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# Microbiota shaping — the effects of probiotics, prebiotics, and fecal microbiota transplant on cognitive functions: A systematic review

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## Abstract

### BACKGROUND

Dementia is a chronic progressive neurological disease affecting millions of people worldwide, and represents a relevant economic burden for healthcare systems. Although its pathogenesis is still unknown, recent findings have reported that a dysregulated gut-brain axis communication, a fundamental relationship mediated by several host and microbial molecules, is associated with cognitive disorders. In addition, gut microbiota manipulation reduces neuroinflammation, improving cognitive function by restoring the functional gut-brain axis.

### AIM

To better define the effects of probiotics, prebiotics, synbiotics, and fecal microbiota transplant (FMT) on cognitive function.

### METHODS

We performed a literature search of human randomized clinical trials to examine the effects of the administration of probiotics, prebiotics, synbiotics, or FMT on cognition outcomes in healthy or sick people of every age, sex, and nationality. We systematically searched Embase, Medline/PubMed, Cochrane Library, central and clinicaltrials.gov databases with a combination of comprehensive terms related to cognition and gut microbiota manipulation. Then we carefully reviewed and synthesized the data by type of study design and setting, characteristics of the studied population, kind of intervention (strain type or mixture type, dosage, and frequency of administration), control treatment, inclusion and exclusion criteria, follow-up duration, and cognitive or memory outcomes.

### RESULTS

After examining the titles and abstracts, the initial literature screening identified

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995 articles, but we added 23 papers in our systematic review. The analyses of these selected studies highlighted that both probiotic supplementation and FMT improved cognitive function regardless of the type and posology of administration and the adopted cognitive tests and questionnaires. We found that most of the studies conducted in healthy people showed a significant positive effect of the intervention on at least one of the performed cognitive tests. Regarding unhealthy subjects, while FMT and especially probiotic administration had multiple beneficial effects on different cognitive functions, supplementation with prebiotics did not provide any cognitive improvement.

**CONCLUSION**

Probiotic supplementation and FMT may represent a promising strategy to restore gut eubiosis and enhance the cognitive functions of healthy people and patients with neurological disorders.

**Key Words:** Dementia; Cognitive disorders; Gut microbiota; Probiotics; Prebiotics; Fecal microbiota transplant

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**Core Tip:** Dementia and cognitive impairment are age-related conditions that are on the rise worldwide. Recent studies have demonstrated the existence of a gut-brain axis and that the manipulation of gut microbiota composition can exert positive effects on cognition. The administration of probiotics, prebiotics, and fecal microbiota transplant may represent a good strategy to counteract gut dysbiosis and ameliorate cognitive dysfunction by reducing neuroinflammation and brain damage.

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**INTRODUCTION**

Global population ageing, defined as the increasing proportion of older people around the globe, represents a deep shift in society and a considerable challenge for the sustainability of healthcare systems due to the rise of geriatric illnesses[1,2]. Currently, the prevalence of cognition impairment, particularly dementia, is estimated worldwide in 50 million people with an economic burden of 818 billion dollars in 2016 and a forecast of about 115 million people by 2050[3,4].

Dementia is an acquired, gradual, and progressive disorder involving multiple adverse neurocognitive changes that can affect learning processes, memory, executive function, language, complex attention, mood, perceptual-motor function or social cognition. Moreover, although its detailed pathological mechanism is still not well understood, dementia often occurs in association with advanced age or the presence of contributing causes, usually Alzheimer's disease (AD), Parkinson's disease (PD), or cerebrovascular pathology[5-7]. Unfortunately, current therapies are only symptomatic, and notably, no treatment stops the disease progression[8].

Recent studies have shown that the gut microbiota, with more than 100 trillion microorganisms carrying three times of human genes, plays a pivotal role in human health; manipulation of the intestinal microbiota can modify the release of neuroactive metabolites, which affect brain health[9,10]. This role can be further explained by the documented existence of the gut-brain axis, a complex bidirectional system in which communication occurs through three parallel and interplaying pathways that involve nervous, endocrine, and immune signals[11]. Therefore, different preclinical and observational studies have demonstrated that the gut dysbiosis is responsible for increased intestinal permeability, which correlates with both neuroinflammation and a decline of cognitive abilities[12-15].

Dietary interventions (in nutritional supplements or specific diets) have often been applied in clinical practice to restore intestinal eubiosis and prevent and treat cognitive disorders. For example, a Mediterranean diet and/or a healthy diet based on fruits, vegetables, and fish seems to stabilize or slow cognitive decline[16].

Nevertheless, the most promising strategy to counteract gut dysbiosis and to maintain cognitive function seems represented by the administration of probiotics, prebiotics, and fecal microbiota transplant (FMT).

Interestingly, administration in animal models of an adequate posology of multistrain probiotics reduces both Firmicutes/Bacteroidetes ratio and intestinal permeability, slowing cognitive decline and reducing neuroinflammation[17,18]. Moreover, using specific prebiotics seems to ameliorate cognitive performance with a direct effect on gut microbiota[19].

Moreover, even FMT has demonstrated remarkable efficacy in healthy subjects and people affected by various diseases caused by gut microbiota perturbation, particularly *Clostridium difficile* infection. It could represent a promising therapy for cognitive impairment improvement because of its capability to re-establish a healthy gut microbial community[20,21].

Therefore, since the evidence derived from human randomized clinical trials (RCTs) is currently limited, this systematic review identified the available RCTs and better defined the effects of probiotics, prebiotics, synbiotics, and FMT on cognitive functions.

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## MATERIALS AND METHODS

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### **Literature search**

Our study followed the PRISMA statement guidelines. A computerized search of the articles published until 24 October 2019 was conducted in Embase, Medline/PubMed, Cochrane Library, central and clinicaltrials.gov databases and other individual journal sources, using the following search string: (memory OR cognition OR dementia) AND (lactobacillus OR bifidobacteria OR streptococcus OR enterococcus OR probiotic OR prebiotic OR symbiotic OR fecal, transplantation). In the PubMed database, we activated the filter “Humans”; in Embase, we selected the filter “Research articles”; in Cochrane Library, we activated the filter “Trials”; and in clinicaltrials.gov, we selected the filter “recruitment: terminated or completed.” The search did not apply filters for language, country, duration of follow-up, and participants’ characteristics (age and sex).

