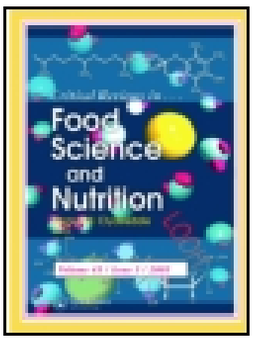

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REVIEW

An appraisal of folates as key factors in cognition and ageing-related diseases

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ABSTRACT

Folic acid (FA) is often consumed as a food supplement and can be found in fortified staple foods in various western countries. Even though FA supplementation during pregnancy is known to prevent severe congenital anomalies in the developing child (e.g., neural tube defects), much less is known about its influence on cognition and neurological functioning. In this review, we address the advances in this field and situate how folate intake during pregnancy, postnatal life, adulthood and in the elderly affects cognition. In addition, an association between folate status and ageing, dementia and other neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis is discussed. While its role in the incidence and severity of these diseases is becoming apparent, the underlying action of folates and related metabolites remains elusive. Finally, the potential of FA as a nutraceutical has been proposed, although the efficacy will highly depend on the interplay with other micronutrients, the disease stage and the duration of supplementation. Hence, the lack of consistent data urges for more animal studies and (pre)-clinical trials in humans to ascertain a potential beneficial role for folates in the treatment or amelioration of cognitive decline and ageing-related disorders.

KEYWORDS

ageing; cognition; folic acid; fortification; neurodegeneration; supplementation

General introduction

Folates are part of the B vitamin family and are crucial players in many vital functions, including the immune response, DNA synthesis, brain functioning, etc. In literature, the terms folate, folic acid (FA), and e.g., 5-methyltetrahydrofolate (5-MTHF) are often used interchangeably. However, it is important to note that the micronutrients addressed by these terms often differ in terms of molecular structure, biological impact and bioavailability (Saini, Nile, and Keum 2016). The term folate is commonly used to address the family of naturally occurring compounds such as 5-MTHF, which are commonly found in green leafy vegetables, liver, fruits, nuts and yeast (Looman et al. 2018; Kim and Cho 2018). In contrast, FA is a synthetic derivative which is often used to fortify staple foods, due to its relatively heightened uptake in the gut and increased molecular stability (Scaglione and Panzavolta 2014; Osterhues, Ali, and Michels 2013). In this review, the term *folates* is used to address the entire family of compounds, including naturally occurring and synthetic variants.

After uptake in the duodenum and jejunum, following hydrolysis of polyglutamated folates, and processing by the designated cells, folates play a key role in e.g. methylation reactions and DNA (purine and pyrimidine) synthesis (Shane 2008; Devlin et al. 2000; Chandler et al. 1991; Imbard, Benoist, and Blom 2013). Throughout these metabolic processes, folates fulfill the role of one-carbon carrier/donor. More specifically, S-adenosyl-L-methionine (SAM) is generated as a consequence of folate metabolism and is in turn converted into S-adenosyl-L-homocysteine. This process, which occurs within the homocysteine-methionine remethylation cycle, will mediate metylation of e.g. DNA. For purine and pyrimidine synthesis, it are respectively the generated 5,10-methylene-tetrahydrofolate and 10-formyl-tetrahydrofolate forms which fulfill crucial roles (Lim et al. 2007). Folate metabolism is also closely intertwined with the thymidylate cycle, homocysteine, choline and vitamin B12 metabolism, which has already been extensively reviewed elsewhere (Hoffer 2004; Brosnan et al. 2015; Nazki, Sameer, and Ganaie 2014).

It has been known for many years that FA food fortification and supplementation can reduce the prevalence of birth defects, whilst low FA and folate intake has been associated with an increased prevalence of such defects (Blom et al. 2006). More specifically, it has been observed that risk for neural tube defects (NTDs) (Blom et al. 2006), cleft palate (Millacura et al. 2017) and some other skeletal defects such axial skeletal malformations and growth plate/metaphyseal bone damage (Schmidt et al. 1983; Fan et al. 2012; Biale and Lewenthal 1984; Oyama et al. 2009; Kappen et al. 2004; Keeling et al. 1986) can be decreased by heightened FA intake. Even though an increased folate intake only rarely decreases the risk of these defects completely to zero

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(Osterhues, Ali, and Michels 2013), its protective efficacy was still sufficient to merit a mandatory food fortification in various countries. These included for example the USA, Australia and the majority of South America (Imbard, Benoist, and Blom 2013).

Even though the use of folates to prevent congenital birth defects has been well explored, major knowledge gaps persist on how this micronutrient affects other health aspects, such as cognition. For this reason, a growing number of studies started to address this issue and focused on the impact of folates on the developing and adult nervous system. A previous review already discussed how folate and vitamin B-12 deprivation is linked to birth defects of the central nervous system (i.e., NTDs), and the authors offered first insights into how such a deprivation is involved in the etiology of neurodegenerative diseases (Reynolds 2006). Continuing along this line, the involvement of FA in neurological disorders of the cerebrospinal fluid, seizures, and Down/fragile X syndrome was already described in detail (Djukic 2007). More recently, Balashova *et al.* discussed how folates are important in neural function and neurodegenerative disease, but epidemiological studies were not discussed in detail (Balashova, Visina, and Borodinsky 2018). In this review, we expand upon this existing literature, by critically discussing to which extent folate status is related to cognition throughout the various stages of life. We compare between the effectiveness of prenatal, postnatal and (young-)adult folate deprivation and supplementation in affecting cognition and offer a detailed description of the underlying mechanisms. Furthermore, we compile the most recent epidemiological and experimental evidence for the involvement of folates in ageing-related neurodegenerative disorders. A better insight into the role of folates in cognition and neurodegenerative disease, will in turn lead to a more optimized supplementation strategy.

Folates and cognition

Aside from the clear association between maternal folate deprivation and the occurrence of severe congenital defects in the unborn child, a series of publications have suggested a link between an altered folate intake and effects on the developing and adult nervous system, for instance in terms of cognition (see Tables 1 and 2 for a detailed overview of epidemiological findings). In corroboration, a behavioral study on adult male Wistar rats also showed an improved short- and long-term memory and an improved motor function after FA injections (Shooshtari, Moazedi, and Parham 2012). The biological mechanisms underlying this association are not fully uncovered, but might encompass a folate-dependent neuronal development, functioning and plasticity. Below, a comprehensive overview of relevant epidemiological and experimental findings on these aspects is provided.

