The GUT-BRAIN study: short-term effect of a high-fiber diet on gut-brain communication

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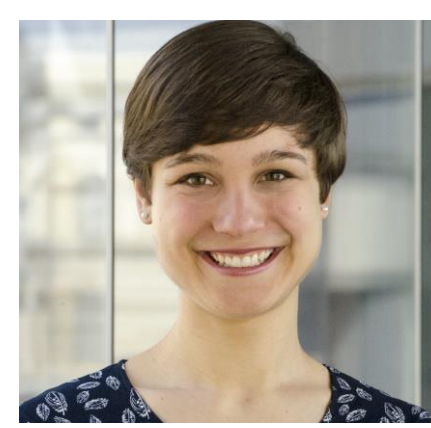
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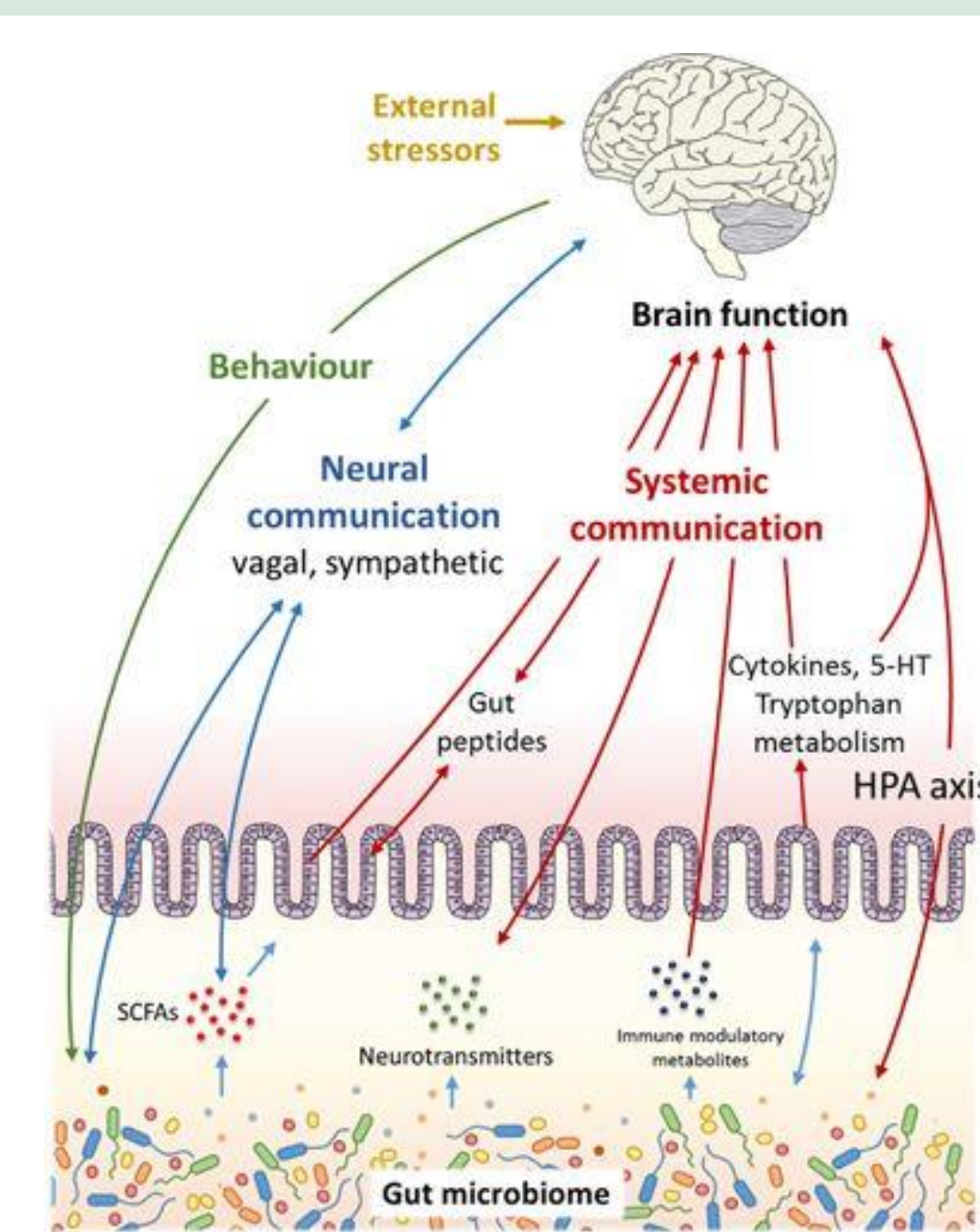
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Background

Communication pathways linking the gut microbiome with brain function.

