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Review

The role of serotonin within the microbiota-gut-brain axis in the development of Alzheimer's disease: A narrative review

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Highlights

- Serotonin (5-HT) alterations are implicated in Alzheimer's disease (AD) development.
- SSRI and 5-HT receptor a(nta)gonists might attenuate AD neuropathology and symptoms.
- Gut microbiota form a viable target in AD for inducing profound 5-HT brain changes.
- Pre-/probiotics, diet and fecal microbiota transplants are promising approaches.

- A shift from animal to human trials in prodromal up to mild AD is a prerequisite.

Abstract

Alzheimer's disease (AD) is the most common cause of dementia, accounting for more than 50 million patients worldwide. Current evidence suggests the exact mechanism behind this devastating disease to be of multifactorial origin, which seriously complicates the quest for an effective disease-modifying therapy, as well as impedes the search for strategic preventative measures. Of interest, preclinical studies point to serotonergic alterations, either induced via selective serotonin reuptake inhibitors or serotonin receptor (ant)agonists, in mitigating AD brain neuropathology next to its clinical symptoms, the latter being supported by a handful of human intervention trials. Additionally, a substantial amount of preclinical trials highlight the potential of diet, fecal microbiota transplantations, as well as pre- and probiotics in modulating the brain's serotonergic neurotransmitter system, starting from the gut. Whether such interventions could truly prevent, reverse or slow down AD progression likewise, should be initially tested in preclinical studies with AD mouse models, including sufficient analytical measurements both in gut and brain. Thereafter, its potential therapeutic effect could be confirmed in rigorously randomized controlled trials in humans, preferentially across the Alzheimer's continuum, but especially from the prodromal up to the mild stages, where both high adherence to such therapies, as well as sufficient room for noticeable enhancement are feasible still. In the end, such studies might aid in the development of a comprehensive approach to tackle this complex multifactorial disease, since serotonin and its derivatives across the microbiota-gut-brain axis might serve as possible biomarkers of disease progression, next to forming a valuable target in AD drug development. In this narrative review, the available evidence concerning the orchestrating role of serotonin within the microbiota-gut-brain axis in the development of AD is summarized and discussed, and general considerations for future studies are highlighted.

Previous

Next

Keywords

Alzheimer's disease (AD); Diet; Fecal microbiota transplantation (FMT); Microbiota-gut-brain axis; Pre-/probiotics; Serotonin (5-hydroxytryptamine; 5-HT); Tryptophan

1. Introduction

1.1. About Alzheimer's disease

Dementia roughly affects 50 million people worldwide, and numbers are expected close to double every 20 years (Prince et al., 2015). Dementia is a broader term for the decline in cognitive function, including memory, learning and thinking, in a more drastic manner than is expected from normal aging (WHO, 2020). This can be caused by a range of conditions, yet, the most common one is Alzheimer's disease (AD) which accounts for 60–70% of all cases as stated by the WHO. Although AD is considered a disease of the elderly, Zhu et al. (2015) estimated that early-onset AD (<65 years) accounts for 6% of cases. Regardless of the age of onset, the course of the disease extends over a period of about 15–25 years as a continuum (Scheltens et al., 2021). At onset of the pathology, the patient may be asymptomatic or experience mild cognitive impairment (MCI). Over time, however, symptoms gradually become worse in function of the progressive neuronal loss (Duyckaerts et al., 2009; Förstl and Kurz, 1999). During all disease stages, a change in mood and behavior is often experienced (Lyketsos et al., 2002). These common neuropsychiatric symptoms include anxiety, depression, irritability, reduced appetite, stereotyped behavior, psychosis and aggression (Craig et al., 2005). Given the cognitive and behavioral alterations, the dementia syndrome forms a burden both on the individual suffering from the disease, as well as on family, caregivers, friends in addition to the entire society. As an indication, the global socioeconomic costs for dementia were calculated to be about 670 billion euros in 2015 (Prince et al., 2015).

Although many gene polymorphisms have been linked to AD, genetics give a far from complete explanation, with an exception for the rare familial (often early-onset) forms of AD (Gatz et al., 2006, Vogrinc et al., 2021). Nevertheless, related genes may give an indication of the possible pathophysiological mechanisms, such as with the apolipoprotein-E (*APOE*) determined allelic risk variation (Scheltens et al., 2021). The general picture of AD consists of the progressive topographic decline in cholinergic, catecholaminergic (dopamine, (nor)adrenalin) and indoleaminergic (serotonergic) neuronal functioning and loss (for review: Šimić et al., 2017), preceded by neurotoxic amyloid-beta (Aβ) plaque aggregation extraneuronally, and, intraneuronally deposited neurofibrillary tangles (NFT) of phosphorylated tau (P-tau), both being histological hallmarks of AD (Braak and Braak, 1991).

Other factors are suspected to be equally involved, such as a blood-brain barrier disintegrity, oxidative stress and mitochondrial dysfunction (Vidal and Zhang, 2021). Another etiological factor is the glycosylation of lipids and proteins, giving rise to advanced glycation end products (Haukedal and Freude, 2021). Furthermore, a substantial amount of evidence suggests that neuroinflammation plays a contributing role in AD development by accelerating the abovementioned processes (Kinney et al., 2018). Especially microglia seem to be involved (Hansen et al., 2017). Finally, the microbiota-gut-brain axis may be involved in the development of AD as well (Bonfili et al., 2021, Doifode et al., 2021I, Generoso et al., 2020, Kesika et al., 2021). All in all, these suspected disease modulators are current targets in the ongoing search for an effective cure (Cummings et al., 2021). At the same time, Livingston et al. (2020) identified 12 potentially modifiable risk factors across the lifespan, accounting for around 40% of worldwide dementias, aiding the development of public health prevention strategies. Of these risk factors, lifestyle in general plays a prominent role.

1.2. Serotonergic neurotransmitter system alterations in Alzheimer's disease: gut involvement

Prominent changes in AD brain expand far beyond Aβ and tau, with a disturbed serotonergic neurotransmitter system as one of the most prominent neurochemical alterations, which is involved in but not restricted to emotional and cognitive dysfunction (Ciranna, 2006). Firstly, a decrease in total brain serotonin content, particularly in the temporal and frontal cortex, has earlier been identified (Aral et al., 1984, Palmer et al., 1987), next to alterations of cerebrospinal fluid (CSF) serotonin levels (Tohgi et al., 1992). Secondly, Cross et al. (1984) found a substantial loss of serotonin (5-hydroxytryptamine, 5-HT) type 1 and 2 receptors in the amygdala, neocortex and hippocampus in post-mortem brains of Alzheimer's patients, and, more recently, Solas et al. (2021) examined involvement of 5-HT7 receptors in psychotic symptoms in AD. A correlation has also been observed between aggressive as well as depressive symptoms and serotonin levels (and its metabolite 5-hydroxyindoleacetic acid (5-HIAA)) in specific brain areas, among which the hippocampus (Vermeiren et al., 2014). Multiple studies also revealed that selective serotonin reuptake inhibitors (SSRI), which act on the serotonin transporter (SERT) (Fig. 1), relief both behavioral and cognitive phenomena in AD patients, among which aggression and anxiety (Rodríguez et al., 2012). Additionally, CSF Aβ-concentrations were shown to be associated with SSRI treatment (Cirrito et al., 2011, Sheline et al., 2014) and the long-term use of antidepressants, such as SSRI, seems to lower the elevated risk on developing dementia in depressed individuals (Kessing et al., 2009). These findings hypothesize (in)direct involvement of serotonergic system alterations and

AD development, making it a valuable target both in terms of prevention and (symptomatic) treatment.