Epidemiological evidence for a folate-dependent nervous system development and cognition

Over the past decade, a series of epidemiological studies have aimed to clarify the role of micronutrients (e.g. folates) in cognition. The importance of adequate nutrient intake for good health is evident, especially in the developing child. However, aside from the anticipated beneficial effects such as stimulated growth and disease prevention, recent studies have addressed some intriguing findings on the influence of micronutrients such as FA on childhood cognition. To note, a distinction needs to be made between observational studies, which focus on general nutritional status and the effect on cognition, and interventional studies, where the overall goal is to fortify specific nutrients in the individual and improve cognition. For a general overview of findings from observational and interventional studies, we refer to Tables 1 and 2.

Observational studies

In the search for a link between metabolic biomarkers and cognition (see Table 1 for an overview), most studies agree on the notion that increased and decreased folate status can be linked to respectively augmented and impaired cognitive functioning. Strikingly, not only prenatal but also postnatal folate status has been shown to alter neurological function, which implies a role for folates in brain development as well as in postnatal brain functioning and plasticity. Contrarily, a meta-analysis by Veena et al., including a total of 38 epidemiological studies, could not identify a clear link between maternal nutritional status during pregnancy (body mass index, various micro and macro-nutrients) and offspring cognition. Yet, these data were stated to be inconclusive and more studies in cohorts with undernutrition are warranted (Veena et al. 2016). Furthermore, most studies observe folate status only at one time point, whilst the duration of the folate-deprived or -augmented state is crucial for a correct interpretation of the results.

Interventional studies

Expanding on purely observational studies, interventional studies where folates are supplemented in the cohort may shed additional light on the cognitive consequences of increased intake. The most recent findings in this category are depicted in Table 2. To our knowledge and according to (Campoy et al. 2011), there is currently no conclusive evidence from interventional studies that folate supplementation during pregnancy affects childhood cognition. Interestingly, combining prenatal and postnatal fortification appears to increase cognition in late-childhood, but not in infants (Christian et al. 2010; Christian et al. 2016). Continuing, multiple micronutrient supplements (MMS) taken exclusively after birth also appear to augment cognition at 7–13 years of age (Kumar and Rajagopalan 2007; Jiang 2006; Kumar and Rajagopalan 2008), but not at younger ages (Siegel et al. 2011; Rauh-Pfeiffer et al. 2014). Because many studies use MMS (including FA) and not standalone FA supplementation, it remains difficult to formulate a definite conclusion for FA-dependent changes in cognition.

Several studies have previously investigated whether different supplements can have varying effects on cognition, as

Table 1. Observational studies on cognitive behavior following prenatal or postpartum folate analysis.

	Age at biomarker analysis	Method of biomarker assessment	Age at cognitive analysis	Method of cognitive assessment	Association folates and cognition?	Sampling size	Reference
PRENATAL FOLATE ASSESSMENT	First and second trimester	Food-frequency questionnaires addressing various nutrients	3 years	Peabody Picture Vocabulary Test III and the Wide Range Assessment of Visual Motor Abilities	Y	1210	Villamor et al. 2012
	19, 26, and 37 weeks of gestation	Maternal blood folate and total homocysteine	5.3 years	Wide Range Achievement Test, Peabody Picture Vocabulary Test, Home screening Questionnaire, Differential Ability Scales, Visual and Auditory Sequential Memory, Knox Cube Test, Gross Motor Scale, Grooved Pegboard	N	355	Tamura et al. 2005
	13.5 weeks of gestation	Maternal plasma folate	6–8 years	Snijders-Oomen Niet-verbale intelligentie Test – revisie (SON-R.2/5-7) and NEPSY-II-NL	Y	256	Ars et al. 2016
	30 weeks of gestation	Maternal plasma folate, B-12 and homocysteine	9–10 years	3 core tests from the Kaufman Assessment Battery for children and adaptations of Atlantis, Word order, Pattern reasoning, Verbal fluency, Kohs' block design and the coding-Wechsler Intelligence Scale for Children-III	Y	536	Veena et al. 2010
POSTPARTUM FOLATE ASSESSMENT	6–16 years	Blood folate and vitamin B-12 measurements	6–16 years	WRAT-R (reading and math) and WISC-R (block design and digit span)	Y	5365	Nguyen, Gracely, and Lee 2013
	12–18 months	Plasma folate, cobalamin, total homocysteine and methylmalonic acid	12–18 months	Bayley Scales of Infant Development II	Y	650	Strand et al. 2013
	25, 32, 45 years	Interviewer-administered CARDIA Diet History	50 years	Rey Auditory Verbal Learning Test, the Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale–III and the Stroop interference test.	Y	3136	Qin et al. 2017
	70 years	Food-frequency questionnaires addressing various nutrients	70 years	MHT (verbal reasoning), Mini-Mental State Examination, National Adult Reading Test and Verbal Fluency, subtests from Wechsler Adult Intelligence Scale-IIIUK, backward digit span, symbol search and digit symbol coding. Wechsler Memory Scale-IIIUK	N	882	McNeill et al. 2011
	79 years	Serum vitamin B-12 and folate	79 years	Moray House test	Y	470	Starr et al. 2005

Y = yes, an association between folates and cognition was observed; N = no association between folates and cognition was observed.

Table 2. Interventional studies on cognitive behavior following folate fortification.

	Supplementation/fortification				Molecular biomarker analysis			Cognitive analysis			
	Age	Period and duration	Carrier and nutrients	Sampling size	Age	Markers	Outcome	Age	Methodology	Association folates and cognition?	Reference(s)
Prenatal supplementation	20th week of pregnancy until birth	daily	400 µg 5-MTHF	161	Week 20, 30 of pregnancy and/or at delivery	Plasma folate of mother and cord blood	Maternal plasma folates were increased at W30 and delivery	6.5 years	Kaufman Assessment battery for Children	N	Campoy et al. 2011
Prenatal and postpartum supplementation	11th week of pregnancy until 12 weeks postpartum	daily	400 µg FA +60 mg iron	676	n.a.	n.a.	n.a.	7–9 years	Universal Nonverbal Intelligence Test, tests of executive function, Movement Assessment Battery for Children and finger-tapping test	Y	Christian et al. 2010
	11th week of pregnancy until 12 weeks postpartum	daily	600 µg FA +27 mg iron	734	n.a.	n.a.	n.a.	2 years	Adapted Bayley scales of infant and toddler development-third edition	N	Christian et al. 2016
Postpartum and childhood supplementation	1 – 36 months	Daily until the age of 36 months	IFA (6.25 mg iron +25 µg FA), 5 mg zinc, or IFA-zinc	367	12 months after start of supplementation	Hemoglobin and serum ferritin	Supplementation lead to significant concentration increase	39 or 52 weeks	Fagan Test of Infant Intelligence and the A-not-B Task of executive functioning	N	Siegel et al. 2011, Tielsch et al. 2006
	4–6 years	Daily for 3.5 months	220 µg FA, 1.1 mg vitamin B2, 0.73 mg B6, 1.2 lg B12 and 130 mg calcium	237	4–6 years	Urinary and blood creatinine, MMA and folate catabolites, ap-ABG and p-ABG	Supplementation lead to increased urinary ap-ABG and full blood folates, whereas plasma homocysteine was reduced	4–6 years	Subtests of the 'Hannover-Wechsler-Intelligenztest fur das Vorschulalter-III' and Wechsler Pre-school and Primary Scale of Intelligence-III, Kaufman-Assessment Battery for Children	N	Rauh-Pfeiffer et al. 2014
	7–11 year	Every day for one year	MMS (used in food preparation)	129	7–11 years, baseline and study end	Hemoglobin, hematocrit, red blood cell count, urinary iodine and serum vitamin A.	Significant increase in in hemoglobin, red cell count, serum vitamin A	7–11 year	NIMHANS (National institute of mental health and neurological sciences, Bangalore, India) memory test	Y	Kumar and Rajagopalan 2007, 2008

