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Randomized double-blind inpatient study of a gluten-free diet for negative symptoms in people with schizophrenia

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ABSTRACT

Background: There are no FDA-approved treatments for negative symptoms in schizophrenia and related disorders (SRD). In an SRD subgroup with systemic and central inflammation and elevated anti-gliadin immunoglobulin G antibodies (AGA IgG+), previous findings suggested that a gluten-free diet (GFD) improved negative symptoms.

Methods: We conducted a five-week double-blind randomized placebo-controlled inpatient trial comparing a GFD versus a gluten-containing diet (GCD) in people with SRD and elevated AGA IgG+ ($N = 39$; $n = 21$ GFD and $n = 18$ GCD). The Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure (CAINS MAP) scale measured the primary outcome of negative symptoms. Secondary outcomes evaluated other symptom domains and serum kynurenine pathway metabolites. Also, we explored inflammatory markers and, in $n = 20$ participants, measured cerebral blood flow (CBF) using Arterial Spin Labeling, and neurochemistry using magnetic resonance spectroscopy.

Outcomes: Relative to a GCD, a GFD was associated with a modest decrease in CAINS MAP scores ($df = 31.2.1$, $F = 2.96$, $p = 0.035$); decrease in kynurenic acid (KYNA; $df = 32$, $F = 9.51$, $p = 0.0042$) and kynurenine ($df = 32$, $F = 11.45$, $p = 0.0019$); and increase in CBF and total creatine in frontal brain regions. KYNA and CAINS MAP change scores were correlated ($r = 0.350$, $p = 0.039$) while cognition was not impacted.

Discussion: Our preliminary data suggests that a GFD may be associated with modest improvements on experiential negative symptoms within an SRD subgroup. A GFD may be associated with reductions in kynurenine pathway metabolites and increased CBF. Larger and longer studies are needed to confirm negative symptom efficacy in this AGA IgG+ SRD subgroup.

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1. Introduction

Schizophrenia and related disorders (SRDs) are characterized by positive (hallucinations, delusions and disorganized thinking) and negative symptoms, chiefly anhedonia and avolition. These experiential negative symptoms have been shown to be the main determinant of social and occupational dysfunction and predictors of long-term functional outcomes (Keefe et al., 2006). There are no FDA-approved treatments for negative symptoms, leaving a critical gap in care for people with SRD (Nuechterlein et al., 2008).

Worldwide SRD rates are lower in areas with little to no wheat consumption (Chan et al., 2015; Dohan et al., 1984; van Os, 2016), and rates of SRD diagnoses were correlated with rates of wheat consumption during World War II (Dohan, 1966a, 1966b). Several clinical trials performed in the 1950s–80s reported symptom improvement (Dohan et al., 1969; Osborne et al., 1982; Potkin et al., 1981; Rice et al., 1978; Sheldon, 1959; Singh and Kay, 1976; Storms et al., 1982; Vlissides et al., 1986) following removal of wheat from the diets of people with SRD; however, these studies lacked a systemic biomarker to define subphenotypes for who were likely to respond (Phillips and Kendler, 2021). The understanding of subgroups is of growing importance, as SRD is a heterogeneous illness, caused by a multitude of complex factors beyond dopamine dysregulation. People with SRD suffer from higher rates of autoimmune disorders (Eaton et al., 2006) and immune dysfunction (Fineberg and Ellman, 2013; Nguyen et al., 2023), based on in vivo (Gupta et al., 1997) and ex vivo studies (Hemmings, 2004). Accumulating evidence suggests that inflammation plays a role in a subset of those with SRD (Kelly and Buchanan, 2022; Kendler, 2019; Pratt et al., 2018).

We identified a subgroup of people with SRD who have an immune response to gliadin, a protein found notably in wheat. We find 33–38% of people with SRD to have elevated Antigliadin Antibodies Immunoglobulin G (AGA IgG+) compared to 10% of the general population (Cihakova et al., 2018; Daniels et al., 2023; Dickerson et al., 2016; Jackson et al., 2014; Lachance and McKenzie, 2014; Okusaga et al., 2013; Sidhom et al., 2012). In this SRD subgroup, AGA IgG+ is correlated with both peripheral inflammatory markers (Daniels et al., 2023; Jackson et al., 2014; Kelly et al., 2018a), brain neurochemistry markers indicative of inflammation (Rowland et al., 2017) and differential T cell abundance and function (Salem et al., 2025). The AGA IgG+ subgroup also has fewer positive symptoms and more negative symptomatology (Jackson et al., 2014) that may improve after removal of gluten from the diet, as evidenced by our previous open-label (Jackson et al., 2012) and randomized double-blind studies (Kelly et al., 2019). The AGA IgG+ subgroup also had high levels of the pivotal tryptophan metabolite kynurenine in the plasma (Okusaga et al., 2016), which decreased after removal of dietary gluten in our previous trial (Friendshuh et al., 2020). Notably, kynurenine and its metabolite kynurenic acid (KYNA) may be related to SRD pathophysiology (Cao et al., 2021; Chen et al., 2024; Orhan et al., 2025; Plitman et al., 2017).

Here, we present results of a five-week double-blind placebo-controlled randomized trial. The primary aim was to evaluate the efficacy of a gluten-free diet (GFD) versus a gluten-containing diet (GCD) for improving negative symptoms in persons with SRD who are AGA IgG+. Secondarily, we examined the effects of a GFD on circulating kynurenine and KYNA levels and other symptom domains and we explored the impact of diet on inflammatory markers, neuroimaging measures of cerebral blood flow (CBF) and neurochemistry in brain areas related to negative symptoms. We hypothesized: 1) that we would see a decrease in negative symptoms, specifically in domains of anhedonia and asociality, 2) that we would see and improvement in cognitive function and decreases in kynurenine and KYNA 3) that in explorative analyses, we would see evidence that CBF increases and peripheral inflammatory markers would decrease with a GFD.

2. Methods

2.1. Study design

This 5-week randomized double-blind clinical inpatient trial was conducted at the Maryland Psychiatric Research Center (MPRC), University of Maryland School of Medicine, Maryland, USA. Screening was performed at the MPRC and Johns Hopkins University School of Medicine, Maryland, USA. The University of Maryland Baltimore institutional review board approved the clinical trial (HP-00075175). The study was reviewed annually by a data safety and monitoring board, approved by the Spring Grove Hospital Center (SGHC) research committee, and was registered in ClinicalTrials.gov (NCT03183609).

2.2. Participants

All participants provided written informed consent after passing the Evaluation to Sign Consent (with score $\geq$ 10/12) (DeRenzo et al., 1998). Over the course of 1–2 screening visits, participants' psychiatric diagnoses were confirmed by the Structured Clinical Interview for Diagnosis of DSM-IV/DSM 5 (SCID) (First et al., 1997). Eligibility was established by medical history and physical examination by a medically accountable physician and a standard blood chemistry panel, complete blood count, urinalysis, and electrocardiography. Before COVID 19, participants could have been admitted from the community into the hospital to participate. Only current inpatients were eligible to participate from COVID 19 onward. A five-week study was selected initially as the feasible duration for inpatient admission. Antipsychotic, antidepressant, and mood stabilizers remained unchanged throughout the 5 weeks as per protocol.