Rogers, G. B., et al. (2016). From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol. Psychiatry; 21(6): 738.
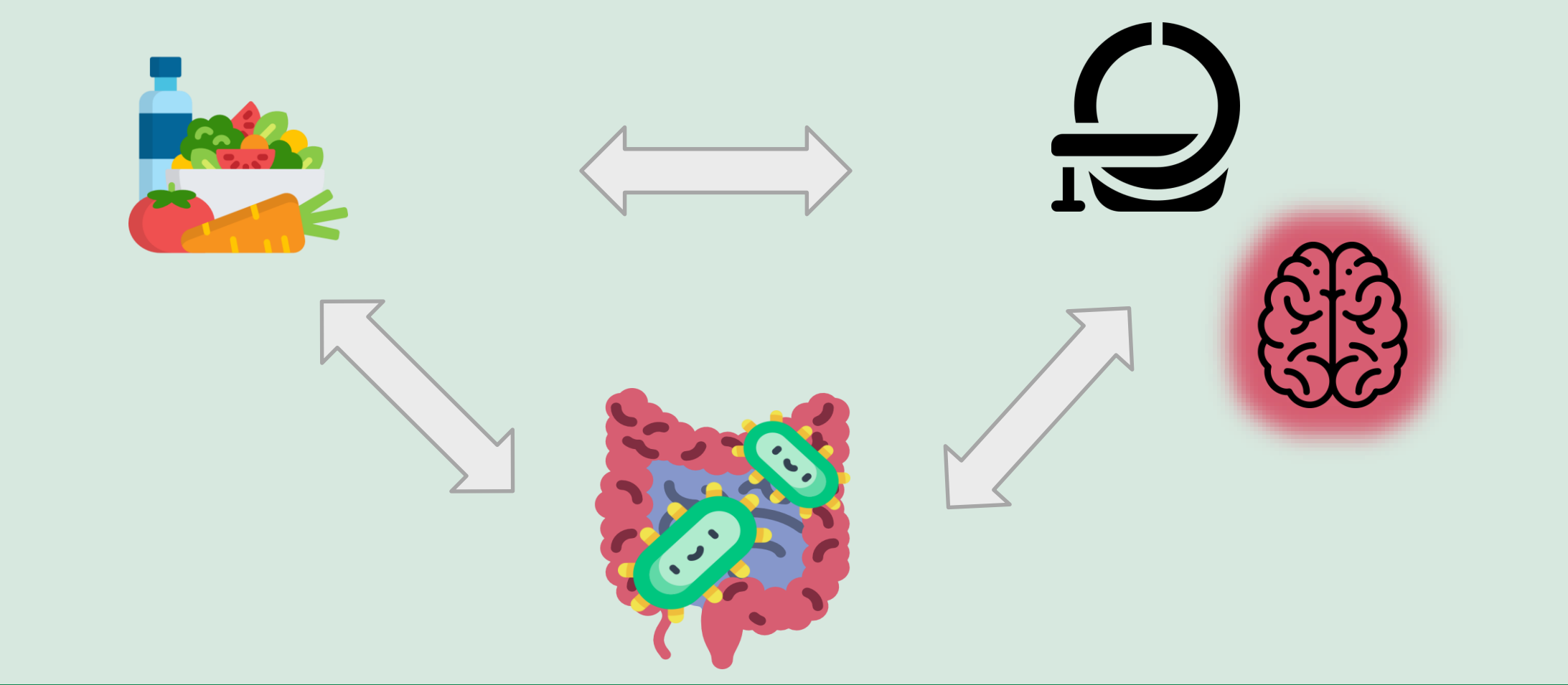
- **gut-brain axis**: bidirectional signaling between the gastro-intestinal tract and the brain[2]
- high-fiber diets, rich in naturally occurring **prebiotics** such as soluble fibers, increase blood levels of circulating **short-chain fatty acids** (SCFAs) which are produced by bacteria in the **gut microbiome**[2,6]
- high-fiber diets are reported to have **beneficial health effects** and might affect brain structure[5] and **cognitive functions**[1,4] through changes in the gut microbiome[3]
- lack of evidence from rando-mized controlled trials in humans: Do fibers affect the brain through **"bottom-up"** metabolic mechanisms via the gut-brain axis?

1 Bagga D, et al. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes; 9: 486–496.
2 Cryan JF, O'Mahony SM (2011). The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil; 23: 187–192.
3 David, LA, et al. (2014). Diet rapidly and reproducibly alters the human gut microbiome. Nature; 505(7484): 559–563.
4 MahmoudianDehkordi S, et al. (2019). Altered bile acid profile associates with cognitive impairment in Alzheimer's disease - An emerging role for gut microbiome. Alzheimer's Dement; 15: 76–92.
5 Ong, IM, et al. (2018). Gut microbiome populations are associated with structure-specific changes in white matter architecture." Transl. Psychiatry; 8(1): 6.
6 Zimmer, J., et al. (2012). A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. European Journal of Clinical Nutrition; 66(1): 53–60.

Research Question

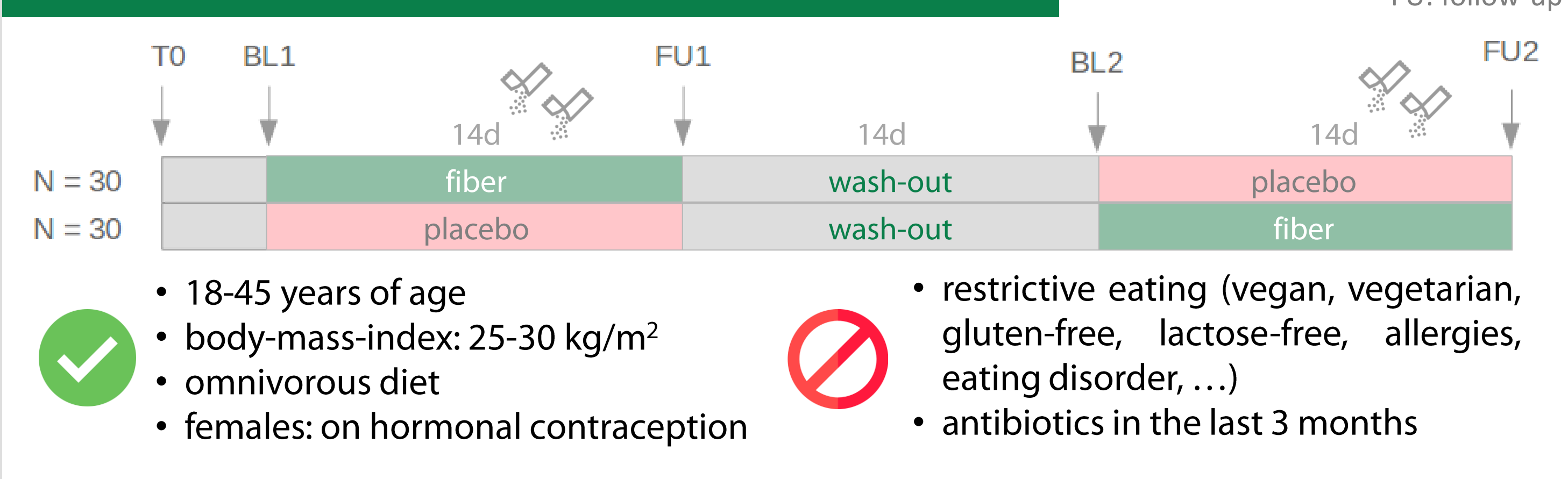Is there a causal link between diet, gut microbial signalling and the brain?