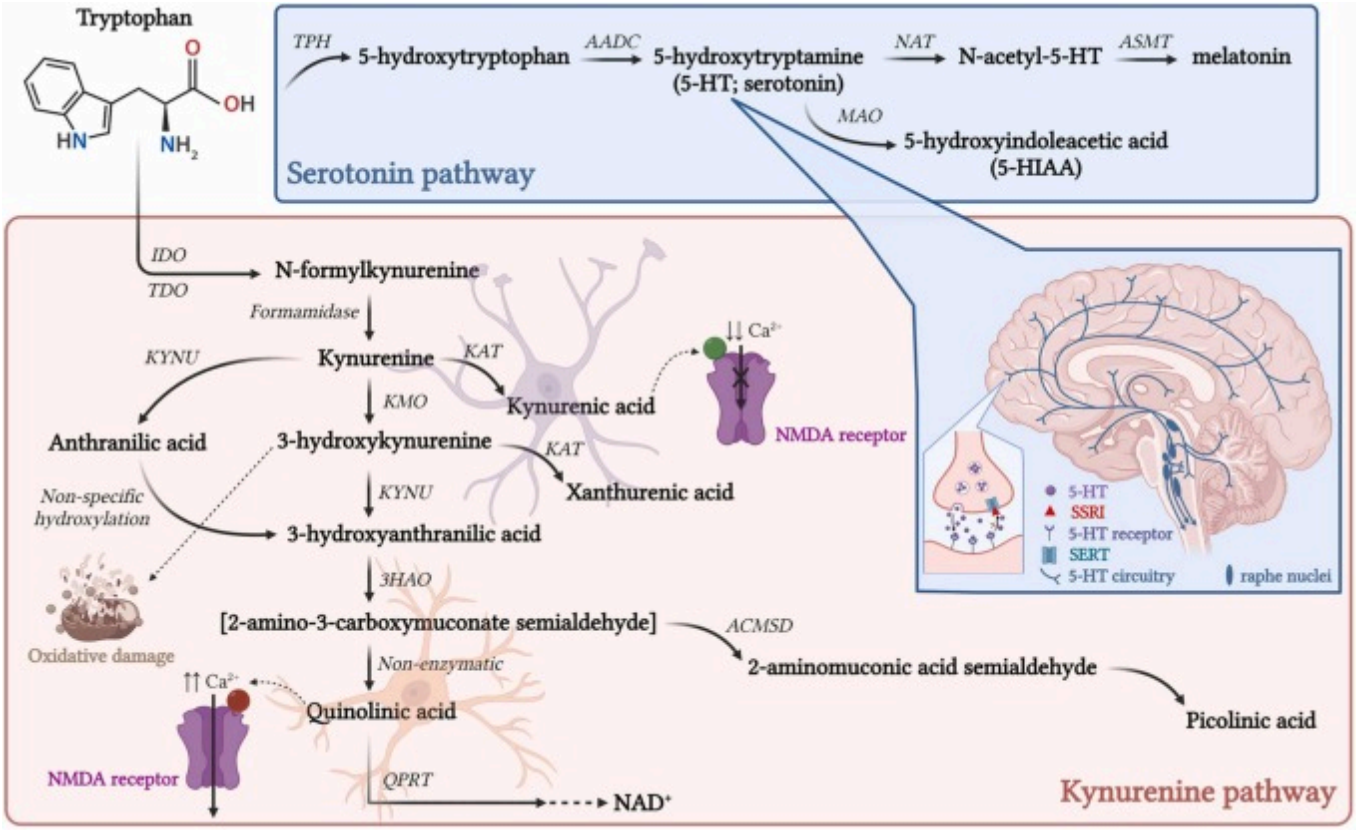

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Fig. 1. Serotonin and kynurenine biosynthetic and metabolic pathways starting from tryptophan. The essential amino acid tryptophan forms the basis for the synthesis of serotonin (5-HT). Its deductive metabolic pathway consists of the kynurenine pathway. Serotonergic brain circuitry all start from the raphe nuclei, a collection of serotonin-producing neurons, located in the brainstem at the height of the pons, and have efferents connecting with the entire neocortex, limbic system (of which amygdala and hippocampus), diencephalon, cerebellum and peripheral/autonomous nervous system (e.g. spinal cord, vagus nerve). The mechanism of action of an SSRI is to block SERT, thus preventing the reuptake of serotonin after its release from the synaptic cleft back into the presynaptic neuron. The kynurenine pathway elicits the formation of both neurotoxic and neuroprotective metabolites. Kynurenic acid is mainly formed in astrocytes (purplish) and is an effective NMDA receptor antagonist, preventing abundant intracellular release of calcium, and, consequently, excitoxicity. Contrariwise, 3-hydroxykynurenine is known as a potent oxidative stressor and free radical donor, leading to mitochondrial damage and the creation of reactive oxygen species. A similar neurotoxic function has been ascribed to

quinolinic acid, an NMDA receptor agonist, with an opposite function compared to kynurenic acid. Quinolinic acid is mainly formed in microglia (pinkish). Abbreviations: 3-HAO: 3-hydroxyanthranilate 3,4-dioxygenase; 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine (serotonin); AADC: aromatic L-amino acid decarboxylase; ACMSD: 2-amino-3-carboxymuconate semialdehyde decarboxylase; ASMT: acetylserotonin O-methyltransferase; Ca^{2+}: calcium; IDO: indoleamine 2,3-dioxygenase; KAT: kynurenine aminotransferase; KMO: kynurenine 3-monooxygenase; KYNU: kynureninase; MAO: monoamine oxidase; NAD^{+}: nicotinamide adenine dinucleotide; NAT: N-acetyltransferase; NMDA: N-methyl-D-aspartate; SERT: serotonin transporter; SSRI: selective serotonin reuptake inhibitor; TDO: tryptophan 2,3-dioxygenase; TPH: tryptophan hydroxylase; QPRT: quinolinate phosphoribosyltransferase. Created with BioRender.com.

On the whole, the total serotonin content in brain is far less than that in gut tissue (Erspamer, 1966, Vermeiren et al., 2016, Vermeiren et al., 2015), and, even more less compared to concentrations in the intestinal lumen. Fecal concentrations give an indication of the latter (Hirabayashi et al., 2020). Total estimates range from 5% to 10% of its production solely in the brain, compared to 90–95% in the gut. The essential aromatic amino acid tryptophan (Bender, 1983, Udenfriend et al., 1956) is the main precursor of serotonin synthesis. After dietary or supplemental ingestion, the amino acid can be converted through a chain of reactions into several products of which serotonin, or, more specifically, 5-hydroxytryptamine (5-HT), is one example. An intermediate in the formation of the neurotransmitter is 5-hydroxytryptophan (5-HTP) (Udenfriend et al., 1956). Following its synthesis, serotonin can in turn be converted into other metabolic products, such as 5-HIAA via the action of monoamine oxidase (MAO) (Fig. 1). Nevertheless, tryptophan can also be metabolized via the kynurenine pathway, which requires the enzyme indoleamine-2,3-dioxygenase (IDO) (for review: Wichers and Maes, 2004). An essential enzyme required for the synthesis of serotonin itself is tryptophan hydroxylase (TPH), which plays a role in the rate-limiting step (Bender, 1983). Both neurons and enterochromaffin cells (ECC) of the gut comprise this enzyme, although slightly different variants exist (Côté et al., 2003, Walther et al., 2003I). TPH1 and TPH2 are the most abundant in gut and brain, respectively. Beside EEC, several microorganisms in the gut are also able to produce hormones and neurotransmitters, including serotonin (for review: Clarke et al., 2014). Escherichia coli k12 and Lactobacillus plantarum, for instance, are examples of bacteria that possess this ability, at least in vitro.

1.3. Its potential importance in Alzheimer's disease

In short, the brain, gut and microbiota all produce serotonin. However, serotonin itself, unlike its intermediates, is hardly able to cross the blood-brain barrier, as evidenced in rats

by the use of radiolabelling techniques (Oldendorf, 1971). This points out the existence of distinct pools of serotonin, which, on the contrary, may be able to interact with one another (Clarke et al., 2013). This notion is supported by the fact that gut and brain are bidirectionally connected via metabolic, hormonal and neural routes as reviewed by Wang and Wang (2016). Short-chain fatty acids (SCFA), metabolites produced by gut microbiota following (mainly) dietary fiber intake, are considered important mediators in this communication with an effect on cognitive function (Dalile et al., 2019). This might be through the impact on gene expression, since SCFA stimulate the transcription of TPH1 (Reigstad et al., 2015). As a logical consequence, interfering with the microbiota (composition) in the gut, either by means of nutrition, fecal microbiota transplantations (FMT) or a combination of pre- and probiotics, has become an emerging potential modulator of brain health, and is likely to affect both distantly related serotonin pools (Liu et al., 2015a).

As an indication of the importance of the indoleamine neurotransmitter serotonin within the gut-brain axis, enrichment of diet with tryptophan has previously been evidenced to enhance learning and memory abilities in aged rats (Musumeci et al., 2017) while decreasing hippocampal apoptosis and intraneuronal Aβ load in transgenic AD mice (Noristani et al., 2012). Musumeci et al. (2015) claim these effects to be the consequence of changes in serotonin and brain-derived neurotrophic factor expression in both frontal cortex and hippocampus. Additionally, FMT is able to modulate Aβ content in the hippocampus as shown in a senescence accelerated mouse model (Cui et al., 2018).

1.4. Research question

In general, AD is a complex multifactorial disease of which the mechanisms remain incompletely understood. There is mostly preclinical evidence that serotonin may play a role in AD-related cognitive decline and neuropathological aspects, and that this might be indirectly modulated through the microbiota-gut-brain axis, both in terms of development and onset. In this narrative review, multiple relevant studies will be discussed aiming to answer the question ‘what is the role of serotonin within the microbiota-gut-brain axis in the development of AD?’. Since there are no studies to date yet that have tackled this issue as a whole, the research question will be subdivided into two subquestions. First, ‘are the alterations in the brain’s serotonergic system implicated in the development of AD?’, followed by ‘is it possible to alter the brain’s serotonergic system through modulation of the microbiota-gut-brain axis?’.

2. Methods

In order to gather literature for this narrative review, two databases were searched. The search was performed in PubMed and Scopus using a set of queries. For each subquestion, specific queries were used. These were: SSRI AND alzheimer * AND (plaque * OR (amyloid AND beta) OR tau OR tangle * OR learning OR memory OR cognit * OR atrophy OR neurodegeneration), ("serotonin receptor" AND (agonist OR antagonist)) AND alzheimer * AND (plaque * OR (amyloid AND beta) OR tau OR tangle * OR learning OR memory OR cognit * OR atrophy OR neurodegeneration), (probiotic * OR prebiotic*) AND (serotonin OR serotonergic) AND brain, (nutrition OR diet*) AND (microbiota OR microbiome) AND (serotonin OR serotonergic) AND brain and ((fecal OR fecal) AND transplant*) AND (serotonin OR serotonergic) AND brain. Occasionally, the techniques forward and backward snowballing were used. Duplicate findings were excluded. The remaining acquired articles were screened by looking at the title and abstract, after which relevant articles were read more thoroughly. Both human and animal in vivo designs, as long as it were intervention studies, were considered eligible for the purpose of this review. In general, review articles were excluded. Exceptions were made for reviews that summarized trials otherwise excluded in this review. For the first subquestion, preclinical randomized controlled trials that included an AD mouse or rat model as well as human clinical trials from the last two decades were found eligible, at least, if they specifically manipulated the brain's serotonergic system. Trials with subjects that had pre-existing mental disorders (such as depression) were excluded. This was also the case for trials that focused on one specific behavioral symptom (such as agitation or depression), instead of a variety of behavioral symptoms, cognition and/or underlying pathology. For the second subquestion, studies involving either healthy subjects or a(n) (induced) disease state related to AD pathology or symptoms that looked at serotonin (related) enzymes, receptors, transporters or concentrations in the brain were included, provided that the studies intervened through prebiotics, probiotics, FMT or nutrition. Furthermore, articles written in another language than English were not considered. Eventually, 67 articles were considered relevant for inclusion in this review, as can be seen in the overview (Fig. 2).

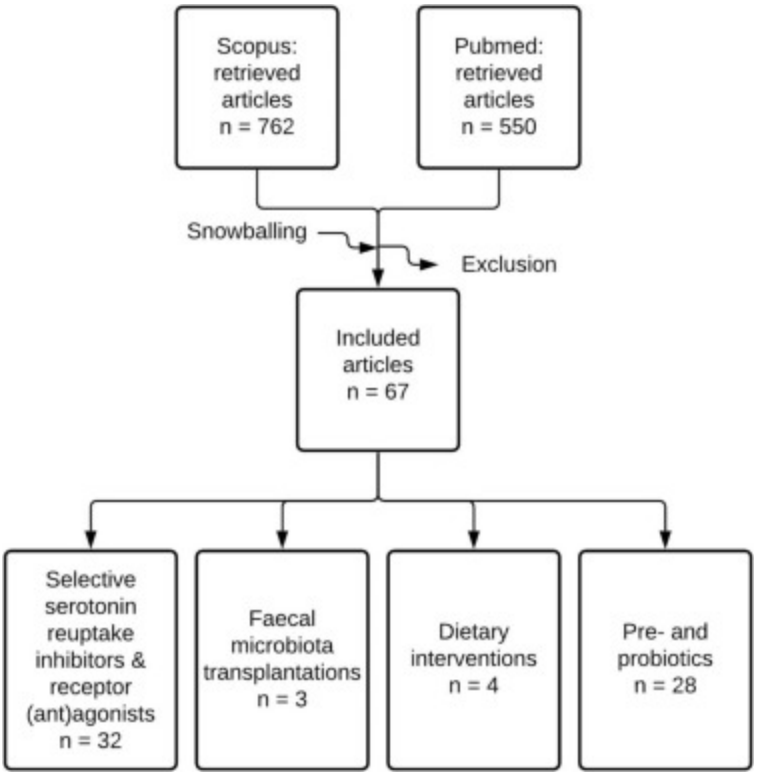

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Fig. 2. **Flowchart of the inclusion and exclusion process for the review.** Created with Lucidchart.com.