Participants ages 18–64 years were eligible based on the following inclusion criteria: (1) diagnosis of schizophrenia or schizoaffective disorder (DSM-IV-TR/DSM-5-TR) and confirmed by the SCID; (2) AGA IgG level > 20 U (AGA IgG+); (3) treatment with the same antipsychotic for at least 4 weeks prior to the study; (4) Scale for the Assessment of Negative Symptoms (SANS) total score $\geq$ 20, OR, a SANS avolition, affective flattening or alogia global item score $\geq$ 3, OR, a SANS anhedonia asociality subscore $\geq$3 (Buchanan et al., 2015).

Exclusion criteria included tTG positivity (presumed celiac disease); adherence to a gluten-free diet prior to the study; active pregnancy or lactation; history of organic brain disorder or intellectual disability; history of a medical condition whose pathology or treatment could alter study participation or safety; gluten ataxia determined by physician with aid of the Brief Ataxia Rating Scale (Schmahmann et al., 2009); and DSM-IV/DSM 5 criteria for alcohol or substance abuse (other than nicotine) within the last month. Additional exclusion criteria for those participating in the optional imaging component included: i) non-removable ferromagnetic metal on or within the body, ii) current claustrophobia, iii) inability to lie supine for 1.5 h.

2.3. Procedures

All enrolled participants were inpatients on the research unit (Treatment Research Unit at MPRC/SGHC). Participants received 15 g of either rice flour (GFD; Bob's Red Mill®) or gluten flour (GCD; Bob's Red Mill®) mixed in twice daily protein shakes each containing water, ice, protein powder (Sunwarrior Plant-Based Protein), and optional syrup of the participants' choice. Bob's Red Mill® was selected because the rice flour is certified gluten-free. Throughout the study, participants in both groups received gluten-free meals, consisting of a 7-day rotating (21 meal) schedule prepared according to the strict gluten-free operating procedures of the hospital kitchen and clinical oversight by a Registered Dietician. The target ingestion of gluten was below 15 mg for those in the GFD group (Catassi et al., 2007). During the day, a 1:1 staff-to-participant ratio was used to ensure protocol adherence and shake consumption. Research nurses communicated daily with the research

team regarding all meals and shake details. All packaged food consumed was confirmed gluten-free. The mean daily calorie level was 2737 per day. The breakdown was 119 g protein (17%), 347 g carbohydrate (51%), 97 g fat (32%) with 343 mg cholesterol, 25.2 (8%) saturated fat, and 3689 mg of sodium.

The study intervention was added to participants' ongoing antipsychotic regimen. Study physicians were encouraged to avoid dose changes of somatic and psychotropic medications during the study. Anticholinergic medications for extrapyramidal side effects (e.g., benztropine and diphenhydramine), propranolol for akathisia and benzodiazepines for anxiety or agitation (e.g., lorazepam) could be prescribed as needed.

2.4. Randomization and masking

Participants, researchers, and clinical team members were blinded to intervention assignment. Treatments were assigned at random, using computer-generated permuted block randomization sequences with varied block sizes to limit imbalance in the number of patients assigned to each group while making it difficult for staff to predict what treatment patients were receiving.

Randomization codes were sent by the study statistician to the unblinded research pharmacist for dispensing. The 15 g packets of identical white flour were weighed and packaged for delivery to the hospital research unit. Twice daily, the research nurse on the unit used a blender to combine the flour with the protein powder and about 24 oz. of water. On the unit, each participant was assigned a blender so that no sharing of blenders occurred. The research nurses documented the time of the shake and were one on one observation during the time of the shake ingestion. All study participants and all staff were blinded in this study with no unblinding during the study.

2.5. Outcomes

2.5.1. Primary outcome

The primary outcome of this trial was negative symptom change using the Clinical Assessment Interview for Negative Symptoms (CAINS) Motivation and Pleasure (MAP) scale (Kring et al., 2013). The CAINS MAP offers advantages over other negative symptom scales including: (1) the incorporation of both observed and subjective report, (2) avoidance of symptoms relevant to other psychopathological dimensions of functioning, (3) providing separate assessment of consummatory vs anticipatory anhedonia (Giordano et al., 2022), and (4) mapping well to functional outcomes (Kring et al., 2013). We note that inclusion criteria were based on a minimum SANS score rather than CAINS MAP, thereby enriching for a broader range of negative symptoms. At the time of study design, CAINS MAP had not been used for inclusion criteria, and we therefore employed established SANS-based criteria (Buchanan et al., 2015).

2.5.2. Secondary outcomes

2.5.2.1. Clinical symptoms. We also measured the SANS total score (Andreasen, 1982; Andreasen and Olsen, 1982), the CAINS Expressivity Scale (EXP) and the 18-item Brief Psychiatric Rating Scale (BPRS) total score (Overall and Gorham, 1962), and the Clinical Global Impression Scale (CGI) (Guy et al., 1976). The BPRS four-item psychosis factor (conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content) (Raskin, 1988) and hostility factor are reported. All these scales were performed at baseline and weekly throughout the study. Raters were required to show agreement with an intraclass correlation coefficient (ICC) >0.8 as compared to gold standard ratings of training tapes, and they regularly maintained ICCs >0.8 in monthly training exercises throughout the course of the study.

2.5.2.2. Cognitive function. Cognition was assessed at baseline and endpoint using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008), both as individual domains and as a composite score standardized to the general population (Kern et al., 2008; Nuechterlein et al., 2008). Executive function was separately assessed using the Tower of London Test (Keefe et al., 2004; Keefe et al., 2006).

2.5.2.3. Kynurenine pathway metabolites. Blood samples were collected at baseline and study endpoint for all laboratory tests, centrifuged then stored at −80 °C until use. Plasma was collected using EDTA tubes. Thawed plasma was diluted (1:2 *v*/v) in ultrapure water on the day of the assay. Two hundred microliters (μL) were acidified with 50 μL of 6% perchloric acid. After centrifugation (16,000 x*g*, 15 min), 20 μL of the resulting supernatant were applied to a 3-μm Reprosil C18 HPLC column (100 mm × 4 mm; Dr. Maisch GmbH, Ammerbuch, Germany). Kynurenine and KYNA were isocratically eluted using a mobile phase containing 50 mM sodium acetate and 5% acetonitrile (pH adjusted to 6.2 with glacial acetic acid) at a flow rate of 0.5 mL/min. Using post-column derivatization with 500 mM zinc acetate, delivered at a flow rate of 0.1 mL/min, both kynurenine and KYNA were measured in the eluate using fluorometric detection [kynurenine; excitation: 365 nm, emission: 480 nm; KYNA; excitation: 344 nm, emission: 398 nm]. The retention times of kynurenine and KYNA were ~ 6 min and ~ 10 min, respectively.

For the measurement of 3-hydroxykynurenine (3-HK), 25 μL of 6% perchloric acid were added to 100 μL of the thawed plasma sample and vortexed thoroughly. After centrifugation (16,000 x*g*, 15 min), 20 μL of the resulting supernatant were applied to a 3-μm HR80 column (80 × 4.6 mm, Thermo-Fisher Scientific, Waltham, MA, USA), using a mobile phase consisting of 1.5% acetonitrile, 0.9% triethylamine, 0.59% phosphoric acid, 0.27 mM sodium EDTA, and 8.9 mM heptane sulphonic acid, and a flow rate of 0.5 mL/min. In the eluate, 3-HK was detected electrochemically (Eicom HTEC-500; San Diego, CA, USA) at an oxidation potential of +0.5 V. The retention time of 3-HK was ~10 min.

