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Letter to the editor

Pro-cognitive effect of a prebiotic in psychosis: A double blind placebo controlled cross-over study

Cognitive impairments in psychosis are highly disabling, and are detectable even at first episode of illness, and remain stable or deteriorate for periods of up to ten years (Bozikas and Andreou, 2011). While cognitive improvement is a key predictor of functional recovery, weight gain is also a common side-effect of antipsychotics contributing to the increased prevalence of obesity in patients (Dickerson et al., 2006). Dietary supplementation with a prebiotic, (a substrate selectively utilized by beneficial gut bacteria), improves cognitive flexibility (Gronier et al., 2018) and prevents olanzapine-induced weight gain (Kao et al., 2018) in rats. These effects may have resulted from suppressed circulating pro-inflammatory factors such as C-Reactive Protein (CRP) and IL-6 (Vulevic et al., 2013), and/or from the beneficial actions of acetate produced from the bacterial fermentation of the prebiotic (Kao et al., 2018). The aim of the present study, was to examine whether the daily ingestion of the prebiotic, B-GOS®, improved cognitive function, attenuated weight gain and/or influenced circulating immune/metabolic markers in medicated, stable psychosis participants.

Ethical approval was provided by South-Central Oxfordshire Research Ethics Committee B (16/SC/0654). Thirty-nine non-hospitalised participants (18–60 years old) with psychosis, stable on antipsychotic medication for at least three months prior to recruitment, and whose global cognitive score was 0.5 standard deviations below the healthy average (see below), were randomized in a double-blind placebo-controlled crossover trial (Fig. S1). Exclusion criteria for B-GOS® and placebo supplementation have been previously described (Schmidt et al., 2015). The study is registered on ClinicalTrials.gov (NCT03153046).

Participants performed the Brief Assessment of Cognition in Schizophrenia (BACS, Keefe et al., 2008), at baseline, 12 and 24 weeks, and results were expressed as a standardized T-score to account for age and gender. The Token Motor Test was presented as a raw value. Subjects also completed the Becks Depression Inventory (BDI, Beck et al., 1961). Body mass index, waist-to-hip ratio, hip and waist circumference were assessed, and blood samples taken, at baseline, 12 and 24 weeks. Sera were stored at −80 °C prior to measures of CRP, IL-6 and acetate concentrations using commercial assay kits (Abcam, UK).

All data were assessed for normality using the Shapiro-Wilk test (SPSS ver.22). Paired *t*-tests examined the overall effects of B-GOS® or placebo on pooled data before and after the administration of supplements. A linear mixed model repeated measures analysis explored the influence of group (placebo vs B-GOS®) and time (0 [baseline], 12 and 24 weeks) on all parameters. The level of significance was set at $p < 0.05$.

A significant increase in the composite T-score (effect size, *Cohen's d* = 0.443) was observed following B-GOS® ($n = 24$) intake, but not placebo ($n = 25$) (Fig. 1A, Tables S1, S2), whereas placebo improved verbal fluency alone (effect size, $d = 0.447$, Table S2). To explore which particular domains led to the prebiotic-mediated overall improvement in cognitive performance, the BACS subtests data were arranged into two groups: 'verbal' (verbal memory, verbal fluency) and 'executive' (digit sequencing [measures verbal working memory], symbol coding, Tower of London) functions. There was a significant pre- versus post- effect of B-GOS® on the executive, but not verbal, domains ($t = -2.114$, $p = 0.045$, $n = 24$, $d = 0.432$, Fig. S2A). Placebo had no influence on these domains (Fig. S2B). The overall effect of B-GOS® on the composite T-scores, therefore, was driven by subtests of executive function.

Linear mixed model repeated measures revealed an overall significant effect of time on the BACS composite T-score in all participants ($F = 6.998$, $p < 0.05$). Estimates of fixed effects indicated that this increase was significant at 0–12 weeks, ($t = -3.638$, $p < 0.05$, $n = 39$), and was driven by the improvement in patients supplemented with B-GOS® (Fig. 1B; $t = -2.410$, $p = 0.033$, $n = 13$), but not in those receiving placebo ($t = -1.443$, $p = 0.186$, $n = 14$). The calculated effect size for B-GOS® in this part of the study was $d = 0.669$. Analysis of the 12–24 week period revealed a non-significant increase in composite T-scores in patients taking the prebiotic, whereas a decrease was observed in the placebo group (Fig. 1B). The overall change in T-scores between 0 and 24 weeks was only significant in subjects completing the trial with the prebiotic (Fig. 1B). A similar analysis of verbal fluency T-scores, (in view of the placebo effect, Table S2), revealed a trend effect of time ($F = 3.026$, $p = 0.07$), but no significant fixed effects at 0–12 weeks or 12–24 weeks ($p > 0.05$). The placebo finding therefore, may have occurred by chance and an upshot of the 'learning effect' observed after repeated cognitive testing (Fig. 1B). There were no significant differences in mood, anthropometric indices or serum levels of acetate, CRP and IL6 after B-GOS® (Table S1) or placebo (Table S2).