3. Results

3.1. Serotonergic alterations in Alzheimer's mouse models and patients

Although a body of evidence supports the existence of serotonergic changes in AD, it does not necessarily imply a causal relationship. Therefore, intervention studies that manipulate serotonin synthesis, metabolization or transport and meanwhile assess its effect on AD brain pathology or clinical symptomatology are required. One well-studied way to manipulate brain serotonin concentrations is the administration SSRI, known for its widespread use as antidepressants. Multiple studies report their effect on Aβ plaques in mouse models of AD, as summarized in Table 1.

Table 1. Preclinical studies in AD mouse models investigating SSRI administration on Aβ plaque and tau tangle load and/or related cognitive and/or behavioral functioning.

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
Ai et al. (2020)	Multiple-armed randomized controlled trial	APP/PS1 mice (1 month old)	Unclear, likely about 12–52	Paroxetine (15 mg/kg/2 days) in drinking water	6 months	Open field test, three chamber test, elevated plus maze and forced swimming test	- Decreased A plaques in cortex and percentage large diamet plaques - No effect on tau - Less memor deficit
Chao et al. (2020)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (8 months)	60	Fluoxetine (50 mg/kg/day), intraperitoneal	2 months	The open field, Morris water maze and Y maze test	- Decreased A and Aβ42 an levels and plaques in H - Promote oligodendro maturation - Prevent oligodendro lineage cell senescence (HC) - Less learnin and memor deficits

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
Cirrito et al. (2020)	Multiple-armed randomized controlled trial	APP/PS1 mice (6 months old)	13	Escitalopram (2.5 and 5 mg/kg/d), intraperitoneal	1 month	–	- Both dosage decreased hippocampa Aβ40/42 pla burden - 5 mg/kg/d reduced plac formation; n effect on pla clearance
Hallida y et al. (2017)	Multiple-armed randomized controlled trial	rTg4510 (tauP301L^{+}) mice (4 months)	48	Trazodone (40 mg/kg/day), intraperitoneal	4 months	Novel object recognition test, burrowing	- Reduced tau burden in th HC - Reduced hippocampa neuronal los - Prevention o memory loss
Huang et al. (2018)	Multiple-armed randomized controlled trial	APP/tau/PS1 mice (4 months)	36	Fluoxetine (10 mg/kg/day), intragastrical	4 months	Morris Water maze, spatial learning test, probe trial	- Decreased A and Aβ42 lev in HC - Improved learning and memory

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
Jin et al. (2017)	Multiple-armed randomized controlled trial	APP/PS1/TauP301L mice (6 months old)	Unclear, likely about 32	Fluoxetine (20 mg/kg/day), intraperitoneal	15 days	Morris water maze, fear conditioning trial,	- Decreased A levels in HC - Increased neuron num and dendriti spine densit DG and HC (CA1) - Enhanced neuronal plasticity (lo term potentiation - No effect on tau; improve learning and spatial mem
Ma et al. (2017)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (16–17 months)	20	Fluoxetine (10 mg/kg/day), intraperitoneal	5 weeks	Morris water maze	- Reduced Aβ plaques in H - Prevented neuronal los DG, but not CA1/CA3 of I - Improved spatial learn

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
Olesen et al. (2016)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (9 months)	Unclear, likely 68	Paroxetine (5–30 mg/kg/day) in drinking water	9 months	Open field test, elevated plus maze, social interaction test	- No effect on plaque load the neocorte - Improved activity, exploration, and less anx
Olesen et al. (2017)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (9 months)	52	Paroxetine (5–30 mg/kg/day) in drinking water	9 months	Y maze test	- Reduced plaques in th HC - No effect on spatial work memory
Qiao et al. (2016)	Multiple-armed randomized controlled trial	APP/PS1 mice (2 months)	Unclear	Fluoxetine (5 mg/kg/day) in drinking water	4 months	Y maze test, water maze test	- Reduced plaques and soluble Aβ40 and Aβ42 - Improved spatial mem
Reddy et al. (2021)	Multiple-armed randomized controlled trial	APP mice (12 months)	40	Citalopram (60 mg/kg/week), intraperitoneal	2 months	Morris water maze, rotarod	- Reduced Aβ4 (but not Aβ4 in whole bra - Less synapti damage, mitochondri

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
							deficits and autophagy - Improved cognitive function
Severino et al. (2018)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (9 months)	147	Paroxetine (5–10 mg/kg/day) in drinking water	3–9 months	Elevated plus maze, open field test, social interaction test	- Reduced survival - No effect on plaques in neocortex - No effect on memory or behavior, exc for locomoti
Torrisi et al. (2019)	Multiple-armed randomized controlled trial	Male Aβ1–42 oligomers injected C57BL/6 mice (2 months)	Unclear, 5–14 per group	Fluoxetine (10 mg/kg/day) and vortioxetine (5 and 10 mg/kg/day), intraperitoneal	21–26 days	Forced swim test, passive avoidance test, object recognition test	- Both SSRI rescued Aβ-induced memory loss and depressi like behavio
Von Linstow et al. (2017)	Randomized controlled trial	APP/PS1 mice (3 month)	20	Escitalopram (5 mg/kg/day), oral drops	6 months	–	- Treatment d not significa reduce Aβ (r in HC nor neocortex)

Author, year	Study design	AD mouse model	Total sample size	SSRI	Duration	Behavioral tests	Overall outcom effect
Zhang et al. (2018)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (6 months)	Likely about 40	Citalopram (10 mg/kg/day), intraperitoneal	28 days	New object recognition task, three chamber social test, odor recognition test, nest building task, marble burying test, TST, sucrose preference test	- Reduced Aβ plaques in cortex and H - Inhibited microgliosis HC and somatosens cortex - Improved short-term memory and depression-l behavior

Abbreviations: Aβ: amyloid-beta; AD: Alzheimer's disease; APP: amyloid-precursor protein; DG: dentate gyrus; HC: hippocampus; PS1: presenilin 1; P-tau: phosphorylated tau; SSRI: selective serotonin reuptake inhibitors; TST: tail suspension test.

Different types of SSRI, including fluoxetine (Chao et al., 2020, Huang et al., 2018, Jin et al., 2017, Ma et al., 2017, Qiao et al., 2016), escitalopram (Cirrito et al., 2020), citalopram (Reddy et al., 2021, Sheline et al., 2014, Zhang et al., 2018) and paroxetine (Ai et al., 2020, Olesen et al., 2017), induce a decrease in Aβ levels and/or plaques in either the whole brain, cortex or hippocampus, of which the latter region is the most studied one. The effect might be region specific, since Olesen et al. (2016), Severino et al. (2018) and Von Linstow et al. (2017) failed to replicate the effect for the neocortex. Another neuropathological hallmark within the AD brain, P-tau depositions, has been studied by Ai et al. (2020) and Jin et al. (2017). However, no significant effect was found of paroxetine and fluoxetine in their used AD mouse models. On the other hand, the findings of Halliday et al. (2017) did reveal improvement in tau burden in Tau P301L positive mice after administering trazodone. A preventive effect on neuronal loss has been repeatedly observed

as well in either the hippocampus (Halliday et al., 2017) or nearby regions, such as the dentate gyrus (Jin et al., 2017, Ma et al., 2017). Other AD-model induced abnormalities seem to be improved likewise, such as microgliosis (Zhang et al., 2018) and mitochondrial deficits (Reddy et al., 2021). Importantly, most of the mentioned preclinical studies also reported protective effects on cognitive function, such as for learning and memory, next to the alterations concerning plaques, tangles and neuronal loss (Ai et al., 2020, Chao et al., 2020, Halliday et al., 2017, Huang et al., 2018, Jin et al., 2017, Ma et al., 2017, Olesen et al., 2016, Qiao et al., 2016, Reddy et al., 2021, Zhang et al., 2018). The positive effect on cognition has been confirmed by the randomized controlled trial of Torrisi et al. (2019). However, this is contradicted by the findings of Olesen et al. (2017) and Severino et al. (2018). The latter also found a decreased survival rate in APP/PS1 mice, which in part questions its utility and safety on the long term, even though chronic SSRI administration via repeated intraperitoneal injections in this particular study may have created a stressful living condition for these mice on the whole. In line with this assumption, one emerged theory suggests that the effects of SSRI on the depression-like phenotype are not determined by the drug per se, but may be induced by the drug, and, driven by the environment. Especially, mice that were administered fluoxetine in an enriched condition overall improved their depression-like phenotype compared to their control littermates, whereas those treated in a stressful living environment showed a distinct worsening (Alboni et al., 2017).

Furthermore, human intervention studies have been executed. This is exemplified by a placebo-controlled trial in cognitively healthy older adults (n = 114) with escitalopram by Sheline et al. (2020). Dosages ranged from 20 to 30 mg and duration from two to eight weeks. A 9.4% larger reduction in CSF Aβ1–42 levels was found in the overall treated groups compared to the non-treated group. Additionally, the small single-dose placebo-controlled crossover trial of Klaassens et al. (2019) showed a protective effect of citalopram (30 mg) on (characteristic) connectivity loss in the precuneus and posterior cingulate cortex, while it failed to show effects on cognition. Cognitive functioning was measured using the NeuroCart test battery, in both mild AD patients (n = 12) and controls (n = 12). Contradictory, a meta-analysis of 14 randomized placebo-controlled trials suggests a beneficial effect of SSRI on cognitive performance in AD patients (Xie et al., 2019). On the whole, the majority of evidence both from animal and human intervention studies support the notion that SSRI are able to alter Alzheimer's neuropathology and symptoms.

