Bifidobacterium longum **1714**: A psychobiotic that modulates brain activity, the stress response and neurocognitive performance in healthy volunteers

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1. Introduction

There is increasing interest in targeting the gut microbiome to affect brain and behavior in humans. Psychobiotics, probiotics that confer a mental health benefit upon the host, represent one such strategy [**1**]. There is existing evidence that chronic administration of multistrain probiotics or fermented milk probiotic products can impact upon the psychological and physiological indices of stress in humans [**2**], as well as upon central nervous system activity [**3**] and cognitive performance [**4**]. However, most of the evidence for psychobiotics comes from animal studies, and there has been a lack of translational selection of strains from preclinical screening to use in human studies.

Previous research from our group has indicated that *Bif longum* **1714**™ can reduce the stress-related behaviours and improve memory performance in mice [**5,6**]**.** We thus investigate the impact of *Bif longum* **1714** on stress, resting brain activity and neurocognitive performance in healthy volunteers.

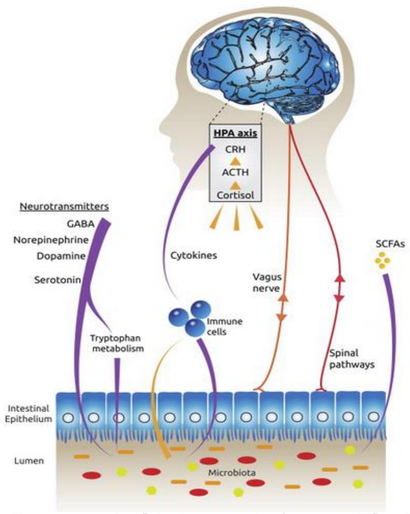


Figure 1 [Adapted from **7**]: The brain and gut microbiota can communicate through various bidirectional routes.

2. Aims & Hypothesis

Aim: Investigate the impact of *Bif Longum* **1714** on stress, cognition and resting brain activity. Hypotheses: *Bif Longum* **1714** would (a). reduce daily stress, (b). attenuate the psychological and physiological response to a controlled, acute stressor, (c). improve cognitive performance and (d). enhance brain activity.

3. Methods

Participants

Healthy male volunteers (N = 22) were recruited (see **Table 1** below for participant characteristics). Exclusion criteria were as follows: having a significant acute or chronic illness; having a condition, following a diet or taking a medication that would interfere with study objectives, pose a safety risk or confound the interpretation of the study results; English not participant's first language; colour blindness, dyslexia/dyscalculia; smoking; habitually taking any probiotic products; any treatment involving experimental drugs.

Age	25.5 +/- 1.2	**Anxiety (STAI)**	29.9 +/- 1.7
BMI	24.8 +/- 0.7	**Depression (BDI)**	3.6 +/- 0.9
Alcohol use	7.5 units/wk +/- 1.3	**Stress (PSS)**	9 +/- 1
Education	18.6 years +/- 0.6	**IQ (NART)**	108 +/- 1.2

Table 1: Participant characteristics (Values are mean +/- SEM)

Procedure

Daily stress: Daily stress was assessed using the Cohen Perceived Stress Scale. Participants completed this via an online survey administered with limesurvey software.

Neurocognitive performance: Participants completed the paired associates learning task (PAL), emotional recognition task and rapid visual information processing tests from the CANTAB platform; the PAL is associated with hippocampal activity (see **Figure 3A**).

Electroencephalography: Resting EEG for 5 minutes was assessed using the Compumedics Neuroscan® Stim system (see **Figure 3B**).

Acute stressor: Participants completed the socially evaluated cold pressor test (SECPT). Participants submerged their hands in water at 0-4^{0}C for up to three minutes, while being evaluated by an cold and unencouraging confederate.

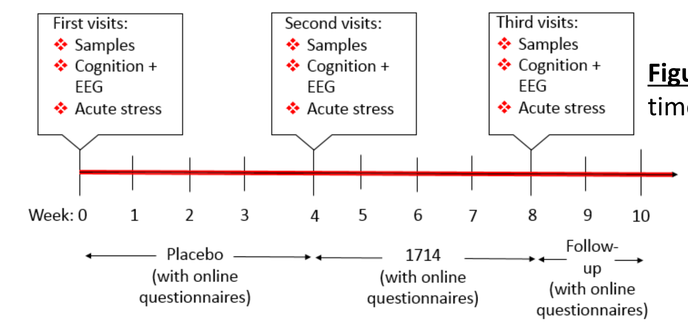


Figure 2: Study timeline

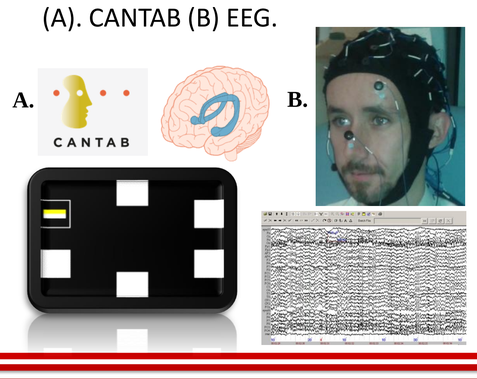
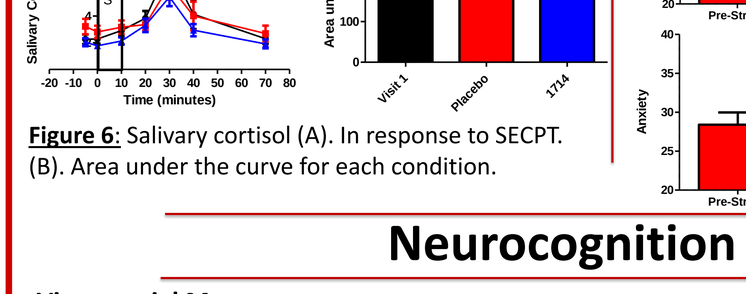


Figure 3: Neurocognitive assessment: (A). CANTAB (B) EEG.

