Towards psychobiotics for stress & cognition: *Bifidobacterium longum* 1714 blocks stress-induced behaviour and physiology and modulates brain activity and neurocognitive performance in healthy human subjects

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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.

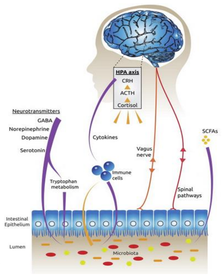

Figure 1 [Adapted from **7**]: The brain and gut microbiota can communicate through various bidirectional routes.

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

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; see **Figure 4**). 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. Saliva samples for cortisol analysis were taken before and after stress exposure.

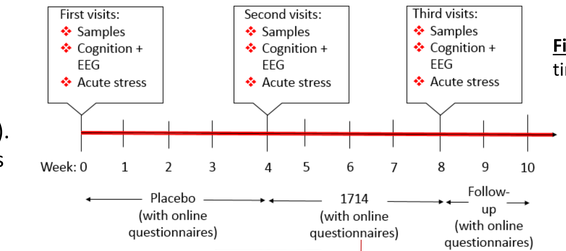

Figure 2: Study timeline

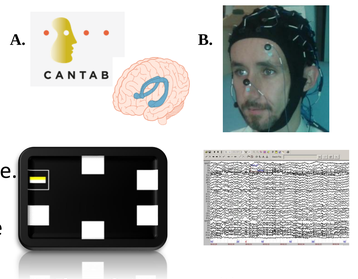

Figure 3: Neurocognitive assessment: (A). CANTAB (B) EEG.

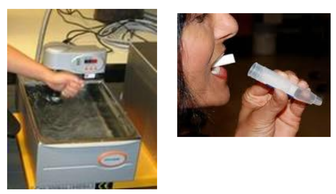

Figure 4: Socially evaluated cold pressor (SECPT)

4. Results

Participants

Healthy male volunteers (N = 22) were recruited (see **Table 1**). Exclusion criteria were: having a significant acute or chronic illness, a condition, following a diet or taking a medication that would interfere with study objectives or pose a safety risk; English not participant's first language; smoking; habitually taking any probiotic products; any treatment involving experimental drugs.

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

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

Daily stress

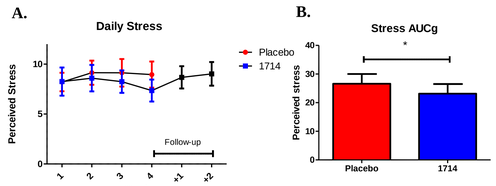

Figure 5: (A). Daily stress for each week of study. (B). Stress area under the curve with respect to ground (AUCg).

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 compared to placebo, $t(18) = 2.32$, $p = .03$ (see **Figure 5B**).

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**).

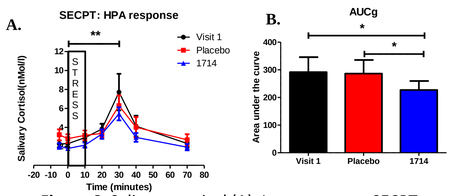

Figure 6: Salivary cortisol (A). In response to SECPT. (B). Area under the curve for each condition.

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**).

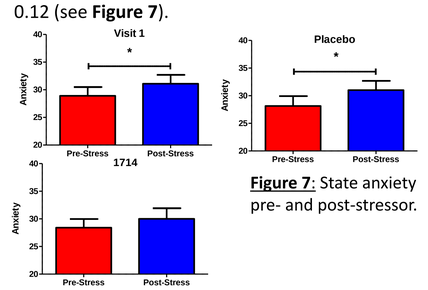

Figure 7: State anxiety pre- and post-stressor.

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**).

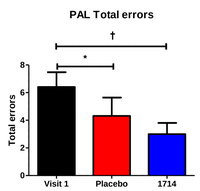

Figure 8: Paired associates learning total errors

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**).

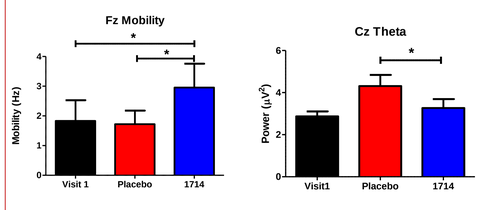

Figure 9: Resting EEG: (A). EEG Mobility at Fz (B). Theta power at Cz.

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 this strain lowered reported daily stress.
- Consumption of this 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 disorders.

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References

[1] Dinan, T.G., et al. 2013. *Biological Psychiatry* 74, 720-726
[2] Messaodi, M., et al. 2011. *British Journal of Nutrition* 105, 755-764
[3] Tillisch, K., et al. 2013. *Gastroenterology* 144, 1394-1401
[4] Chung, Y., et al. 2014. *Journal of Functional Foods* 10, 465-474
[5] Savignac, H.M. et al. 2014. *Neurogastroenterology & Motility*, 26, 1615-27
[6] Savignac, H.M. et al. 2015. *Behavioral Brain Research*, 287, 59-72.
[7] Dinan, T.G., et al., 2015. *Journal of Psychiatric Research* 63, 1-9

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