Besides SSRI, a variety of other compounds are able to modulate the serotonergic system, such as serotonin (5-HT) receptor antagonists and agonists. Firstly, it has been shown that 5-HT6 receptor antagonists have positive effects on cognition in preclinical trials (Hashemi-Firouzi et al., 2018, Shahidi et al., 2019), however, clinical trials with actual AD

patients fail to prove significant effects (for review: Andrews et al., 2018; Khoury et al., 2018). Not only the 5-HT6 receptor, but also the 5-HT1A receptor has gained interest. The partial 5-HT1A receptor agonist tandospirone has been shown to improve anxiety, depression, agitation, irritability and delusion in AD and vascular dementia patients, as assessed with the Neuropsychiatric Inventory and Mini-Mental State Examination score (Sato et al., 2007). Similarly, NAD-299, a high affinity 5-HT1A receptor antagonist, has been shown to produce numerous effects in a streptozotocin-induced AD rat model, both on Aβ plaque load in the cortex and hippocampus (Afshar et al., 2018), as well as on hippocampal oxidative stress, damage and neuronal connections (Afshar et al., 2019). Remarkably, similar effects were observed by Afshar et al. (2019) after administration of the 5-HT2A receptor agonist TCB-2. On the contrary, pimavanserin, an inverse 5-HT2A receptor agonist, has been shown to reduce Aβ in the cortex, hippocampus and CSF, accompanied by improvement in cognitive function in APP/PS1 mice (Yuede et al., 2021). Cognition was improved as well in a trial with the 5-HT2A receptor antagonist desloratadine, using the same type of transgenic mice (Lu et al., 2021). Additional findings include improved microglial phagocytosis, microglial-plaque interaction and neuronal plasticity, accompanied by reduced neuroinflammation, and, decreased Aβ plaques in the CA1 region of the hippocampus. Furthermore, two types of 5-HT4 receptor agonists (RS 67333 and SSP-002392) showed promising effects on learning and memory, in combination with decreased Aβ plaques in several brain regions of transgenic AD mice (Giannoni et al., 2013, Tesseur et al., 2013). However, the effect on plaques seems dependent on treatment duration and onset, as Tesseur et al. (2013) and Giannoni et al. (2013) failed to replicate these effects in some of the intervention arms. The decrease in Aβ plaques in the hippocampus combined with improved cognition was also reported after administration of a 5-HT7 receptor agonist named AS19 (Shahidi et al., 2018). This agonist has also shown to decrease hippocampal apoptosis and improve plasticity in an AD model of male Wistar rats (Hashemi-Firouzi et al., 2017, Shahidi et al., 2018). Finally, a clinical trial has been conducted with the 5-HT3 receptor antagonist ondansetron, which failed to show any effect on cognitive parameters (Dysken et al., 2002). Overall, these studies suggest that 5-HT1A/2A/4/6/7 receptor (ant)agonists exert varying effects related to AD pathology and clinical symptomatology (Table 2).

Table 2. Preclinical studies in AD mouse models or human intervention trials investigating the effect of serotonin receptor (ant)agonists administration on Aβ plaque load and/or related cognitive and/or behavioral functioning.

Author, year	Study design	Human subjects or AD mouse/rat model	Total sample size	Serotonin receptor (ant)agonist	Duration	Behavioral tests	Overal effect
Afshar et al. (2018)	Multiple-armed randomized controlled trial	Male Wistar rats (adult), injected with streptozotocin	54	5-HT1A receptor antagonist (5 micrograms/day), intracerebrally injected	1 month	Novel object recognition test, open field test and passive avoidance task	- Dec pla and - Dec los - Dec los
Afshar et al. (2019)	Multiple-armed randomized controlled trial	Male Wistar rats (adult), injected with streptozotocin	50	5-HT1A antagonist and 5-HT2A agonist (5 micrograms/day), intracerebrally injected	1 month	–	- Dec hip oxi dar con
Dysken et al. (2002)	Double blinded placebo-controlled trial	Probable AD patients (mild to moderate)	185	Selective 5-HT3 receptor antagonist: ondansetron (20–100 microgram/day)	24 weeks	Alzheimer's Disease Assessment Scale-Cognitive Subscale, Clinician's Interview-Based Impression of Change	- No cog fun
Giannoni et al. (2013)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (1–2 months)	59	5-HT4 receptor antagonist and/or partial agonist RS67333 (2	1–3 months	Novel object recognition test	- The red pla cor

Author, year	Study design	Human subjects or AD mouse/rat model	Total sample size	Serotonin receptor (ant)agonist	Duration	Behavioral tests	Overal effect
				mg/kg/week), intraperitoneal			ent effe dep dur (yo trea din pre ant trea - The red and you - The pre cog dys
Hashemi-Firouzi et al. (2017)	Multiple-armed randomized controlled trial	Male Wistar rats (adult), injected with streptozotocin	40	5-HT7 receptor agonist: AS19 (1 microgram/day), intracerebrally injected	1 month	–	- Dec hip apc - Imp pla

Author, year	Study design	Human subjects or AD mouse/rat model	Total sample size	Serotonin receptor (ant)agonist	Duration	Behavioral tests	Overal effect
Hashemi-Firouzi et al. (2018)	Multiple-armed randomized controlled trial	Male Wistar rats (adult), injected with streptozotocin	38	5-HT6 receptor antagonist SB258585 (dose unclear), intracerebrally injected	1 month	Novel object recognition, passive avoidance learning test	- Dec apc - Imp and
Lu et al. (2021)	Multiple-armed randomized controlled trial	Male APP/PS1 mice (7 months)	40	Selective 5-HT2A receptor antagonist: desloratadine (20 mg/kg/day), by oral gavage	3 months	Y maze, Morris water maze, new object recognition test	- Rec pla reg - Dec neu - Imp ter in I - Inc ass mic - Enh mic pha - Imp fun
Sato et al. (2007)	Open-label trial	AD or vascular dementia patients	30	Partial 5-HT1A receptor agonist: tandospirone (mean: 19.6 mg/day)	± 2 months	NPI and MMSE	- Imp anx dep agi

Author, year	Study design	Human subjects or AD mouse/rat model	Total sample size	Serotonin receptor (ant)agonist	Duration	Behavioral tests	Overal effect
							irri del
Shahid i et al. (2018)	Multiple-armed randomized controlled trial	Male adult Wistar rats, injected with Aβ	40	5-HT7 receptor agonist (1 microgram/day), intracerebrally injected	1 month	Novel object recognition test and passive avoidance task	- Dec hip apc - Dec pla - Imp pla - Imp and
Shahid i et al. (2019)	Multiple-armed randomized controlled trial	Male Wistar rats (8–10 weeks), injected with Aβ	30	Selective 5-HT6 receptor antagonist: SB-258585 (24 microgram/kg/day), intracerebrally injected	1 month	Open field test, passive avoidance learning test, novel object recognition test,	- Imp ter or s pla - Les me

Author, year	Study design	Human subjects or AD mouse/rat model	Total sample size	Serotonin receptor (ant)agonist	Duration	Behavioral tests	Overal effect
Tesseur et al. (2013)	Multiple-armed randomized controlled trial	hAPP/PS1 mice (4–13 months)	42	5-HT4 receptor agonist: SSP-002392 and RS67333 (5 and 1 mg/kg/day), by oral gavage	26–37 days and 4 months, respectively	Morris water maze	- SSP red pla cor RS6 - Bot spa and
Yuede et al. (2021)	Multiple-armed randomized controlled trial	APP/PS1 mice (2 months)	265	5-HT2A inverse receptor agonist (3–6 mg/kg/day), subcutaneous pump	4 months	Open field test, sensorimotor battery, Morris water maze, elevated plus maze, novel object recognition,	- Rec pla HC - Imp fun

Abbreviations: 5-HT: 5-hydroxytryptamine (serotonin); AD: Alzheimer's disease; APP: amyloid-precursor protein; DG: dentate gyrus; HC: hippocampus; PS1: presenilin 1; CSF: cerebrospinal fluid; MMSE: Mini-Mental State Examination Score; NPI: neuropsychiatric inventory.

3.2. Brain serotonergic alterations in response to fecal microbiota transplantation

The role and manipulability of microbiota in brain serotonergic alterations in AD can be studied using FMT. Unfortunately, such studies are currently lacking in both AD mouse models, as well as patients. Nevertheless, Hata et al. (2019) conducted such a transfer from

four anorexia nervosa patients, as well as four healthy age-matched individuals, to four-week old germ-free female mice (n = 72). A decrease in serotonin content of the brainstem was significantly observed afterwards, in addition to a trend of decreased serotonin and increased 5-HIAA content in other brain regions. Behavioral testing (i.e. open field and marble burying) indicated promising alterations. More specifically, mice receiving FMT from the anorexia nervosa patients showed more anxiety-like and compulsive behavior. Correspondingly, a study in which FMT was conducted from 11 schizophrenia patients to five-week old antibiotics-treated (pathogen-free) mice in comparison with FMT from ten control individuals, showed an increase in hippocampal and striatal serotonin, prefrontal cortex and striatal kynurenine and hippocampal TPH-1 expression (Zhu et al., 2020). These findings were accompanied by an increase in learning and memory impairment as assessed with the elevated plus maze, reciprocal social interaction, forced swim test, open field test, Barnes maze, three chamber sociability test and novel object recognition test. Both studies thus evidenced that FMT has the ability to affect the serotonergic neurotransmission in addition to clinical functioning, at least in germ-free mice. Moreover, a human intervention study including Caucasians (n = 24) aged 50–70 with treatment-naïve metabolic-syndrome showed a positive trend in both hypothalamic and thalamic SERT binding after FMT from post-gastric bypass patients compared to oral butyrate supplementation (Hartstra et al., 2020). The serotonin transporter was visualized in both regions with region of interest analysis using single photon emission computed tomography (SPECT) after injection of ^{123}I-ioflupane as the radioligand. Additionally, significant differences in microbiota composition between the two groups were measured in the fecal microbiota analysis. In conclusion, these handful of studies indicate that FMT is able to exert serotonergic changes in the brain and may even have profound subsequent effects on both cognitive and behavioral aspects.