### **Study selection**

Two authors independently reviewed the titles and abstracts of the collected articles, applying predefined inclusion/exclusion criteria. The inclusion criteria were as follows: RCTs; availability of full text; patients regardless of age, nationality, sex, and health status; comparison between oral intake of probiotics, prebiotics, or symbiotic and control treatment or placebo; and outcome as cognitive or memory evaluation. The adopted exclusion criteria were as follows: Studies with fewer than 10 participants; reviews, articles, and case reports; or studies with incomplete outcomes.

### **Data extraction**

The same two authors performed analyses of the full text and data extraction with the intervention of a third author in case of poor agreement or discrepancies. Each reviewer independently recorded the data in a predefined data extraction form. The following data, if reported, were obtained from each selected trial: First author name, year of publication, study design, setting (institution, city, and country), characteristics of the studied population (mainly age and health status), number of total participants and their gender, number of subjects in both treatment and control groups, characteristics of the intervention (strain type or mixture type, dosage and frequency of administration), control treatment, inclusion and exclusion criteria, follow-up duration, cognitive or memory outcomes and compliance data.

### **Outcome assessment**

For each selected study, cognitive functions were assessed through specific tests which evaluated the eight main cognitive skills: sustained attention, speed of information processing, cognitive flexibility and control, multiple simultaneous attention, working memory (short-term memory), category formation, pattern recognition, and response

inhibition[22]. A detailed description of all cognitive tests performed in the selected papers for this systematic review is annexed in [Supplementary material](#).

## RESULTS

### Study selection

The initial literature screening identified 995 papers. Eight studies were excluded for duplication and another 964 papers were removed after the title and abstract screening because they did not respect inclusion criteria. The selection process, in accordance with the PRISMA statement 2009, is illustrated in [Figure 1](#).

### Characteristics of the included studies

An overview of the 23 studies included in this systematic review is reported in [Table 1](#). All 23 included papers were RCTs published from 2007 to 2019[23-45]. The total number of participants was 1285 (491 males and 650 females); unfortunately, both articles published by Tamtaji *et al*[44,45] did not report the gender of the participants. Regarding the age of the enrolled subjects, one study was conducted in healthy scholars (7-9 years)[31], four studies enrolled young adults (19-30 years)[25,36,40,43], and most of the studies involved adults or older people (48-95 years)[23,24,26-30,32-35,37-39,40,42,44,45]. Most studies (four) were performed in Iran[22,24,44,45]; three in the United States[26-28] and Japan[34,37,39]; two in the United Kingdom[29,31], South Korea[33,35], and Spain[30,41]; and one in Austria[25], Italy[32], Ireland[36], Malaysia[38], Poland[42], Wales[43] and the Netherlands[40].

Concerning the patients' health state, most studies enrolled healthy people[25,29,31,33-36,40,43], whereas three studies involved patients with AD[23,24,44] or cirrhotic subjects with recurrent encephalopathy[26-28]. The other studies were focused on stressed adults[38], patients with PD[45], human immunodeficiency virus (HIV)-1-infected individuals[32], subjects affected by fibromyalgia syndrome[41], people with major depression[42], elderly with frailty syndrome[30], and adults with forgetfulness[39] and mild cognitive impairment[37].

In the trials, subjects were administered probiotics[22-25,26,29,32-42,44,45], prebiotics[30,31,43], or FMT[27,28] and its duration lasted a maximum of 24 wk[32] and a minimum of 4 h[43]; however, the trials continued for 12 wk for most of the studies[23,24,31,33-35,37,38,44,45]. No studies have reported the administration of synbiotics. In the studies examining the effects of probiotics, a total of 21 different bacterial species were administered (alone or in combination) in a dosage ranging from  $1 \times 10^9$  CFU/mL to  $2.5 \times 10^{10}$  CFU/mL; the most represented species were *Lactobacillus plantarum*, *L. acidophilus*, and *Bifidobacterium bifidum*. On the other side, the administered prebiotics was composed of inulin or galacto-oligosaccharides (GOS), in a dosage that ranged from 5 g/d to 7.5 g/d. In FMT studies, subjects were administered a capsule containing 550  $\mu$ L stool and buffer solution or enema infusion of 90 mL FMT solution. Lastly, only five studies reported their compliance[31,33-35,44,45], and it was generally considered high because it ranged from 82.69% to 100%.

### Effects of probiotics and prebiotics on the cognitive functions of healthy people

Regarding the healthy subjects, three studies showed no significant difference between probiotic and placebo groups[29,31,36]. In comparison, five studies showed a significant positive effect of the intervention on at least one of the performed cognitive tests[25,33,35,40,43].

In Benton *et al*[29], the healthy enrolled subjects ingested fermented milk containing *L. casei* Shirota daily for 3 wk. However, no significant differences between the probiotic and placebo groups were reported regarding episodic and long-term memory, assessed with the Wechsler Memory Scale test and the ability to remember the capitals of 30 countries. Moreover, the healthy people treated with *L. rhamnosus* supplement in Kelly *et al*[36] did not report any cognitive improvement, as assessed with the Paired Associates Learning, Attention Switching Task, Rapid Visual Information-Processing task (RVIP), Emotion Recognition Task and electroencephalography tests.

Considering the five studies reporting a significant cognitive improvement, Bagga *et al*[25] found that 4 wk administration of a multistrain probiotic increased Positive and Negative Affect Schedule (PANAS) score (paired with the response accuracy to unpleasant stimuli test) and showed the activation of the cingulum, pre-cuneum and cerebellum areas, involved in decision making and memory process.

