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ARTICLE

Ketogenic diet-derived faecal microbiota transplantation improved sensorimotor gating deficit in an acute NMDA-receptor antagonist model of schizophrenia in mice

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Ketogenic diets (KDs) show promise as a novel treatment for schizophrenia, although its mechanisms of action are still unclear. KDs have been shown to modify the gut microbiota and may exert some of its brain-directed effects through that. We hypothesised that KD-induced changes in the gut microbiota mediate some of the therapeutic effects of KDs in a preclinical model of schizophrenia. To test this hypothesis, we transplanted the gut microbiota through faecal matter obtained from mice maintained on KD to standard diet-fed mice (faecal microbiota transplantation; FMT) and assessed its effect on a translationally validated endophenotype of psychotic disorders, the sensorimotor gating deficit induced by the NMDA-receptor antagonist MK-801, in mice. Faecal samples were collected from male C57Bl/6 mice fed a KD for 4 months and prepared into a liquid for inoculation. Ten-week-old male C57Bl/6 mice maintained on standard diet (SD) received 3 inoculations every second day. One week after the last inoculation, animals received 0.2 mg/kg MK-801 (dizocilpine) to induce schizophrenia-like sensorimotor gating deficit as measured by the pre-pulse inhibition (PPI) of startle. MK-801 reduced PPI, which was attenuated by the faecal microbial transplant derived from mice fed with KD. We showed for the first time that FMT through inoculation with KD faeces improved a highly translatable behavioural endophenotype of schizophrenia. Our novel findings confirm that some of the beneficial effects of KDs in schizophrenia are mediated by the gut microbiota.

Introduction

Metabolic alterations exist across the psychosis spectrum [1]. *In vivo* imaging and postmortem samples of individuals with schizophrenia demonstrate glucose hypometabolism, leading to bioenergetic dysfunction, and impairing synaptic activity and maintenance [2-4]. Antipsychotics rely on partially understood disease pathophysiology [5] and are ineffective in a significant segment of patients, with side effects leading to secondary disease conditions [6-11]. Therefore, novel treatment strategies considering the most recent advances in our understanding of the disorder's pathophysiology are needed.

Ketogenic diets (KD; very low carbohydrate, high fat and medium protein containing diet) provide the body and brain with an alternative fuel in the form of ketone bodies, which are metabolised into Acetyl-Coenzyme-A and feed into the tricarboxylic acid (TCA) cycle bypassing the presumably impaired glycolytic processes in schizophrenia. KDs have been shown to be effective in pre-clinical [12-14], case studies [15-18] and clinical trials [19, 20] for the treatment of schizophrenia. The wider distribution of KDs for schizophrenia is challenging due to compliance issues [20], limited food choice, stress, social implications [21] and cost. Therefore, understand the mechanisms by which KDs may exert their beneficial effects on schizophrenia is crucial for identifying new therapeutic targets. We previously have demonstrated that administration of beta-hydroxybutyrate (BHB), the main circulating ketone body produced by the liver during KDs, improves a schizophrenia-like phenotype in an acute N-methyl-D-aspartate (NMDA) receptor antagonist model of schizophrenia, which might be an alternative to KDs [22]. Modifying the gut microbiota might provide another potential novel treatment approach, creating the need to understand the interaction between KDs, schizophrenia and the gut microbiota. No study so far has investigated the effects of KDs on the gut microbiota in schizophrenia. This raises the question, of whether KDs might reduce schizophrenia symptoms by altering the gut microbiota.

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A bidirectional communication between the brain and gut microbes occurs through the gut-brain axis regulating processes such as metabolism [23], the immune system [24] and behaviour [25, 26]. Pathophysiology and factors such as diet and medications have been associated with altered gut microbiota composition [27]. KDs can create a rapid shift in gut microbiota composition [28-32]. Similarly, individuals with schizophrenia have an altered gut microbiota composition [33-40]. Current treatment options for schizophrenia, antipsychotics, have an impact on the gut microbiota by reducing the species diversity [41, 42].

Studies investigating gut microbiota composition with behaviour are mostly correlational and fail to investigate a causal effect. Faecal microbial transplant (FMT) studies and bacterial depletion studies can support the understanding of the causal role of the intestinal microbiota [43]. Transfer of the gut microbiota through FMT has been shown to result in the transfer of disease [44] and behavioural alterations [45].

