Interactions between gut microbiota signatures and CNS status in a HIV cure strategy

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BACKGROUND

The microbiome-gut-brain axis interplay is a major player in regulating the neurocognitive functioning.

The BCN02-Neuro study[1] investigated the effects of the HIV latency reversing agent romidepsin (RMD) on the central nervous system (CNS) in early-treated HIV-infected individuals (**Figure 1**), showing no significant alterations in cognitive and functional outcomes. Although, participants with lower cognitive functioning (standardized neuropsychological test score covering 6 cognitive domains, NPZ-6) showed a trend toward progressive improvement over time (**Figure 2**).

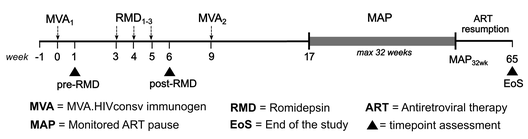

***Figure 1**. Study design.*

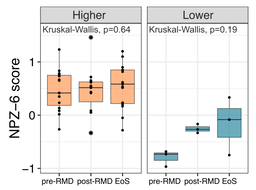

***Figure 2**. Longitudinal changes of NPZ-6 score.*

Additionally, the BCN02-Microbiome study[2] identified host and gut microbial pro-inflammatory signatures as potential predictors of immune-mediated HIV-1 control during 32-weeks of monitored antiretroviral pause.

OBJECTIVES

I. To characterize the gut microbiota composition and functions in participants with lower and higher cognitive functioning in the BCN02-Neuro study.

II. To identify potential gut microbial signatures for predicting cognitive functioning evolution.

III. To validate microbial predictive signatures in two BCN02 sub-cohorts.

METHODS

Participants with lower (≤-0.5, n=3) and higher (>-0.5, n=15) NPZ-6 score at the study entry and with characterized gut microbiome (shotgun metagenomics data analyzed using Metaphlan2 and Humann2) were included in the study. Assessments were performed before (pre-RMD) and after RDM administration (post-RMD) and at the end of the study (EoS) (**Figure 1**).

Associations between microbial taxa, cognitive functioning and functional outcomes (CNS-related symptoms, emotional status, daily functioning, and quality of life) were characterized in HIV-1 viremic controllers and non-controllers (C-NC, n=11) and RMD-intervention and RMD-no-intervention (I-NI, n=16) sub-cohorts from the paternal BCN02 study[3].

Differentially abundant taxa were estimated by Random forest and discriminant LEfSe analysis. Spearman's correlations and BH-adjusted p-values were calculated by R/*rcorr* and microbiome profiling assessed using R/*phyloseq*.

HIV-infected early-treated patients presenting worse cognitive functioning and enriched in neurological-linked bacteria showed recovery in the BCN02-Neuro study

RESULTS

I. Taxonomic and functional signatures associated with different cognitive functioning

Participants with lower NPZ-6 score at pre-RMD were enriched in bacterial species previously described in autism spectrum disorder (ASD) and other neurological disorders[4] (**Figure 3a**). Also, this group was functionally enriched in 1,2-propanediol degradation (pathway of propionic acid synthesis) at pre-RMD (**Figure 3b**). Previous evidence suggests that propionic acid is produced by gut bacteria related to ASD, such as *Desulfovibrio spp* and *Clostridium spp*[5].

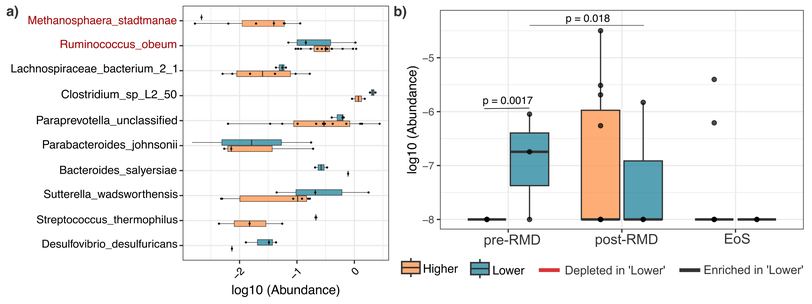

***Figure 3**. **a)** Differentially abundant bacterial species between Lower NPZ-6 and Higher NPZ-6 groups (p<0.05) at pre-RMD. **b)** Longitudinal changes of L-1,2-propanediol degradation (PWY-7013) pathways.*