Table 1 Summarizing of all selected studies

Ref.	Study design	Setting	Characteristics of the studied population	Number of participants (M/F)	Intervention	Comparison	Duration of intervention	Outcomes	Compliance
Agahi <i>et al</i> [23], 2018	RCT	Cities: Emam Ali, Golabchi, Miad, Barekat; Country: Iran	Patients with Alzheimer disease; Age: 65-90 yr; Control group: 80.57 ± 1.79 yr; Intervention group: 79.70 ± 1.72 yr	Total: 48; Control group = 23 (10/13); Intervention group = 25 (7/18)	1 capsule with <i>L. fermentum</i> , <i>L. plantarum</i> , <i>B. lactis</i> and 1 capsule with <i>L. acidophilus</i> , <i>B. bifidum</i> , and <i>B. longum</i> ( $3 \times 10^9$ CFU)	Placebo	12 wk	TYM	-
Akbari <i>et al</i> [24], 2016	RCT	Cities: Golabchi, Sadeghyeh; Country: Iran	Patients with Alzheimer disease; Age: 60-95 yr; Control group: 82.00 ± 1.69 yr; Intervention group: 77.67 ± 2.62 yr	Total: 60; Control group = 30 (24/6); Intervention group = 30 (24/6)	200 mL/d probiotic milk containing <i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i> , and <i>L. fermentum</i> ( $2 \times 10^9$ CFU each)	Placebo	12 wk	MMSE	-
Bagga <i>et al</i> [25], 2018	RCT	City: Graz Country: Austria	Healthy volunteers; Age: 20-40 yr; Control group (placebo): 27.25 ± 5.78 yr; No intervention group: 23.87 ± 4.97 yr; Intervention group: 28.27 ± 4.2 yr	Total: 45; Control group = 15 (9/6); No intervention group = 15 (7/8); Intervention group = 15 (7/8)	1 sachet/d with 3 g freeze-dried powder containing <i>L. casei</i> W56, <i>L. acidophilus</i> W22, <i>L. paracasei</i> W20, <i>B. lactis</i> W51, <i>L. salivarius</i> W24, <i>L. lactis</i> W19, <i>B. lactis</i> W52, <i>L. plantarum</i> W62 and <i>B. bifidum</i> W23( $7.5 \times 10^6$ CFU/g)	Placebo or no intervention	4 wk	PANAS, SCL-90, ADS, LEIDS, RM task, ED task	-
Bajaj <i>et al</i> [26], 2014	RCT	City: Richmond, Virginia Country: United States	Patients with hepatic encephalopathy; Age: 18-65 yr; Control group: 58.5 ± 4.5 yr; Intervention group: 58.4 ± 3.8 yr	Total: 30; Control group = 16 (12/4); Intervention group = 14 (10/4)	<i>L. rhamnosus</i> GG (ATCC 53103)( $> 50$ billion CFU/gm)	Placebo	8 wk	NCT-A, NCT-B, DS, BDT	-
Bajaj <i>et al</i> [27], 2017	RCT	City: Richmond, Virginia Country: United States	Patients with hepatic encephalopathy; Mean age: 62 yr; Control group: 62.9 ± 9.8 yr; Intervention group: 64.5 ± 5.1 yr	Total: 20; Control group = 10 (10/0); Intervention group = 10 (10/0)	FMT units (90 mL total) instilled by enema and retained for 30 min	Standard of care	20 wk	EncephalApp-Stroop, PHES	-
Bajaj <i>et al</i> [28], 2019	RCT	City: Richmond, Virginia Country: United States	Patients with hepatic encephalopathy; Control group: 64.2 ± 6.2 yr; Intervention group: 63.3 ± 4.2 yr	Total: 20; Control group = 10 (8/2); Intervention group = 10 (8/2)	FMT capsules (550 µL of stool and buffer solution)	Placebo	20 wk	EncephalApp-Stroop, PHES	-
Benton <i>et al</i> [29], 2007	RCT	City: Swansea Country: Wales	Healthy volunteers; Age: 48-79 yr; Average age 61.8 ± 7.3 yr	Total: 126 (51/75)	65 mL of milk drink containing <i>L. casei</i> Shirota ( $10^8$ /mL)	Placebo	3 wk	POMS, WMS, VFT, NART, Ability to recall the capital cities of countries	-
Buigues <i>et al</i> [30], 2016	RCT	City: Valencia Country: Spain	People with frailty syndrome; Age: 66-90 yr; Control group: 73.4 ± 1.8 yr; Intervention group: 74.2 ± 1.6 yr	Total: 50; Control group = 22 (6 /16); Intervention group = 28 (9/19)	7.5 g/d of Darmocare Pre® (Inulin 3375 mg, FOS 3488)	Placebo	13 wk	MMSE	-

