Electroacupuncture reshapes the microbial co-occurrence networks related to the behavioral and psychological symptoms of dementia in Alzheimer’s disease

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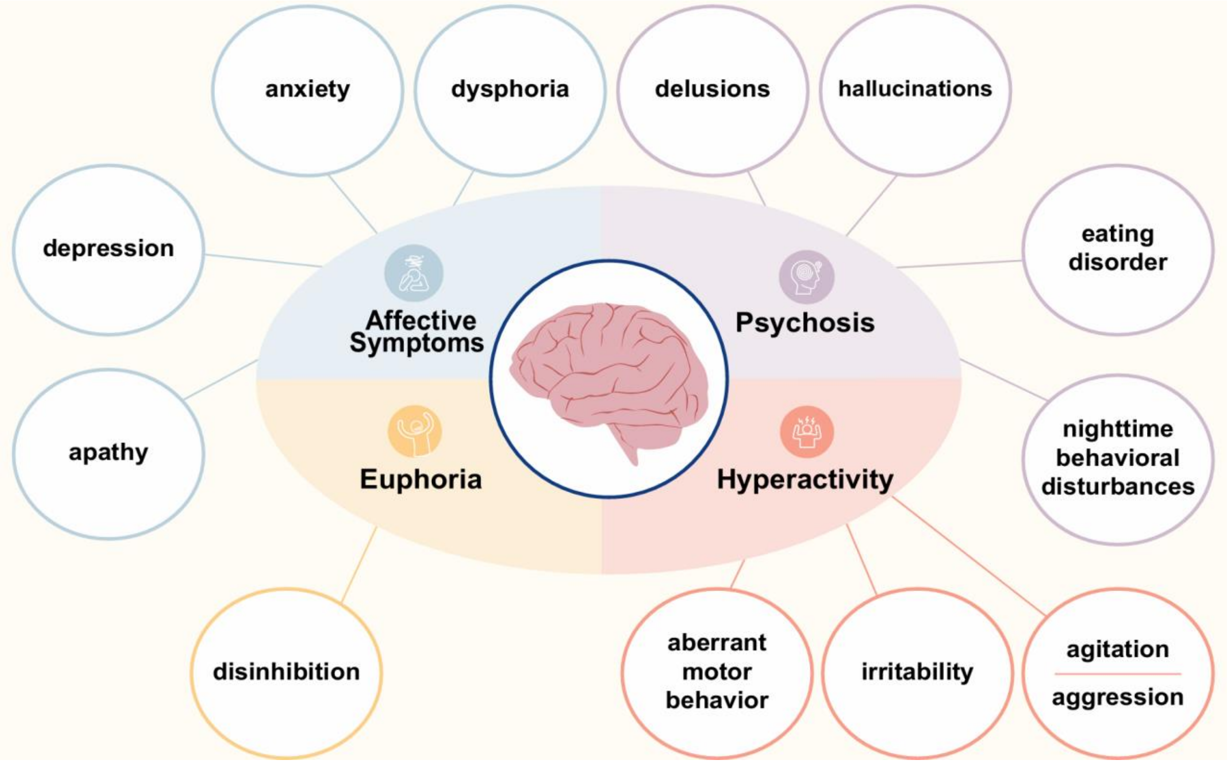
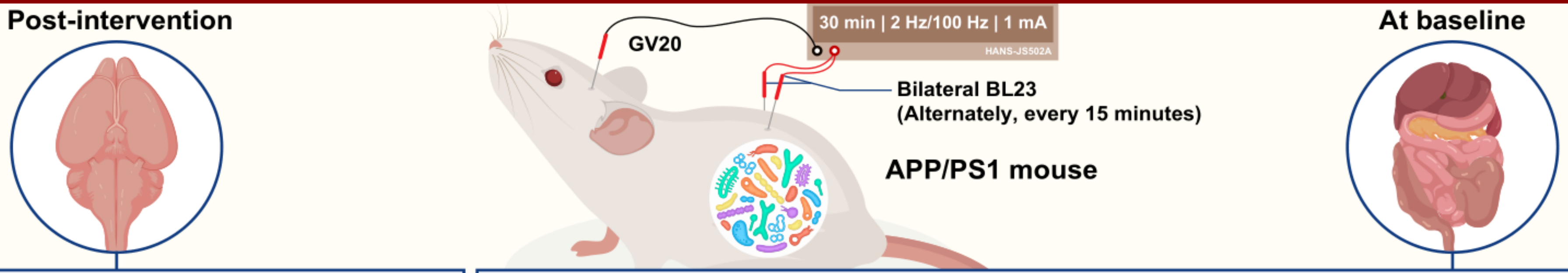
Introduction



