Biomarker Research in ADHD: the Impact of Nutrition part 2 (2ndBRAIN)

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We aim to examine the effects of an FFD on ADHD symptoms, inhibition-related brain responses and taxonomic composition and functional capacity of the gut microbiota.

Ethical review	Approved WMO
Status	Pending
Health condition type	Psychiatric and behavioural symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON57033

Source
ToetsingOnline

Brief title
2ndBRAIN study

Condition

- Psychiatric and behavioural symptoms NEC

Synonym
ADHD, attention deficit hyperactivity disorder

Research involving
Human

Sponsors and support

Primary sponsor: Wageningen Research
Source(s) of monetary or material Support: Porticus;a philantropic organization

Intervention

Keyword: ADHD, Biomarker, Gut microbiome, Nutrition

Outcome measures

Primary outcome

- ADHD symptoms over the three main measurement points T1 (before FFD or control period), T2 (after FFD or control period) and T3 (after challenge)

If a significant effect is found on the ADHD symptoms:

- Neural activation in the precuneus during the stop-signal task measured by functional magnetic resonance imaging (fMRI), at T1, T2 and T3.
- Taxonomic composition and functional capacity of the gut microbiota at T1, T2 and T3.

Secondary outcome

- Metabolomic, hormonal and immune signatures in urine and peripheral blood
- Taxonomic composition of the oral microbiota
- Ethylene (inflammation), Nitric Oxide (inflammation), Methane (gut microbiota functioning), Short-chain fatty acids (gut microbiota functioning) in exhaled breath
- PUFA levels in peripheral blood
- Physical complaints
- ODD symptoms
- Whole brain neural activation during the stop-signal task
- Performance on the stop-signal task and stop-signal anticipation task

Study description

Background summary

Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent childhood behavioral disorder with a complex, multifactorial etiology. Current treatment primarily involves behavioral and pharmacological therapies, although there are concerns about side effects and long-term efficacy of medication use. Previous studies have shown promising effects of a few-foods diet (FFD), which led to significant improvements in ADHD symptoms in 33-64% of children. However, following an FFD and the subsequent food reintroduction phase requires an enormous effort of both the child and parents, limiting its applicability as an approach to treat ADHD. Therefore, the Biomarker Research in ADHD, the Impact of Nutrition (BRAIN) study conducted in Wageningen in 2018-2020 aimed to identify the mechanism behind the effect of an FFD on ADHD symptoms and to identify biomarkers that predict which children will respond to an FFD. In this study, 63% of participants responded positively an FFD showing a reduction in ADHD symptoms by at least 40%. This reduction was associated with increased activation in the precuneus during inhibitory tasks. Changes in ADHD symptoms after the FFD were also linked to gut microbiome composition. Differences were also observed in genes related to gut microbial pathways, depending on the species they were encoded by. The microbiome composition correlated with the change in precuneus activation after the FFD. Although this study shows indications that the microbiome-gut-brain (MGB) axis may be involved in the how an FFD affects ADHD symptoms, the exact mechanism remains unclear. Here, we propose a second study, 2ndBRAIN, in which we will test the effects of an FFD in children with ADHD on ADHD symptoms, brain activation and the MGB axis. In this follow-up study, we will include an control group that will not follow an FFD but instead receive a daily polyunsaturated fatty acid (PUFA) supplement. The control group will be used to minimize the possible effects of treatment expectations of the children and parents. Children with ADHD have significantly lower plasma and blood concentrations of polyunsaturated fatty acids. Although a recent Cochrane Review concluded there was little evidence that polyunsaturated fatty acids supplementation improved symptoms of ADHD in children and adolescents on average, in children with PUFA deficiencies supplementation might result in behavioral improvements. By comparing an FFD to the control we aim to test whether the behavioral, brain, and MGB-axis changes observed in the BRAIN study are specific to the FFD group and thereby test the possibility of a causal relationship. Furthermore, a challenge phase will follow after the FFD and control condition in which all children will consume their baseline diet again. Including this challenge will allow us to see whether behavioral, MGB and brain changes persist after returning to the baseline diet. We hypothesize that, on average, the FFD group will show improvements in ADHD symptoms, and changes in brain activation (increased inhibition-related precuneus activation in responders) and MGB functioning after following the FFD. We hypothesize that after the challenge phase, these changes will have gone back to baseline. Furthermore, in the control group we hypothesize that the ADHD symptoms, MGB functioning and brain activation on

average remain relatively stable over time.