							and urinary iodine					
9 to 11 years	Daily for 37 days	0.625 mg riboflavin, 0.512 mg thiamin, 0.365 mg nicotinic acid, 0.13 mg FA	101	9–11 years, samples were collected on days 1, 20, and 37 of the fortification period	Urinary riboflavin excretion and erythrocyte glutathione reductase activity coefficient, erythrocyte transketolase activity	Supplementation increased urinary riboflavin and thiamin pyrophosphate and decreased erythrocyte glutathione reductase activity	9–11 years	AYP index	Y	Jiang 2006
9–13 years	Once weekly, twice weekly or daily for one year	IFA (100 mg iron +0.5 mg FA)	161	9–13 years	Pre-and post-intervention hemoglobin	Intervention increased hemoglobin levels	9–13 years	Digit span maze test visual memory test clerical task scores	Y	Sen and Kanani 2009

FA = folic acid; IFA = iron + folic acid; MMS = multiple micronutrient supplement; LNS = lipid-based nutrient supplement; N = no; Y = yes.

other nutrients than FA might affect cognition. For example, in anemic or undernourished mothers, maternal MMS supplementation improved child (3.5 y) motor function and cognition over maternal IFA supplementation (Prado et al. 2012). These findings were supported by an improved cognitive performance in 9–12 year old children of mothers who received multiple micronutrient supplementation in comparison to children that only received IFA tablets (Prado et al. 2017). However, these findings are debated, as another study could not identify a difference between prenatal IFA, MMS and FA supplementation (Li et al. 2015). It is however important to note the lack of standardization between different studies when MMS are formulated. One example of a micronutrient that appears not to be beneficial to cognition is zinc, as maternal and/or child zinc supplementation in addition to IFA conferred no added benefit to cognition in early school age (Li et al. 2015; Christian et al. 2011). The concept that not individual nutrients, but the combined diet affects child cognition is not new but has only been scientifically addressed in detail in recent years. For example, a dietary study indeed suggested a link with dietary patterns and altered child cognition and psychomotor development (Leventakou et al. 2016). Variation in nutrient dosage, supplementation frequency and age in-between studies should however be taken into account to better comprehend the combined effect as well as the individual roles of different micronutrients on cognitive functioning. For now, we conclude from Table 2 that a daily postpartum and adult supplementation of 0.13–0.5 mg FA has the most beneficial effect, but more studies are required before we can fully support that this is an optimal dose range. Furthermore, before we can conclude whether even higher doses of FA have a positive or negative impact on cognition, more studies are required that cover a broader FA dose-range. Furthermore, intestinal uptake of nutrients such as folates should be taken into consideration, which is not only dependent on its chemical characteristics, but also on the presence of other (e.g., phenolic) compounds and on individual-based metabolic activity. Hence, nutrient uptake may vary depending on whether a single nutrient or an MMS was given, or whether the supplement was processed in food (Halsted 1979; Lemos et al. 2007). Furthermore, it is important to not underestimate the importance of the formulation and preparation of the vehicle through which FA will be supplemented, as food processing (e.g., milling and cooking) can affect folate integrity. Studies that carefully address proper design of the vehicle indeed appear to get more pronounced positive test results (Kumar and Rajagopalan 2007; 2008).

Small-scale epidemiological studies in a healthy, well-nourished cohort may not have the statistical power to uncover significant effects of folate supplementation. Hence, most of the epidemiological studies discussed in Table 2 focus on cohorts with potential malnutrition. These data should however be interpreted with caution, since only few studies clinically validated malnutrition within the cohort (Prado et al. 2012). Furthermore, augmented maternal folate levels might not be directly linked to an increased folate