Capitão <i>et al</i> [31], 2020	RCT	Cities: Swindon, Milton Keynes, London Country: United Kingdom	Healthy scholars; Age: 7-9 yr; Control group: 9.12 ± 1.02 yr; Intervention group: 8.54 ± 0.79 yr	Total: 35; Control group = 18 (12/6); Intervention group = 17 (12/5)	5.5 g/d of Bimuno (B-GOS, Lactose, Glucose, Galactose)	Placebo	12 wk	BAS-III, CogTrack™ battery, STAIC, MFQ	High (> 80%)
Ceccarelli <i>et al</i> [32], 2017	RCT	City: Rome Country: Italy	HIV-1 infected individuals; Median age: 48 (IQR: 38-54) yr; Intervention group: 45 (35-52.5) yr; Control group: 43 (38.2-53) yr	Total: 35; Control group = 26 (24/2); Intervention group = 9 (9/0)	Sachet containing <i>L. plantarum</i> DSM 24730 <i>S. thermophilus</i> DSM 24731, <i>B. breve</i> DSM 24732, <i>L. paracasei</i> DSM 24733, <i>L. delbrueckii subsp. bulgaricus</i> DSM 24734, <i>L. acidophilus</i> DSM 24735 <i>B. longum</i> DSM 24736, and <i>B. infantis</i> DSM 24737 (450 × 10 <sup>9</sup> bacteria)	Control group	24 wk	ROCF, RAVLT, STEP, VST, PVF, SVF, SPM, DS, CBTT, AAT, TMT A, TMT B	-
Chung <i>et al</i> [33], 2014	RCT	City: Jeonju Country: Korea	Healthy volunteers; Age: 60-75 yr; Control group: 64.50 ± 4.84 yr; Intervention group (500 mg): 64.50 ± 2.17 yr; Intervention group (1000 mg): 64.43 ± 4.47 yr; Intervention group (2000 mg): 66.56 ± 4.98 yr	Total: 36; Control group = 10 (4/6); Intervention group (500 mg) = 10 (9/1); Intervention group (1000 mg) = 7 (2/5); Intervention group (2000 mg) = 9 (5/4)	Daily doses of 500, 1000, or 2000 mg. of tablet containing <i>L. helveticus</i> IDCC3801	Placebo	12 wk	DS, SRT, VLT, RVIP, SCWT	> 70%
Inoue <i>et al</i> [34], 2018	RCT	City: Hyogo prefecture, Country: Japan	Healthy volunteers; Average age: 70.3 ± 3.1 yr; Control group: 70.9 ± 3.2 yr; Intervention group: 69.9 ± 3.0 yr	Total: 38; Control group = 18 (7/11); Intervention group = 20 (7/13)	Sachet containing lyophilised powder of <i>B. longum</i> BB536, <i>B. infantis</i> M-63, <i>B. breve</i> M-16V and <i>B. breve</i> B-3 (1.25 × 10 <sup>10</sup> CFU each)	Placebo	12 wk	MoCA, Modified flanker task, PHQ-9, GAD-7	> 99%
Hwang <i>et al</i> [35], 2019	RCT	City: Jeonju Country: South Korea	People with mild cognitive impairment; Age: 55-85 yr; Control group: 69.2 ± 7.00 yr; Intervention group: 68.0 ± 5.12 yr	Total: 100; Control group = 50 (14/36); Intervention group = 50 (20/30)	Mixture of fermented soybean powder and <i>L. plantarum</i> C29 (1.25 × 10 <sup>10</sup> CFU/g)	Placebo	12 wk	VLT, DS, ACPT	> 90%
Kelly <i>et al</i> [36], 2017	RCT	City: Cork Country: Ireland	Healthy volunteers; Age: 20-33 yr; Placebo/Probiotic group: 23.6 ± 0.97 yr; Probiotic/Placebo group: 25.64 ± 1.14 yr	Total: 29; Placebo/Probiotic group = 15 (15/0); Probiotic/Placebo group = 14 (14/0)	Active capsules contained corn starch, magnesium stearate, silicon dioxide and <i>L. Rhamnosus</i> (1 × 10 <sup>9</sup> CFU)	Placebo	8 wk	MOT, PAL, AST, RVIP, ERT, Emotional Stroop	-
Kobayashi <i>et al</i> [37], 2019	RCT	City: Tokyo Country: Japan	People with memory complaints; Age: 50-80 yr; Control group: 61.6 ± 6.37 yr; Intervention group: 61.5 ± 6.83 yr	Total: 117; Control group = 58 (29/29); Intervention group = 59 (29/30)	1 capsule per day with <i>B. breve</i> A1 (> 2 × 10 <sup>10</sup> CFU)	Placebo	12 wk	RBANS, MMSE	-
Lew <i>et al</i> [38], 2019	RCT	Cities: Penang, Kubang Kerian Country: Malaysia	Stressed adults; Age: 18-60 yr; Control group: 32.1 ± 11.4 yr; Intervention group: 31.3 ± 10.8 yr	Total: 103; Control group = 51 (12/39); Probiotic group = 52 (12/40)	<i>L. plantarum</i> P8 (10 <sup>10</sup> CFU/sachet per day)	Placebo	12 wk	PSS-10, DASS-42, CBB	-
Ohsawa <i>et al</i> [39], 2018	RCT	Country: Japan	People with forgetfulness; 50-70 yr; Control group: 57.8	Total: 60; Control group = 29 (13/16); Intervention	One bottle per day (190 g per bottle) of a <i>L. helveticus</i> -fermented	Placebo	8 wk	RBANS, POMS	-

			± 5.9 yr; Intervention group: 58.5 ± 6.5 yr	group = 31 (13/18)	milk contained 2.4 mg of lactononadecapeptide				
Papalini <i>et al</i> [40], 2019	RCT	City: Nijmegen Country: The Netherlands	Healthy volunteers; Age:18-40 yr; Control group: 22 yr (SE = 0.5); Intervention group: 21 yr (SE = 0.4)	Total: 58; Control group = 29 (0/29); Intervention group = 29 (0/29)	2 g/d of powder diluted in water or milk containing <i>B. bifidum</i> W23, <i>B. lactis</i> W51, <i>B. lactis</i> W52, <i>L. acidophilus</i> W37, <i>L. brevis</i> W63, <i>L. casei</i> W56, <i>L. salivarius</i> W24, <i>L. lactis</i> W19 <i>L. lactis</i> W58( $5 \times 10^9$ CFU)	Placebo	4 wk	BDI, LEIDS-r, Emotional face-word Stroop task, Emotional face-matching paradigm, SCWT, DS, SECP	-
Roman <i>et al</i> [41], 2018	RCT	City: Almeria Country: Spain	Fibromyalgia patients; Control group: 50.27 ± 2.03 yr; Intervention group: 55.00 ± 2.09 yr	Total: 31; Control group = 15 (2/13); Intervention group = 16 (1/15)	4 pills/d containing <i>L. Rhammosus</i> GG <sup>®</sup> , <i>L. casei</i> , <i>L. acidophilus</i> , and <i>B. Bifidus</i> ( $6 \times 10^6$ bacteria per capsule)	Placebo	8 wk	MMSE, BDI, IGT, Two-choice Task	-
Rudzki <i>et al</i> [42], 2019	RCT	City: Bialystok Country: Poland	People with major depression; Control group: 38.90 (12) yr (SD); Intervention group: 39.13 (9.96) yr	Total: 60; Control group = 30 (10/20); Intervention group = 30 (7/23)	2 capsules/d containing <i>L. plantarum</i> 299v ( $10 \times 10^9$ CFU per capsule)	Placebo	8 wk	HAM-D 17, SCL-90, PSS-10, APT, RFFT, TMT A, TMT B, CVLT Stroop Test parts A and B	-
Smith <i>et al</i> [43], 2015	RCT	City: Cardiff Country: Galles	Healthy volunteers; Age: 19-30 yr; Mean age 23.0 yr	Total: 47 (19/28)	One sachet of Inulin per day (5 mg)	Placebo	4 h	Mood, Performance Tasks, Memory Tasks, Psychomotor Tasks, Selective Attention Tasks, Sustained Attention Task	-
Tamtaji <i>et al</i> [44], 2019	RCT	City: Kashan, Shahrekord Country: Iran	Patients with Alzheimer disease; Age: 55-100 yr; Control group: 78.5 ± 8.0 yr; Intervention group (Selenium): 78.8 ± 10.2 yr; Intervention group (Selenium + probiotic): 76.2 ± 8.1 yr	Total: 79; Control group = 26; Intervention group (Selenium) = 26; Intervention group (Selenium + probiotic) = 27	Selenium (200 µg/d) and probiotic containing <i>L. acidophilus</i> , <i>B. bifidum</i> , and <i>B. longum</i> ( $2 \times 10^9$ CFU/d each)	Placebo or only selenium (200 µg/d)	12 wk	MMSE	100%
Tamtaji <i>et al</i> [45], 2019	RCT	City: Kashan Country: Iran	Patients with Parkinson disease; Age: 50-90 yr; Control group: 67.7 ± 10.2 yr; Intervention group: 68.2 ± 7.8 yr	Total: 60; Control group = 30; Intervention group = 30	Probiotic containing <i>L. acidophilus</i> , <i>B. bifidum</i> , <i>L. reuteri</i> , and <i>L. fermentum</i> (each $2 \times 10^9$ CFU/g)	Placebo	12 wk	MDS-UPDRS	90%