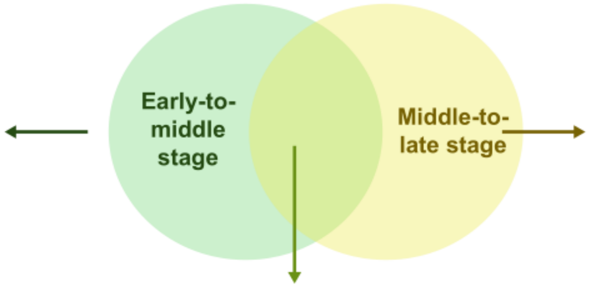
- BPSD belongs to the spectrum of neuropsychiatric syndromes (NPS), encompassing more than twelve complex symptoms divided into four major categories.
- Microbial keystone species and gut microbiota composition are highly variable during the pathological development of BPSD in AD.
- Age stratification reveals stage-specific gut microbial signatures in AD-related BPSD.

Highlights



- **Structural network changes driven by *Ruminococcus gnavus* post-electroacupuncture**
- **Behavioral improvement post-electroacupuncture (↓ anxiety, hyperactivity)**

Potential microbial markers



Lactobacillus vaginalis, Ruminococcus gnavus

Alistipes finegoldii, Desulfovibrio C21_c20, Faecalibacterium prausnitzii, Alistipes massiliensis, Clostridium celatum

Bifidobacterium pseudolongum, Lactobacillus hamsteri, Parabacteroides distasonis, Akkermansia muciniphila, Clostridium cocleatum, Ruminococcus flavefaciens

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Co-occurrence networks

Early-to-middle stage: Keystone species

- *Mucispirillum schaedleri*
- *Clostridium perfringens*
- *Subdoligranulum variabile*