When investigating behaviour in animal studies, it is important to use translatable behavioural paradigms to assess potential benefits of novel treatments. Sensorimotor gating is the ability to filter incoming sensory information to support efficient functioning [46]. Sensorimotor gating deficits are highly translatable and are commonly seen in patients with schizophrenia ~~patients~~, resulting in an overload of sensory input [46, 47]. One paradigm to measure sensorimotor gating is the prepulse inhibition of startle (PPI) paradigm [46]. The PPI paradigm measures motor startle reflexes induced by an unexpected strong sensory stimulus such as an eye puff or loud noise called the startle response [48]. This startle response can be reduced if the strong sensory stimulus (startle) is preceded by a weaker sensory stimulus (prepulse) demonstrating the filtering of incoming sensory information or also termed sensorimotor gating [48, 49]. PPI values can vary depending on methodological factors such as stimulus intensity, duration, frequency and interstimulus interval (ISI) [48]. ISI is the delay between the prepulse and the startle stimulus [48]. Short ISI (30 ms) have been considered as preconscious, reflecting brainstem level processing [50]. ISI 100 is an indicator for conscious information processing [51 50].

Here, we investigated for the first time if the beneficial behavioural effects of KDs can be transferred using KD donor faeces and transplanting these faeces into standard diet-fed mice in an acute NMDA receptor antagonist model (MK-801). We hypothesised that ketogenic diet-derived FMT will mitigate MK-801 induced PPI deficits.

Methods

Animals and procedure

All experiments were approved by the Animal Ethics Committee of James Cook University (A2373) and in accordance with NHMRC/AVCC Statement and Guidelines on Research Practice (1997). Guidelines for reporting on animal faecal transplantation (GRAFT) and ARRIVE guidelines were used to ensure transparency and reproducibility [52, 53]. The 3Rs of animal research (Reduction, Refinement and Replacement) were considered at all stages of the experiment. Ten-week-old male C57Bl/6 mice (n=35) bred in-house were caged (4-5 mice per cage) in standard housing conditions (12-hour light/dark cycle at 22 ± 1 °C, Type II open polycarbonate cages). Throughout the experiment, all animals received *ad libitum* standard diet (Goldmix Stockfeeds, Norco, Lismore, NSW, Australia; Table 1)[54, 55] and access to shredded paper as environmental enrichment. After a one–week acclimation period, mice were randomly assigned (without blinding) to ketogenic diet-derived FMT or saline as control. Mice were placed prior to the first inoculation into clean cages. Inoculations via oral gavage were performed every other day for a total of three occurrences. The cage was used as the experimental unit as mice exhibit coprophagy. One week after the last ketogenic diet-derived FMT, animals were tested for PPI. Thirty minutes before behavioural testing, mice were randomised to receive an acute intraperitoneal injection of 0.2 mg/kg MK-801 (dizocilpine; Sigma, Australia) [54, 56] or saline as the respective control. We investigated four experimental groups: (1) Saline - Saline, (2) Saline - MK-801, (3) ketogenic diet-derived FMT - Saline and (4) ketogenic diet-derived FMT - MK-801. The day after behavioural testing, the mice were killed by decapitation.

Table 1: Diet composition of Standard and Ketogenic diet

Component	Standard Diet (NORCO Rat & Mouse Nut)	Ketogenic Diet 77.6% Fat (SF14-063)
Protein (%)	17.65	9.50
Total Fat (%)	3.08	77.60
Carbohydrate (%)	60.85**	~8–10 (very low; minimal starch)
Crude Fibre (%)	4.06	4.70
Sugar (%)	1.85	None added
Ash (%)	7.78	~2.4–2.5†
Moisture (%)	10.64	Not specified
Digestible Energy (MJ/kg)	12.77	30.8
Energy from Lipids (%)	8.9*	93.8

Note: *Percentage energy values for the Standard Diet are calculated using physiological fuel factors (37 kJ/g for fat and 17 kJ/g for protein) and total digestible energy (12.77 MJ/kg). They are estimates and may differ slightly from laboratory-determined energy values. ** Carbohydrate for the Standard Diet is calculated by difference: 100 − (Protein + Fat + Ash + Moisture).