3.3. Brain serotonergic alterations as a result of dietary interventions

Less drastic, but, at the same time, more difficult to control for, is the dietary approach. Firstly, a randomized controlled preclinical trial focussed on the western diet, defined by its high fat content, compared to a standard diet as a possible modulator of the gut-brain axis (Ohland et al., 2016). Composition of the diets were 28% and 29% protein, 49% and 55% refined carbohydrates, and, 33% and 13% fat, respectively. The study had a small sample size of only three to four male mice (6 weeks old) per group. After the three-week intervention period, behavioral tests such as the elevated Barnes maze and latency to step down were performed. The diet group showed a decrease in anxiety-like and exploratory behavior. Also, neurotransmitter analyses of the brain revealed an enhancing effect on tryptophan levels in the hippocampus. Nevertheless, hippocampal serotonin levels and TPH2 expression

remained unchanged. The larger study of Beilharz et al. (2018) also reported on the effects of the western diet compared to a standard diet, although for a total of about four weeks in male rats (n = 60). Importantly, the diet increased 5-HT1A while it decreased 5-HT2C receptor gene expression in the hippocampus. These effects were absent in the perirhinal cortex. Behavioral tests (elevated plus maze, object recognition task and place recognition task) revealed negative effects on spatial memory, but not anxiety. Additional findings were the decreased microbial diversity. Remarkably, the observed effects on spatial memory and microbial diversity could be prevented by a two-week treatment of the probiotic containing Bifidobacterium *longum, infantis* and *breve,* Lactobacillus *acidophilus, paracasei, bulgaricus* and *plantarum*, as well as Streptococcus salivarius. In another randomized controlled trial male rats (n = 12) were also fed a high fat diet for four weeks, although in this case, until obesity. These findings even revealed a decrease in whole brain serotonin, accompanied by the overgrowth of Bacteroides as assessed from fecal samples (Labban et al., 2020).

Secondly, Egerton et al. (2020) investigated the effect of a specific dietary component, namely fatty fish oil, combined with fluoxetine added to a standard diet for two weeks in maternally separated male rats (n = 58). Behavioral tests, such as the elevated plus maze, open field test and forced swim test, revealed improvement in depression and anxiety. In contrast, the subsequent biochemical analysis showed no significant difference in brainstem serotonin levels. Unfortunately, no other brain regions were investigated, complicating the interpretation of findings. However, both fatty fish oil and fluoxetine, separately or combined, did lower the level of serotonin's main metabolite, 5-HIAA, in the brainstem. The change of gut microbiota composition and SCFA production thus suggest a potential modulatory role in this effect. For instance, increased prevalence of Bacteroidetes and Prevotellaceae in combination with reduced levels of butyrate seemed characteristic for the fatty fish oil group.

Finally, the most compelling evidence so far, even though it was not a whole diet approach, comes from Musumeci et al., 2015, Musumeci et al., 2017 and Noristani et al. (2012), as previously mentioned. Noristani and colleagues examined reduced CA1 hippocampal intraneuronal Aβ in the triple transgenic AD mouse model following an acute one month increase of dietary tryptophan intake (0.40 g tryptophan/100 g), whilst Musumeci et al. (2015) provided direct evidence that an alike diet increased the serotonergic neurotransmission, particularly in the hippocampus of aged rats. In the same way, tryptophan-deprived (non-AD) mice recently showed significant reduction in 5-HT and 5-HIAA levels in a brain region-specific manner, namely in hippocampus, brainstem, cortex and striatum (Zhang et al., 2022).

3.4. Brain serotonergic alterations induced by pre- and probiotics

A variety of studies highlight the effect of pre- and/or probiotics on the brain's serotonergic system, often in combination with behavioral and cognitive changes. Details of all the included studies can be found in Table 3.

Table 3. Preclinical intervention studies in animal models investigating the effect of pre- and probiotics on brain serotonin levels, receptors, transporters, enzymes and related gene expression.

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
Barrera-Bugueño et al. (2017)	Male Sprague–Dawley rats (3 weeks)	59	14	–	*Lactobacillus casei* 54-2-33 and inulin (synbiotic)	- The synbic decreased density of HT1A rece HC, increas HT1A mRN expression and exerte anxiogenic
Borrelli et al. (2016)	Male and female zebrafish of heterozygous "wild type" strain (4–6 months)	24	28	–	*Lactobacillus rhamnosus* IMC 501	- The probic increased expression TPH1/2, SL and MAO i - The probic enhanced explorativ behavior a attention/a

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
Chen et al. (2019)	Male SPF BALB/c mice (3–4 weeks)	24	30	CMS	*Lactobacillus reuteri*	- CMS induc decrease i brain 5-HT HT-positiv the DRN. - Probiotic e whole brai and the nu 5-HT-posit in the DRN **the effect of L. without CMS v studied*
Corpuz et al. (2018)	Senescence-accelerated mouse prone 8 (14 weeks)	36	280–301	Accelerated aging model	*Lactobacillus casei subsp. casei* 327 and *Lactobacillus paracasei* K71	- The probic increased l HT levels a downregul MAO - It reduced related cog decline
Davis et al. (2016)	Wild-type zebrafish (adult)	Unclear	± 30	CMS	*Lactobacillus plantarum*	- The probic induced th upregulati HT transpo SLC6A4a, b SLC6A4b

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						- It also had anxiolytic **the effect of tl probiotic on he non-stress indi zebrafish was studied*
Desbonnet et al. (2008)	Male Sprague-Dawley rats (adult)	20	14	–	*Bifidobacterium infantis* 35624	- The probic increased concentrat tryptopha decreased in frontal c - No effect c HT/5-HIA the frontal no effect o 5-HT level
Engevik et al. (2021)	Swiss Webster germ-free mice (adult)	50	14	–	*Bifidobacterium dentium*	- The probic increased expression region of H - It increase acetate lev
Fleming et al. (2019)	Naturally farrowed intact male	24	31	–	polydextrose and galactooligosaccharide	- The prebio decreased hippocamp striatal 5-H

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
	pigs (new-born)					- The probic improved recognitio memory a explorator behavior - Hippocam correlated explorator behavior, b with recog memory
Ibrahim et al. (2018)	Chicks (1 week)	12	42	Induced stress (with a higher density of chicks per square meter)	*Enterococcus faecium*	- A higher d chick per s meter incr brain 5-HT - The probic lowered bı levels, hov only in the density gr
Kao et al. (2018)	Female Sprague-Dawley rats (6–8 weeks)	24	7	–	galacto-oligosaccharides	- The prebio no effect o 5-HT2A re protein an levels

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
Li et al. (2019)	Male Wistar rats (age not mentioned)	50	28	CMS	*Bifidobacterium longum, Lactobacillus rhamnosus* (probiotics) and fructo-oligosaccharide and galacto-oligosaccharide (prebiotics)	- CMS decre TPH2 and while it in IDO levels and fronta - Pre- and p enhanced and 5-HT, decreased levels in H frontal cor **the effect of tl and prebiotics CMS was not s*
Liang et al. (2015)	Male specific-pathogen-free (SPF) Sprague–Dawley rats (adult)	32	26	Chronic restraint stress	*Lactobacillus helveticus* NS8	- Stress dete cognition, and depre - The probic restored 5- levels in H improved (memory), and depre
Liu et al. (2015b)	Male pups (2 weeks) from timed-pregnant female C57BL/6J	32 pups	28	Early life stress	*Lactobacillus plantarum* PS128	- 5-HT level decreased, alterations HIAA level stressed m non-stress

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
	mice, and, naïve adult male C57BL/6J mice (8 weeks)					- The probic reduced 5- stressed m naïve mice reduced 5- but increas - The probic increased locomotor and decrea anxiety in naïve and mice - It decrease depressive behavior i stressed m
Liu et al. (2016)	Male germ-free C57BL/6JNarl mice (6 weeks)	18	16	–	*Lactobacillus plantarum* PS128	- The probic increased 5-HIAA lev striatum, h not in pref cortex or H - It decrease anxiety-lik behavior a increased locomotor

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
Liu et al. (2019)	Male Wistar rats (7–8 weeks)	24	28	CMS	*Lactobacillus fermentum* PS150	- CMS induc memory a learning d and a drop whole brai - Probiotic p the memo learning d and the dr whole brai **the effect of tl probiotic with was not studie*
Luo et al. (2014)	Specific-pathogen-free male Sprague-Dawley rats (adult)	18	14	hyperammonaemia-induced neuroinflammation	*Lactobacillus helveticus*	- Hyperamn increased metabolis (increased unchange cerebellun prefrontal - It induced like behav cognitive dysfunctio - The probic improved and reduc anxiety; it 5-HT (not

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						in HC and cerebellun
Mika et al. (2017)	Male Fischer 344 rats (3 weeks)	126	28	Inescapable stress	*Galactooligosaccharide and polydextrose*	- Inescapabl induced a in 5-HT1A mRNA leve amygdala - The prebio attenuated induced de in 5-HT1A mRNA leve amygdala rostral late not other p the DRN - The prebio enhanced *Lactobacill* feces
Mika et al. (2018)	Male Fischer 344 rats (± 3 weeks)	28	28	–	Galacto-oligosaccharides (prebiotic) in combination with lactoferrin and milk fat globule membrane	- Diet-induc increase in *Lactobacill* correlated positively HT1A rece mRNA in t dorsoventr of the DRN

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						HT2C rece the lateral amygdala - The diet re anxiety-lik behavior
Pandey et al. (2015)	Charles foster male albino rats (adult)	56 days	48	1,2-Di-methylhydrazine-induced systemic oxidative stress	*Escherichia coli* CFR 16	- The induce oxidative s decreased HT levels - The probic enhanced HT levels **the effect of th probiotic in ra induced oxidat was not studie*
Savignac et al. (2016)	Male CD1 mice (6–8 weeks)	18	21	Lipopolysaccharide-induced sickness and anxiety	Non-digestible galacto-oligosaccharide	- LPS induce increase in 5-HT2A re levels and anxiety - The prebio counteract effects on 5-HT2A re levels, and anxiety

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						**there was no significant diff cortical 5-HT2 receptor levels control mice re prebiotics*
Sun et al. (2018)	Male C57BL/6 mice (6–8 weeks)	30	28	CMS-induced depression	*Clostridium butyricum* WZMC1018	- CMS reduc levels in H induced depressive behavior - The probic elevated th hippocamp levels and improved depressive behavior **the effect of th probiotic in he mice without C not tested*
Szklany et al. (2020)	Male BALB/c mice (new-born) and their mothers (adult)	20 pups, 11 dams	77	–	Galacto-oligosaccharides and long-chain fructo-oligosaccharide	- The prebio decreased tryptopha HT levels i prefrontal and enhan HT/5-HIAA the somat cortex; no