Hypotheses

1. Changes in the
   a) gut microbial composition (e.g. higher α- and β-diversity) and in
   b) carbohydrate-specific meta-bolic path-ways (e.g. short-chain fatty acid synthesis)
   may mediate potential effects of the high-fiber diet.

2. Supplementary high-fiber com-pared to placebo intake modulates food wanting and memory performance and its neuronal correlates.

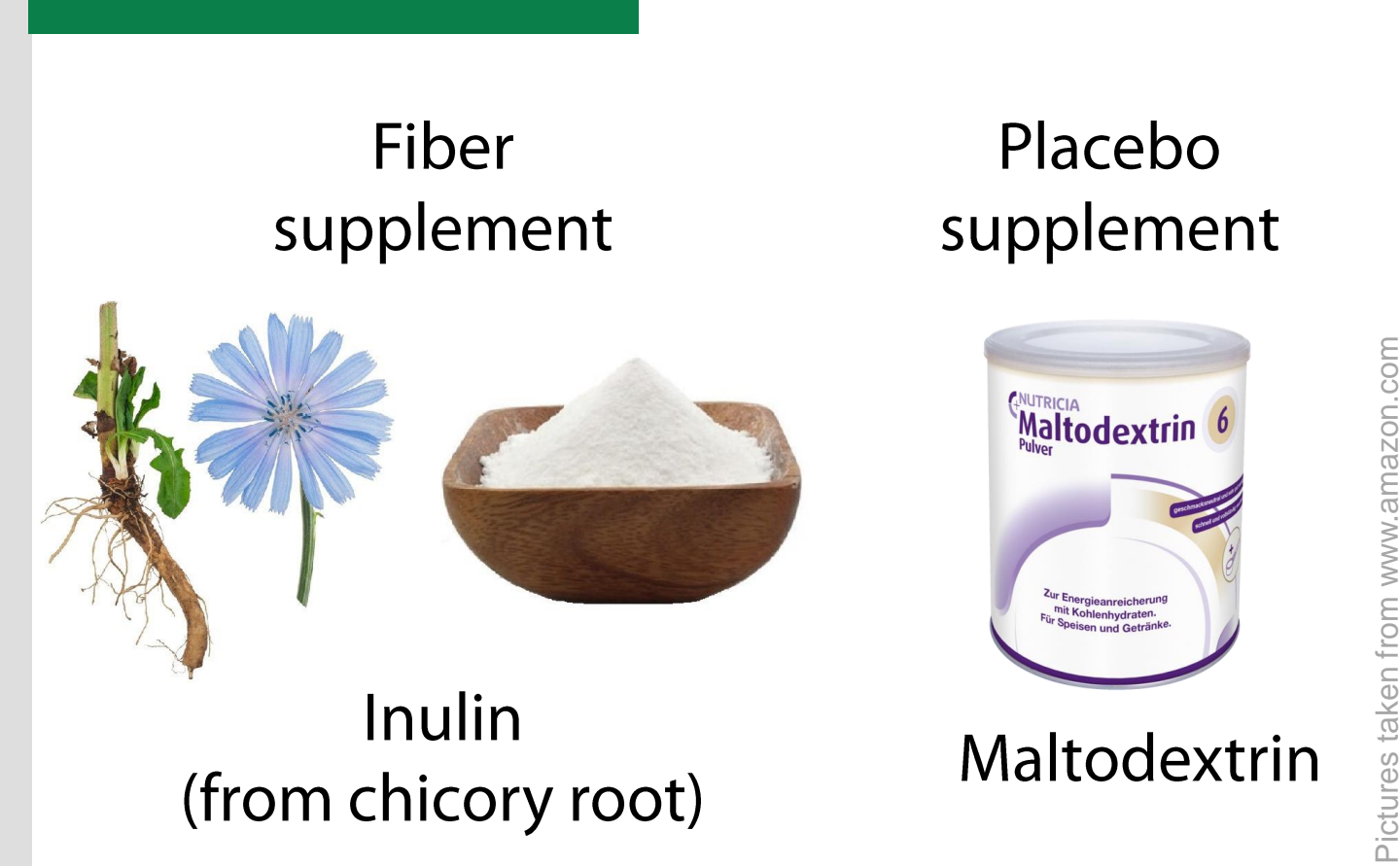3. A high-fiber diet induces higher well-being and higher satiety.
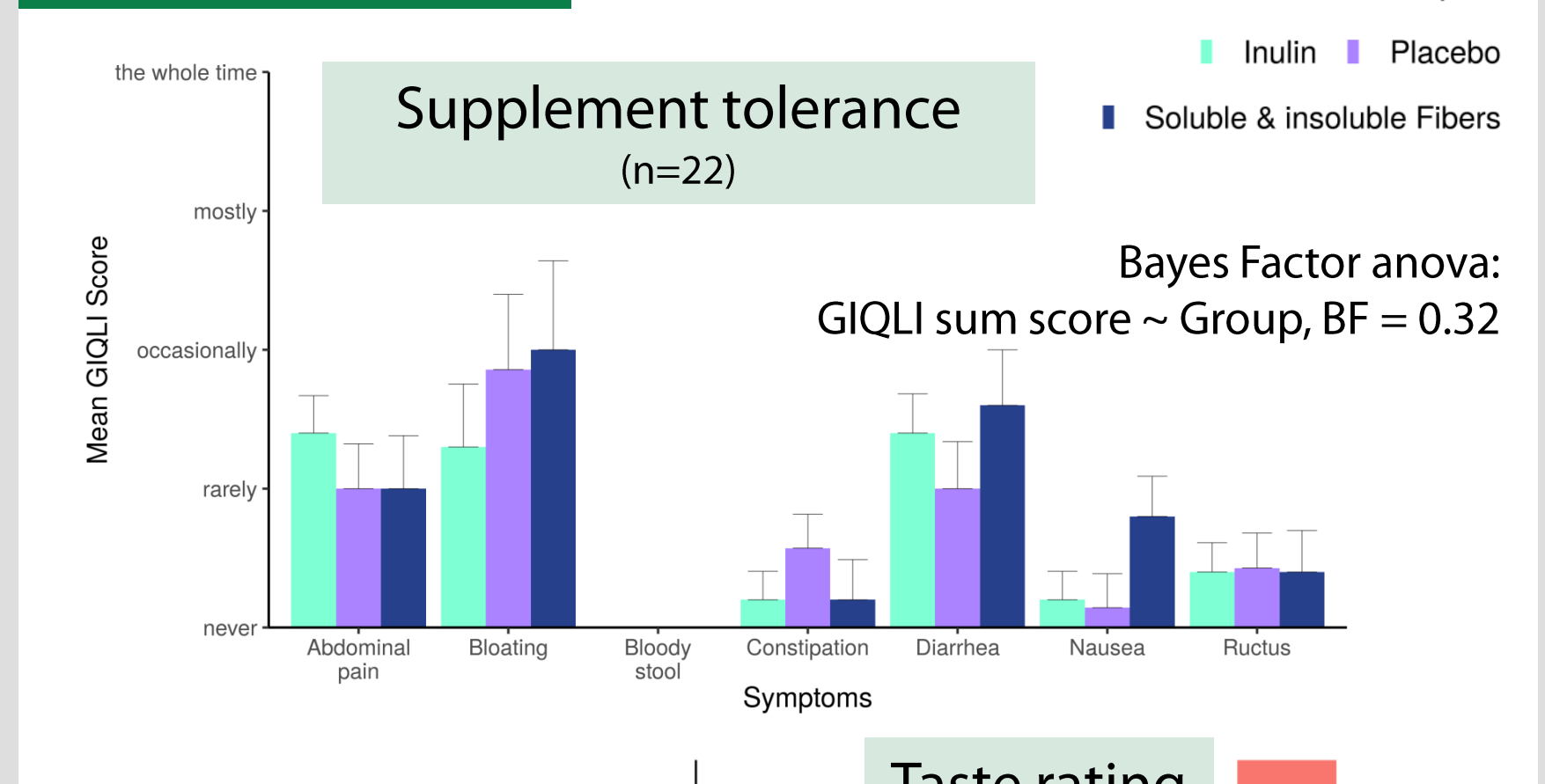