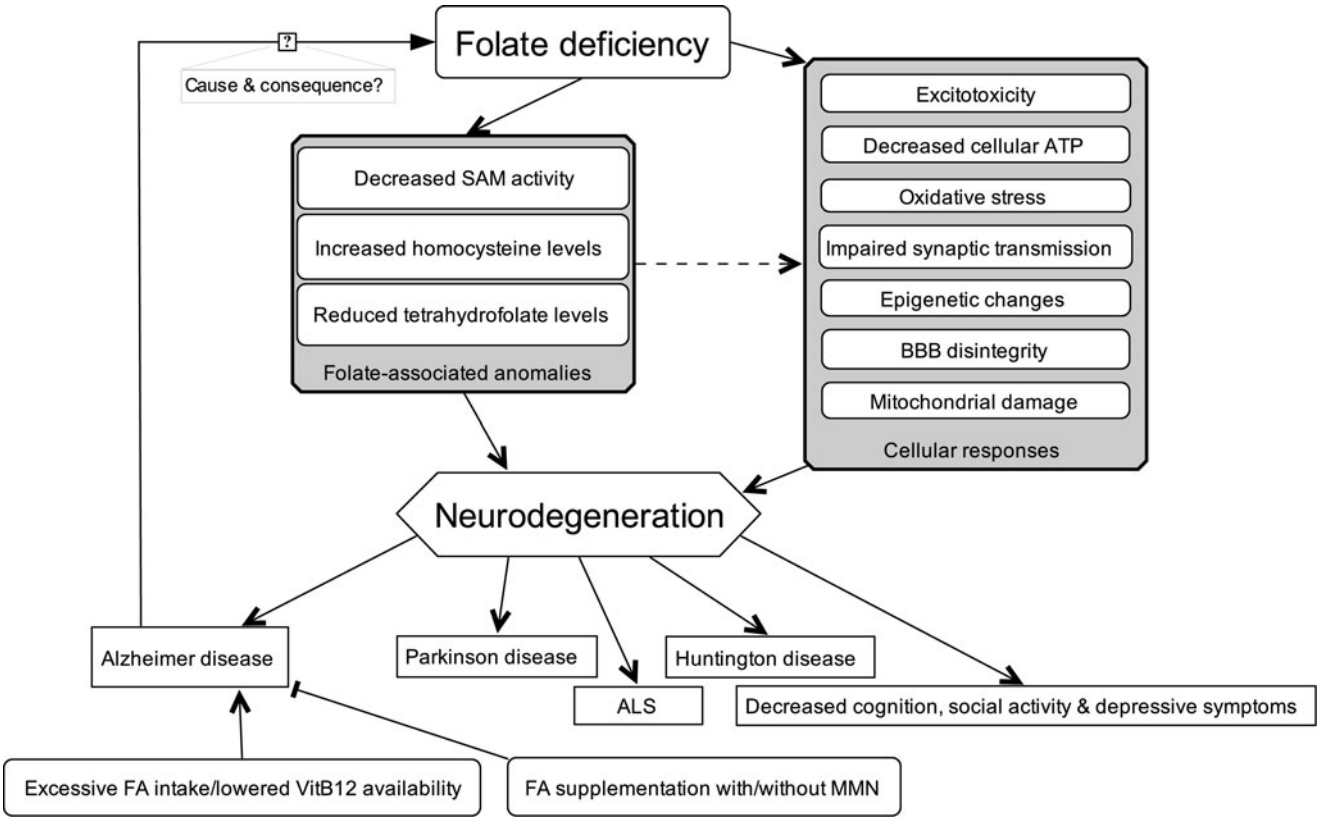

Figure 1. Schematic overview of folate deficiency and its association to ageing-related neurodegenerative diseases and disorders.

concentration in the embryo. Indeed, transport of folates across the placenta and within the embryo is strictly regulated (Kur et al. 2014; Zhao et al. 2011) and folate transport is known to be saturable (Spector and Lorenzo 1975). Nevertheless, a retrospective study revealed that the use of FA supplementation above the upper limit of $\geq$1000 μg/d during pregnancy negatively impacts cognition in children at ages 4-5 years (Valera-Gran et al. 2017). Hence, even though there is no linear correlation between maternal and embryonic folate concentrations, care must still be taken in terms of proper FA dosage. Besides, confounding dietary factors should also be taken into account, as was illustrated for alcohol consumption by a study of Hutson and colleagues. In particular, alcohol consumption during pregnancy was shown to increase maternal plasma folate levels, whilst reducing folates in fetal cord blood (Hutson et al. 2012). Finally, even if increased maternal plasma levels induce elevated embryonic or fetal folate concentrations, it has become evident from mouse studies that a perturbed embryo/fetal folate metabolism can still negate the beneficial role of supplemental folates (Fleming and Copp 1998). Next to uncertainties in folate uptake, the fact that most epidemiological studies were not originally designed to assess cognition, but were rather aimed at treating malnutrition, can be considered a major drawback. As such, these opportunistic cohorts lacked a proper control group (Li et al. 2015; Zeng et al. 2008; Siegel et al. 2011; Tielsch et al. 2006).

In all, the above described factors severely compromise our understanding on the exact role of folates in cognition, and warrant further research using well-designed human cohorts as well as appropriate experimental models.

Implementation of folates in nervous system development and plasticity: experimental evidence

Cognition and cognitive development, encompassing the ability for thinking, reasoning, memorizing, socializing etc., is dependent on a multitude of brain functions and is strictly regulated throughout development. Since folates have been associated with many aspects of brain development and plasticity, this might provide insight into its association with cognition, and shed light on the importance of adequate folate intake.

The role of folates in neuronal proliferation has been studied in both embryonic and adult nervous tissue, using both *in vitro* and *in vivo* approaches. For example, an increased FA bioavailability has been suggested to stimulate cellular proliferation, potentially mediated by an elevated expression of Notch1 and Hes5, in cultured rat neural stem cells (Liu et al. 2010). Likewise, increased folate levels in cultured neurospheres from fetal rat cortices was shown to induce cell proliferation and reduce apoptosis in a dose-dependent manner, possibly via increased ERK1/2 map kinase phosphorylation (Zhang, Huang, et al. 2009). In support hereof, FA depletion in cultured primate embryonic stem cells was shown to reduce cell proliferation and induce anomalous rosette and embryoid body formation, accompanied by a decreased differentiation of embryonic stem cells

into neuronal cells (Chen et al. 2012). *In vivo* studies in mice further suggested that a maternal folate-deprived state during neurogenesis resulted in a decreased cellular proliferation in various regions (e.g., hippocampus and neocortex) of the developing brain (Craciunescu, Johnson, and Zeisel 2010; Craciunescu et al. 2004). However, these data have been debated, since a recent study demonstrated that folate deprivation, starting 6 weeks before mating, does not significantly alter the rate of mitosis in the hippocampus of 3-week old mice (Jadavji et al. 2015). Curiously, mice that were folate deprived during adulthood, for an extended period of 3.5 months, did however show a significantly decreased proliferation of hippocampal progenitor cells (Kruman et al. 2005), being the prime brain region involved in memory and learning. Moreover, a decreased proliferation and apoptosis was unveiled in a folate-deprived hippocampal cell line (Akchiche et al. 2012). These apparent discrepancies might possibly be explained by a difference in onset and duration of folate deprivation, which critically determines the cellular response in discrete regions of the brain. In addition, the age at which cellular proliferation was assessed may also be crucial and should be carefully considered in future studies.

Importantly, the role of folates in brain development is suggested to be multifactorial, covering aspects of cell growth, survival and functionality. Indeed, an *in vitro* study by Akchiche et al. revealed not only a decrease in proliferation and apoptosis in folate-deprived hippocampal cells, but also a decreased hippocampal cell polarity, vesicular transport, neurite outgrowth and synaptic plasticity (Akchiche et al. 2012). In addition, increased expression of several histone deacetylases was observed, suggesting epigenetic effects (Akchiche et al. 2012). In agreement herewith, FA was also shown to increase neural connectivity in cultured chick dorsal root ganglia. More specifically, low folate was linked to a dose-dependent reduction in neurite length, whilst also hindering pathfinding of the growth cones, thus suggesting a possibly hindered synapse formation (Wiens et al. 2016). Furthermore, a study on Wistar rats suggested that a folate and choline deficient diet, starting one month before mating, reduced cerebellar synapsin expression in the progeny at 21 days after birth, presumably mediated by an impairment of the ER-alpha pathway (Pourie et al. 2015). The implication of folates in various pathways that regulate neuronal function has been further strengthened in a study by Budni and Lobato, who have found the inhibition of glycogen synthase kinase-3β (GSK-3β) and activation of PPAR gamma to be crucial in the antidepressant-like role of FA in the forced swim test (Budni et al. 2012). In contrast to maternal FA supplementation, extremely little is known about the role of methyl donors in the paternal diet on offspring cognition. Interestingly, paternal FA supplementation in mice prior to mating appears to result in F1 offspring with deficits in hippocampus-dependent learning and memory, impaired hippocampal synaptic plasticity and reduced hippocampal theta oscillations. These observations may be linked to downregulated Mat2a and Kcnmb2, following abnormal promotor methylations in methyl donor rich F1 mice (Ryan et al. 2018).