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						differences measured amygdala - It decrease expression HT1A rece mRNA in t prefrontal but not an or HC - TPH2 was unaffected prebiotic - It decrease anxiety-lik repetitive behaviors enhanced behavior i adulthood - It enhance acetate, pr and butyra in fecal sa
Tian et al. (2019a)	Male C57BL/6J mice (6 weeks)	24–32	35	CMS	20 different lactic acid bacteria strains, which can be subdivided into *Bifidobacterium longum subsp., Infantis, Bifidobacterium*	- E41, S60 a increased 5-HT and HC

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
					longum subsp. Longum, Bifidobacterium breve, Lactobacillus helveticus, Lactobacillus rhamnosus, Lactobacillus fermentum, Lactobacillus plantarum	- Probiotics suggested improve depressior behavior - F45BB and increased propionate butyrate; I increased in cecum s **the effect of tl probiotics on h mice without (not tested*
Tian et al. (2020)	Male C57BL/6 mice (6 weeks)	40	42	CMS	*Bifidobacterium breve* CCFM1025	- CMS induc depressior anxiety-lik symptoms decreased hippocamp levels - The probic enhanced hippocamp HIAA level HT) - No effect c or SLC6A4

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						expressior was obser - The probic increased levels in th **the effect of th probiotic with was not studie*
Tillmann et al. (2018)	Male adult rats	30	70	Model of depression: Flinders Sensitive Line of rats (compared to resistant line)	*Lactobacillus helveticus* R0052 *and Bifidobacterium longum* R0175	- Probiotics affect hipp or prefron 5-HT or its metabolite HIAA) - The probic no signific on anxiety memory o behavior
Xie et al. (2020)	Male C57BL/6 mice (8 weeks) and retired male CD-1 breeder mice	40	28	Chronic social defeat stress	*Lactobacillus reuteri 3*	- Stress decr TPH1 mRN increased and IDO m the prefro cortex - The probic reversed th decrease ir mRNA, and

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						increase in and IDO m - No signific differences SLC6A4 or mRNA wer between c with(out) j - No signific effects on S levels in fe observed
Yaghoubfar et al. (2020)	C57BL/6J male mice (8 weeks)	30	28	–	*Akkermansia muciniphila* strain ATCC BAA-835,	- The probic increased hippocamp levels; it in TPH2 expr HC - The probic decreased SLC6A4 an receptor 1A expression
Zaydi et al. (2020)	Male Sprague Dawley rats (8 weeks)	36	84	Induced aging with D-galactose injections	*Lactobacillus plantarum DR7*	- D-galactos injections cognitive f memory, a and TPH1 expression

Author, year	Population	Total sample size	Duration (days)	Disease model	Pre- and/or probiotic	Overall outco effect
						- The probic increased ' expressior improved (function, r and anxiet **the effect of th probiotic was r studied in heal*

Abbreviations: 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine (serotonin); 5-HTP: 5-hydroxytryptophan; Aβ: amyloid-beta; AD: Alzheimer's disease; APP: amyloid-precursor protein; CMS: chronic mild stress; DG: dentate gyrus; DRN: dorsal raphe nucleus; HC: hippocampus; IDO: indoleamine 2,3-dioxygenase; MAO: monoamine oxidase; PS1: presenilin 1; P-tau: phosphorylated tau; SSRI: selective serotonin reuptake inhibitors; SCFA: short-chain fatty acid; TPH: tryptophan hydroxylase.

Firstly, nine randomized controlled preclinical trials reported the effects of a probiotic containing Lactobacillus plantarum. An anxiolytic effect of the probiotic was confirmed by several studies (Davis et al., 2016, Liu et al., 2016, Liu et al., 2015b, Morshedi et al., 2018, Zaydi et al., 2020). The same holds true for improvement in learning (Morshedi et al., 2020) and memory (Zaydi et al., 2020). Besides cognitive alterations, Zaydi et al. (2020) showed the enhancing effect of the probiotic on serotonin-related enzymes, in this case TPH1, in a D-galactose-induced rat model of aging. Additionally, the probiotic increased serotonin in the whole brain (Mustafa et al., 2020), with the hippocampus in specific (Morshedi et al., 2020), next to the amygdala (Morshedi et al., 2018). Also, an increase in the expression of the serotonin transporter (5-HTT or SLC6A4) in healthy rats has been reported (Reza et al., 2019). This is confirmed in stressed Zebrafishes, specifically for the serotonin transporter subtype SLC6A4a (Davis et al., 2016). Findings seem contradicting in the case of its metabolite 5-HIAA. Liu et al. (2016) showed an increase in the striatum, but not prefrontal cortex or hippocampus of male germ-free mice, while Liu et al. (2015b) showed an overall decrease in male mice with early life stress.

Other *Lactobacillus* strains show similar effects. Borrelli et al. (2016) and Xie et al. (2020) reported an increased DNA expression of serotonin-related enzymes in the brain, as well as the serotonin transporter, in zebrafish and male adult mice, respectively. Notably, Xie et al. (2020) found only effects of the probiotic when stress was induced. Furthermore, related preclinical trials observed enhancement of brain serotonin levels, either in a specific region such as the hippocampus, or, the whole brain (Chen et al., 2019, Liang et al., 2015, Liu et al., 2019, Wei et al., 2019). On the contrary, serotonin was found to be reduced in the hippocampus and cerebellum of rats with hyperammonaemia-induced neuroinflammation, as reported by Luo et al. (2014). Administration of the probiotic combined with inulin enhanced both the expression and density of the 5-HT1A receptor in the dentate gyrus and hippocampus of rats (Barrera-Bugueño et al., 2017). Moreover, improvement of anxiety (Barrera-Bugueño et al., 2017, Liang et al., 2015, Luo et al., 2014, Wei et al., 2019) and cognitive function, including learning and memory, have been reported (Liang et al., 2015, Liu et al., 2019, Luo et al., 2014).

Four randomized placebo-controlled preclinical trials with *Bifidobacterium* are contradicting. For instance, Tian et al. (2020) found an increase in hippocampus, but not prefrontal cortex, of serotonin levels in chronically-stressed adult male C57BL/6 mice fed with the *infantis* strain. With the same strain, Desbonnet et al. (2008) found decreased 5-HIAA levels in the frontal cortex, albeit in rats, while the 5-HIAA/5-HT ratio, as a measure of catabolic turnover, and, overall serotonin content remained unaffected. On the other hand, Tian et al. (2019b) reported an increase in serotonin levels in the prefrontal cortex, but not the brainstem, of chronically stressed adult male C57BL/6J mice after administration of the *Breve* strain. Furthermore, Engevik and colleagues showed that administration of the *dentium* strain to germ-free mice enhanced the expression of the 5-HT2A receptor primarily in the CA1 subregion of the hippocampus. Changes were accompanied by SCFA composition changes in feces in some cases. Acetate was found to be increased in the trial with the *dentium* strain (Engevik et al., 2021), while acetate, n-butyrate, propionate and isobutyrate were found to be decreased with the *infantis* strain (Tian et al., 2019b).

Four other types of probiotics were also found to enhance serotonin levels in the brain. Pyrroloquinoline quinone-producing *Escherichia coli* affected whole brain serotonin levels in subcutaneously 1,2-dimethylhydrazine-injected rats (Pandey et al., 2015), while Clostridium (Sun et al., 2018) and *Akkermansia* (Yaghoubfar et al., 2020) both affected hippocampal levels in male stressed and non-stressed mice, respectively. In addition, *Clostridium* also decreased MAO, SLC6A4 and 5-HT1A/2A/5/6 receptor expression, while simultaneously increasing TPH2 expression in the hippocampus. Next, *Clostridium* also improved

depressive-like behavior (Sun et al., 2018). On the other hand, Enterococcus faecium had the opposite effect on whole brain serotonin content in stressed goslings (Ibrahim et al., 2018).

Combinations of several probiotics improved age-related cognitive decline (Corpuz et al., 2018) and possibly depression in mice or rats (Tian et al., 2019a, Tillmann et al., 2018). No effect was found on anxiety, social behavior or memory, as reported by Tillmann et al. (2018). In general, brain serotonin levels were increased in the whole brain of senescence-accelerated mice (Corpuz et al., 2018). In rats, the same effect was found specifically in the hippocampus (Li et al., 2019, Tian et al., 2019a) and frontal cortex (Li et al., 2019). However, Tillmann et al. (2018) found no effect in the prefrontal cortex and hippocampus in a genetic rat model of depression. Nevertheless, the probiotic mixture, enriched with prebiotics, showed an increase in TPH2 and a decrease in IDO in both hippocampus and (pre)frontal cortex of male Wistar rats (Li et al., 2019). Apart from TPH2, MAO levels were observed to be downregulated in an alike probiotic mixture intervention too (Corpuz et al., 2018).

Finally, the use of only prebiotics has been previously looked at with regards to brain serotonin levels albeit by few studies so far. Firstly, it affected cognitive function in pigs (Fleming et al., 2019), as well as anxiety and behavior in new-born mice and their mothers (Szklany et al., 2020). Secondly, findings on the effect on expression of serotonin receptors 5-HT2A, 5-HT2C and 5-HT1A are rather contradictive between prebiotic type and/or study (Kao et al., 2018, Mika et al., 2017, Mika et al., 2018, Savignac et al., 2016, Szklany et al., 2020). Thirdly, serotonin levels were found to be decreased in specific areas of the brain in pigs and male BALB/c mice (Fleming et al., 2019, Szklany et al., 2020).

4. Discussion

The involvement of the microbiota-gut-brain axis in AD with possible implications for prevention and treatment have been highlighted previously (Arora et al., 2020, Kesika et al., 2021, Liu et al., 2020). Additionally, the suggestion of a(n) (in)direct link between the axis and AD development due to neurotransmitter alterations (serotonin, gamma aminobutyric acid) has recently been raised by a Mendelian randomization analysis (Zhuang et al., 2020). Notably, there is also a phase three trial ongoing with GV-971, a pharmaceutical drug derived from seaweed extracts (sodium oligomannate), targeting the gut microbiota (NCT04520412; for review: Cummings et al., 2021). These recent developments highlight the importance of the axis in the search for disease-modifying therapies, apart from the modifying role of serotonin and its derivatives within the microbiota-gut-brain axis in the development of AD in particular.