Middle-to-late stage: Keystone species

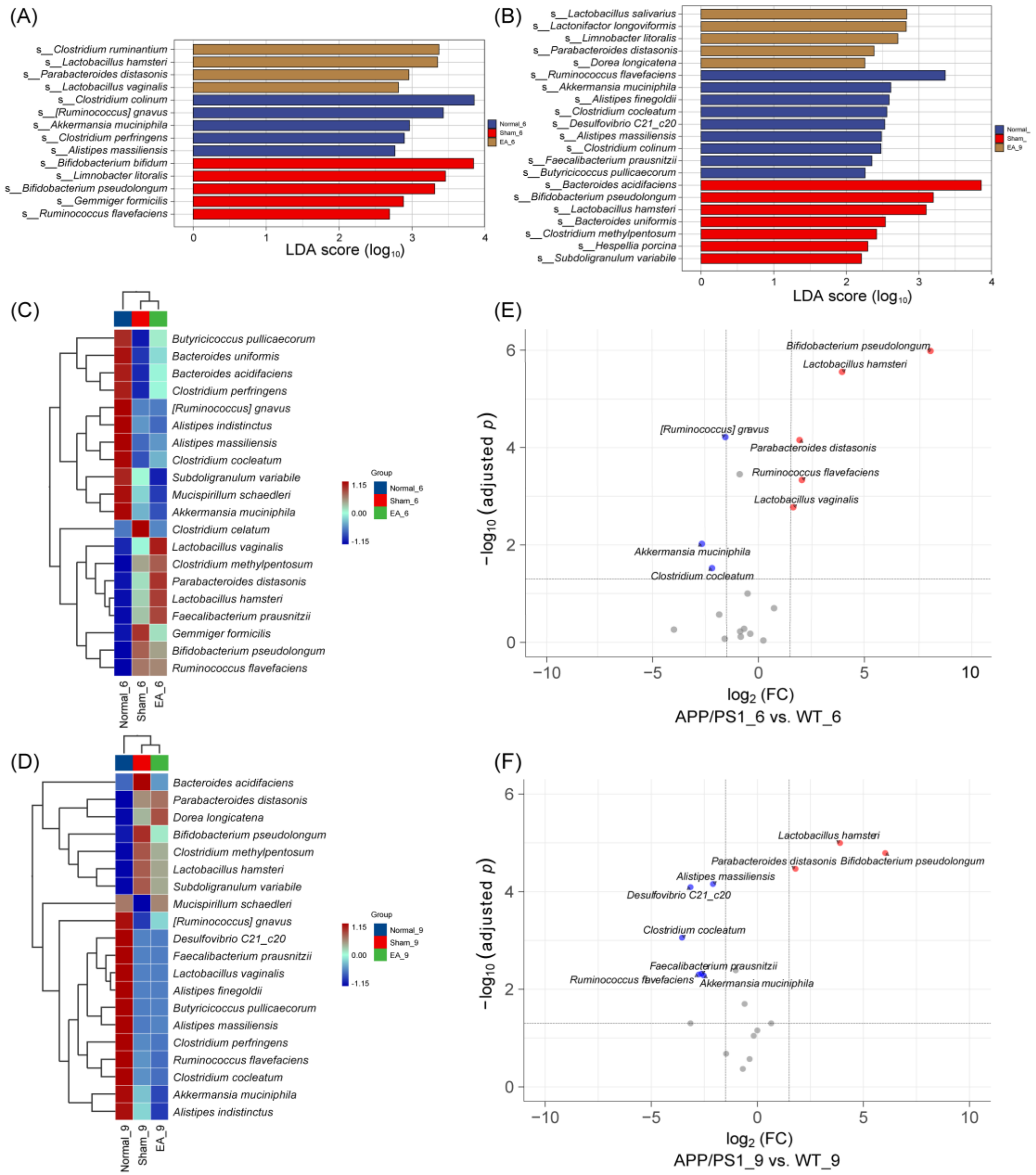
- *Bifidobacterium pseudolongum*
- *Lactobacillus hamsteri*
- *Butyricicoccus pullicaecorum*
- *Clostridium celatum*

Metabolic pathway changes

- Early-to-middle stage → ↑ Glucose degradation
- Middle-to-late stage → ↑ L-arabinose degradation, gallate degradation, and chlorophyllide A biosynthesis

