


## REVIEW ARTICLE

# Functional MRI technologies in the study of medication treatment effect on Alzheimer's disease

Hui Guo<sup>1,2,3</sup> | Lukas Grajauskas<sup>1,2</sup> | Baraa Habash<sup>1,4</sup> | Ryan CN D'Arcy<sup>1,2,4,5</sup> | Xiaowei Song<sup>1,2,4,5</sup> 

<sup>1</sup>SFU ImageTech Laboratory, Surrey Memorial Hospital, Surrey, BC, Canada

<sup>2</sup>Health Sciences and Innovation, Surrey Memorial Hospital, Fraser Health, Surrey, BC, Canada

<sup>3</sup>Department of Diagnostic Imaging, Tianjin Medical University General Hospital, Tianjin, China

<sup>4</sup>Department of Engineering Science, Simon Fraser University, Burnaby, BC, Canada

<sup>5</sup>Department of Computing Science, Simon Fraser University, Burnaby, BC, Canada

## Correspondence

Xiaowei Song, SFU ImageTech Laboratory, Surrey Memorial Hospital, Surrey, BC, Canada.

Email: xiaowei.song@fraserhealth.ca

## Funding information

Canadian Institutes of Health Research, Grant/Award Number: CSE-125739; China's Scholarship Council; Canada's National Science and Engineering Research Council; Surrey Hospital and Outpatient Centre Foundation, Grant/Award Number: FHREB2015-030

## Abstract

Alzheimer's disease (AD) is the most common cause of late-life dementia. Characterized by progressive neurodegeneration, the disease is expressed as gradual memory loss together with decline in cognitive abilities and other brain functions. Despite extensive research over the past decade, the cause and cure of AD both remain largely unknown. Several AD-associated deficits have been targeted for interventions, including those based on amyloid-beta, tau, and inflammation hypotheses. Only 2 types of medications—cholinesterase inhibitors and memantine—have been approved, to control the cognitive symptoms of AD such as the loss of memory, language, and executive function. Noninvasive in vivo functional magnetic resonance imaging (MRI) technologies, including the blood oxygen level-dependent functional MRI, arterial spin labeling-based perfusion MRI, and the proton magnetic resonance spectroscopy have been used to study the effect of ChEIs and memantine in the brain. Most of these studies have demonstrated increased functional activation and connectivity, increased regional brain blood flow and volume post-treatment, and positive responses of critical brain metabolites reflecting neuronal status and functionality in patients with AD and mild cognitive impairment. The findings have contributed to the understanding of the mechanisms underlying the medication treatments and support the crucial role of functional MRI technologies in the development and refinement of AD medication therapies.

## KEYWORDS

Alzheimer's disease, brain function, dementia, magnetic resonance imaging, medication treatment

## 1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of late-life dementia, characterized by an insidious onset and progressive deterioration of memory and other brain functions.<sup>1-3</sup> Alongside the impact to the individual, AD has greatly challenged global socioeconomic systems due to its high prevalence and costs.<sup>4-7</sup> Pathogenesis

of AD is complex and heterogeneously presented in individuals,<sup>8</sup> for example, extracellular deposition of amyloid- $\beta$  peptide and neuritic plaques, intracellular accumulation of hyperphosphorylated Tau protein as neurofibrillary tangles, and reactive microgliosis and widespread damages of the neurons, synapses, and white matter integrity.<sup>9,10</sup> Mechanisms underlying AD neuropathological changes can involve both combined environmental and genetic effects.<sup>11</sup>

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2018 The Authors. *Aging Medicine* published by Beijing Hospital and John Wiley & Sons Australia, Ltd.

Over the last 3 decades,  $\beta$ -amyloid has been the centre of a great deal of clinical trials for new drug development, but to date, none have proven successful.<sup>8,12</sup> Drug development has also targeted the Tau pathology with unproven effect.<sup>12,13</sup> Approaches that have proven successful for the treatment of the symptoms of AD and amnesic mild cognitive impairment (MCI) have targeted the cholinergic system to slow down regression.<sup>14</sup> The US Food and Drug Administration (FDA) approved medications include 3 cholinesterase inhibitors (ChEIs: donepezil, galantamine, and rivastigmine), memantine (that targets the glutamatergic system), and a combined treatment of ChEI and memantine.<sup>15-17</sup>