2.5.3. Exploratory outcomes

2.5.3.1. Neuroimaging. Neuroimaging was performed on all participants who met neuroimaging criteria and agreed to have a scan ($N = 20$; 16M/4F) at baseline and week 5 using a 3T MR system (Prisma, Siemens Medical Solutions, Inc., Erlangen, Germany) equipped with a 64-channel head coil. Imaging protocols used in this study are described elsewhere (Kochunov et al., 2016; Rowland et al., 2016). 800-micron HCP T1-weighted structural data were collected for anatomical reference. Gray and white matter CBF was measured using three-dimensional pseudo-continuous Arterial Spin Labeling (pcASL) with background suppressed gradient and spin-echo sequence consisting of 13 pairs of labeled and control scans. The acquisition parameters were: spatial resolution = 2.5 mm × 2.5 mm × 2.5 mm, matrix size = 96 × 96 with 58 axial slices, repetition time/echo time (TR/TE) = 4000/37 ms, flip angle = 120°, field of view (FoV) read = 220 mm, FoV phase = 100%, post-label delay = 1700 ms, and labeling duration = 1650 ms. Furthermore, a volume of M_0 image was acquired without background suppression to normalize the control-label difference for CBF quantification. The M_0 image was smoothed with a 5 mm Gaussian-kernel to suppress noise. CBF data analysis was performed with the FSL software package. Perfusion was estimated by using a standard single compartment ASL model, and partial volume effects correction was performed with a spatially regularized method (Chappell et al., 2011). CBF maps were used to extract the average regional CBF signals using the volumetric Desikan-Killiany (DK) atlas. Supplementally, we report data using the human Brainnetome (BNE) atlas to visualize greater regional specificity using an atlas with 246 regions.

Neurochemical measures were determined with magnetic resonance

spectroscopy (MRS) methods as reported previously (Rowland et al., 2016; Wijtenburg et al., 2017). Spectra were acquired from a voxel placed in the medial frontal region, an area involved in negative symptoms, with a phase rotation STEAM: TR/TM/TE = 2000/10/6.5-ms, VOI ~24 cm^3, NEX = 128, 2.5-kHz spectral width, 2048 complex points, and phases: φ1 = 135°, φ2 = 22.5°, φ3 = 112.5°, φADC = 0°. A water reference (NEX = 16) was also acquired for phase and eddy current correction as well as quantification. Spectroscopy post-processing methods are detailed in the Supplementary Methods.

2.5.3.2. Inflammatory markers and AGA IgG. For cytokines and AGA IgG, blood was collected in serum separator tubes, and serum was assayed at the Cihakova lab at Johns Hopkins University (Baltimore, MD). AGA IgG were analyzed using semi quantitative ELISA assays from Inova Diagnostics (San Diego, CA; catalog # 708650). Cytokines were measured using EMD Millipore's MAP Human Cytokine Magnetic Bead panel (Luminex bead-based immunoassays (Millipore, Billerica NY)); (IL-1β, IL-1ra, IL-2, IL-6, IL-10, IL-12, IL-17A, TNF-α, and IFN-gamma). The readout was completed using a multiplex Bioplex 200 platform (Biorad, Hercules, CA). IL-23 was measured using an ELISA assay from R and D systems and a readout on a Spectramax 384 plate reader.

2.5.4. General medical and side effect monitoring

At baseline and endpoint, we administered the Short Form-36 for general health assessment (McHorney et al., 1994), the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989), and the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994). Participants had vital sign assessments weekly, were administered the 15-item Gastrointestinal Symptom Rating Scale (GSRS) (Revicki et al., 1998), the Simpson-Angus Extrapyramidal Symptom Rating Scale (SAS) (Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS) (Barnes, 1989, 2003), and the 23-item Side Effect Checklist (SEC). Other spontaneous adverse events were also recorded. Body mass index (kg/m^2), complete blood count (CBC), and a complete metabolic panel (CMP,14-item) were also assessed.

2.6. Statistical analysis

Baseline demographic and clinical data were evaluated using Kruskal-Wallis tests and Chi-Squared analyses for continuous and dichotomous variables.

2.6.1. Primary outcome

For the primary outcome of negative symptoms, we compared the GFD to GCD over 5 weeks using a mixed model ANCOVA for repeated measures, including all data (including noncompleters) for those treated with the diet for at least 1 week (a priori criteria), with treatment differences adjusted for baseline scores. We examined treatment x time interactions to detect differences between groups over the full course of 5 weeks of treatment. Graphically we display the CAINS MAP data over 5 weeks. A sample size of 16 participants per group was estimated to be sufficient to detect significant effects at week 5 with a power ≥ 0.80 based on the prior double-blind trial (Kelly et al., 2019).

2.6.2. Secondary outcomes

Secondary clinical symptoms and cognitive measures were also analyzed using ANCOVAs, adjusting for baseline scores and examining treatment x time interactions using data collected at all five weeks. Kynurenine pathway metabolites were collected only at baseline and endpoint, thus only including 2 points in the ANCOVA analysis.

2.6.3. Exploratory outcomes

All exploratory analyses were conducted using Cohen's D effect size only to detect an effect as we were not powered to show an effect.

2.6.3.1. ASL and MRS. The final neuroimaging sample included 20 participants and data is presented using a heat map change to visualize differences in the effect sizes. For ASL analysis we used the Desikan-Killiany (DK) atlas, a widely used parcellation scheme that divides the brain into 34 cortical and 7 subcortical brain regions from each hemisphere, based on gyri and sulci.

Effect sizes are also calculated for MRS neurochemicals including, total choline (glycerophosphocholine + phosphocholine), myoinositol, glutamate, glutamine, glutamate + glutamine, glutathione, total *N*-acetylaspartate (*N*-acetylaspartate+ *N*-acetylaspartylglutamate), and total creatine (creatine + phosphocreatine).

2.6.3.2. Inflammatory markers. Inflammatory markers were drawn at baseline and endpoint. We log transformed the values due to non-normal distribution of the values for data analysis.

2.6.4. Safety data

We report safety labs, movement disorder scales and gastrointestinal side effects using a repeated measures ANCOVA controlling for baseline using baseline and endpoint changes. We descriptively report side effects and adverse events.

For all analyses we used a significance threshold of $p \leq 0.05$, at $\alpha < 0.05$ (two-tailed). Trend-level findings were noted when $p > 0.05$ and ≤ 0.10.

3. Results

From October 2017 to November 2023, a total of 43 participants were randomized, and 39 met a priori criteria for study inclusion ($N = 2$ food violations week 1, $N = 1$ refused to get assessments and N = 1 did not want to do the diet. All data were included for both those who discontinued or completed (see CONSORT trial profile, Fig. 1). The baseline characteristics are reported in Table 1. Of the $N = 39$ participants, five participants withdrew from the study as follows: COVID-19 outbreak (N = 1, GCD), stomach discomfort (N = 1, GCD), insufficient food (N = 1, GCD), or discharge from the inpatient unit (N = 1, GCD; N = 1 GFD). Two in the GFD group had their 4-week data used as endpoint as both had a COVID infection during week 5 (N = 2, GFD), Existing gastrointestinal disorders did not differ by group, with about 1/3 having baseline disorders.