AAT: Aachener Aphasia Test; ACPT: Auditory Continuous Performance Test; ADS: Allgemeine Depressionsskala; APT: Attention and Perceptivity Test; AST: Attention Switching Task; BAS-III: British Ability Scales III; BDI: Beck Depression Inventory; BDT: Block Design Test; CBB: Cogstate Brief Battery; CBTT: Corsi Block Tapping Test; CFU: Colony-forming unit; CVLT: California Verbal Learning Test; DASS-42: Depression Anxiety and Stress Scale questionnaire; DS: Digit Symbol Test; ED: Emotional Decision Making; ERT: Emotion Recognition Task; F: Female; GAD-7: Generalised Anxiety Disorder Questionnaire-7; HAM-D 17: Hamilton Depression Rating-17; IGT: Iowa Gambling Task; LEIDS: Leiden Index of Depression Severity; M: Male; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MMSE: Mini Mental State Evaluation; MoCA: Montreal Cognitive Assessment instrument; MOT: Motor Screening Test; NART: National Adult Reading Test; NCT-A: Number Connection Test A; NCT-B: Number Connection Test B; PAL: Paired Associates Learning; PANAS: Positive and Negative Affect Schedule; PHES: Psychometric Hepatic Encephalopathy Score; PHQ-9: Patient Health Questionnaire-9; POMS: Profile of Mood States; PSS-10: Perceived Stress Scale-10; PVFT: Phonological Verbal Fluency (PVF) test; RAVLT: Rey Auditory Verbal Learning Test; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RCT: Randomized controlled trial; RFFT: Ruff Figural Fluency Test; RM: Emotional Recognition Memory; ROCF: Rey-Osterrieth Complex Figure Test; RVIP: Rapid

Visual Information-Processing task; SCL-90: Symptom Checklist 90; SCWT: Stroop Color and Word Test; SECPT: Socially Evaluated Cold Pressor Test; SPM: Raven's Standard Progressive Matrices; SRT: Story Recall Test; STAIC: State-Trait Anxiety Inventory for Children; STEP: Test of Time and Weights Estimation; SVF: Semantic Verbal Fluency test; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TYM: Test your memory; VFT: Verbal Fluency test; WMS: Wechsler Memory Scale MFQ: Children Mood and Feelings Questionnaire; VLT: Verbal Learning Test; VST: Visual Search Test.

Papalini *et al*[40] tested a probiotic multistrain mixture in women who underwent a stressful condition for 4 wk. The results showed that the trial reduced the unfavorable stress effect on working memory performance measured by the DS backward test. In addition, Chung *et al*[33] demonstrated a significant improvement in Verbal Learning Test, Story Recall Test, RVIP and Stroop Color and Word Test after 12 wk administration of *L. helveticus* in healthy subjects compared to placebo. Finally, Inoue *et al*[34] demonstrated that intervention with *Bifidobacterium spp.* for 12 wk, added to resistance training, significantly improved response accuracy and reaction time tests in healthy elderly subjects. Regarding the cognitive effects of prebiotic administration, the study conducted in healthy children by Capitão *et al*[31] reported that 12 wk GOS supplement only improved memory retrieval speed assessed with the CogTrack™ test battery. By contrast, Smith *et al*[43] investigated the acute effects of inulin intake on healthy volunteers and reported improving memory tasks, especially immediate free and delayed recall. No FMT intervention has been carried out in healthy subjects. Hence, although three of eight studies conducted in healthy subjects showed no significant difference between intervention and placebo groups, probiotics resulted were more effective in improving cognitive function than prebiotics.

### **Patients with different pathologies and the impact of probiotics/prebiotics/FMT on cognitive functions**

The effects of probiotics, prebiotics, and FMT on cognitive functions were also assessed in different diseases, of which the most represented were hepatic encephalopathy (HE) and AD. Bajaj *et al*[26] conducted three studies on HE. In particular, the authors first investigated the effect of *Lactobacillus GG* administration on HE but did not report changes in cognition. However, they also treated HE patients with FMT *via* enema and reported a significant improvement in PHES and EncephalApp Stroop tests[27]. Moreover, Bajaj *et al*[28] evaluated the treatment with FMT capsules effects on HE patients, and they reported only a significant improvement in the EncephalApp Stroop test.