As such, it is becoming more clear that folates are not only limited to influencing proliferation, but various other crucial neuro-functional aspects as well, that might ultimately impact on cognition.

Involvement of folates in brain functioning at the genetic, epigenetic and enzymatic level

Although knowledge about the working mechanism of folates is limited, especially in terms of folate-dependent functioning of the postnatal brain, it appears linked to a variety of mechanisms, ranging from genetic and epigenetic to enzymatic functions.

First, some insights were provided from folate-deprivation studies, investigations of genetic polymorphisms and the interactions thereof. Methotrexate (MTX) is commonly used as chemotherapy for e.g., acute lymphoblastic leukemia (ALL), and functions as an inhibitor of dihydrofolate reductase, in turn limiting folate metabolism within the organism. Children treated with MTX have been observed to demonstrate MTX-related clinical neurotoxicity, although these detrimental effects appear only transient (Bhojwani et al. 2014). Continuing, adverse consequences of folate deprivation might be coupled to genetic background. For example, several polymorphisms of genes involved in folate metabolism can modulate cognitive function in childhood survivors of ALL MTX chemotherapy. More specifically, it has been suggested that polymorphisms such as 10-methylenetetrahydrofolate reductase (MTHFR) 1298A > C and methionine synthase 2756A > G might exacerbate the low-folate status in children treated with MTX and reinforce cognitive decline, such as attention deficits (Kamdar et al. 2011). In support of this, elderly (age 55–90) with the MTHFR 1793 G/A genotype also appear more prone to cognitive decline when exposed to a folate-limited diet (Cai et al. 2016). In contrast, other folate gene polymorphisms appear to be related to increased IQ. More specifically, underrepresentation of the cystathionine beta-synthase 844ins68 allele, which contributes to transsulfuration of homocysteine to cystathionine, was linked to elevated IQ in children (Barbaux, Plomin, and Whitehead 2000).

Folate-induced epigenetic changes that impact cognition may be apparent both at the histone and the DNA level. Epigenetic effects were observed in an ND7 cell line, derived from dorsal root ganglion cells, and treated with FA. Here, modulation of posttranslational histone modification genes such as H3K9, H3K18, and H3K19 acetylation and H3K27 methylation were observed following the addition of FA, which were linked to an increased proliferation and decreased differentiation to sensory neurons (Boshnjaku et al. 2011). Yet another study suggested that FA supplementation during mouse gestation substantially altered DNA methylation patterns in various genes in the cerebral hemispheres of postnatal offspring (P1). A link with cognition was however not experimentally assessed (Barua et al. 2014).

Other mechanisms, less covered in literature, discuss in more detail the role of individual enzymes and mitochondrial function in the folate metabolic pathway and provide a link with cognition and behavior in rodents. For example, the SHMT1 enzyme catalyzes the conversion of serine and tetrahydrofolate to glycine and 5,10-methylene tetrahydrofolate. Previously, expression of SHMT1 was observed in the mouse hippocampus, including the granule cell layer of the dentate gyrus, and SHMT1 deficiency was linked to abnormal neurogenesis and fear responses in mice (Abarinov et al. 2013). A recent review by Du J. and colleagues discussed the role of folate in mitochondrial dysfunction (Du et al. 2016). For example, folate-deprivation is commonly associated with increased homocysteine, which is toxic to mitochondrial function, which has in turn been linked to depression. Indeed, this decreased folate state was in turn linked to abnormal metabolism of serotonergic and other amines within the mitochondria, an observation previously associated with mood disorders (Du et al. 2016).

Altogether, even though initial insight has been gathered, the mechanisms underlying and modifying the role of folates in the young and adult brain are varied and remain elusive, warranting a more in-depth investigation of the cellular response to augmented/decreased folate availability or FA intake and the implications for cognitive functions.

Folates, ageing and age-related diseases

Although underlying mechanisms are poorly understood, folates are believed to be important players in many ageing processes and are linked to several ageing-related and neurodegenerative diseases (see Fig. 1 for a schematic overview of the hereunder described paragraphs).

Folates in ageing and dementia: epidemiological evidence and mode of action

The first epidemiological studies on folates and the risk of ageing and mental decline date back to the 1980's. In a cohort of 34 megaloblastic anemia patients, showing folate deficiency and harboring abnormally large and few numbers of red blood cells, two-third of the patients displayed neuropsychiatric abnormalities and one-third showed mental changes (Shorvon et al. 1980). A first correlation between folate status and cognition in healthy elderly (aged $\geq$60 years) was found in 1983, where subjects with low folate levels showed a decrease in cognition, and more specifically in abstract thinking ability (Goodwin, Goodwin, and Garry 1983). In the following years, many more epidemiological studies have been conducted, among which a meta-analysis of seniors aged >65 years, showing an association between low serum folate levels and cognitive impairment, however only in male individuals (Michelakos et al. 2013). Although very informative, epidemiological studies that focus on the elderly are often inconsistent and difficult to interpret when studying countries with high FA fortification, including the US and Canada (Agnew-Blais et al. 2015; Corrada et al. 2005; Luchsinger et al. 2007; Nelson et al. 2009; Morris et al. 2006). This inconclusiveness also applies for interventional studies that have been conducted in these countries (Clarke et al. 2014), being in contrast to two European clinical trials that showed a beneficial role for FA treatment on cognitive function and prevention of brain atrophy in the elderly (Durga et al. 2007; Douaud et al. 2013). Recently, in a French population-based cohort of people aged 65 years or older, with a relatively low baseline folate status, a correlation between higher folate intake and decreased risk of dementia was also found (Lefevre-Arbogast et al. 2016). Of note, in one of the clinical trials conducted in the UK, elderly subjects with increased risk for dementia and Alzheimer's disease (AD) were treated with a B-vitamin supplement that contained not only FA but also vitamin B6 and B12, and showed a striking 7-fold reduction in brain atrophy (Douaud et al. 2013). Furthermore, in a Korean cohort consisting of subjects with mild cognitive impairment, dietary intake of B vitamins resulted in cognitive improvement, and a positive correlation was found for all vitamins (B2, B6, B12 and folate) (Kim, Kim et al. 2014). Thus, the use of folates to treat ageing-associated cognitive decline seems promising but is likely to be enhanced in presence of other B-vitamins, which together hold great promise for future treatment of elderly patients.