4.1. Modulatory effects of the serotonergic system in Alzheimer's disease

The literature search was aimed at finding out if and how serotonergic alterations and AD development are related. In this regard, the majority of enlisted studies, mainly preclinical but also a few human intervention trials, show that SSRI and serotonin receptor (ant)agonists may very well modify the underlying neuropathology, with inclusion of clinical symptoms. Though the effectiveness of treatment might be dependent on the disease stage, as already highlighted by the trial of Giannoni et al. (2013). The suggested modulatory involvement of the serotonergic system is further strengthened by mechanistic in vitro studies. This is exemplified by the work undertaken by Hornedo-Ortega et al. (2018), who showed that serotonin is able to prevent destabilization of Aβ oligomers and fibrils and thus insoluble plaque formation. This effect could be established by disruption of salt bridges between and within Aβ42 protofibrils, as well as beta-sheet structure (Gong et al., 2021). Apart from the effect on plaque burden, serotonin might also exert neuroprotective effects mediated via its action on heat shock protein 70, SIRT-1 and SIRT-2 gene expression, as evidenced in rat cells (Hornedo-Ortega et al., 2018).

On the contrary, few trials, failed to replicate the effects of SSRI on Aβ plaque reduction in the hippocampus (Von Linstow et al., 2017) alongside mitigating the cognitive dysfunction (Klaassens et al., 2019, Olesen et al., 2017, Severino et al., 2018). In the case of Klaassens et al. (2019), this could be due to the small sample size and the single administration dosage. The unexpected findings of the three animal trials might be partially explained by administration route, since the trials belong to the minority that administered the SSRI orally. Other factors, such as sample size, intervention duration and type of AD model, do not seem to be crucially different as compared to the other animal trials that did find an effect. Furthermore, the effects of SSRI on P-tau remain ambiguous, since the findings of Halliday et al. (2017) and Jin et al. (2017) contradict each other even though both trials involved mice that overexpressed the human tau mutation. Finally, the effect of SSRI on the neocortex plaque load, and, 5-HT3 receptor antagonists on cognition, seem absent, although again this might be due to the administration route. Nevertheless, the majority of included studies supports the overall hypothesis that brain serotonergic neurotransmitter system alterations are intrinsically involved in AD pathophysiology, thereby suggesting that interfering with its evolution from the earliest stages onwards could be a viable target for prevention, and, possibly (symptomatic) treatment. This notion is consistent with the review of Joshi et al. (2020) concerning multiscale and multilevel serotonergic modeling approaches for AD.

4.2. The potential of the microbiota-gut-brain axis in modulating the brain's serotonergic system

The question hereafter remained whether these serotonergic alterations could be prevented or prohibited by modulating the microbiota-gut-brain axis. Indeed, nutrition, probiotics, prebiotics and FMT seem to affect serotonin levels, serotonin receptors, related enzyme expression (TPH1, TPH2, MAO, IDO) and serotonin transporter (SLC6A4) expression in the brain. This observed connection between gut and brain with respect to serotonin, might be the consequence of multiple different interactions as visualized in Fig. 3. One example could be modulation of vagus nerve activity similarly as is the case with SSRI (McVey Neufeld et al., 2019). In this study, for instance, oral SSRI administration enhanced vagus nerve activity, and, vagotomy subsequently removed its antidepressant effect. More recently, bacterial tryptophan metabolites have even been linked to vagus nerve stimulation, through the activation of epithelial sensory enteroendocrine cells of the intestine (Ye et al., 2021). In addition, serotonergic changes in the included studies were often accompanied by cognitive or behavioral changes. As an example, the prebiotic trial of Liu et al. (2019) revealed both cognitive improvement as well as whole brain serotonin level enhancement. Although improvement in brain function might be a direct effect of the enhanced serotonin level (Fig. 3), it could also be related to the alternative fate of dietary tryptophan, namely the kynurenine pathway. Metabolites of this pathway, such as quinolinic acid (Fig. 1), have shown to be neurotoxic through a variety of mechanisms like agonizing the N-methyl-D-aspartate receptor (for review: Lugo-Huitrón et al., 2013). Thus, inhibiting the formation of such compounds through the action of microbiota, for instance by lowering the activity of IDO or availability of tryptophan, might reduce neurotoxicity which is logically beneficial for overall brain health. Accordingly, Yu et al. (2015) showed the positive effect of IDO inhibition on cognition, Aβ formation and neuronal loss, while Parrott et al. (2012) highlighted a preventive effect on anxiety- and depressive-like symptoms, both in AD mouse models. Notably, not all metabolites of the kynurenic pathway are necessarily detrimental for the brain. Nicotinamide adenine dinucleotide (NAD^+), which is an essential cofactor important for mitochondrial function, gained interest as a possible modulator of age-related diseases (for review: Castro-Portuguez and Sutphin, 2020; Verdin, 2015).

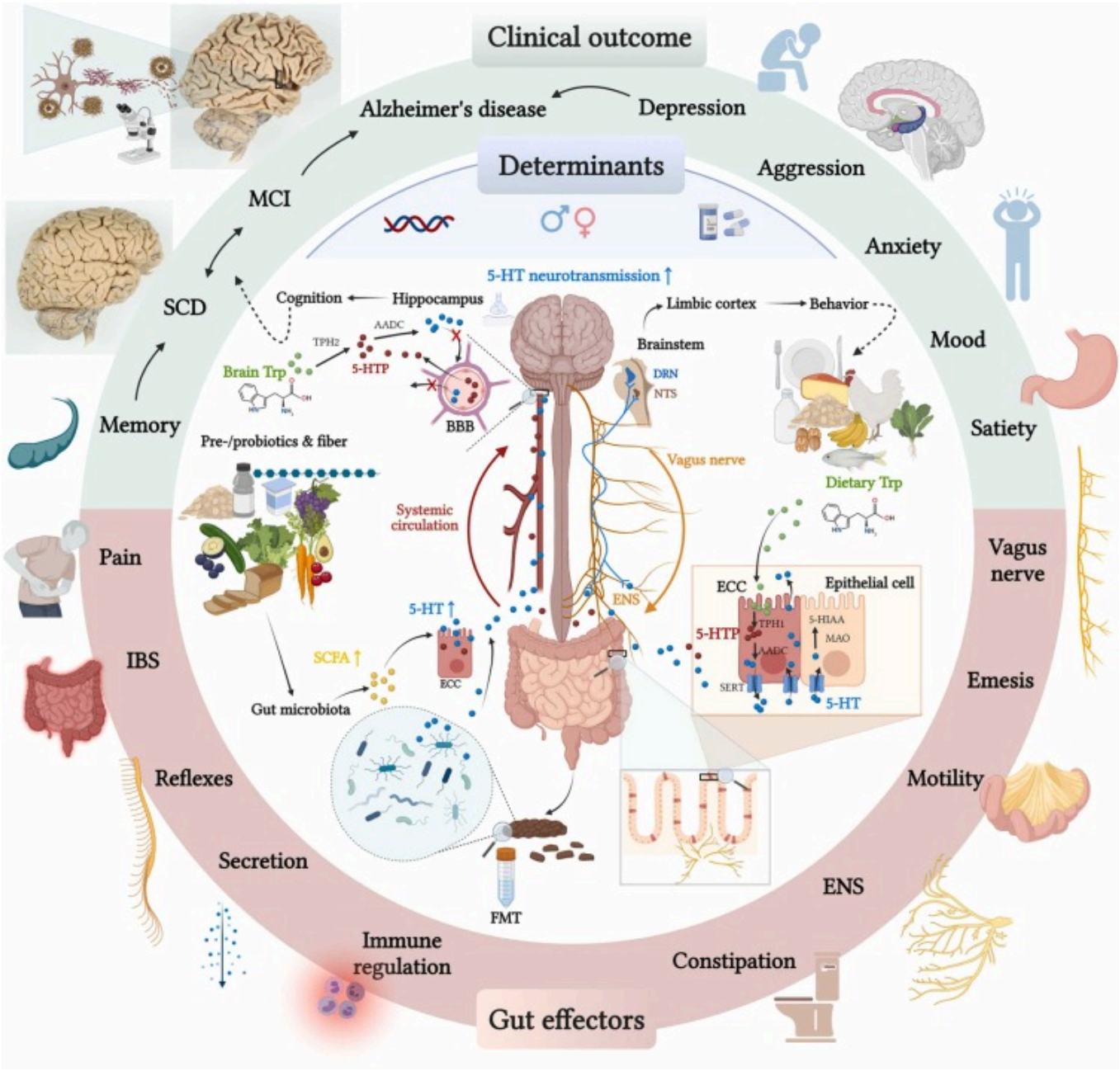

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Fig. 3. **Serotonergic functions mediated by gut-brain crosstalk in relation to potential enhancers.** Serotonin (5-HT) is a critical modulator of microbiota-gut-brain axis signaling and exerts multiple functions throughout the human body that relate to both brain and gut (outer circle). Its production, availability and activity is influenced in various ways, with gender, genetics (e.g. enzymatic activity, receptor distribution) and medication (e.g. SSRI) as main external or physiological (internal) determinants. Firstly, dietary or supplemental tryptophan (Trp) can be transformed in the gut by the enterochromaffin cells (ECC) to 5-hydroxytryptophan (5-HTP) by the action of tryptophan hydroxylase (TPH)1, and, subsequently, to serotonin by aromatic L-amino acid decarboxylase (AADC). Following its

release, 5-HT interacts with receptors on the enteric nervous system to modulate gut motility among others, and, to induce further signaling along the vagus nerve. Vagal afferents further propagate the signal to the dorsal raphe nuclei and the nucleus of the solitary tract. Both nuclei connect with emotion-regulating brain networks that control mood, which in effect may further determine eating behavior. Secondly, 5-HT production via the ECC can also be effectuated by the intake and digestion of dietary fiber or related prebiotics, following which the microbiota produce short-chain fatty acids (SCFA; e.g. propionate, butyrate, acetate). These SCFA stimulate the ECC for additional 5-HT synthesis. Particular strains of gut microbiota can also synthesize neurotransmitters themselves. Importantly, the intermediate of 5-HT synthesis, 5-HTP, can pass the blood-brain barrier from the systemic circulation, whereas 5-HT cannot. In neurons, Trp is transformed into 5-HTP by the action of TPH2, and, further to 5-HT via AADC. The vagus nerve can be considered as the highway along which 5-HT modulates the gut-brain connection, having a reciprocal interaction. With regard to Alzheimer's disease (AD) development, fecal microbiota transplantations, diet and pre-/probiotics could enhance the abovementioned pathways, and boost brain serotonergic neurotransmission in the end (e.g. hippocampus; limbic cortex). This could result in altered behavioral and cognitive outcomes, or, depending on the disease stage, prevent, attenuate or delay neuroinflammation and thus subsequent plaque or tangle formation (upper left corner). Further involvement of the alternative fate of dietary Trp, i.e. the kynurenine pathway, related to neuroinflammatory processes in AD progression has not been included in this figure. Abbreviations: 5-HIAA; 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine (serotonin); 5-HTP: 5-hydroxytryptophan; AADC: aromatic L-amino acid decarboxylase; BBB: blood-brain barrier; DRN: dorsal raphe nuclei; ECC: enterochromaffin cell; ENS: enteric nervous system; FMT: fecal microbiota transplantation; IBS: irritable bowel syndrome; MAO: monoamine oxidase; MCI: mild cognitive impairment; NTS: nucleus tractus solitarius (nucleus of the solitary tract); SCD: subjective cognitive decline; SCFA: short-chain fatty acids; SERT: serotonin transporter; SSRI: selective serotonin reuptake inhibitors; TPH: tryptophan hydroxylase; Trp: tryptophan. Brain images (12% formalin-fixated) are at the courtesy of the picture archive of the Neurobiobank of the Institute Born-Bunge (Antwerp, Belgium; FAGG registration no. 190113). Created with BioRender.com.