Preparation of faeces for ketogenic diet-derived FMT

Collection: Ten-week-old male C57Bl/6 mice donor mice (n=5, 1 cage), breed in house, were placed for four months on KD (SF14-063; Specialty Feeds, Western Australia; Table 1) as used by us in previous studies [54, 55, 57]. Donor mice were housed in the same condition as experimental mice. For one-week faecal samples were collected daily from donor mice by scuffing the mouse at irregular timepoints throughout the day. Storage: Faecal samples were directly placed into sterile Eppendorf's. Faecal samples in Eppendorf's were kept on ice until all samples for that day were collected and stored at -80°C for longer term storage. Processing: Faeces of all mice were pooled. Twelve faecal pellets were defrosted for 10-15 minutes on ice, then added to 800 µl of cooled, autoclaved and filtered water and homogenised. The mixture was strained through a 40 µm nylon filter. The filtrate was diluted to a volume of 2.5 ml (procedure for eight mice)[58]. Each mouse received 300 µl of the diluted filtrate at each inoculation. Filtrate was freshly produced on the day of inoculation and immediately administered.

Behavioural testing

One hour before behavioural testing, animals were transported from the holding room to the behavioural testing room to acclimatize and reduce stress (temperature 22 ± 1 °C, light level 690 lx). Behavioural testing was done during the light phase of the circadian cycle.

PPI was chosen as it is a highly translatable task between rodents and humans [56, 59] and clinical manifestation of schizophrenia [60]. In brief, PPI and startle were assessed as described previously [22, 54] using automated startle chambers producing background noise and acoustic stimuli, as well as recorded whole-body startle (SR-Lab; San Diego Instruments, San Diego, CA, USA). Animals were subjected to the following: (1) 3 min of acclimatisation, (2) 8 pulse-alone startle stimuli (40 ms burst of 115 dB white noise), (3) 88 pseudo-randomized trials (16 startle stimuli, four groups of 8 prepulse-pulse trials at 2, 4, 8, and 16 dB over baseline with an interstimulus interval (ISI) of either 30 ms or 100 ms, and 8 NOSTIM trials (no stimulus)). The 72 trials were concluded with a further 8 startle stimuli. Between trials, chambers were cleaned with 70 % ethanol.

Statistical analysis

Analysis was conducted with R-studio, R version 4.4.3. Packages used: car, tidyverse, dplyr, ggpubr, ggsignif, ggstatsplot, ggsci, rstatix, reshape2, ez, afex, lme4, effectsize. Two mice were identified as outliers in Microsoft excel as their averages were outside mean ± 3 SD and were listwise deleted. Percent PPI was calculated according to the following formula: PPI% = (100 − (100 × startle amplitude on prepulse followed by pulse trial)/(startle amplitude on pulse trial alone)) [48]. Levene's test for homogeneity of variances were met. Data was not normally distributed according to Shapiro-Wilk and QQ Plots. Despite this, we used parametric test as ANOVAs are considered robust enough if all other assumptions are met. Average PPI and Startle: We conducted a two-way analysis of variance (ANOVA) with Bonferroni-corrected pairwise comparison. For Individual pre-pulse intensities: We used a 2x2x4 mixed ANOVA repeated with Bonferroni-corrected pairwise comparison. When Mauchly's Test of sphericity was violated, we reported whole degrees of freedom and reported Greenhouse-Geisser correction. All data were expressed as the mean ± standard error of the mean (SEM). A p-value of < 0.05 was considered to be statistically significant. Code used and data is available within the supplementary materials. Although the study was not pre-registered the analysis was planned prior to conducting the experiment and follows the same methodology as in our previous publications [54, 61] with the only exception that the analysis was primarily conducted in R and replicated with SPSS.

Results

ISI 30

We have previously demonstrated that a ketogenic diet improved sensorimotor gating deficits in an acute MK-801 induced animal model of schizophrenia [54]. However, it has not yet been explored if the beneficial behavioural effects of KDs can be transferred using KD donor faeces and transplanting these faeces into standard diet-fed mice using the same acute MK-801 induced animal model of schizophrenia. Short ISI, such as ISI 30 ms, have been considered as preconscious, reflecting brainstem level processing. PPI was dependent on pre-pulse intensity ($F_{3,87} = 130.044$, $p < 0.001$, partial $\eta^2 = 0.818$). MK-801 reduced PPI ($F_{1,29} = 33.593$, $p < 0.0001$, partial $\eta^2 = 0.537$), which was dependent on pre-pulse intensity ($F_{3,87} = 3.330$, $p = 0.033$, partial $\eta^2 = 0.103$, Figure 1 B). FMT treatment resulted in an increase in PPI ($F_{1,29} = 22.147$, $p < 0.0001$, partial $\eta^2 = 0.433$), which was independent of pre-pulse intensity ($F_{3,87} = 1.469$, $p = 0.235$, partial $\eta^2 = 0.048$). Ketogenic diet-derived FMT treatment significantly influenced the effect of MK-801 treatment on average PPI ($F_{1,29} = 4.856$, $p = 0.035$, partial $\eta^2 = 0.143$; Figure 1 A & B). Bonferroni-corrected post hoc analysis showed that MK-801 in mice receiving saline gavage significantly reduced average PPI ($p < 0.001$), which was attenuated by ketogenic diet-derived FMT ($p < 0.001$) (Figure 1 A). In sum, MK-801 reduced PPI, which was improved by ketogenic diet-derived FMT treatment at ISI 30.