Folate depletion results in an increased homocysteine cytotoxicity, which in turn has been conferred to have a role in ageing, neuronal plasticity and neurodegenerative diseases such as AD, Parkinson's disease (PD) and Huntington's disease (HD) (see also section 2.2 and reviewed in (Obeid and Herrmann 2006)). In healthy individuals, plasma folate levels decrease and homocysteine levels increase with age (Andersson et al. 1992; Brattstrom et al. 1994; Magnus et al. 2009), with a steep increase in plasma homocysteine concentration between the age of 40 and 90 years (Mattson 2003). This goes side by side with a decreased appetite and intestinal malabsorption in the elderly with a concurrent decline in uptake of essential nutrients such as folates and other B vitamins (Selhub et al. 2000; de Benoist 2008). The cytotoxic impact of homocysteine is further exemplified in transgenic mice displaying hyperhomocysteinemia (cystathionine-beta-synthase heterozygotes, methionine fed), in which homocysteine-induced oxidative stress and epigenetic changes affected blood-brain barrier integrity, eventually leading to neuronal toxicity and neurodegeneration (Kalani et al. 2014). Of interest, a protective role for dietary FA supplementation was proven in this study, through a reduction in these pathogenic events and epigenetic alterations (Kalani et al. 2014). Apart from disturbing blood-brain integrity, homocysteine also exerts its detrimental role via promotion of excitotoxicity through NMDA receptor stimulation (Kruman et al. 2000), which has been associated with several neurodegenerative disorders (Lipton et al. 1997). In line herewith, FA addition has been shown to reverse glutamate-induced excitotoxicity in hippocampal slices, which might involve modulation of PI3K/GSK-3β-catenin pathway and inhibition of inducible nitric oxide synthase (iNOS) (Budni et al. 2018). In addition, smaller brain volumes and silent brain infarcts have been associated with higher plasma

homocysteine levels, even in healthy individuals, which could induce dementia and stroke (Seshadri et al. 2008). Another role for homocysteine in the mediation of neurodegenerative events has been ascribed to a depletion of cellular ATP, needed for DNA repair, which has been implicated in the development of AD, PD and HD (Mattson and Shea 2003; Mattson et al. 1999; Grunewald and Beal 1999). This depletion in ATP might be directly related to mtDNA damage and mutagenesis resulting from a lack of folates in the ageing brain, with a consequent brain dysfunction and neuronal loss (Kronenberg et al. 2011). Reduced folate levels may also interfere with brain ageing and functioning through a decreased SAM activity, suggested to impact synaptic transmission and epigenetic regulation in the aging brain (Selhub, Troen, and Rosenberg 2010). Furthermore, 5-MTHF, the active form of folate, has been directly implicated in DNA repair and DNA replication, being indispensable for a proper adult neurogenesis in the hippocampal dentate gyrus and thus for correct learning and memory (Araujo et al. 2015; Morris 2012). Finally, at the molecular level, a change in expression of nerve growth factor (NGF) was found in the frontal cortex, the amygdala and the hippocampus of mice subjected to a FA-deficient diet, which they correlated to stress response, increased anxiety and hippocampal-dependent memory decline and neurodegeneration (Eckart et al. 2013).

Folates in Alzheimer's and Parkinson's disease

Alzheimer's disease

AD is characterized by β-amyloid (Aβ) plaque depositions and hyperphosphorylation of tau protein, which results in senile plaques and neurofibrillary tangles with a concurrent cognitive decline, memory loss and neurodegeneration. Strikingly, AD patients displayed lower serum and cerebrospinal folate levels as compared to healthy controls (Clarke et al. 1998; Chen et al. 2015; Snowdon et al. 2000; Hinterberger and Fischer 2013; Serot et al. 2001; de Wilde et al. 2017). In line herewith, a change in folate status, either from a (inherited) defective folate metabolism or altered intake, may result in an increased risk for neurodegenerative disorders such as AD. One example of an inherited heightened risk to develop AD is in case of a MTHFR C677T polymorphism, as demonstrated in a recent meta-analysis including 41 studies (Rai 2017). Furthermore, in a study of non-demented healthy elderly with a mean age of 75 years, low folate status and/or hyperhomocysteinemia was correlated with an increased AD risk within a 2.5 year- (Fischer et al. 2008), 3 year- (Wang et al. 2001), and 4-year (Ravaglia et al. 2005) longitudinal follow-up. In terms of homocysteine levels and its association to folates and AD, there are however still some uncertainties and conflicting results that should be addressed. For instance, in a longitudinal study of non-demented elderly, no association was found between homocysteine levels and AD pathology (Luchsinger et al. 2004), which is in contrast to another study that reported AD development to be dependent on high homocysteine levels, while being independent of circulating folate levels (Haan et al. 2007; Hooshmand et al. 2010). It should however be noted that the studies by Haan et al. and by Hooshmand et al. did not include subjects with low folate levels, which might partly explain the discrepancies and which stress the importance of adequate serum folate levels, either with or without the direct influence of homocysteine levels. To add to this complexity, a recent study found a decrease in folates and hyperhomocysteinemia to be primarily associated with subcortical vascular dementia (sVAD) and to a lesser extent to AD (Moretti et al. 2017). Clinical features of sVAD are in part caused by a disruption of cortical and subcortical circuits, and are represented by intellectual decline and severe cognitive disabilities (Capizzano et al. 2000). Still, based on their calculations, the risk to develop AD decreased by 9% with increasing folate levels (Moretti et al. 2017).

In recent years, an association between folates, its derivatives and amyloid toxicity has been clearly demonstrated. For instance, an epidemiological study on healthy young individuals showed a correlation between higher neurotoxic Aβ1-42 aggregate levels, high homocysteine levels and low 5-MTHF levels (Oikonomidi et al. 2016). This hyperhomocysteinemia, associated with a lack of folate and its active form 5-MTHF, is believed to be involved in an enhanced expression of γ-secretase which is an important player in the formation of amyloid plaques (Zhang, Wei et al. 2009). Furthermore, hyperhomocysteinemia has been described to induce a hypomethylation of PPM1 via upregulation of PS1 genes (Leulliot et al. 2004), with a concurrent increase in Aβ1-42 production as well as hyperphosphorylation of tau protein, being another crucial hallmark of AD pathology (Fuso et al. 2008, Oikonomidi et al. 2016). A folate-dependent amyloid toxicity was further corroborated *in vitro*, where incubation of mouse hippocampal neurons in FA-deficient medium was shown to induce Aβ toxicity, possibly resulting from an impaired one-carbon metabolism and hippocampal DNA repair (Kruman et al. 2002). The involvement of one-carbon metabolism in AD pathology was also put forward in other studies, where it was suggested to be involved in the upregulation of PSEN1 (presenilin 1) and BACE (beta-site amyloid precursor protein (APP) cleaving enzyme 1), shown both *in vitro* and *in vivo* using animal models (Fuso, Nicolia, Pasqualato et al. 2011, Fuso et al. 2005). In addition, in APP mutant mice, an increased cellular damage and hippocampal neurodegeneration could be confirmed when put on a FA-deficient diet (Kruman et al. 2002). Furthermore, phosphorylation of tau was evidenced in patients with neurological disorders (Obeid et al. 2007) and in Wistar rats fed a homocysteine-rich diet and showing increased plasma folate levels, and was generally ascribed to a disturbed methylation process (Obeid et al. 2011; Nicolia et al. 2010). In fact, DNA methylase and demethylase activities are modulated by one-carbon metabolism and thus sensitive to folate deficiency (Fuso, Nicolia, Cavallaro et al. 2011). In accordance, in mouse neuro-2a cells expressing human APP695 and in AD transgenic mouse brains, a role for folates in increasing methylation of the JAK-STAT signaling pathway was established, which may decrease the cellular