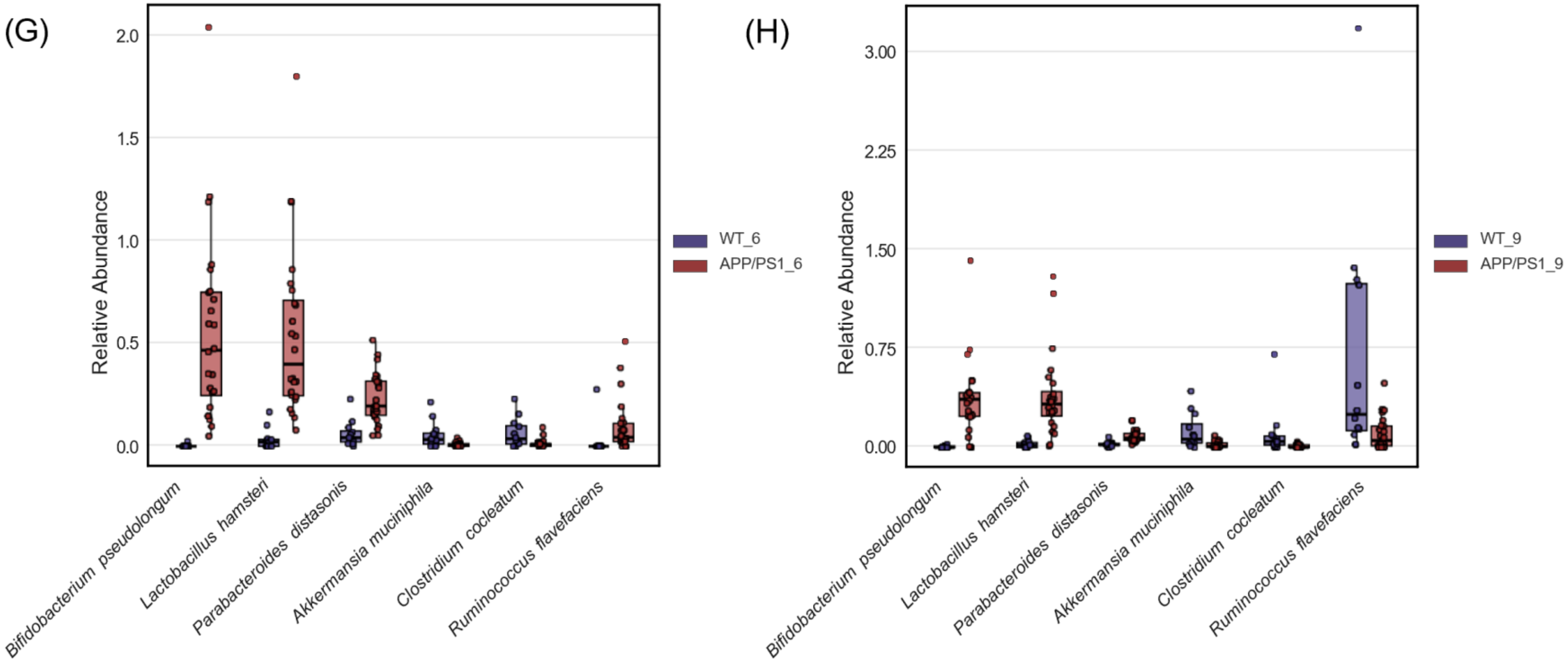
Results

Profiles of disease-discriminatory microbial markers



- Our analyses demonstrated that *Bifidobacterium pseudolongum*, *Lactobacillus hamsteri*, and *Parabacteroides distasonis* were significantly enriched, while *Akkermansia muciniphila* and *Clostridium cocleatum* were significantly depleted in both 6- and 9-month-old APP/PS1 mice.

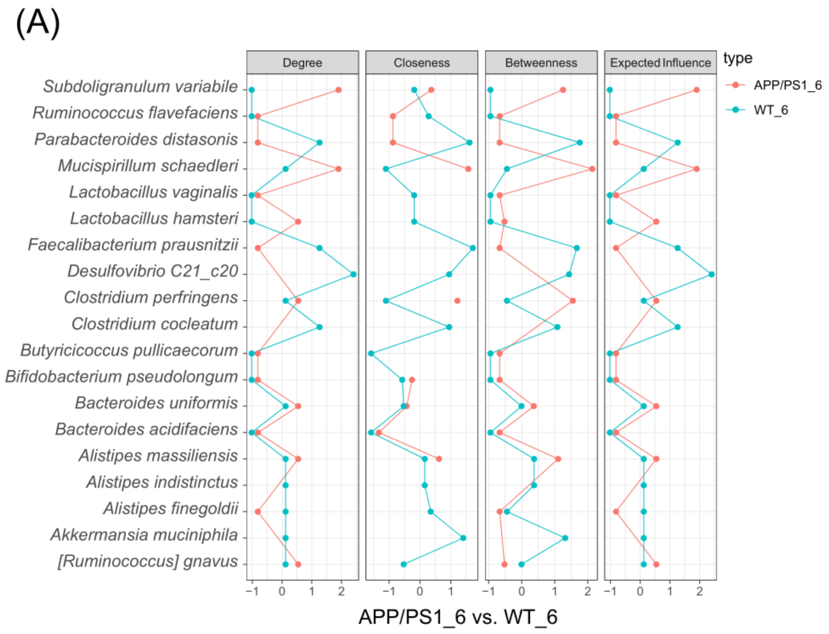
Age-stratification reveals stage-specific microbiota signatures