Study Design

Double-blind within subject cross-over design

BL: baseline
FU: follow-up

- 18-45 years of age
- body-mass-index: 25-30 kg/m²
- omnivorous diet
- females: on hormonal contraception

- restrictive eating (vegan, vegetarian, gluten-free, lactose-free, allergies, eating disorder, …)
- antibiotics in the last 3 months

The effector

Fiber supplement

Placebo supplement

Inulin (from chicory root)

Maltodextrin

Pictures taken from www.amazon.com

Pilot study

Supplement tolerance (n=22)

Bayes Factor anova:
GIQLI sum score ~ Group, BF = 0.32

Taste rating (n=9)

Bayes Factor anova:
Taste rating ~ supplement*subject, BF = 0.49

Neuroimaging

fMRI tasks

EPI BOLD sequence. TR 2000ms; TE 23.6ms; flip angle 80° ; FOV 204x204x136mm²; (2.0mm)³; gap 0.26mm; multi-band 3
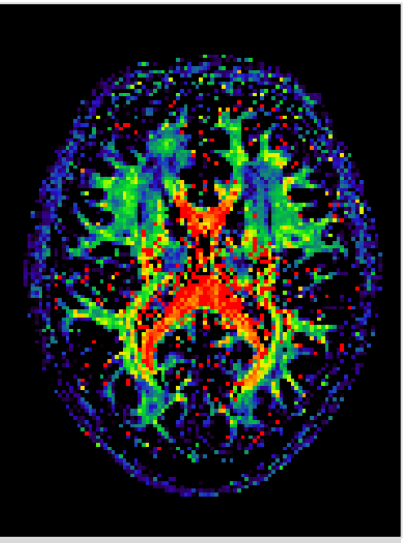
Structural scans