3.1. Primary outcome: CAINS MAP scores

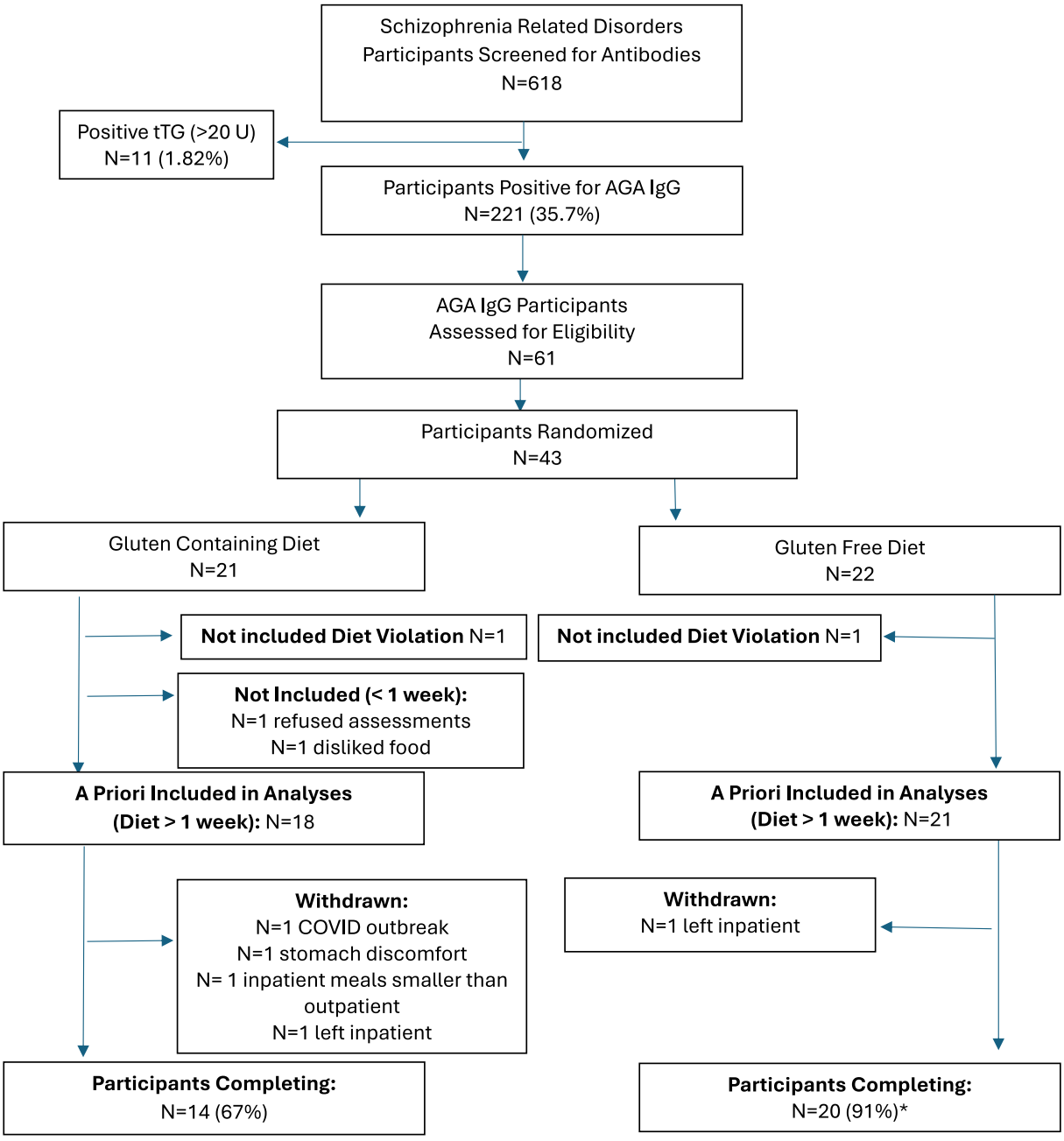
We observed a significant treatment X time interaction on change in CAINS MAP scores showing a greater improvement over time with the GFD relative to the GCD ($F = 2.96$, $df = 4,31.2$, $p = 0.035$, ES = 0.39). This is illustrated in Fig. 2. The GFD group had 10/21 (47.6%) who had a 20% decrease in CAINS MAP scores vs 5/18 (27.8%) in the GCD group (Chi-square = 1.61, df = 1, $p = 0.20$). There was a 13% decrease from baseline to 5 weeks in the GFD group (absolute change GFD = −2.02, GCD = 0.36).

3.2. Secondary outcomes

3.2.1. Clinical psychiatric symptoms

As indicated in Table 2, no other symptoms measures showed significant improvement with the GFD, relative to GCD including CAINS EXP ($p = 0.87$, ES = 0.06), SANS total ($p = 0.57$, ES = 0.33), SANS anhedonia/asociality ($p = 0.15$, ES = 0.3), BPRS total ($p = 0.18$, ES = 0.28), BPRS hostility ($p = 0.32$, ES = 0.22) or CGI-severity ($p = 0.91$, ES = 0.11). There was a trend for BPRS positive symptom improvement ($p = 0.085$, ES = 0.16) in the GFD relative to GCD but the effect size was small.

Additionally, there were no significant changes in cognition as measured by the MCCB and Tower of London (Table 3).



*2 participants contracted COVID infection, were in isolation and incomplete data during week 5, week 4 data used.

Fig. 1. CONSORT flow diagram.

3.2.2. *Kynurenine pathway metabolites*

As shown in Table 4, both KYNA ($F = 9.51$, $df = 1,32$, $p = 0.0042$, ES = 1.145) and kynurenine ($F = 11.45$, $df = 1,32$, $p = 0.0019$, ES = 0.879) levels decreased in the GFD group compared to the GCD group, with no change in 3-HK ($F = 2.56$, $df = 1,32$, $p = 0.120$, ES = −0.101). Ratios of 3-HK to KYNA and kynurenine, respectively showed a trend-level treatment effect in the 3-HK/KYNA ratio ($F = 3.22$, $df = 1,32$, $p = 0.0822$, ES = −0.727) but not in the 3-HK/kynurenine ratio ($F = 0.34$, $df = 1,32$, $p = 0.563$, ES = −0.944). The change in KYNA, but not in kynurenine, was correlated with the improvement in the CAINS MAP score ($r = 0.350$, $p = 0.039$).

3.3. *Exploratory outcomes*

3.3.1. *Cerebral blood flow (pcASL)*

Based on the small sample of $N = 20$, neuroimaging results are considered exploratory. We present bilateral increases in CBF in frontal and parietal regions in the GFD group relative to the GCD (Fig. 3) using effect size heat mapping. Notably the largest effect sizes (Cohen's d > 0.7) are noted in the insula, paracentral lobule and the transverse temporal gyrus (see Supplementary Table 1).