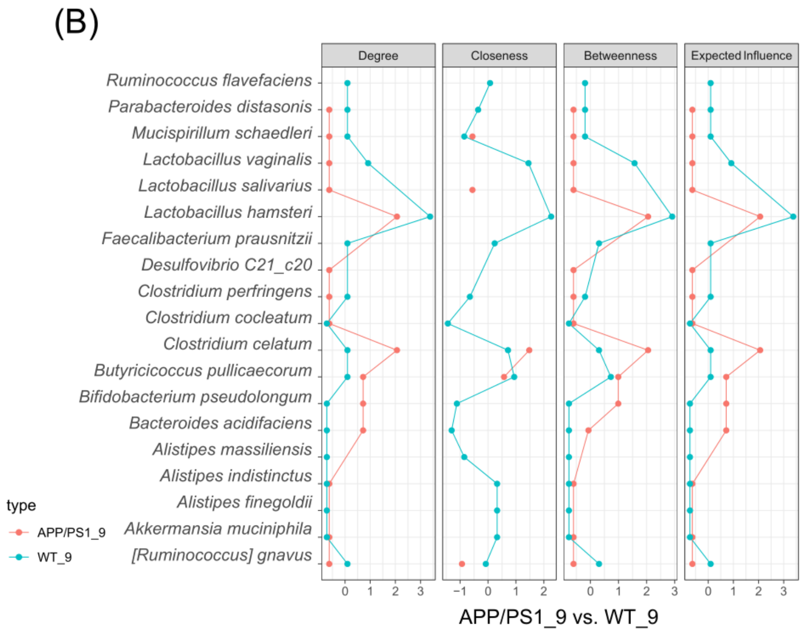
- The specific microbial markers that distinguished 6-month-old APP/PS1 mice from age-matched wild-type (WT) mice included *Lactobacillus vaginalis* and *Ruminococcus gnavus*, while those that distinguished 9-month-old APP/PS1 mice from age-matched WT mice included *Alistipes finegoldii*, *Desulfovibrio C21_c20*, *Faecalibacterium prausnitzii*, *Alistipes massiliensis*, and *Clostridium celatum*.

- Due to the marked variation in the abundance of *Ruminococcus flavefaciens* in both age groups of WT mice, the comparison between AD and WT mice exhibited an opposing trend: a higher abundance in 6-month-old APP/PS1 mice but a lower abundance in 9-month-old APP/PS1 mice when compared to age-matched WT mice.

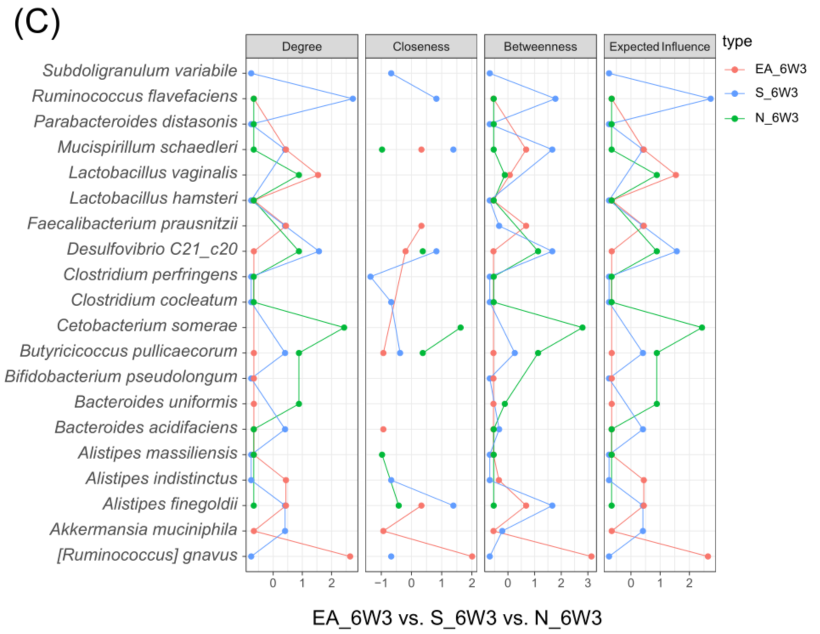
Centrality score indicators for microbiota