The B-GOS®-mediated improvement in global cognition in participants with psychosis is a novel finding, and is consistent with previous work demonstrating improved cognitive flexibility in rats (Gronier et al., 2018), and attentional vigilance in healthy volunteers (Schmidt et al., 2015) following prebiotic intake. Neurocognitive impairment in psychosis has been hypothesized to originate from central *N*-methyl-D-aspartate receptor (NMDAR) hypo-function (Coyle, 2012). Given that B-GOS® elevates brain NMDARs and D-serine in rats (Kao et al., 2018; Savignac et al., 2013), their increase in psychosis patients may have mediated the enhancement in cognitive function.

The current study also demonstrated that B-GOS® supplementation did not affect weight, BMI, central adiposity or circulating candidate metabolic/immune markers. This is in contrast to our recent observation in rats, where B-GOS® administration attenuated olanzapine-induced weight gain (Kao et al., 2018). However, since a majority of participants had been treated for several years, it is possible that B-GOS® is ineffectual once olanzapine-induced metabolic side effects are established.

In conclusion, this investigation provides the first proof-of-concept that the consumption of the prebiotic B-GOS® confers significant cognitive benefits in medicated participants with psychosis, possibly driven by improvements in specific executive functions. Future studies to corroborate our findings and to test other prebiotics, should include clinical

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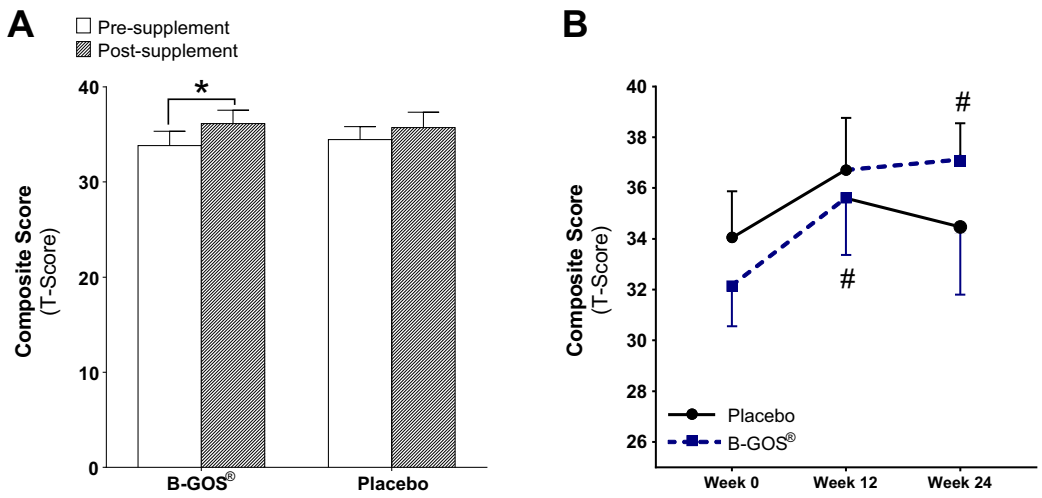

Fig. 1. Effect of B-GOS® ($n = 24$) and placebo ($n = 25$) on composite T-score represented by (A) the change in T-Score before and after supplementation and (B) over the 24-week study. $^{*}p < 0.05$ with paired t-tests; $^{\#}p < 0.05$ compared to baseline (week 0), with linear mixed model repeated measures.

symptom assessments to reveal the overall therapeutic utility of prebiotics in psychosis, and measures of gut microbiome composition to define the associations between bacterial communities and cognition in participants.

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Conflict of interest

Clasado Biosciences Ltd. provided the B-GOS® and placebo supplements 'in-kind', but made no financial contributions to the study. The authors disclose no financial interests or any other conflicts of interest.

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The Governance of the University of Oxford played no role in the design, analysis, write-up or decision to submit this manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.03.003.

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