In Supplementary Fig. 1 and Supplementary Table 2, we also show these effect sizes for CBF ASL results using the BNE reference atlas for

Table 1
Demographic and clinical characteristics of participants.

	GCD (n = 18)	GFD (n = 21)
Age, years	39.7 (8.6)	36.8 (11.2)
Sex		
Male	13 (72.2%)	16 (76.2%)
Female	5 (27.8%)	5 (23.8%)
Race		
White	3 (16.7)	7 (33.3)
Black	14 (77.8)	12 (57.1)
American Indian	1 (5.6)	0 (0)
Asian	0 (0)	1 (4.8)
Ethnicity		
"Yes" to Hispanic or Latino	0 (0%)	1 (4.8%)
"No" to Hispanic or Latino	18 (100%)	19 (90.5%)
Level of education, years	11.7 (1.6)	11.7 (2.2)
Age at symptom onset, years	17.1 (5.4)	15.9 (5.5)
Gastrointestinal symptoms at baseline		
"Yes"	6 (33.3%)	7 (33.3%)
"No"	12 (66.7%)	14 (66.7%)
Antipsychotic use at baseline*		
Clozapine	9 (50.0%)	8 (38.1%)
Olanzapine	3 (16.7%)	6 (28.6%)
Aripiprazole	2 (11.1%)	5 (23.8%)
Fluphenazine	1 (5.6%)	4 (19.1%)
Haloperidol	4 (22.2%)	3 (14.3%)
Risperidone	3 (16.7%)	2 (9.5%)
Ziprasidone	0 (0.0%)	1 (4.8%)
Lurasidone	0 (0.0%)	1 (4.8%)
Chlorpromazine	1 (5.6%)	0 (0.0%)
Paliperidone	1 (5.6%)	0 (0.0%)
Cariprazine	1 (5.6%)	0 (0.0%)
Chlorpromazine (CPZ) equivalent dose (mg)	418.1 ± 322.9	345.6 ± 388.2

* May be on more than one antipsychotic.

the GFD relative to the GCD. We note large effect sizes observed (Cohen's d > 0.9) in regions of the insula, superior frontal gyrus, inferior frontal gyrus and the paracentral lobule.

3.3.2. Neurochemistry (MRS)

A representative spectrum with corresponding voxel images is shown in Supplementary Fig. 2. For the MRS data we see large effect sizes (>0.70) showing an increase in total creatine in GFD relative to GCD (see Supplementary Table 6).

3.3.3. Inflammatory markers

Of the 10 cytokines included we observed a small to medium effect favoring a decrease in the GFD relative to GCD in 5 of these: (IL-17a (d = 0.39), IL-2 (d = 0.32), IL-1ra (d = 0.50), IL-12 (d = 0.36) and IFN-ɣ (d = 0.49) All data is presented in Supplementary Table 4. There was no change in AGA IgG ($F = 1.7$, $df = 1,35$, $p = 0.172$).

3.4. Laboratory measures and general health

There were no differences between groups observed for general health, neurologic symptoms or pain ($p > 0.05$). While the GSRS changes did not reach significance, there was a trend towards less constipation in the GFD compared to the GCD ($F = 3.79$, $df = 1,37.2$, $p = 0.059$). There were no differential effects over 5 weeks in any component of CBC or CMP (see Supplementary Table 5 and Table 6, respectively).

3.5. Side effects and adverse events

There were no significant differences in the SAS ($F = 0.0808$, $df = 1,37$, $p = 0.778$), BAS ($F = 0.822$, $df = 1,37$, $p = 0.370$) or mean weight, BMI and vital signs (see Supplementary Table 7). Albumin levels ($F = 4.4$, $df = 29$, $p = 0.045$) increased in the GFD. Side effects from the SEC are shown by group (see Table 5) and adverse events included: new onset diabetes mellitus (N = 1, GFD), knee pain increase (N = 2, GFD), skin lesions (N = 1, GFD), acid taste in mouth (N = 1, GFD), stomach bloating (N = 1, GCD), somatic concern (N = 1, GCD), and COVID 19 infection (N = 2, GFD).

4. Discussion

4.1. Primary outcome: negative symptoms

To our knowledge, this is the first double-blind randomized controlled inpatient trial using a GFD in people with SRD with corresponding neuroimaging data to examine gluten's effect on brain

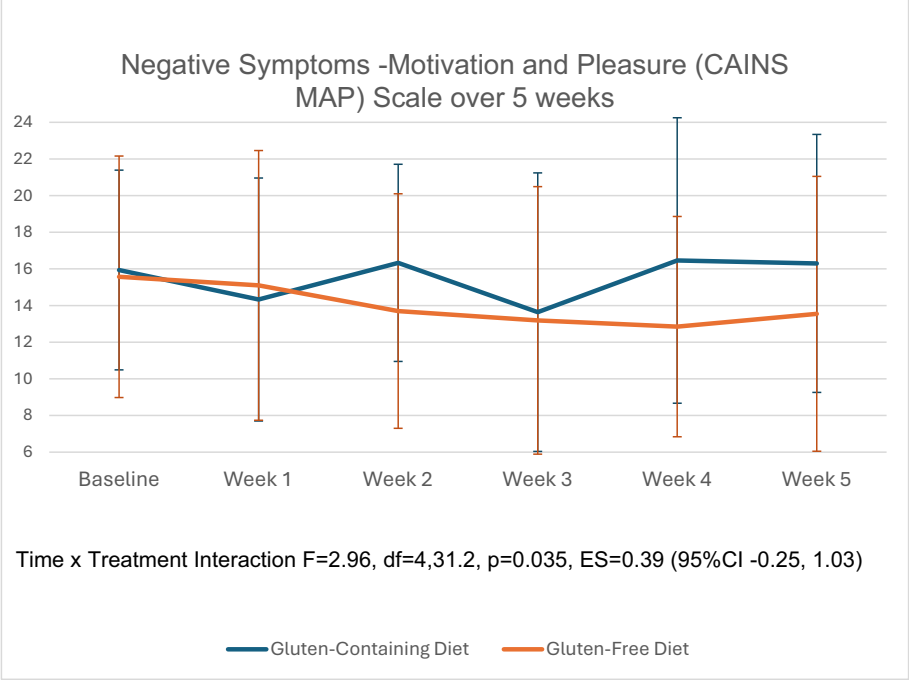


Fig. 2. Change in the clinical assessment interveiw for negative symptoms -motivation and pleasure (CAINS MAP) scale over 5 weeks.

Table 2
Secondary psychiatric symptom rating scales.