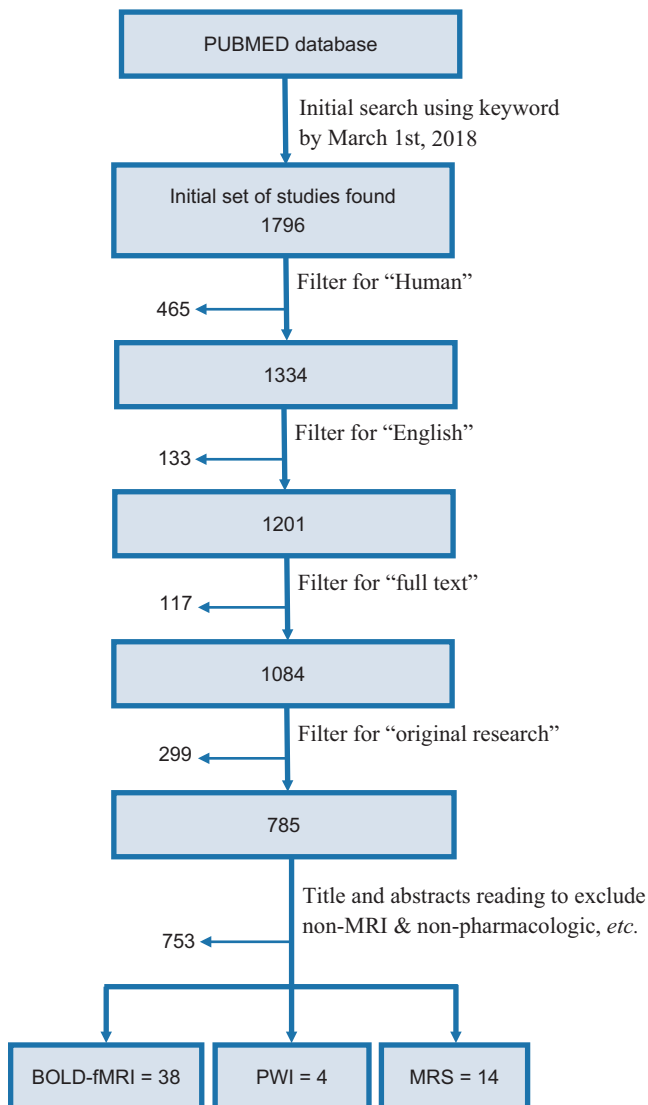
Based on the cholinergic hypothesis, AD is associated with reduced synthesis of the neurotransmitter acetylcholine (a neurotransmitter involved in memory, attention, arousal, and motivation) in the basal forebrain.<sup>14</sup> During synaptic transmission, acetylcholine is released into the synaptic cleft to activate receptors on the post-synaptic neurons. After transmission, acetylcholinesterase breaks

down acetylcholine, so it can be reused by the presynaptic neuron. AD damages the cholinergic neurons, thereby reducing the amount of acetylcholine in the system. A ChEI slows down the loss of acetylcholine by blocking the activity of acetylcholinesterase, helping compensate for the damage of brain cells.<sup>18</sup> The other type of current AD medication, memantine, acts as a NMDA (*N*-methyl-D-aspartate) receptor antagonist on the glutamatergic system, blocking NMDA glutamate receptors to prevent overstimulation from excessive glutamate synthesis. While ChEIs are typically used in treating early AD and MCI symptoms, memantine is used to treat moderate-to-severe symptoms of AD.<sup>19,20</sup>

Advances of functional magnetic resonance imaging (MRI) technologies have been used to understand medication effect on AD treatment. Blood oxygen level-dependent functional MRI (BOLD-fMRI) maps hemodynamic responses to neural activity,<sup>21,22</sup> based on the paramagnetic differences between oxygenated and deoxygenated hemoglobin, which allows the detection of activated brain areas as their oxygen demand increases.<sup>21,22</sup> BOLD-fMRI can be divided into 2 categories: task phase and resting phase. The former uses relative changes of BOLD signal intensity from baseline when performing a task or handling a stimulus, to infer brain areas that are activated.<sup>23</sup> The latter measures spontaneous low-frequency fluctuations in the BOLD signal without an explicit task to investigate the status of brain functional connection.<sup>24</sup> Resting-phase fMRI can be particularly useful in patients who are not able to do fMRI tasks because they are limited by their disease condition, for example, AD.<sup>25</sup>

Perfusion-weighted imaging (PWI) represents another important functional MRI modality. PWI is used for noninvasively assessing cerebral hemodynamics (cerebral blood flow [CBF] and volume),<sup>26</sup> which traditionally has relied on technologies that require use of a tracer that releases ionizing radiation. CBF is the volume of blood flowing through a mass of brain tissue over a certain period of time (reported as mL/100 g/min).<sup>26,27</sup> PWI can be divided into dynamic perfusion imaging, which requires exogenous contrast tracers (eg, dynamic contrast enhancement imaging or dynamic susceptibility contrast), and arterial spin labeling which does not require exogenous contrast tracers,<sup>28</sup> in which radio frequency pulses are optimized to label inflowing blood water, allowing the measurement of arterial blood flow.<sup>29</sup> The latter technique is completely noninvasive and can be used to map brain activity, making it the preferable PWI method.