Study objective

We aim to examine the effects of an FFD on ADHD symptoms, inhibition-related brain responses and taxonomic composition and functional capacity of the gut microbiota.

Study design

Open-label randomized control trial with researchers blinded during sample processing and initial data analyses.

Intervention

In the FFD group, after a 2-week baseline period (regular diet), participants will follow a 5-week FFD preceded by a 1-week transition period followed by a (maximum) 3-week challenge phase preceded by a 1-week transition period. In the control group, after the 2-week baseline period participants are instructed to take daily PUFA supplements and to eat their diet as usual during 5 weeks, followed by a three-week challenge phase preceded by a 1-week transition period.

Study burden and risks

This type of paradigm poses no significant risk. From the baseline period until the last measurement (12 weeks) parents will record food intake, daily activities and behavior of the child. The child will record stool frequency and type. During the screening (T0) the child will be examined by a pediatrician who will confirm the ADHD diagnosis or make a research diagnosis and perform a physical examination. If included in the study children will have a mock-fMRI session (15 min). On the three measurement days (before start FFD or control period (T1), at the end of FFD or control period (T2) and after the challenge period (T3)) blood (15 ml) and saliva will be collected from the children after an overnight fast, and stool and urine samples will be self-collected. Furthermore, children will have a 30 min fMRI scan and perform a 5 min cognitive task. Parents will complete questionnaires about the child*s physical symptoms and behavior. Children in the intervention group will be asked to follow a five-week FFD while children in the control group will be asked to take daily PUFA supplements and continue their diet as usual during 5 weeks. After following the FFD or control period, both groups will be asked to adhere to their baseline diet until the last measurement. Parents can contact the examiners as soon as their child*s behavioral symptoms reappear during the challenge phase to schedule the final measurement as soon as possible. For the FFD group, adhering to the FFD can be considered challenging, but may also reduce ADHD symptoms. Additionally, all participants will invest time in

several measurements and sample collections. Because of the previous findings that an FFD can ameliorate behavior in significant proportion of children with ADHD (Nigg et al., 2012; Pelsser et al., 2011; Hontelez et al., 2021), this study can be considered therapeutic.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:
• Meeting DSM-5 criteria of ADHD
o Of the combined subtype
o Current severity at least moderate
AND
Having an ARS score above 98th percentile for their age and gender

• Fluent in Dutch
• Aged 8 up to and including 11 years old
• Right-handed
• Children have given assent and both parents have provided informed consent
• Children are willing, and able to miss 4 days of school
• Children have permission from their principal to miss 4 days of school
In the Dutch Compulsory Education law (Leerplichtwet 1969) article 11 it is stated that *parents/guardians are exempted from the obligation to ensure that the child regularly attends the school at which he is enrolled, if the child is prevented by other important circumstances from attending the school.* Regarding these important circumstances, article 14 mentions *The head may grant leave [..] for a maximum of ten days per school year in respect of the same child.* part of the number of days he is obliged to attend school under Article 4c.* Therefore, the decision on whether participating in academic research falls under *important circumstances* is then up to the principal.

Exclusion criteria

• Current use of ADHD medication or behavioral therapy
• Diagnosed chronic gastrointestinal disorder, i.e. inflammatory bowel disease, irritable bowel syndrome, celiac disease, non-celiac gluten-intolerance (gluten-sensitivity) or lactose-intolerance
• Auto-immune disorder (e.g. diabetes mellitus type 1)
• Vegetarian/vegan
• Family circumstances that may compromise following or completion of the diet, including but not limited to family relational problems such as ongoing divorce/separation, conflict in the household, behavioral problems of a sibling
• Having a contra-indication to MRI scanning (including, but not limited to): pacemakers and defibrillators, intraorbital or intraocular metallic fragments, ferromagnetic implants, claustrophobia. In line with international safety standards fMRI eligibility of implants and devices is based on the MRI safety list of Shellock, https://www.mrisafety.com/TMDL_list.php
• Formal diagnosis Autism Spectrum Disorder
• Formal diagnosis Developmental Coordination Disorder
• Oxygen deprivation during birth: the newborn was ventilated with oxygen, had convulsions or had no sucking or swallowing reflex.
• Use of systemic antibiotics, antifungals, antivirals or antiparasitics in the past six months

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2024
Enrollment:	120
Type:	Anticipated

Ethics review

Approved WMO

Date:	07-10-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85531.091.24