	No.	GCD	No.	GFD	F	df	*p* value	Effect size
CAINS Expressive Deficit (EXP), mean (SD)								
Baseline	18	6.9 (3.2)	21	7.7 (3.9)	..	..	..	..
5 weeks	13	5.4 (4.1)	18	5.9 (3.8)	0.31	30.1	0.870	0.06
SANS Total, mean (SD)								
Baseline	18	36.2 (10.5)	21	38.2 (10.6)	..	..	..	..
5 weeks	13	34.4 (13.8)	18	31.8 (8.2)	0.74	28.0	0.570	0.33
SANS Anhedonia/Asociality, mean (SD)								
Baseline	18	2.4 (0.7)	21	2.5 (0.9)	..	..	..	..
5 weeks	13	2.3 (1.0)	18	2.1 (0.8)	1.84	29.5	0.150	0.30
BPRS, mean (SD)								
Baseline	18	38.2 (10.7)	21	37.3 (10.2)	..	..	..	..
5 weeks	13	37.3 (16.2)	18	32.6 (9.1)	1.67	28.6	0.180	0.28
BPRS-psychosis, mean (SD)								
Baseline	18	10.9 (5.2)	21	10.0 (4.9)	..	..	..	..
5 weeks	13	11.3 (5.7)	18	8.9 (3.2)	2.28	28.6	0.085	0.16
BPRS-hostility, mean (SD)								
Baseline	18	6.3 (2.7)	21	5.5 (3.1)	..	..	..	..
5 weeks	13	5.8 (2.6)	18	4.3 (1.7)	1.22	26.9	0.320	0.22
CGI-severity, mean (SD)								
Baseline	18	4.4 (0.8)	7	4.5 (0.7)	..	..	..	..
5 weeks	12	4.4 (0.8)	18	4.2 (0.7)	0.24	32.4	0.910	0.11

Table 3
Cognitive function.

	No.	GCD	No.	GFD	F	df	p value	Effect size
MCCB-composite, mean (SD)								
Baseline	18	24.7 (16.3)	20	26.4 (15.6)	..	..	..	..
5 weeks	17	27.0 (16.6)	17	32.6 (14.5)	0.63	31.0	0.435	0.066
MCCB-processing speed, mean (SD)								
Baseline	18	27.2 (16.0)	20	30.0 (15.2)	..	..	..	..
5 weeks	17	30.6 (15.9)	17	35.3 (16.8)	0.00	31.0	0.956	0.004
MCCB-attention/vigilance, mean (SD)								
Baseline	18	35.1 (14.5)	20	31.2 (13.1)	..	..	..	..
5 weeks	17	34.7 (14.0)	17	32.9 (13.5)	0.37	31.0	0.546	0.128
MCCB-working memory, mean (SD)								
Baseline	18	31.3 (13.9)	20	34.6 (10.9)	..	..	..	..
5 weeks	17	34.2 (15.5)	17	37.2 (10.0)	0.45	31.0	0.506	0.161
MCCB-verbal learning, mean (SD)								
Baseline	18	32.2 (8.6)	20	34.0 (10.4)	..	..	..	..
5 weeks	17	33.5 (8.5)	17	37.6 (11.0)	0.80	31.0	0.378	0.147
MCCB-visual learning, mean (SD)								
Baseline	18	29.6 (13.1)	20	34.9 (14.4)	..	..	..	..
5 weeks	17	30.7 (14.1)	17	38.9 (13.7)	0.26	31.0	0.613	0.021
MCCB-spatial reasoning, mean (SD)								
Baseline	18	42.9 (9.9)	20	43.1 (12.1)	..	..	..	..
5 weeks	17	42.2 (10.4)	17	47.7 (12.8)	2.45	31.0	0.127	0.369
MCCB-social cognition, mean (SD)								
Baseline	18	36.7 (13.7)	20	36.4 (11.4)	..	..	..	..
5 weeks	17	36.8 (10.0)	17	38.8 (11.1)	0.02	31.0	0.412	0.047
Tower of London, mean (SD)								
Baseline	17	13.2 (6.5)	20	14.9 (4.9)	..	..	..	..
5 weeks	17	13.5 (7.0)	17	17.6 (3.0)	1.96	31.0	0.170	0.185

MCCB = MATRICS Consensus Cognitive Battery.

function. These results strengthen the evidence of our previous two pilot studies (Jackson et al., 2012; Kelly et al., 2019), showing that GFD was associated with reduced negative symptoms. We specifically tested this approach in an SRD subgroup with AGA IgG+ and, notably, report negative symptom improvement in the domains of motivation and pleasure. The CAINS MAP assesses deficits related to motivation and frequency for social and recreational activities and relationships. This "experiential" negative symptom domain is known to be a major determinant of social and occupational dysfunction and a significant predictor of poor long-term one-year outcomes (Galderisi et al., 2020; Mucci et al., 2021).

It is also important to point out that the CAINS MAP effect size was small to medium. To date the CAINS MAP has not been widely adapted yet into clinical trials, making comparison with other studies challenging. However, a recent pilot study testing the efficacy of a digital intervention on improving motivation and pleasure reported a clinically meaningful reduction in mean CAINS MAP of 17.6% with a corresponding 3.6 (1.3, 5.8) point reduction over 7 weeks (Goenjian et al., 2025), similar to our finding of a 13% reduction over 5 weeks. Likewise, the SANS asociality/anhedonia subfactor also had a nonsignificant but small effect size (ES = 0.30) and the change in CAINS MAP scores were correlated to changes in the SANS asociality/anhedonia domain ($r = 0.608$, $p = 0.0035$). It is important to point out that we see no effect of a GFD on the 'expressive' domain of negative symptoms (i.e. blunted affect, alogia), depression, or cognitive function. This is important as negative symptoms are not treated by antipsychotic medications. Previously, we observed a Cohen's d of 0.5 for negative symptoms in our last 5 week double blind randomized trial in a smaller

Table 4
Kynurenic acid, kynurenine and related metabolites.

	No.	GCD	No.	GFD	F	df	p value	Effect Size
KYNA (fmoles/μL), mean (SD)								
Baseline	17	30.361 (12.08)	21	29.524 (13.61)	..	..	..	..
5 weeks	17	42.967 (19.57)	18	27.403 (10.56)	9.51	32	0.004	1.145
Kynurenine (pmoles/μL), mean (SD)								
Baseline	17	1.238 (0.53)	21	1.565 (0.80)	..	..	..	..
5 weeks	17	1.557 (0.71)	18	1.173 (0.43)	11.45	32	0.002	0.879
3-HK (fmoles/μL), mean (SD)								
Baseline	17	28.088 (11.12)	21	21.352 (9.54)	..	..	..	..
5 weeks	17	34.100 (9.52)	18	27.172 (7.84)	2.56	32	0.120	-0.101
3-HK:KYNA ratio, mean (SD)								
Baseline	17	1.024 (0.54)	21	0.880 (0.58)	..	..	..	..
5 weeks	17	0.933 (0.45)	18	1.107 (0.44)	3.22	32	0.082	-0.727
3-HK:kynurenine ratio, mean (SD)								
Baseline	17	25.309 (10.83)	21	16.239 (9.34)	..	..	..	..
5 weeks	17	25.997 (12.64)	18	25.638 (10.45)	0.34	32	0.563	-0.944

KYNA = kynurenic acid, 3-HK = 3-hydroxy-kynurenine.