T1 (MPRAGE).
ADNI protocol:
TR 2300ms; TE 2.98ms;
flip angle 9° ;
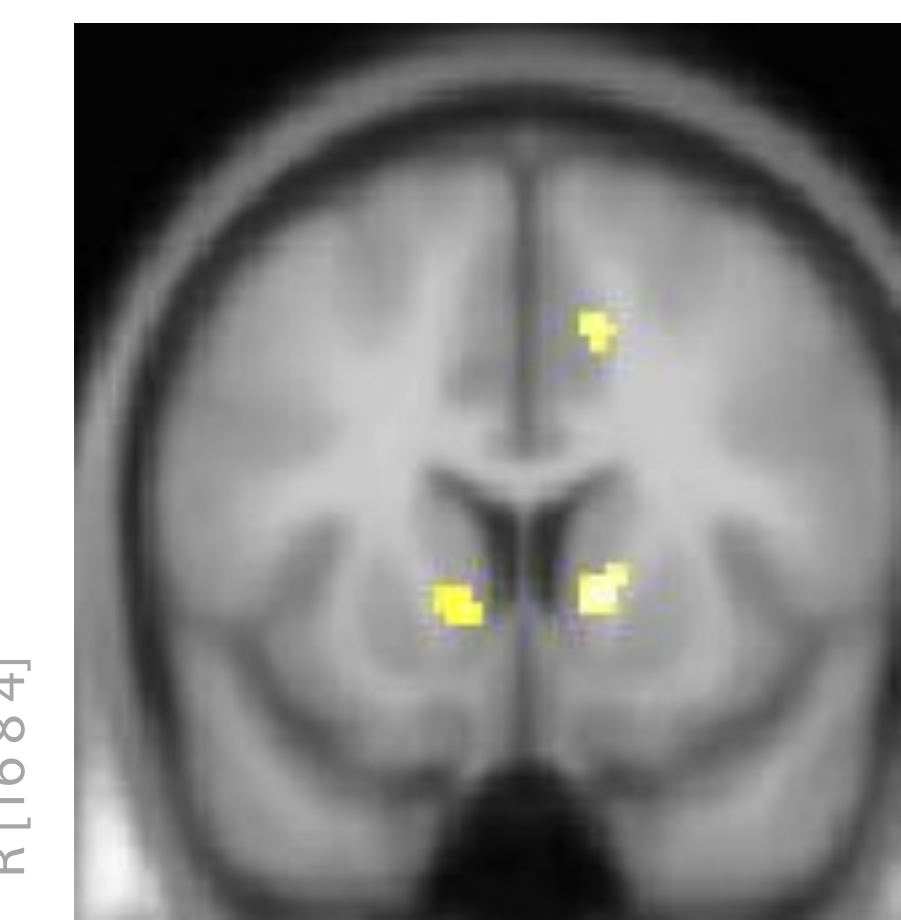FOV 240x256x176mm³;
resolution 1.0mm³
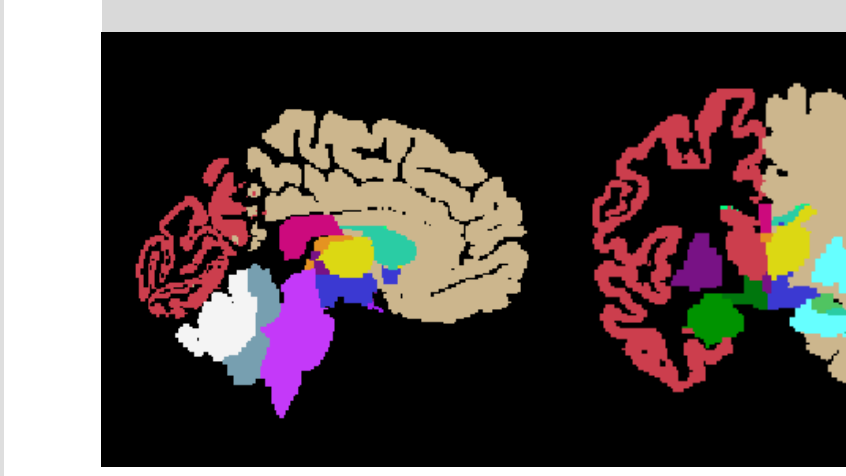
Diffusion-weighted imaging (DWI).