Regarding AD, Agahi *et al*[23] administered two different multistrain probiotic capsules to patients affected by severe disease for 12 wk, but no effect on TYM cognitive tests were reported. By contrast, Akbari *et al*[24] found that daily administration of probiotic milk enriched with *Lactobacillus spp.* led to a decline in Mini Mental State Evaluation (MMSE) score in AD patients compared to placebo. Moreover, Tamtaji *et al*[44] found that a probiotic and selenium co-supplement in AD patients was responsible for a significant increase in MMSE score. In addition, Hwang *et al*[35] found that people with mild cognitive impairment showed an improvement in a

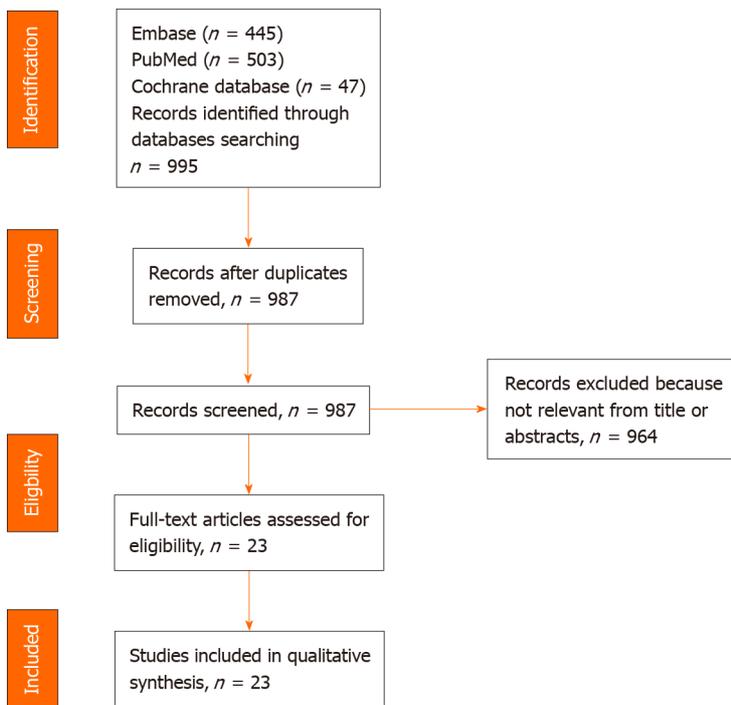


Figure 1 PRISMA flow diagram.

battery of tests related to verbal memory and attention domains after ingesting a mixture of *L. plantarum* C29 and fermented soybean powder. Finally, Lew *et al*[38] reported that daily administration of *L. plantarum* P8 for 12 wk in stressed adults led to a reduction of stress score and enhanced cognition and verbal learning memory, assessed through the CBB. Another study, conducted by Roman *et al*[41], explored the effect of a multispecies probiotic on fibromyalgia patients and found a significantly reduced number of impulsive choices. Moreover, Kobayashi *et al*[37] carried out a 12-wk treatment with *Bifidobacterium breve* A1 in elderly subjects with memory complaints, documenting a significant decline of total scores of both Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and MMSE tests. Regarding patients affected by PD, Tamtaji *et al*[45] highlighted a favorable reduction of the Movement Disorders Society-Unified PD Rating Scale (MDS-UPDRS) after ingesting a probiotic mixture for 12 wk. In addition, Ohsawa *et al*[39] reported improved attention, coding, and delayed memory scores (assessed with RBANS) in people with forgetfulness after 8 wk intake of a *L. helveticus* fermented milk drink. Also, Rudzki *et al*[42] reported a significant improvement in CVLT and APT in people with major depression treated with *L. plantarum* 299v. Moreover, Ceccarelli *et al*[32] demonstrated a significant improvement in several cognitive functions in HIV-1 infected patients ingesting a multistrain probiotic for 24 wk (primarily in the following neurocognitive tests: Rey-Osterrieth Complex Figure, Rey Auditory Verbal Learning Test, Test of Time and Weights Estimation, Phonological Verbal Fluency Test, Corsi Block Tapping Test and Trail Making Test A). Finally, the only study which assessed the effectiveness of a prebiotic intake (inulin and fructooligosaccharides), conducted by Buigues *et al*[30] on elderly affected by frailty syndrome, the MMSE did not report significant cognitive improvement. As a result, while the FMT and especially probiotics played multiple beneficial effects on different cognitive functions of unhealthy subjects, the prebiotics' supplementation did not provide any cognitive improvement, maybe because of their short-term administration.

## DISCUSSION

Dementia is a chronic, gradual, and progressive neurological disease that affects millions of people in both industrialized and rural countries. Cognitive decline and daily activities impairment limits patients' self-care and causes a severe burden to parents, friends, caregivers, and especially to the healthcare systems[46,47]. Increasing evidence suggests that the prevalence of dementia rises with age and is strongly

associated with other comorbidities, including AD and cardiovascular risk factors such as hypertension and hypercholesterolaemia[48].

Although the specific dementia pathogenesis is not yet understood and current therapies only attempt to counterbalance the disturbance, several studies recently highlighted the central role of the gut microbiota in brain health and the onset and persistence of neurodegenerative diseases[49,50]. Nevertheless, our systematic review of human RCTs reported contradictory results due to the diverse type, posology, and duration of interventions and the different responses of healthy or diseased people to the treatment.