stress response and induce long-term depression (LTD) which is impaired in AD (Li et al. 2016).

A link between folate levels and Aβ pathology has also been attributed to changes in vitamin B12 absorption and a subsequent change in inflammatory cytokines and Aβ senile plaques (Das 2008, Chen et al. 2016). Indeed, concomitant with the well-established role of inflammatory cytokines in AD development (Wang et al. 2015), researchers found a causal relationship between a high FA diet and a lowered natural killer cytotoxicity in aged C57Bl6 mice, having an impact on the innate immune response (Sawaengsri, Wang et al. 2016) and possibly on the development of age-related disorders such as AD. Thus, not only low but also high folate levels can have a negative impact on ageing and AD development. Mechanisms are starting to be discovered, and a polymorphism of the vitamin B12 transport protein (TCN2), responsible for a lowered bio-availability of vitamin B12, was associated with excessive FA intake in elderly (Sawaengsri, Bergethon et al. 2016). In other words, caution must be taken in consuming the right amount of FA-fortified food and supplements, and a thorough analysis of long-term adverse effects, which is often neglected, will be imperative in the elderly people at risk for neurodegenerative diseases. Besides, while folate depletion has been recognized as a cause for AD, the question remains whether folate deprivation might also be a consequence of AD (Farkas et al. 2013; Clarke et al. 1998). Another subject of debate is whether a lack of folates and a concurrent hyperhomocysteinemia merely potentiates neurodegeneration or also modulates the microvasculature. Hereto, in case of sVAD, a hyperhomocysteinemia-dependent caspase-3 activation is thought to promote Aβ accumulation in smooth muscle cells, leading to a dysregulation of cerebral blood flow, sVAD symptoms and an exacerbation of AD pathology (Chung et al. 2016; Moretti et al. 2017). A cardioprotective effect of folates was further corroborated in a triple-transgenic (3xTg) Alzheimer mouse model, proposing a role in alleviating heart injury caused by AD (Lin et al. 2018). In line herewith, the protective effect of Fortasyn, which is a nutrient combination including vitamins such as FA, on AD onset and development in aging apoE4 mice is suggested to be related to the improvement of cerebrovascular health and as such of functional connectivity (Wiesmann et al. 2016).

In all, the implication of folates in AD pathology is a topic of growing interest, with a clear role for folates in amyloid pathology. Confounding factors such as homocysteine toxicity and the importance of immune system modulation through other related vitamins should however be further investigated in future studies.

Parkinson's disease

Although less studied when compared to AD, other neurodegenerative disorders were also associated with a change in folate status. One such example is Parkinson's disease (PD), defined by dopaminergic neuron loss in the substantia nigra and affecting the motor system, cognition and in some cases leading to anxiety and depression. In this case, most associations were however based on homocysteine levels, which are thought to be negatively correlated to available folate levels. For instance, a link between increased plasma homocysteine levels and human PD pathology has been uncovered (Isobe et al. 2005; O'Suilleabhain et al. 2004), while an increased risk to develop PD has been found in individuals with a MTHFR C677T genotype that display elevated homocysteine levels (Yasui et al. 2000). Increased homocysteine levels have indeed been shown to be toxic for dopaminergic neurons in the substantia nigra (Duan et al. 2002; Imamura et al. 2007), and localized homocysteine injection in the substantia nigra of rats has been documented to cause parkinsonian behavioral phenotypes and loss of dopaminergic neurons, with oxidative stress and mitochondrial dysfunction as putative mechanisms to induce this neurotoxicity (Bhattacharjee and Borah 2016). Meanwhile, PD patients treated with L-dopa, which is considered as the golden standard to treat the disease, have been found to be exposed to increasing levels of neurotoxic homocysteine, which is correlated to motor fluctuations and so-called L-dopa dyskinesia in these individuals (Carta et al. 2006; Ceravolo et al. 2013). Hence, there is a clear need for reduction of homocysteine levels in PD treated patients, possibly through FA supplementation. Surprisingly, a human meta-analysis showed no difference in folate levels in PD patients *vs* healthy individuals, nor a lowered PD risk after dietary FA intake (Shen 2015). On the other hand, in animal models for PD, a neuroprotective role for folates has been put forward. This was exemplified in mice systemically injected with MPTP (1-methyl-4-phenyl-1.2.3.6-tetrahydropyridine) to induce PD pathology, in which dopaminergic neurons in the substantia nigra were found to be more prone to degeneration after administration of a FA deficient diet (Duan et al. 2002). Besides, a mouse model with experimentally induced PD (striatal 6-OHDA injection) showed an attenuation of PD pathology when subjected to a high folate intake, whereas homocysteine levels were increased in these mice, thereby indicating that the folate-mediated anti-PD effect was independent of homocysteine in this study (Haghdoost-Yazdi et al. 2012). In addition, in a fly model transgenetically modified to develop a PD phenotype (*parkin* (Srivastav et al. 2015) and *pink1* (Lehmann et al. 2017) mutants), a beneficial role for folinic acid to prevent dopaminergic degeneration (Lehmann et al. 2017) and for FA in ameliorating mitochondrial dysfunction, oxidative stress, low metabolic activity and locomotor defects (Srivastav et al. 2015) was demonstrated.

As already shortly discussed for AD, folate deficiency and a concurrent increase in homocysteine might indirectly affect PD via damage to cerebral blood vessels and induction of cardiovascular diseases (Verhaar, Stroes, and Rabelink 2002; Firoz et al. 2015). Besides, hyperhomocysteinemia has been associated with endothelial dysfunction of the carotid artery (Faraci and Lentz 2004), which is predictive for stroke but also marks the progression of AD and PD (Silvestrini et al. 2011; Kim, Oh et al. 2014).