ap/pa-encoded b0-images for distortion correction;
TR 5200ms; TE 75ms;
flip angle 90° ;
FOV 220x220x150mm³;
resolution (1.7mm)³;
6 b0-images;
b=1000s/mm²; 60 directions;
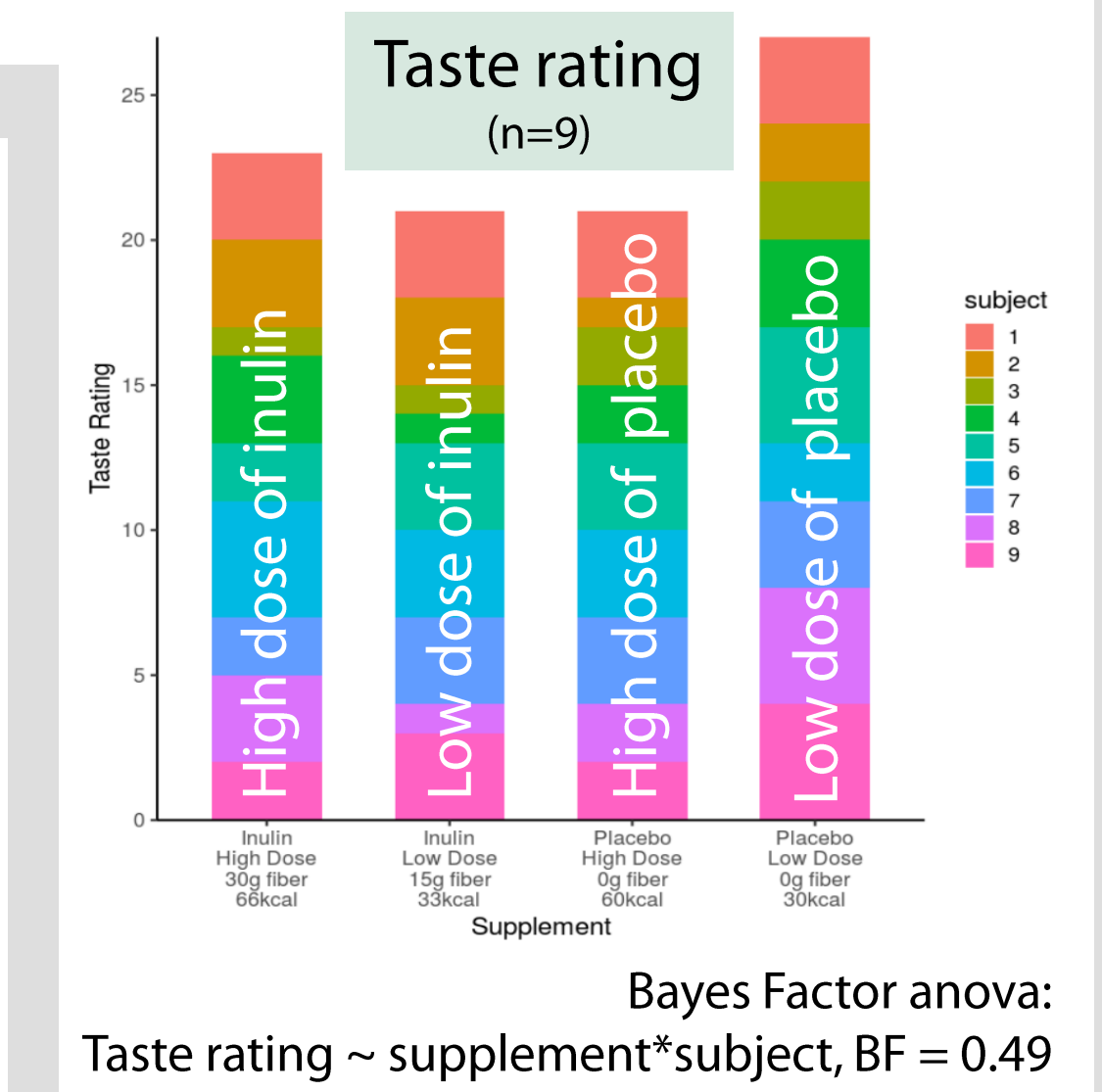