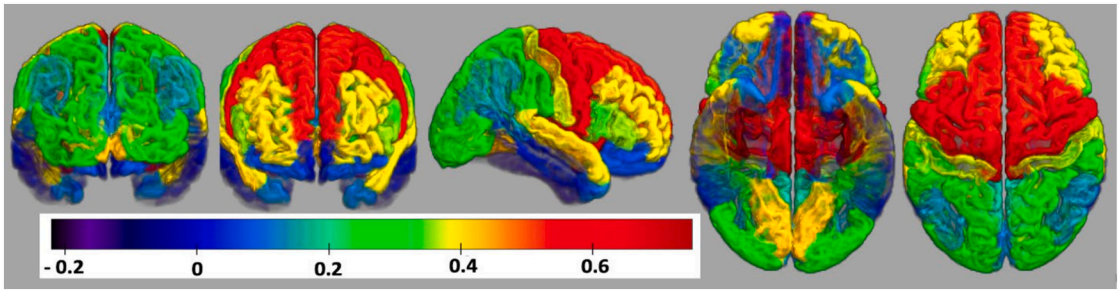


Fig. 3. Cerebral blood flow: effect size differences (Cohen's d) between the gluten-free diet relative to the gluten-containing diet using Desikan-Killiany (DK) Atlas Defined Regions.

Table 5
New and emergent side effects (during the 5 weeks).

	GCD (n = 18)	GFD (n = 21)
Constipation	6 (33.3%)	8 (38.1%)
Sedation	9 (50.0%)	7 (33.3%)
Dry Mouth	6 (33.3%)	7 (33.3%)
Headache	5 (27.8%)	7 (33.3%)
Insomnia	5 (27.8%)	7 (33.3%)
Abdominal Pain	5 (27.8%)	6 (28.6%)
Anorexia	3 (16.7%)	6 (28.6%)
Restlessness	6 (33.3%)	6 (28.6%)
Malaise	1 (5.6%)	6 (28.6%)
Dizziness	5 (27.8%)	5 (23.8%)
Nausea	4 (22.2%)	4 (19.0%)
Diarrhea	3 (16.7%)	4 (19.0%)
Mucous	2 (11.1%)	4 (19.0%)
Rash	2 (11.1%)	4 (19.0%)
Stiffness	1 (5.6%)	4 (19.0%)
Throat pain	1 (5.6%)	4 (19.0%)
Weight Loss	7 (38.9%)	3 (14.3%)
Tremors	5 (27.8%)	3 (14.3%)
Tinnitus	4 (22.2%)	3 (14.3%)
Vomiting	4 (22.2%)	3 (14.3%)
Enuresis	2 (11.1%)	3 (14.3%)
Urticaria	2 (11.1%)	3 (14.3%)
Salivation	3 (16.7%)	2 (9.5%)
Fever	0 (0.0%)	1 (3.8%)
Bruising	0 (0.0%)	0 (0.0%)

sample (Kelly et al., 2019). This signal was likely tempered by COVID 19 lockdowns and lack of opportunity of socializing (as described in limitations below), however, our findings add to the existing data that this subgroup may have negative symptom improvement. Future larger studies will help establish negative symptom improvements as well as establish norms and guidelines for clinically significant changes on the CAINS MAP.

4.2. Secondary outcomes

4.2.1. Kynurenine pathway metabolites

We observed a significant and robust decrease in the plasma levels of both kynurenine and KYNA in the GFD group with corresponding large effect sizes. Previously, we reported reductions in kynurenine and KYNA with a GFD in this AGA IgG+ group (Friendshuh et al., 2020). The present results are also in line with findings from a study of 950 people with SRD, in which elevated circulating kynurenine levels were found to be related to high AGA IgG (Okusaga et al., 2016). Kynurenine and KYNA are two metabolites of the kynurenine pathway, the major degradative route of the essential amino acid tryptophan in mammals (Pocivavsek et al., 2024). Both of these catabolites have neuroimmune properties that impact not only cognitive dysfunction but may also affect negative symptomatology (Schwarcz et al., 2012).

As abnormal tryptophan metabolism has been shown in adults with gluten disorders, such as celiac disease (CD), the reductions in both KYNA and kynurenine observed here with a GFD could reflect a normalization of kynurenine pathway metabolism (Kowlessar et al., 1964). Notably, we found that the change in the CAINS MAP significantly correlated with the change in plasma KYNA levels, raising the possibility that a connection between negative symptoms and KYNA is indeed of biological significance (Schwarcz et al., 2012). However, we acknowledge that correlation does not establish mediation, and a formal mediation or pathway analysis would require larger samples.

4.2.2. Other clinical ratings

In our previous study we found moderate effect size in cognitive function improvements in the GFD compared to the GCD group. Here we do not see any significant changes in cognitive function over the 5 weeks

between groups.

4.3. Exploratory findings

4.3.1. Cerebral blood flow (pcASL)

We observed that a GFD was associated with large effects on CBF in frontal- and parietal-cortical regions (e.g., orbital, inferior, and middle frontal gyri; insula, superior parietal cortex) across the 5-week intervention. These frontal and parietal regions have been implicated in SRD and are responsible for a broad range of associative functions including motivation and planning, the disruption of which could contribute to anhedonia and avolition. Notably, we saw large effects suggesting an increase in CBF for the insular regions that play a crucial role in motivation (Deng et al., 2021; Moran et al., 2019; Sheffield et al., 2020) and are vulnerable to greater inflammation-associated psychopathology (Koren et al., 2021; Mansson et al., 2022). A well-known case related to blood flow changes describes a 33-year-old patient with SRD and severe symptoms of CD, who upon a GFD had drastic improvement in SRD and gastrointestinal symptoms, and an increase in brain blood flow assessed by single photon emission computed tomography ((99mTc) HMPAO SPECT), reversing hypoperfusion of frontal brain areas (De Santis et al., 1997).

Notably, no association between a decrease in kynurenine or KYNA and an increase in CBF was observed in this study. Although speculative, the observed increase in CBF in the context of reduced kynurenine and KYNA could relate to NMDA and alpha7 receptor function and neurovascular coupling in prefrontal circuits associated with motivation and affective processing (Schwarcz et al., 2012). Future studies with sufficient power are needed to examine potential links among these outcomes and negative symptom improvement.

4.3.2. Neurochemistry (MRS)

Using MRS, we previously found that levels of AGA IgG antibodies were correlated to myoinositol and total choline levels (Rowland et al., 2017), i.e. neurochemicals involved in inflammation (Chang et al., 2013). In this study, GFD was associated with an increase in medial frontal total creatine, which could reflect increased energy metabolism since phosphocreatine and creatine are involved in ATP generation (Rackayova et al., 2017). Blood and CBF levels of AGA IgG have been reported to be correlated, suggesting that both may permeate the blood-brain barrier (Severance et al., 2015). Together, our finding of beneficial effects of a GFD associated with increased CBF and total creatine in frontal parietal brain regions is novel and may add to the emerging data to support this subgroup.