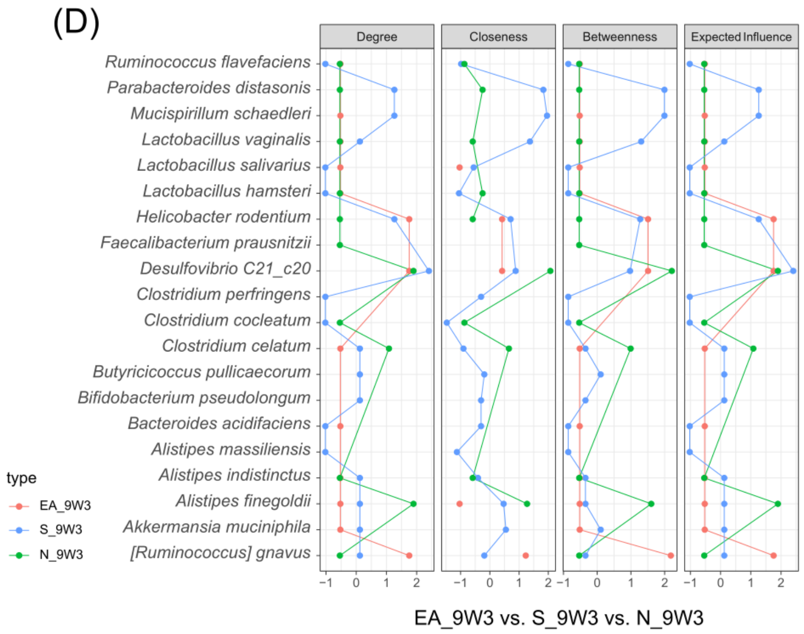
APP/PS1_6 vs. WT_6



APP/PS1_9 vs. WT_9



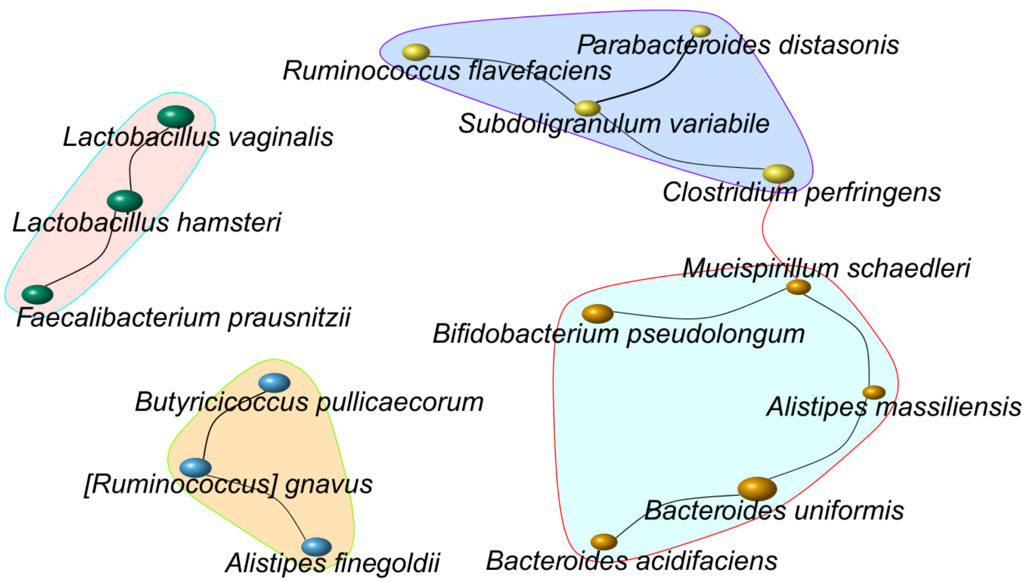
EA_6W3 vs. S_6W3 vs. N_6W3