Figure 4: Socially evaluated cold pressor

4. Results

Daily stress



Daily stress was marginally lower at week 4 of the probiotic condition compared to placebo, $t(18) = 1.95$, $p = .07$, and increased again at follow-up (see **Figure 5A**). Overall stress was lower in the **1714** condition, $t(18) = 2.32$, $p = .03$ (see **Figure 5B**).

Figure 5: (A). Daily stress for each week of study. (B). Stress area under the curve with respect to ground (AUCg).

Acute stress response

Salivary cortisol

The socially evaluated cold pressor increased cortisol at all visits (p's < .001) (see **Figure 6A**). *Bif longum* **1714** reduced cortisol output in comparison to placebo and visit 1, $\chi^2(2) = 8.67$, $p < 0.05$ (see **Figure 6B**).

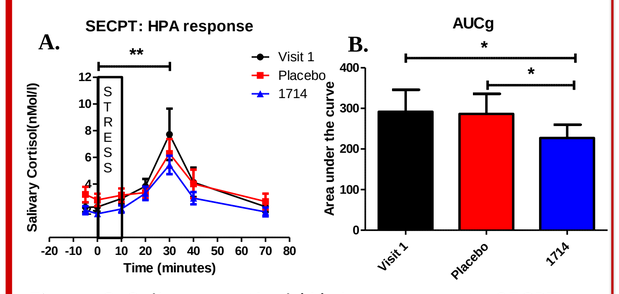


Figure 6: Salivary cortisol (A). In response to SECPT. (B). Area under the curve for each condition.

Anxiety

State anxiety increased in response to the SECPT at visit 1, $T = 8.58$, $p < .05$, and post-placebo, $T = 7.7$, $p < .01$. However, this increase in anxiety was no longer significant post-**1714,** $T = 9.13$, $p > .05$, $r = 0.12$ (see **Figure 7**).

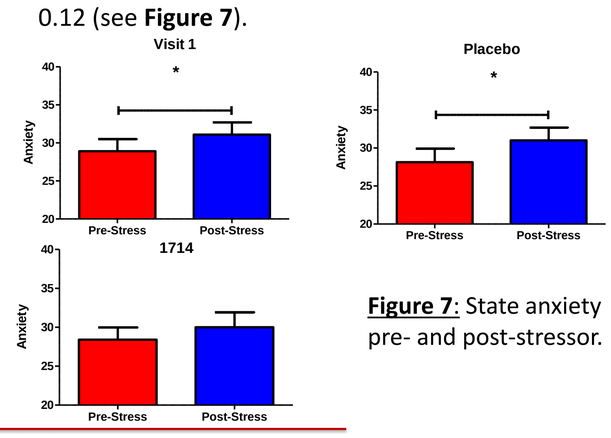


Figure 7: State anxiety pre- and post-stressor.

Neurocognition

Visuospatial Memory

Total errors differed across condition on the Paired Associates Learning (PAL) test, $\chi^2(2) = 10.46$, $p < 0.01$. Participants made fewer errors post-**1714** compared to Visit 1, a greater effect than post-placebo (see **Figure 8**).

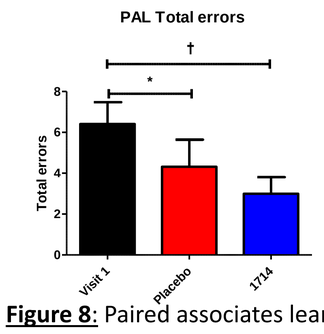


Figure 8: Paired associates learning errors

Resting EEG

Participants had higher mobility at Fz post-1714 compared to post-placebo or visit 1, , $\chi^2(2) = 13.37$, $p = 0.01$ (see **Figure 9A**). Theta at Cz was lower post-**1714** compared to post-placebo, $\chi^2(2) = 10.31$, $p < 0.01$ (see **Figure 9B**).

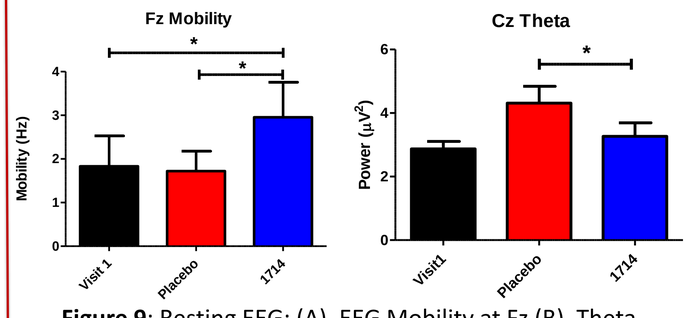


Figure 9: Resting EEG: (A). EEG Mobility at Fz (B). Theta power at Cz.

5. Discussion & conclusions

- The **1714** strain attenuated acute stress response to the socially evaluated cold pressor test, which elevated cortisol levels at all visits.
- Consumption of the **1714** strain lowered reported daily stress.
- The **1714** strain is associated with subtle enhancements in visuospatial memory on a paired associates learning test.
- Frontal mobility was enhanced and midline theta was reduced post-**1714**.
- The current research translates psychobiotic findings from preclinical research to healthy human volunteers.
- Further research is warranted to examine the impact of this psychobiotic strain in stress-related disorder.

6. Acknowledgements & Disclosure

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7. References

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