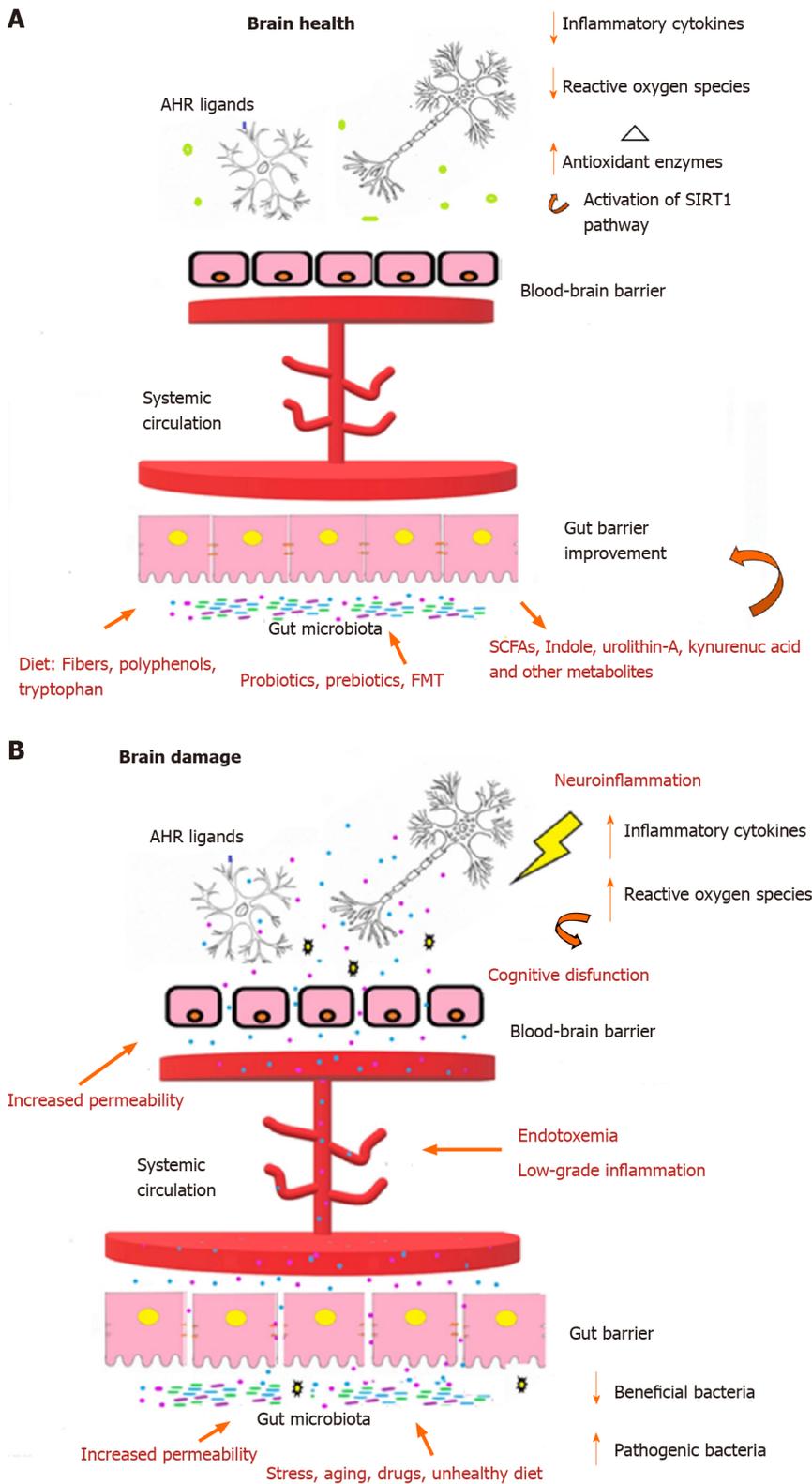
In general, supplementation with probiotics and prebiotics determined the positive effects on healthy subjects. Five (63%) out[25,33,34,40,43] of the eight studies conducted in volunteers reported beneficial effects on the cognitive functions, while the other three[29,31,36] studies did not find any difference between the intervention and control groups.

Regarding the different evaluated patients, only 3 (20%)[23,26,30] of the 15 studies did not report an amelioration of cognitive functions for other possible reasons. For example, the probiotics' administration performed by Bajaj *et al*[26] probably did not last for a sufficient time to obtain cognitive improvement in patients with HE. In contrast, with 13 wk of prebiotics' supplementation, Buigues *et al*[30] did not observe effects on cognitive behaviour because MMSE does not represent a sensitive tool to detect the small changes in cognition that may occur after inulin and FOS supplementation. In addition, in the study conducted by Agahi *et al*[23], the 12 wk probiotic administration did not lead to cognitive amelioration in patients with AD; a probable explanation could be the enrollment of only patients with advanced disease.

Probiotic supplementation improves cognitive functions in many different diseases such as HIV[32], PD[45], fibromyalgia, major depression[42], AD[24,44], and other mild cognitive deficits[35,37-39]. Furthermore, studies evaluating the effects of FMT on patients with HE highlighted a significant amelioration in cognitive functionality[27, 28]. It is well established that a balanced gut microbiota composition (eubiosis condition) plays a crucial role in our health; a dysbiotic status (meaning a reduced gut microbiota diversity) is related to many human gastrointestinal, immunological, and neurodegenerative diseases[51]. Concerning neurological impairments, recent findings elucidated the importance of the gut microbiota in the bidirectional communication between the central and enteric nervous systems, called the gut-brain axis[52]. Hence, the main factors responsible for intestinal dysbiosis such as stress, unbalanced diet, and drug abuse also determine an alteration of the gut-brain axis by causing a loss of epithelial integrity. The loss of this barrier functionality allows microbial-derived molecules to enter the systemic circulation, promoting endotoxemia, oxidative stress and low-grade inflammation responsible for the blood-brain barrier disruption[53,54] (Figure 2); these factors represent a signature for neurodegenerative disorders, especially AD. Consequently, given the importance of the intestinal barrier integrity for the prevention of neuroinflammation and brain damage, gut microbiota modulation by psychobiotics, namely beneficial bacteria (probiotics) or support for such bacteria (prebiotics) and FMT, represent an excellent strategy to restore the intestinal permeability and prevent the consequences of a leaky gut[55-57].

However, although several studies have highlighted the local beneficial effects of probiotics, prebiotics and FMT (*e.g.*, modification of the gut microbiota composition, strengthening of the gut epithelial barrier and modulation of the local (mucosal) immune system), they also exerted systemic effects, in particular on the central nervous system[58,60]. More specifically, recent studies have reported that the intestinal microbiota affects neurodevelopment and diverse brain functions by regulating the gut-brain axis, for example, by acting on the electrophysiological thresholds of the enteric nervous system neurons, which interact *via* neurotransmitters (adrenaline, noradrenaline, and acetylcholine) with the central nervous system[61].

Another important neuronal pathway in gut-brain communication involves the vagus nerve, and many effects of probiotics strains influence its activity[62]. Furthermore, since the gut houses the most extensive collection of lymphoid tissues in the human body and various intestinal immune cells can cross the blood-brain barrier, gut microbiota manipulation represents a key indirect route for communication between the gut microbiota and the central nervous system[63]. Intriguingly, specific probiotic formulations have also been shown an ability to stimulate the production of neurotransmitters (*e.g.*, GABA, serotonin, and dopamine) or are even microbially neuroactive. These microbial metabolites can trigger epigenetic signals on human brain genes involved in various complex networks or act as a ligand for specific human receptors[64].