ISI 100

ISI 100 is an indicator for conscious information processing [51 50]. Similarly to ISI 30, PPI was significantly dependent on pre-pulse intensity ($F_{3,87} = 97.211$, $p < 0.001$, partial $\eta^2 = 0.770$). MK-801 injection reduced average PPI ($F_{1,29} = 14.652$, $p < 0.001$, partial $\eta^2 = 0.336$), which was contingent on pre-pulse intensity ($F_{3,87} = 4.302$, $p = 0.007$, partial $\eta^2 = 0.129$). With ISI 100, ketogenic diet-derived FMT treatment did not impact average PPI ($F_{1,29} = 2.848$, $p = 0.102$, partial $\eta^2 = 0.089$). Ketogenic diet-derived FMT did not impact the MK-801 induced PPI deficit ($F_{1,29} = 0.800$, $p = 0.378$, partial $\eta^2 = 0.027$, Figure 1 C & D). Concluding, MK-801 reduced PPI, which was not attenuated by ketogenic diet at ISI 100.

Startle

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PPI is defined relative to the startle response (pulse-alone trials) [48]. Startle is a measure of general reactivity, if Startle is altered PPI results should be considered with caution. Startle was not affected by MK-801 ($F_{1,29}$ =1.295, p=0.265, partial η^2 = 0.043) nor ketogenic diet-derived FMT treatment ($F_{1,29}$ =0.005, p=0.946, partial η^2 < 0.01) and the two treatments did not interact with one another ($F_{1,29}$ =0.003, p=0.959; partial η^2 < 0.01).