Overall, as for AD, studies have elucidated the importance of folates in PD pathology. Yet, this view and possible intervention for the elderly population is still severely challenged by the lack of consistent human and animal

data, and the apparent complex role of homocysteine in PD etiology.

Amyotrophic lateral sclerosis

Already in 1984, a possible involvement of the folate cycle in the pathogenesis of amyotrophic lateral sclerosis (ALS) has been put forward (Yoshino 1984). Since then, studies have attempted to further unravel this hypothesis, however with little overall progress and conflicting results. ALS is an adult-onset fatal disease characterized by a selective degeneration of upper and lower motor neurons, atrophy of skeletal muscles and paralysis (Rowland and Shneider 2001). Elevated levels of homocysteine have been suggested to play a key role in the disease (Zhang et al. 2008), and its cytotoxicity might be ascribed to the involvement in several of the pathways that underlie motor degeneration: An increased inflammation via conversion of resting to activated microglia (Zou et al. 2010), ROS production and oxidative stress (Sung et al. 2002; Sibrian-Vazquez et al. 2010), excitotoxic over-activation of NMDA receptors (Lipton et al. 1997; Foran and Trotti 2009) and endothelial dysfunction (Garbuzova-Davis et al. 2010; Lai and Kan 2015). Conjointly with increased homocysteine concentrations, lowered levels of FA and its metabolically active form 5-MTHF were found in the plasma, spinal cord and cortex at the middle/late and early disease stages, respectively, in an ALS superoxide dismutase 1 ($SOD1^{G93A}$ transgenic mouse strain, suggesting 5-MTHF to be a potential biomarker for early detection of ALS (Zhang et al. 2010). The potential of B-vitamins, including FA, to reduce homocysteine levels and to ameliorate ALS progression, was assessed by Zhang et al. in $SOD1^{G93A}$ ALS mice (Zhang et al. 2008). As anticipated, oral administration of FA or FA + vitamin B12 both resulted in a marked reduction in homocysteine levels and extension of disease onset. On top, the activation of microglia and astrocytes was shown to be inhibited, the amount of oxidative stress was reduced and pro-apoptotic genes such as cleaved caspase-3 were downregulated (Zhang et al. 2008). This thus indicates the therapeutic potential for B-vitamin supplementation, although the sole administration of vitamin B12 did not seem to affect ALS pathogenesis in this mouse model. Contrarily, in a hybrid cell culture of motor neurons and neuroblastoma cells, 5-MTHF administration was not able to reduce homocysteine-induced neuronal cell death, whereas a neuroprotective role was shown for vitamin B12.

Collectively, vitamin supplementation seems to be an exciting avenue to further explore in the treatment of ALS, although the intricate role of the different vitamins and supplemental forms herein needs to be explored and better defined.

FA as a potential nutraceutical in neurodegenerative diseases

As pointed out throughout this review, reduced folate levels are correlated to an increased risk of dementia, cognitive decline and ageing-related diseases such as AD or PD. Increased FA intake is expected to reduce the risk of sporadic, and possibly also of familial AD cases. Keeping in mind that the risk for developing AD markedly increases when homocysteine levels rise above 10 µM, dietary supplementation with 400 µg of FA can decrease homocysteine levels by 2–5 µM in most individuals (Mattson 2003). Hence, FA food supplementation and nutritional intervention holds great promise to counteract the risk of AD (Moore et al. 2018), although only in an early stage of the disease. Unfortunately, administering food supplements is not straightforward in individuals without obvious disease symptoms. Another reason for concern when administering FA is the potential deleterious effects of excessive intake in individuals with high basal levels. Furthermore, we have to keep in mind the link of FA with other vitamins. For instance, FA administration could mask vitamin B12 deficiency (Reynolds 2006), which is in fact a primary reason why FA fortification is still not mandatory in many countries. Still, it might be opted to supplement FA to specific groups of people with folate deficiency and high levels of homocysteine, with a proper evaluation of bioavailability of other vitamins such as vitamin B12, which could act synergistically (Paul and Selhub 2017; Araujo et al. 2015).

Translation of these findings in a clinical setting, i.e., assessing the efficacy of FA supplementation to reduce cognitive decline and neurodegenerative disease symptoms in patients, remains however controversial. For example, no positive effect of FA treatment was found on cognitive function in elderly patients with/without dementia, although in healthy elderly, long-term FA supplementation favored cognitive functions (Malouf and Grimley Evans 2008). Furthermore, a recent meta-analysis by Zhang et al. could not demonstrate improvement in cognition in AD/dementia patients supplemented with B vitamins including folates (Zhang et al. 2017). Contrarily, in favor for a positive correlation, clinical trials using the nutraceutical compound Souvenaid® (combination of vitamins and minerals containing folate, Nutricia N.V., the Netherlands) could show an increased synaptic plasticity and significant improvement of memory performance in dementia/AD/frontotemporal dementia patients (Pardini et al. 2015; Scheltens et al. 2012), with a favorable safety profile and clinically detectable effects in patients with early AD (Cummings et al. 2017). On top, another clinical trial showed an improvement in cognition after folate supplementation in elderly patients with mild to moderate dementia (Nilsson, Gustafson, and Hultberg 2001).

In any case, more research and (pre)clinical trials are needed to unveil the potential of folates in ameliorating childhood and ageing-related cognitive disorders, either solely administered or through a mix of different minerals and vitamins. This concern was also addressed in a recent review, pointing out the lack of clinical significance, insufficient follow-up and undesirably high variation in cognitive measurements in adults at risk for cognitive decline which were given so-called 'over-the-counter' supplements containing FA (Butler et al. 2018). Furthermore, a closer look at neurodegenerative diseases such as PD, HD and ALS is

warranted, and the difference in susceptibility between men and women – especially during menopause - should not be ignored (Hanamsagar and Bilbo 2016; Mazure and Swendsen 2016; Duarte et al. 2018). This would help the disease outcome but might also aid in a better understanding of the working mechanisms of folates.

General conclusions and future directions

In this review, we took a closer look at existing literature on the role of folates in cognition and its putative involvement in neurodegenerative diseases such as AD, PD, and ALS. Although many studies show a positive correlation between folate concentrations/FA intake and cognition, a strong and direct link between folate status and neurodegenerative diseases remains to be proven. One of the reasons for this uncertainty is the question whether folate deficiency is cause or rather a consequence of neurodegenerative events, and to what extent other vitamins can interfere with the folate cycle and its downstream physiological effects. Before being able to draw a solid conclusion, there is a need for more (pre)-clinical studies, using well-designed epidemiological cohorts and experimental models, with a better consideration of all types of neurodegenerative disorders. This can in turn lead the way for better nutritional guidelines and the potential applicability of folate as a nutraceutical, especially in our elderly population at risk for ageing-related disorders.

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