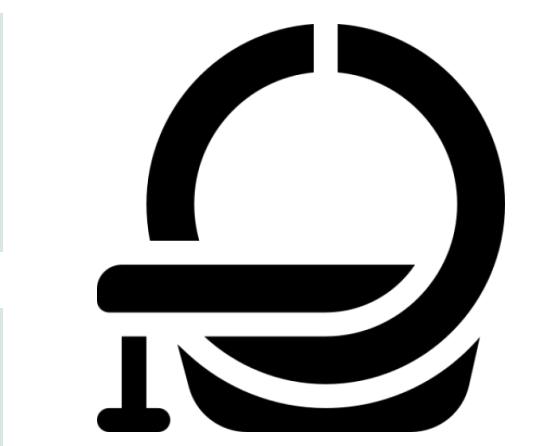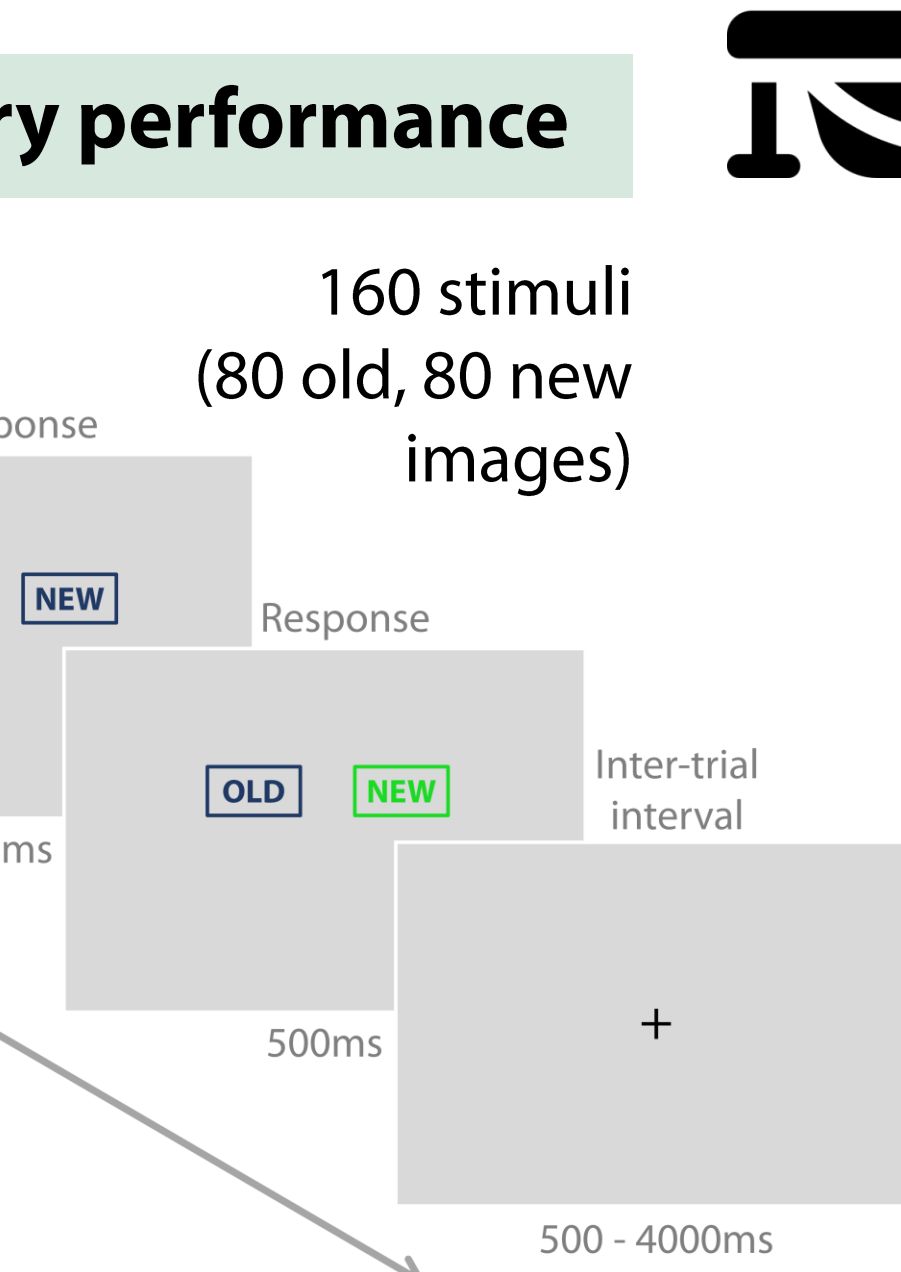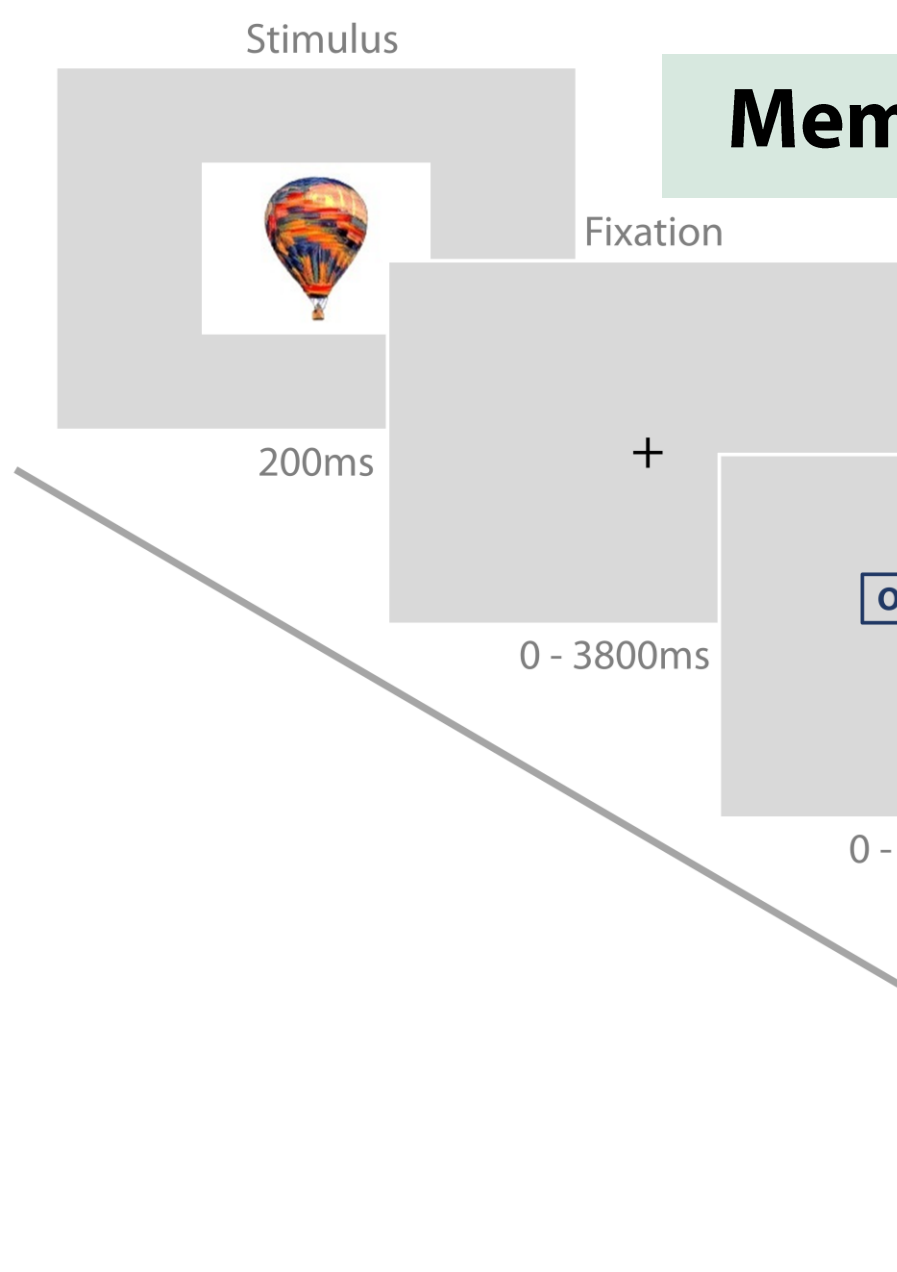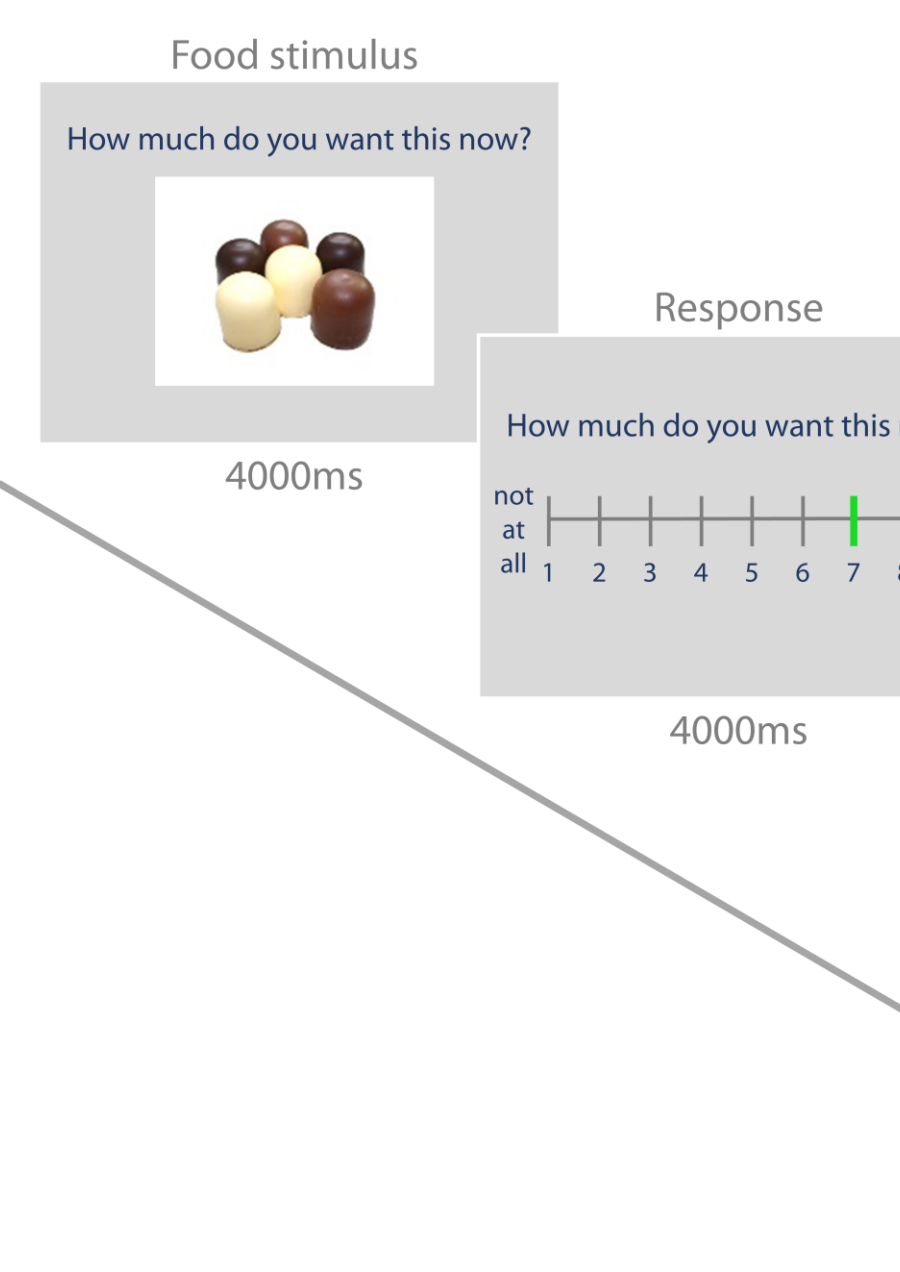partial Fourier 7/8;
multi-band 2; GRAPPA 2