Observed (beneficial) serotonergic alterations, however, are not consistent in all included intervention trials. For example, the impairment of learning and memory is accompanied by an increase in hippocampal serotonin levels in one of the FMT trials. This seems contradictory to the hypothesis that decreased (hippocampal) serotonin levels in AD affect cognition in addition to the previously described positive effects of SSRI in AD animal models. As for two of the included dietary interventions, serotonin itself seemed unaffected,

although serotonin-related changes (e.g. tryptophan or 5-HIAA levels) were observed next to effectively modulated behavior. However, it should be noted that only serotonin levels in the brainstem were measured in one trial, compared to a very small sample size in the other. Moreover, there were only a few dietary trials available, investigating a limited variety of analytical neurochemical measures. Dietary enrichment with high levels of tryptophan, however, revealed to reduce Aβ load in a transgenic AD mouse model (Noristani et al., 2012). Unfortunately, the researchers could not reveal direct serotonergic changes in hippocampus nor raphe nuclei related to the higher tryptophan intake, apart from increased sprouting of hippocampal serotonergic fibers in the transgenic AD mouse model (irrespective of diet) as a potential defense mechanism against Aβ accumulation (Noristani et al., 2012). One proposed neuroprotective mechanism by which serotonergic sprouting in the vicinity of plaques in AD brain might exert its effects, is via the hyperpolarization of nearby neurons through activation of 5-HT1A/B receptors, and subsequent opening of K^+ channels. Hyperpolarisation in turn limits Ca^{2+} entry, and, hence, excitoxicity, since voltage-gated calcium channels then will remain closed and the Mg^{2+} block of NMDA receptors becomes favored (Rodríguez et al., 2012).

Finally, pre- and probiotics seem to differ widely in their impact on the brain, which highlights the importance of strain choice. Lactobacillus *plantarum* is one of the most studied strains and seems potent in modulating brain serotonin with beneficial effects on both cognition and behavior. On the other hand, Enterococcus faecium lowered brain serotonin levels in density-stressed goslings. This effect was also observed in two prebiotics trials in the hippocampus of pigs, and the prefrontal cortex of mice. The largest limitation for most included strains is the lack of replication studies, as well as the inconsistency in study endpoints. Some studies focus on enzymes and receptors, while others focus exclusively on serotonin and its metabolite levels. Another variation can be found in the targeted region for measurements: some were done in whole brains, several others in only a few regions. On the whole, the mentioned limitations make it difficult to draw final conclusions, apart from the general observation that diet, FMT, pre- and probiotics, as well as bacterial strain choice seem intrinsically linked with serotonergic changes, irrespective of the direction of change (increase or decrease) and measured analyte (whether whole levels, or, receptors, enzymes or transporters).

4.3. Meanings of the above findings for possible clinical applications

The implications of the discussed interventions for AD development remain to be determined, since neither of the included trials similarly assessed (i) serotonin levels both in gut and brain (or associated biofluid), (ii) entry route (e.g. pre-/probiotics, diet, FMT), and,

(iii) cognitive and/or behavioral outcome in involved (iv) AD mouse models or patients at (v) different disease stages. Furthermore, it should be kept in mind that everyone has their own individual microbiota composition, which is likely to impact their personal response to FMT, diet, pre- and probiotics. This is not represented in the included FMT trials, since effects on the brain's serotonergic system were measured in subjects that underwent antibiotic treatment prior to FMT. Consequently, it remains unclear whether the microbiota from the transfer could colonize the gut sufficiently, and, consequently, alter gut-brain communication in actual humans with their own initial microbiota composition. In clinical studies with FMT transfers from healthy subjects to (irritable bowel disorder or depressive) patients, psychiatric symptoms did improve, however, this benefit lasted only for about three to six months (Chinna Meyyappan et al., 2020). Noteworthy, one case study observed rapid improvement of cognitive and behavioral symptoms following FMT in an AD patient that suffered from an infection with *Clostridioides difficile*. Stool from the patient's 85-year-old wife as a donor was used. The improvement was noticeable up to six months post-intervention (no further data provided) (Hazan, 2020). The same question about effectiveness in humans could be raised for the pre- and probiotic trials, especially since several included trials used gnotobiotic or germ-free mice. Meanwhile, a randomized controlled trial that investigates the effect of Bifidobacterium (three months administration) on microbiota composition, brain networks and cognition in individuals with amnestic MCI is ongoing (NCT03991195), next to an alike trial in which both *Bifidobacterium* and *Lactobacillus* strains will be supplemented to AD patients for 12 weeks (NCT05145881). Brain serotonin measurements are unfortunately not part of the outcome measures in neither studies. Finally, external factors in preclinical studies should also be vigorously investigated and controlled for before actual translation to the human situation, since SSRI treatment efficacy, for instance, has been hypothesized to be largely dependent on environmental influences, with even a chance of significant worsening rather than improvement if under stressful living conditions (Alboni et al., 2017, Severino et al., 2018). In this context, one proposed mechanism might be the enhanced neuronal plasticity following increased serotonergic neurotransmission, rendering the individual more susceptible to the quality of the living environment.

4.4. Limitations and reflections

Some methodological limitations and reflections need to be considered firstly. For instance, the narrow focus of the review, which is mostly on serotonin only. Metabolites and precursors related to its synthesis and metabolization pathways, such as melatonin, tryptophan, and, the neuroinflammatory kynurenine pathway (e.g. quinolinic and kynurenic acid), are beyond the scope of this review. Their importance should certainly not be

underestimated and can be placed in a general conceptual framework of neuroinflammation in AD (for review: Gheorghe et al., 2019; Maitre et al., 2020). Another important aspect to take into account, is the fact that the observed correlations between altered brain serotonin content and improved clinical outcome and/or attenuated AD pathology, for instance, following SSRI treatment, do not necessarily imply causality. The same goes for the observed serotonergic effects in brain of the enumerated preclinical studies researching pre- and probiotics, FMT, and, whole diet approaches/dietary restrictions. Given that the serotonergic neurotransmitter system both in gut and brain may serve as an intermediate nexus for neighboring and alike neurotransmitter systems, such effects may be rather indirect. It remains to be evidenced still whether serotonin degeneration may be a downstream effect of AD pathology or may have a causative role after all. SSRI treatment does not unequivocally interfere in the progression of human AD, perhaps because of complex effects of chronic SSRI treatment on multiple serotonin receptor subtypes (Gründer and Cumming, 2021). The discrepancy between animal studies with a successful outcome and the lack of replication in clinical trials is often witnessed in that regard. It is, therefore, a difficult enterprise to attribute a causal link for serotonin systems, however, a handful of studies so far have emerged, revealing modifying effects via direct structural and molecular interactions between serotonin and Aβ. A final limitation might be the exclusion of studies that measured serotonin levels, receptors, enzymes or transporters solely in gut and/or blood. These endpoints are often used in human trials due to more expensive, and, perhaps, somewhat more invasive in vivo brain measurements (e.g. PET scans). Although these do not necessarily provide relevant information on brain serotonin content and alterations, such studies certainly could contribute to the overall understanding of serotonin across the microbiota-gut-brain axis. As for imaging studies, these are very much wanted in view of our proposed hypothesis, however, these should be executed with suitable radioligands, and, preferentially, in combination with peripheral analyses of serotonin synthesis or metabolism.

5. Conclusions and general considerations

All in all, current reviewed evidence suggests that the brain's serotonergic neurotransmitter system is intrinsically involved in the development of AD. Additionally, this system could be modulated through the microbiota-gut-brain axis, using pre- and probiotics, FMT and nutrition, at least as evidenced in various preclinical studies. A next step would be executing randomized placebo-controlled trials focused on pre- and probiotics, FMT and diet, in actual AD mouse models, at different ages of the disease pathology. In this regard, transgenic mouse models that cover at least both the tau and Aβ abnormalities should be preferred (such as APP/PS1/TauP301L transgenic mice). Study endpoints should ideally cover cognitive

aspects, neuropsychiatric symptoms (such as depression and aggression), and, central (brain) as well as peripheral (CSF; blood; gut (biopt or fecal materials)) measurements of serotonin levels, receptors, enzymes (IDO, MAO, TPH2, TPH1) and/or transporter expressions. A distinction could be made between neurochemically and behaviorally important brain regions, such as the hippocampus, brainstem, amygdala and frontal cortex. Functional metagenomics approaches using fecal materials to further identify how bacterial metabolites might (in)directly affect serotonergic signaling remain a very powerful tool in this effort (Jameson et al., 2020). Next, largescale human randomized placebo-controlled intervention trials are required to determine in which stage of the Alzheimer's continuum these modulators (e.g. pre-/probiotics; FMT; diet) of the serotonergic system might have the most promising effect, preferably spanning from the prodromal stages, such as subjective cognitive decline or MCI due to AD, up to the milder AD stages, where both high adherence to such therapies, as well as sufficient room for noticeable enhancement are feasible still. In the end, such trials might facilitate the development of a comprehensive approach to tackle this complex multifactorial disease, since serotonin and its derivatives across the microbiota-gut-brain axis might serve as potential biomarkers of disease progression (Tajeddinn et al., 2016), next to forming a valuable target in AD prevention strategy and drug development.

CRediT authorship contribution statement

Emma Aaldijk: Conceptualization, Methodology, Investigation, Visualization (Fig. 2), Writing – original draft. **Yannick Vermeiren**: Conceptualization, Investigation, Visualization (Fig. 1, Fig. 3), Writing – review & editing, Project administration, Supervision.

Declaration of Competing Interest

None.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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