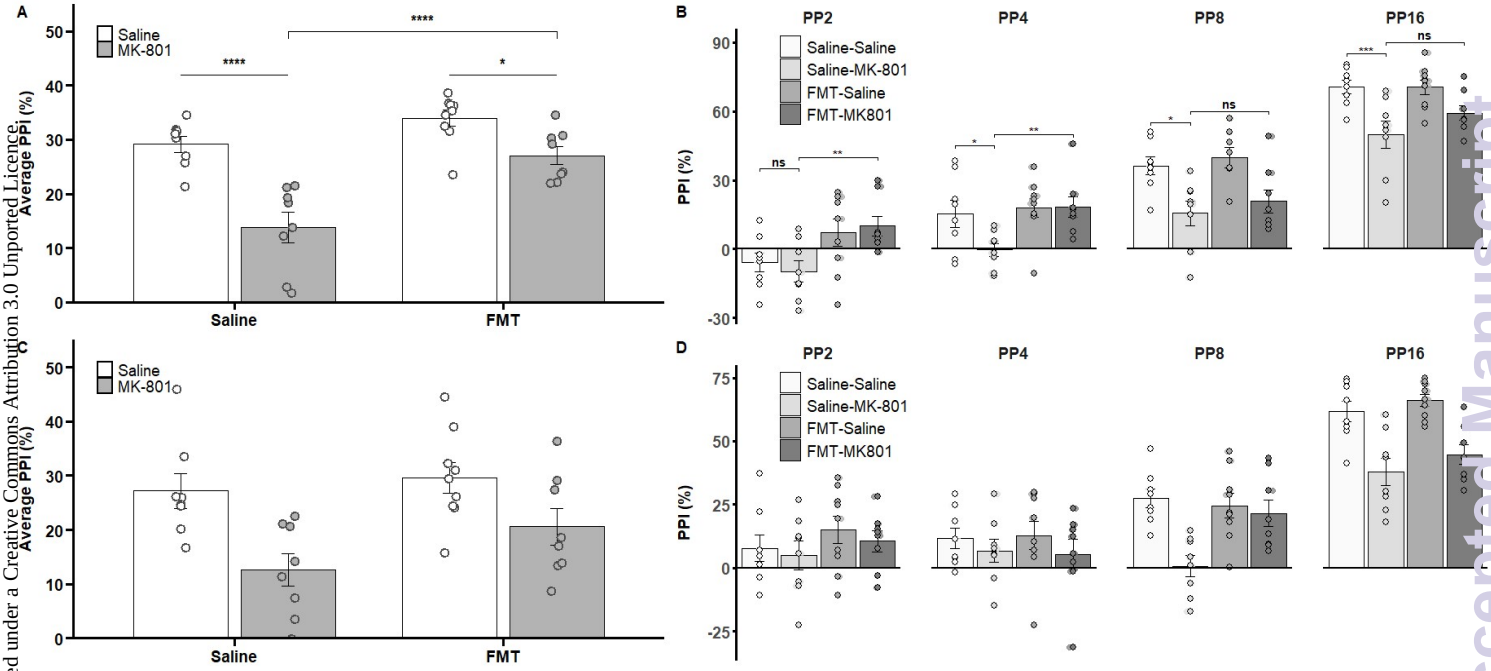

Figure 1: Ketogenic diet-derived FMT improves the PPI deficit in an interstimulus interval dependent manner. (A) MK-801 significantly reduced average PPI, which was increased by ketogenic diet-derived FMT at ISI30, (B) particularly at lower pre-pulse intensities. (C) MK-801 reduced average PPI, which was not improved by ketogenic diet-derived FMT at ISI100 (D) which was consistent across different pre-pulse intensities. Prepulse-pulse trials at 2, 4, 8, and 16 dB over baseline (PP2, PP4, PP8, PP16) * p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. n=8-9 mice per group.

Discussion

The aim of this study was to investigate the effects of ketogenic diet-derived FMT on sensorimotor gating (PPI) within a NMDA-receptor antagonist mouse model of schizophrenia (MK-801). Here, for the first time, we show that inoculation with faeces obtained from KD fed mice significantly mitigates PPI deficits induced by MK-801 compared to mice maintained on standard diet at ISI 30 while startle amplitude remained unaffected. These findings support the hypothesis that some of the behavioural improvements with KDs might be mediated by the gut microbiota.

We previously demonstrated that 3 weeks of KD attenuates PPI deficits in the same hypoglutamatergic preclinical model (47, 53). Similarly, 3 weeks of chronic 2mmol/kg beta-hydroxybutyrate (BHB), the main circulating ketone body produced by the liver during KDs, administration resulted in improvements of sensorimotor gating deficits induced by acute MK-801 administration. Interestingly, our previous findings show that KD normalises PPI deficits at both ISI (30 ms and 100ms) [54] (supplementary materials). BHB improves average PPI at ISI 100 and has no effect at ISI 30 [22] (supplementary materials), whereas ketogenic diet-derived FMT displays the reverse pattern by improving average PPI at ISI 30 but not at ISI 100 (Table 2).

PPI depends on pre-pulse intensity and inter-stimulus interval (ISI) [62]. Here, ketogenic diet-derived FMT improved sensorimotor gating deficits only at ISI 30 not at ISI 100 (Table 2) suggesting that ketogenic diet-derived FMT strengthened the gating of stimuli arriving in the initial 30 ms [63]. This might be an indicator that ketogenic diet-derived FMT is protective of interference by stimuli in immediate temporal proximity but have no impact on interference by stimuli at longer latencies [63]. Short ISI, such as 30 ms, have been considered as preconscious, reflecting brainstem level processing. Our results suggest improvement of automatic gating deficits, these deficits are commonly seen in schizophrenia patients [64]. In contrast, our previous findings show that 3 weeks of chronic BHB injections improve average PPI at ISI 100 [22] and has no effect at ISI 30 (Table 2). ISI 100 is an indicator for conscious information processing [51].