EA_9W3 vs. S_9W3 vs. N_9W3

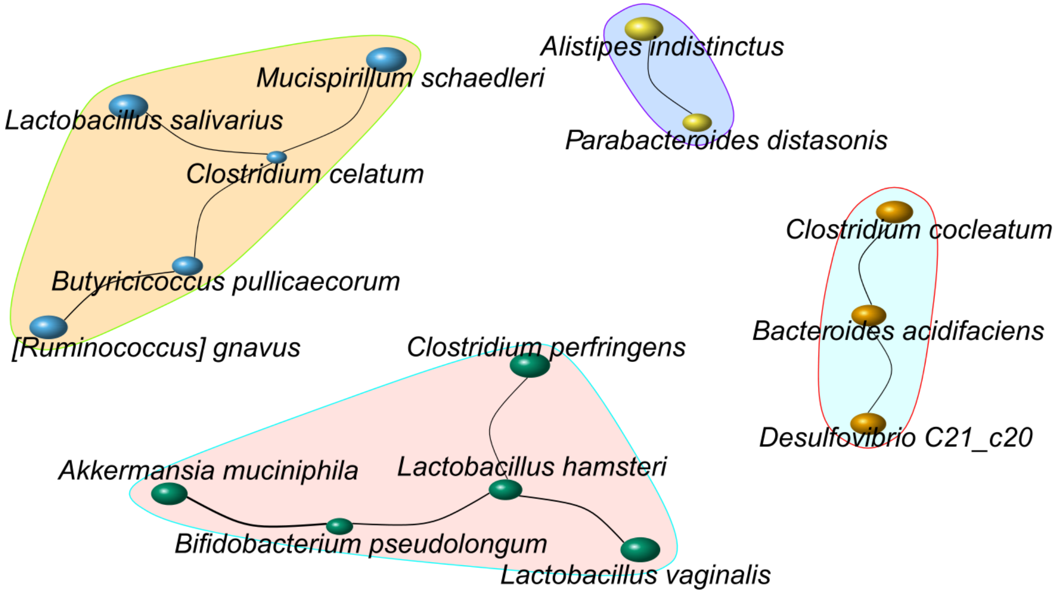
Dynamics of the microbial co-occurrence network

(E)



APP/PS1_6

(F)