II. Microbiome-based index for NPZ-6 score evolution

To investigate the evolution of NPZ-6 score-associated bacteria over time, an index was obtained by calculating the log ratio of geometric means of taxon abundances enriched in the Lower NPZ-6 group (p-val < 0.05) over taxa depleted in Lower NPZ-6 group (p-val < 0.05), compared to the Higher NPZ-6 group, as following[6]:

$$\textbf{\textit{Index}} = \log_{10}\left(\frac{\sqrt[n]{x_1 x_2 \dots x_n}}{\sqrt[m]{y_1 y_2 \dots y_m}}\right)$$

x= *Desulfovibrio desulfuricans, Streptococcus thermophilus, Sutterella wadsworthensis, Bacteroides salyersiae, Parabacteroides johnsonii, Paraprevotella unclassified, Clostridium sp L2 50, Lachnospiraceae bacterium_2_1_58FAA* **at pre-RMD**

y= *Ruminococcus obeum, Methanosphaera stadtmanae* **at pre-RMD**

The index was negatively correlated with NPZ-6 score at pre-RMD (**Figure 4a**) and positively correlated with delta NPZ-6 score (EoS – pre-RMD) (**Figure 4b**).

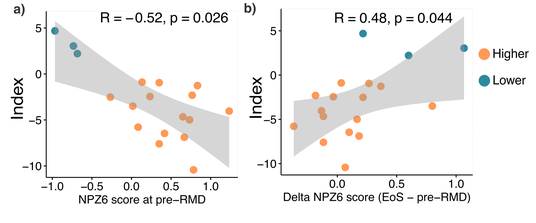

***Figure 4**. Correlations between microbiome-based Index and NPZ-6 score.*

RESULTS

Also, in the participants with lower NPZ-6 score, the microbiome-based index showed a significant longitudinal decrease from pre-RMD to EoS (p=0.039) (**Figure 5**).

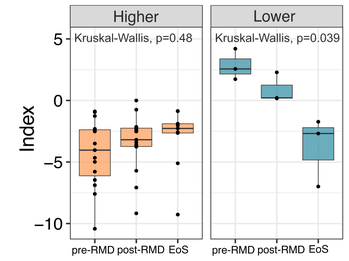

***Figure 5**. Longitudinal evolution of microbiome-based index in Lower and Higher NPZ-6 groups.*

III. Microbiome-based index evaluation in BCN02 sub-cohorts

BCN02 sub-cohorts showed no differences in the microbial index values (**Figure 6a**). In the BCN02 subcohorts, bacteria associated to neurological disorders **negatively** correlated with NPZ-6 score, quality of life and daily functioning and **positively** with CNS related symptoms, depression, stress and anxiety. An opposite trend was observed in bacteria enriched in participants with higher NPZ-6 score and typically described as anti-inflammatory (*R. obeum* and *M. stadtmanae*)[7] (**Figure 6b**).

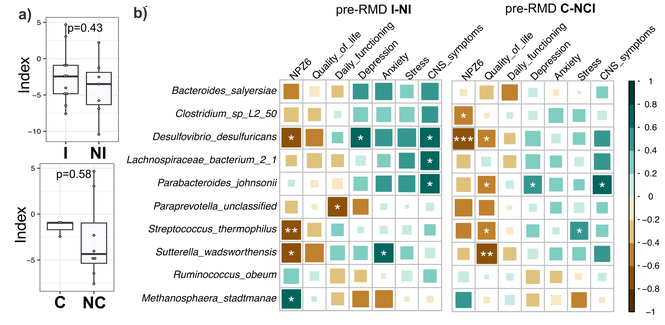

***Figure 6**. **a)** Microbiome-based index comparison in the BCN02 sub-cohorts at pre-RMD. **b)** Correlations between differentially abundant bacteria, cognitive functioning and functional outcomes significance in the BCN02 sub-cohorts at pre-RMD. Significance after FDR adjustment is indicated by asterosks (*p < 0.05; **p < 0.01; ***p < 0.001).*

CONCLUSIONS

- ✓ In participants presenting worse cognitive functioning at study entry and progressive NPZ-6 score recovery, the abundance of bacterial species related to neurological alterations is significantly reduced over time.
- ✓ Bacterial species related to neurological alterations showed global negative correlation with cognitive functioning and quality of life and positive correlation with emotional status.
- ✓ The microbial index might represent a potential predictor of cognitive functioning evolution.

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