4.3.3. Inflammatory markers

We noted small to medium effect size associated with the GFD relative to the GCD in 5 of 10 cytokines: IL-17a ($d = 0.39$), IL-2 ($d = 0.32$), IL-1ra ($d = 0.50$), IL-12 ($d = 0.36$) and IFN-ɣ ($d = 0.49$). A GFD is thought to have anti-inflammatory effects as part of its mechanism (Niland and Cash, 2018; Philip and White, 2022) and we see findings supporting this hypothesis. While the pathways by which inflammation may be affected are not entirely clear, a small signal from IL-17a and IL-2 are not surprising. IL-17a was found previously by our group to be higher in AGA+ SRD compared to AGA- SRD (Daniels et al., 2023) and we previously saw that a GFD was associated with a decrease in this cytokine (Friendshuh et al., 2020). Also, we saw a small effect in IL-2, a growth factor regulating T-cells (Huang et al., 2022). We highlight this cytokine since we previously found different T cell populations are associated with negative symptom severity in SRD (Kelly et al., 2018b), and this relationship may be specifically unique to the SRD AGA IgG+ subgroup (Salem et al., 2025) and related to high kynurenine levels (Salem et al., 2023). The relationship between IL-2 and negative symptoms in SRD, particularly anhedonia and avolition, is in line with previous work (Kelly et al., 2018b) as well as data showing elevated IL-2 predicting of poor functional outcomes (Gonzalez-Blanco et al., 2019). While a different psychopathology, it is interesting to note that others found that, in patients with CD, gluten promotes IL-2 elevation and rapid onset of gluten-induced T-cell activation (Cartee et al., 2022).

We also acknowledge that serum cytokines are sensitive to changes in temperature and thawing (Ashworth et al., 2021), problems that may have compounded by collecting samples during a pandemic.

4.3.4. Safety and side effects

The GFD was well-tolerated in our inpatient study since side-effects occurred comparably between groups, and only one person discontinuing participation (citing 'not enough food' as the reason). We did not observe significant improvements in gastrointestinal issues as in our previous study; however, baseline gastrointestinal issues were low in all participants – possibly due to the aggressive treatment of gastrointestinal symptoms at admission. We did note a treatment effect favoring the GFD for constipation, though, despite similarly very low rates recorded at study baseline.

4.4. Limitations

Primary limitations of this study included the short duration of the trial and the small sample size. Five weeks may not have been long enough to see full negative symptom effects or potential improvements in other domains such as positive symptoms and cognitive impairments. The half-life of AGA IgG is about 21–23 days; thus 6 to 9 months is needed on a strict gluten-free diet to completely eliminate these antibodies from the bloodstream (Birdsall, 2015). As such, the maximal improvement in inflammation and response to symptoms may not have occurred with the short duration allowing for only early detection of treatment response, and more extended improvements may be likely. While the study was powered to find an effect, larger samples could have provided more insight into secondary outcomes.

Additionally, as we mentioned above, a minimization of true negative symptom improvement may have been obscured due to the COVID-19 pandemic, which involved quarantines, lockdowns, periods of isolation, lingering social effects, and fearfulness, a nearly insurmountable challenge to the study of social and motivational behaviors. As a form of systematic error, these unpredictable circumstances may have led to behaviors that resembled negative symptomatology in response to chronic unpredictable stress across treatment groups, such that our ability to detect greater reductions in negative symptoms and treatment response was hampered. This is notable as our negative symptom effect size was slightly less robust than we had observed previously (Jackson et al., 2012; Kelly et al., 2019). Similarly, negative symptoms, such as anhedonia and avolition, as well as anxiety and depression, were noted to be higher during the pandemic compared to pre-pandemic (Strauss et al., 2022) which may contribute to social isolation (Li et al., 2021). We also point out that while the sample was enriched for negative symptoms (using the SANS), it was not specifically enriched for only those with prominent anhedonia and asociality. At the time of the study design, the use of CAINS MAP for inclusion has not been previously used and we opted for broader range negative symptoms using criteria previously described (Buchanan et al., 2015).

The exploratory outcomes were not corrected for multiple comparisons; therefore, only effect sizes are presented, and results should be interpreted with caution. Further, while AGA IgG antibodies are not impacted by antipsychotics (Chong-Thim et al., 1993), we did not control for antipsychotic type, dose, or lifetime burden of antipsychotic treatment (Lincoln et al., 2010). Although macronutrient content and caloric intake were controlled and both groups followed an identical 21-meal rotating weekly menu, we cannot rule out differences in fiber, micronutrients, food processing, or microbiome effects that may have contributed to the observed changes. It is also possible that gluten removal itself influenced the microbiome, which could have contributed to the findings. Finally, although our study may have been limited by the inclusion of inpatients only, the strict inpatient setting provided

stringent 24-hour monitoring and less outside confounds which may not be controlled for in an outpatient setting.

4.5. Conclusion

In conclusion, our study provides preliminary but promising additional support suggesting that negative symptomatology and circulating levels of kynurenine and KYNA may decrease with the removal of gluten in an AGA IgG+ SRD subgroup. This is notable as this well-defined AGA IgG+ subgroup represents about 1/3 of all patients with SRD, a population where negative symptoms are likely untreated. This study not only strengthens findings and compliments earlier GFD benefits in this subgroup, but also adds to the literature in showing that a GFD is associated with an increase in CBF measured by ASL and total creatine measured by MRS. The GFD was well tolerated, with few side effects reported and only one person dropping out because of the diet. To further understand the unique characteristics of this subgroup and investigate the mechanistic role that the kynurenine pathway and inflammation may play, as well as to explore related areas like changes in the microbiome, additional research in larger samples is warranted. Future discussions will consider whether testing for AGA IgG should be considered to help identify a subgroup which gluten removal may help improve negative symptoms. Together with other accumulating evidence (Ahmed et al., 2018; Dacquino et al., 2015; Saether et al., 2023), our findings suggest that the identification of more homogenous subgroups of people with SRD may be important for developing new treatments (Kelly and Buchanan, 2022).

CRediT authorship contribution statement

Deanna L. Kelly: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Christopher M. Lee:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Gopal Vyas:** Writing – review & editing, Investigation. **Robert W. Buchanan:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Daniel J. Roche:** Writing – review & editing. **Valerie Harrington:** Writing – review & editing. **Laura M. Rowland:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **S. Andrea Wijtenburg:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Bhim M. Adhikari:** Writing – review & editing, Formal analysis. **Korrapati V. Sathyasaikumar:** Writing – review & editing, Data curation. **Peter Kochunov:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Monica V. Talor:** Writing – review & editing, Methodology, Data curation. **James Waltz:** Writing – review & editing. **Fang Liu:** Writing – review & editing, Formal analysis. **Stephanie Hare:** Writing – review & editing. **Heather A. Adams:** Writing – review & editing. **Robert Schwarcz:** Writing – review & editing. **Deepak Salem:** Writing – review & editing. **James M. Gold:** Writing – review & editing. **Sarah M. Clark:** Writing – review & editing. **William W. Eaton:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Role of the funding source

The funding source played no role in the design or conduct of the study.

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Declaration of competing interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. DLK served on advisory boards for Karuna, Boehringer Ingelheim, and Alkermes, RWB served as a DSMB member for Merck, Newron, and Roche and on an advisory board for Acadia, Karuna, Merck, and Neurocrine. RS is a co-founder of Kynexis BV, which develops kynurenic acid synthesis inhibitors for the treatment of cognitive dysfunctions in people with schizophrenia. No other authors have disclosures or conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2026.01.006.

Data availability

Fully deidentified data will be considered for sharing with appropriate IRB approvals. This is available with a request to the corresponding author. A smaller subset of data for those participants approving online sharing in the National Database for Clinical Trials (NDCT) is available.

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