Table 2: Comparison of the efficacy of ketogenic diet-related interventions on the acute NMDA receptor antagonist induced sensorimotor gating impairment at different ISIs in mice

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	30 ms ISI	100 ms ISI	Reference
Ketogenic diet (3 weeks)	Normalised*	Normalised*	54
Chronic BHB 2 mmol/kg (3 weeks)	No Change*	Improved	22
FMT	Improved	No Change	As presented above

*Inferential statistics are provided in supplementary materials

Our findings suggest that ketogenic diet-derived FMT and chronic BHB have distinct biological pathways which might contribute to the broad effects on PPI seen with KD. BHB might work through epigenetic regulation of gene expression, which would explain the effect on attention processes as indicated by ISI 100. Histone deacetylase (HDAC) inhibitors are important in memory formation, consolidation and extinction [65]. BHB has been shown to be a natural HDAC inhibitor [66]. Previous literature has shown that a HDAC inhibitor (Entinostat) rescued PPI deficits in an early life stress animal model of schizophrenia at ISI 100 [67].

The exact mechanism by which the gut microbiota alterations induced by KDs might cause more effective attentional filtering is not known. Several downstream changes resulted by the alterations in the abundance of different bacterial species may take place, including the increased production of short chain fatty acids (SCFAs, e.g. propionate, butyrate, etc.), alterations of enteric neurotransmitter synthesis, (serotonin, in particular) and the activation of vagal neural afferents [68]. One published study is available to support the potential role of SCFAs or enteric neurotransmitters on sensorimotor gating. This study investigated the effects of propionic acid, a SCFA, on sensorimotor gating [69]. Propionic acid is important for immune regulation; however, high doses of propionic acid clinically model some autistic symptoms [70]. Acoustic startle response decreased with higher doses of propionic acid, whereas, percent PPI was not influences by propionic acid [69]. Additionally, subdiaphragmatic vagal deafferentation (cutting the vagus nerve below the diaphragm) impairs sensorimotor gating assessed using prepulse inhibition of startle paradigm [71]. Therefore, it is conceivable that the ketogenic diet-derived FMT activates afferent vagal processes in the host animal to influence the MK-801-induced PPI deficits. Future studies need to confirm if the proposed mechanisms, epigenetic regulation and neurotransmitter synthesis within the gut, resulted in the observed improvements in attentional filtering with BHB, ketogenic diet-derived FMT and KD at different ISI intervals.

Whilst this is an impactful and highly novel study demonstrating a causal role of the gut microbiota in regulating beneficial effects of KD in a validated animal model of schizophrenia it does have some limitations to consider. Currently no standard protocol for FMT inoculation in mouse models exist creating differences in procedure which include the preparation of the donor stool and the preparation of the recipient for FMT and timing such as chronic exposure [53, 72]. Aerobic stool processing may have decreased bacterial viability [72]. Future studies should investigate different inoculation schedules and procedures. Schizophrenia is a chronic disorder with a set of behaviours; therefore, it will be important to investigate the effects of ketogenic diet-derived FMT on other schizophrenia-like behaviours, such as impairments in social interactions and working memory deficits, in chronic animal models of schizophrenia. Within this proof of principle study, we could not perform sequencing on the faecal samples, future studies should compare taxonomic changes of KD faeces and ketogenic diet-derived FMT. At this point, it is not certain if it is the combination of several bacteria species or individual specific bacteria species, which produce the beneficial behavioural effects. Here using KD faeces, we investigated a specific combination of the whole gut microbiota (Bacteria, Fungi, Viruses, Archaea, Parasites) and not just particular bacteria. Therefore, it will be important to investigate the role of microbiota and virome separately.

Conclusions

This study is the first to demonstrate that transplanting KD faecal matter improves a core and highly translatable schizophrenia-like behavioural endophenotype. Our novel finding confirms that some of the beneficial effects seen with KD are due to a modulation in the gut microbiota.

Author contributions

Conceptualisation: Ann-Katrin Kraeuter and Zoltan Sarnyai
Data curation: Ann-Katrin Kraeuter
Formal Analysis: Ann-Katrin Kraeuter
Investigation: Ann-Katrin Kraeuter
Methodology: Ann-Katrin Kraeuter and Zoltan Sarnyai
Project administration: Ann-Katrin Kraeuter and Zoltan Sarnyai
Writing- original draft: Ann-Katrin Kraeuter
Writing- review and editing: Ann-Katrin Kraeuter and Zoltan Sarnyai
Visualisation: Ann-Katrin Kraeuter

Conflicts of interest

There are no conflicts to declare.

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Data availability

The datasets and codes used and/or analysed during the current study are available within the supplementary materials.

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Data availability

The datasets and codes used and/or analysed during the current study are available within the supplementary materials.