to measure dietary compliance and then will be randomized to a double-blind placebo-controlled crossover challenge for 3 days each, of 2 consecutive weeks. The challenge materials are either 225mg of mixed powder AFC (i.e., Red No. 40, Red No. 3, Yellow No. 5, Yellow No. 6, Blue No. 1, Blue No. 2) disguised in chocolate cookies, or placebo chocolate cookies with no AFC.

Chocolate cookies work well for blinding since when these colors are mixed together, they are close to brown in color. The mixture of AFC was chosen to incorporate the colors most often consumed in the diet, and the amount of each AFC used was half of the Estimated Daily Intake (EDI) of a high-consumer, as determined by the FDA. Powdered AFC will be used to avoid any possible confounding effects from propylene glycol or sodium benzoate which are commonly used in liquid food coloring. A 4-day washout period was implemented to avoid carry-over effects. The CNSVS cognitive testing, ASRS, and EEG recordings will be repeated at the end of each 3-day exposure.

Adult ADHD Self-Report Scale (ASRS)

The ASRS-v1.1 is a reliable and valid scale used for assessing ADHD symptoms based on the DSM-IV-TR criteria in the adult population. The ASRS includes 6 questions in Part A that are considered most predictive of adult ADHD and 12 questions in Part B that further probe at specific symptom profiles. Scoring is based on the frequency of symptoms asked in each question, ranging from 0 for "never" to 4 for "very often", with a higher score indicating a higher likelihood of ADHD. The ASRS is a screener for adult ADHD and asks about symptoms over

the last 6 months, however participants were asked to answer questions based on the week leading up to the testing to capture potential short-term effects of AFC. Additionally, ASRS questions were broken up into "inattentive" or "hyperactive" sub-classifications based on CNSVS protocol for adult ADHD testing, resulting in 9 inattentive questions and 9 hyperactive questions, and then these were scored. Thus, each participant will receive an inattentive, hyperactive, and total ASRS score.

CNSVS Cognitive Testing for Attention

CNS Vital Signs ® (CNSVS) software will be used to test simple and complex attention. Simple attention is measured using a Continuous Performance Test (CPT) to analyze the correct response rate and to assess whether the correct responses are more frequent than commission errors. Complex attention is a composite score created from performance on a Stroop task, CPT, and Shifting Attention Task.

Quantitative Electroencephalography (EEG)

Participants will sit in a comfortable chair facing a computer monitor in an air-conditioned, sound attenuated room. Four minutes of eyes-closed resting-state data will be collected at baseline and at the end of each challenge period. Participants will be instructed to remain as still as possible while being relaxed, but awake.

EEG recording will be completed using g.tec equipment (http://www.gtec.at). Twenty-five Ag/AgCL g.SCARABEO Z electrodes (16x10x5 mm, 125 cm lead) will be used with an adult size cap (g.GAMMAcap2) according to the International 10-20 System (FP1, FP2, , F3, F4, F5, F6, F7, F8, Fz, AF3, AF4, C3, C4, Cz, T7, T8, , P3, P4, P7, P8, P9, P10, Pz, O1, O2) with the reference on the right earlobe and the ground electrode placed at Fpz. Impedance remained

below 5 kOhm for all electrodes. A sampling rate of 256 Hz, input signal filter of 0.5-60 Hz, and a 60 Hz notch filter were applied online.

EEG recordings will be analyzed in EEGLab and The Batch Electroencephalography Automated Processing Platform (BEAPP). In BEAPP, a bandpass filter will be applied (1 Hz-50 Hz). To remove artifacts, Independent Component Analysis (ICA) with multiple artifact rejection algorithm (MARA) will be used. The data will be re-referenced to the average and segmented into 2-second epochs, with time points rejected if more than 0.01% of the epoch was >150μV. Power spectral density (PSD) will be calculated using the Fast Fourier Transform (FFT) with a Hanning window. Mean power and relative power will be calculated for delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-50 Hz) frequency bands. Mean power is the sum of the power values of each frequency band divided by the frequency bandwidth, a

measure similar to absolute power. Relative power is the absolute power of a specific frequency band divided by the absolute total power of all bands. The theta-beta ratio (TBR) will also be calculated. Each band and ratio was then averaged over frontal electrodes (Fp1, Fp2, F3, F4, F5, F6, F7, F8, Fz, AF3, AF4), central electrodes (Cz, C3, C4), and posterior/temporal electrodes (Pz, P3, P4, P7, P8, P9, P10, T7, T8, O1, O2).

Statistical Analysis Plan (SAP)

All data will be analyzed in SPSS ® V25.0. Baseline comparisons between the ADHD and controls for demographic and anthropometric data will be run using Wilcoxon rank sum test for non-normal continuous variables, Student's t-test for normal continuous variables, or Chi-Square test for categorical variables. Baseline comparisons of mean and relative EEG power between groups will be analyzed using Wilcoxon rank sum test. Challenge week analyses for the ADHD and EC group will be run using General Linear Modeling (GLM) with the within-

subjects variable being the challenge week material (AFC/placebo) and the between-subjects variable being the order of challenge materials. GLMs will be run for ASRS scores (inattentive, hyperactive, and total), simple attention measures, complex attention measures, and each frequency band of interest or TBR in the frontal, central, and posterior regions. At least 75% of the EEG data segments will need to be usable after preprocessing for the participant data to be included in the statistical analyses.

Since this is the first pilot study on this topic, a power analysis for sample size was not able to be performed. Therefore, uncorrected p-values will be reported to a significance level of $p=0.05$ to note possible effects of AFC across all measures.