**Figure 2** Gut-brain axis in eubiosis and dysbiosis condition. A: Eubiosis; B: Dysbiosis condition. AHR: Aryl hydrocarbon receptor; FMT: Fecal microbiota transplant; SCFA: Short-chain fatty acid; SIRT1: Sirtuin 1.

For instance, the probiotic activated Sirtuin 1 pathway, which regulates the brain antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, could favor cognitive improvements by preventing oxidative stress and deposition of beta-amyloid in the brain[65]. Even the modulation of kynurenine metabolism, the primary route for tryptophan catabolism, which is closely related to the structural and functional dynamics of the gut microbiota, could positively affect brain health[66]. Indeed, *in vivo* *L. plantarum* administration demonstrated a beneficial reduction of

kynurenines as most act as neurotoxic compounds[42,67,68]. Notably, although *L. plantarum* was administered to healthy or ill people in most of our selected RCTs, its positive effects have been probably underestimated because of the unknown impact of the other components of the probiotic formula that include it.

By contrast, indole-3-lactic acid (ILA) is an interesting neuroprotective tryptophan metabolite mainly produced by *Bifidobacterium spp.* acting as an aryl hydrocarbon receptor (AhR) agonist, expressed by intestinal and neuronal cells[69,70]. In detail, microbial agonists produced by *L. bulgaricus* and *L. reuteri* could activate microglia and astrocytes AhRs, suppressing pro-inflammatory signals and preventing neuronal damage[71-73]. Furthermore, the administration of some probiotics (especially *L. helveticus*, *L. casei* and *L. rhamnosus*) and prebiotics could also improve cognitive functions by stimulating the production of short-chain fatty acids as they enhance the transcription of the brain-derived neurotrophic factor that stimulates neuronal plasticity, protecting against neuroinflammation and neuronal apoptosis[74-78]. Moreover, the FMT represents a very promising strategy to re-establish gut eubiosis and improve cognitive functions. For instance, in transgenic mice, FMT significantly improved cognitive deficits, beta-amyloid accumulation, and neuroinflammation while reducing UPDRS score and tremor in people with Parkinson disease[79].

Finally, our recent study demonstrated that age-associated shifts of the microbiota have a detrimental impact on the central nervous system's protein expression and critical functions. Still, FMT represents an excellent strategy to restore a young-like microbiota and improve cognitive functions[80]. Therefore, although the modulation of intestinal microbiota represents a new precious therapeutic opportunity, it also shows some restrictions and risks. In particular, even if probiotics are generally considered safe and have many advantages such as a tolerated mode of administration (orally) and the possibility to integrate them with other pharmacological/non-pharmacological approaches, they displayed some limitations mainly due to potential side effects, especially in some patients (including immunocompromised people), or to their long-term safety[81]. Besides, even if probiotics can promote the production of several compounds such as lactic acid, bioamines, bile salts and other molecules that could play detrimental effects on the host, most of them are sold as dietetic supplements, and the regulatory agencies do not require safety studies in humans before their commercialization[82,83].

Although reported to be fairly safe in most clinical trials, FMT can be responsible for acute or prolonged adverse effects such as diarrhea, abdominal pain, nausea, headaches, and fatigue[84]. In particular, immunological concerns have been raised regarding safety assessments for both probiotics and the FMT because either indigenous or transient microorganisms could impact the immune system's functionality. Hence, the FMT application or the administration of probiotics to specific vulnerable populations and stressed or aged people, immunocompromised patients, newborns or pregnant women must be well evaluated to prevent microbial translocation and sepsis[85-87]. Moreover, the current literature lacks information about the long-term administration of probiotics; therefore, the possible horizontal transfer of antibiotic resistance genes favored by their supplementation cannot be excluded. Likewise, because stool contains thousands of microorganisms and a vast number of metabolites, FMT represents a constant risk of pathogens or commensals transfer to donors that may harmfully affect them[88].

## CONCLUSION

As a final note, the different defects found in the evaluated studies highlighted some methodical limitations such as small sample sizes, the limited sampling time and the wide range of other cognitive tests. Supplementation of probiotics and FMT could represent a non-invasive successful strategy to restore gut eubiosis and enhance cognitive functions in healthy people and patients with different neurological/neurodegenerative diseases. Of course, further specific and clinical studies with numerous patients are needed to confirm this encouraging hypothesis.

## ARTICLE HIGHLIGHTS

### Research background

Due to the global population aging, cognitive impairments will affect approximately

115 million people by 2050. Since current therapies only attempt to counterbalance cognitive disorders, many recent studies recently highlighted the central role of the gut microbiota in brain health.

### **Research motivation**

The pathogenesis of several cognitive disorders is still not fully understood; however, it has been recently established that a dysregulated gut-brain axis communication is associated with the onset and persistence of neurodegenerative diseases. Thus, gut microbiota manipulation could restore a functional gut-brain axis improving cognitive functions.

### **Research objectives**

Since the evidence derived from human randomized clinical trials (RCTs) is currently limited, the main purpose of this systematic review was to detect the currently available RCTs, to define better the effects of probiotics, prebiotics, and fecal microbiota transplant (FMT) on cognitive functions.

### **Research methods**

We systematically searched Embase, Medline/PubMed, Cochrane Library, central and clinicaltrials.gov databases with a combination of comprehensive terms related to cognition and gut microbiota manipulation. Then, we carefully reviewed and synthesized the data by types of study design and setting, characteristics of the studied population, kind of the intervention (strain type or mixture type, dosage and frequency of administration), control treatment, inclusion and exclusion criteria, follow-up duration, and cognitive or memory outcomes.

### **Research results**

The analysis of the 23 included in our systematic review highlighted that, although the different type and posology of administration and the various cognitive tests and questionnaires adopted, both probiotics supplementation and FMT improved the cognitive functions in most of healthy people and patients affected by different neurological pathologies.

### **Research conclusions**

The gut microbiota manipulation could represent a good strategy to counteract gut dysbiosis and so ameliorate cognitive dysfunction.

### **Research perspectives**

The supplementation of probiotics and FMT could represent a non-invasive successful strategy to restore gut eubiosis and enhance cognitive functions in healthy people and patients with different neurological/neurodegenerative diseases.

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