Food Wanting

160 stimuli (80 food, 80 artistic non-food images)

Memory performance

160 stimuli (80 old, 80 new images)

Brain activation

L [-12 6 2]
R [16 8 4]

ventral striatum
(modulated by food wanting scores);
pilot participant;
$p_{uncor} < .001$
80 stimuli

post-scan reward

food with highest ratings

Brain activation

L [-34 -34 -22]
R [36 -34 -19]

hippocampus
(memory recall vs. manual response);
pilot participant;
$p_{FWE} < .05$
160 stimuli

Anthropometry

Body-mass-index (BMI) [kg/m²]
Percentage body fat measured by bioimpedance analysis
Waist-to-hip ratio
Blood pressure

Blood sample

Glucose metabolism
Lipid metabolism
Hormones
Inflammation
Dietary markers
Amino Acid Profile
General health markers

Attention Network Test

executive control   alerting   orienting

- 3 blocks x 5min computer-based task
- subjects' reaction time and error rate
- Assessment of three different types of attention

Fan et al., J Cog Neur (2002)

Questionnaires

State (BL1, FU1, BL2, FU2)

Trait (T0)

Anxiety
Art knowledge   Personality traits
Eating disorders   Physical activity
Eating habits   Sleep
Impulsivity   Well-being

Anxiety   Physical activity
Depression   Positive and Negative
Food Frequency   Affect Scale
    Questionnaire   Profile of Mood States
Gastrointestinal   Sleep
    Quality of Life   Well-being
Personality states

Stool sample

16S rRNA gene sequencing:
α and β microbial diversity
Metabolomics:
i.a. short-chain fatty acids (SCFAs)

analyses in cooperation with
Ulrike Rolle-Kampczyk and
Sven-Bastiaan Haange

Neuroendocrinology and Brain Imaging Conference, Rome, Italy, June 2019