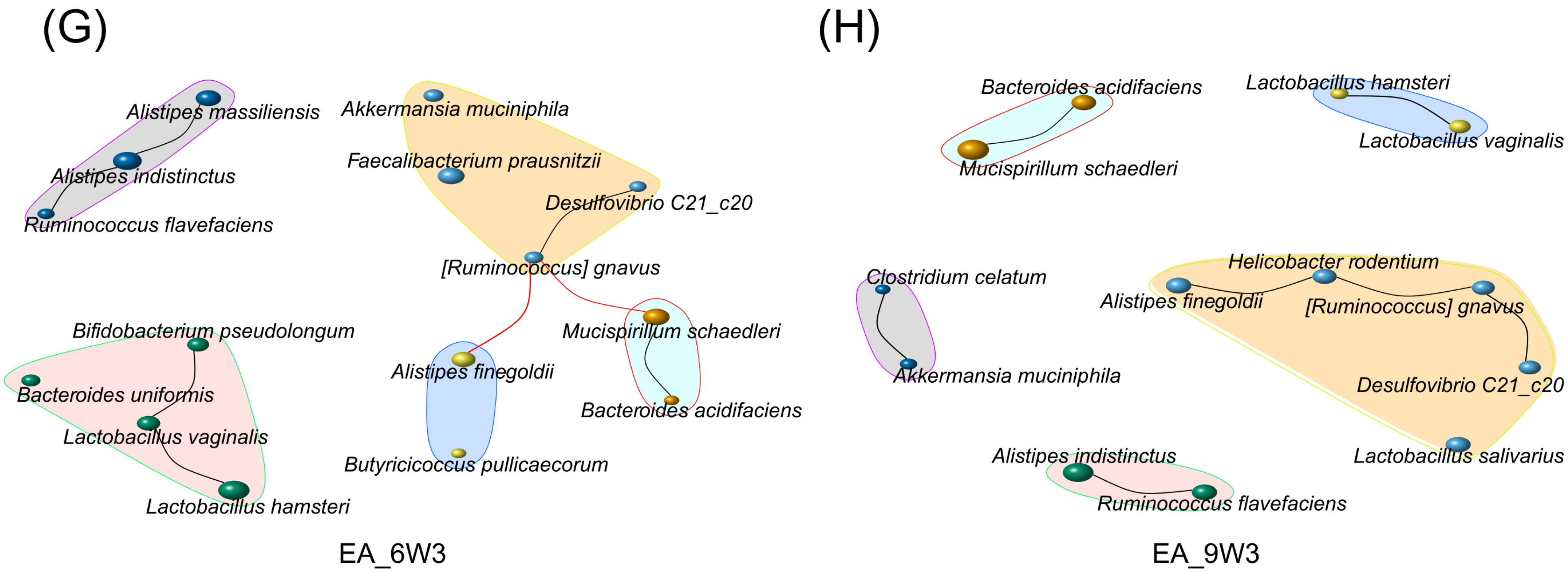


APP/PS1_9

- In the microbial co-occurrence network of 6-month-old APP/PS1 mice, *Mucispirillum schaedleri* and *Clostridium perfringens* were negatively correlated and identified as keystone species, together with *Subdoligranulum variabile*, a diabetes-related species.

- In the microbial co-occurrence network of 9-month-old APP/PS1 mice, *Bifidobacterium pseudolongum*, *Lactobacillus hamsteri*, and *Butyricicoccus pullicaecorum*, which have anti-inflammatory effects and produce short-chain fatty acids, and *Clostridium celatum*, a risk factor for type 2 diabetes, were identified as keystone species.

Electroacupuncture reshaped microbial co-occurrence network module



- In the co-occurrence network of 6- and 9-month-old APP/PS1 mice post-electroacupuncture, *Ruminococcus gnavus*, which is related to inflammatory bowel disease (IBD) and produces polysaccharides, was identified as a likely keystone species.

Summary

- Our findings support our hypothesis on the co-regulation of glucose, L-arabinose, and gallate degradation with chlorophyllide A biosynthesis in the gut microbiota of AD-related BPSD following electroacupuncture intervention.

- Our findings suggest that electroacupuncture can ameliorate AD-related BPSD by driving keystone species in the microbial co-occurrence network and by regulating the composition and functional metabolic pathways of core microbiota.

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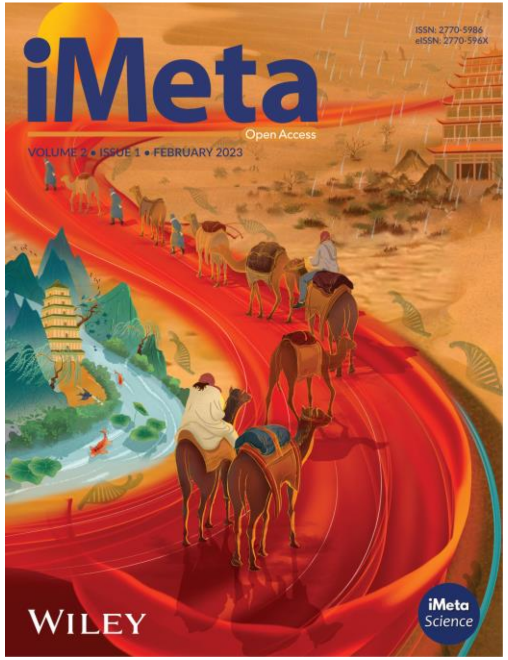

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