The *in vivo* proton magnetic resonance spectroscopic (MRS) had also gained some popularity in AD research.<sup>30</sup> Based on the magnetic resonance properties of the hydrogen proton, MRS can be used to quantify levels of neurometabolites in the living brain.<sup>23,31,32</sup> When excited in the magnetic field, each hydrogen nucleus inside a metabolite goes through a tiny shift in resonant frequency (ie, chemical shift), expressed in parts per million (ppm). Depending on factors in the chemical environment (eg, atom negativity, electron density, magnetic field strength), an MRS signal is generated. MRS acquisition can either be in localized brain regions (ie, single-voxel MRS) or as chemical shift imaging (MRSI). The most commonly studied brain metabolites are *N*-acetyl aspartate (NAA), creatine (Cr), choline (Cho),



**FIGURE 1** Flowchart showing the literature search process

**TABLE 1** Studies that used blood level-dependent functional magnetic resonance imaging (fMRI) with FDA-approved medications

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	fMRI experiment	Main fMRI findings on treatment effect
Rombouts SA	2002	Mild AD = 7	Rivastigmine	3 mg	Single dose	2 Scans: 3 h post-treatment and after 7-d drug-free period	1.5T, EPI, block design, visual face-encoding and n-back working memory tasks	(1) Increased activation in bilateral fusiform gyrus in face-encoding task; (2) enhanced activation in the left middle and superior frontal gyri in working memory task; (3) increased activation in left middle frontal gyrus, right superior and inferior frontal gyri, decreased activation in the right middle and superior frontal gyri with increased working memory load
Goekoop R	2004	MCI = 28	Galantamine	8 mg single dose, 4 mg bid 120 h	120 h over 6 weekdays	3 Scans: baseline, after single dose, end of treatment	1.5T, EPI, block design, visual face-encoding and n-back working memory tasks	(1) Increased activation during both tasks with prolonged treatment; (2) in anterior cingulate gyrus, left prefrontal areas, occipital areas, and posterior hippocampus with face encoding; (3) in right precuneus and right middle frontal gyrus with working memory task
Saykin AJ	2004	MCI = 9 HC = 9	Donepezil on MCI	5 mg/d for 4 wk, 10 mg/d after initial 4 wk	~12 wk	2 Scans: baseline and at end of treatment	1.5T, sequence unknown, block design, auditory n-back working memory task	(1) Increased frontal activity after treatment relative to controls; (2) level of fMRI activation increase was correlated with hippocampal volume
Kircher TT	2005	AD = 10 HC = 10	Donepezil on AD	5 mg/d for 4 wk, 10 mg/d for 6 wk	10 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	1.5T, EPI, block design, visual face-encoding task	(1) Baseline: more activation of right fusiform gyrus in HC than AD; (2) follow-up: after treatment fusiform gyrus activated in AD similar to HC
Goekoop R	2006	AD = 18 MCI = 28	Galantamine	8 mg single dose, 4 mg bid 120 h	120 h over 6 weekdays	3 Scans: baseline, after single dose, end of treatment	1.5T, EPI, event-related design, face recognition task	(1) MCI: single dose increased activation in posterior cingulate, left inferior parietal, and anterior temporal lobe; prolonged exposure decreased activation relative to baseline in similar posterior cingulate areas and bilateral prefrontal areas; (2) AD: single dose increased activation in bilateral hippocampal, whereas prolonged exposure decreased activation relative to baseline in these areas
Grön G	2006	MCI = 10	Galantamine	4 mg bid	7 d	2 Scans: baseline and at end of treatment	1.5T, EPI, block design, spatial navigation task	Post-treatment relative to baseline: increased activations in right middle occipital and middle temporal gyri, fusiform gyrus, posterior cingulate, hippocampus, and left anterior parahippocampal gyrus

(Continues)

TABLE 1 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	fMRI experiment	Main fMRI findings on treatment effect
Shanks MF	2007	AD = 9 HC = 9	Galantamine on AD	16 mg bid	20 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	1.5T, EPI, block design, semantic association, and target detection tasks	(1) Semantic association: activation in left prefrontal cortex, anterior cingulate gyrus, and medial frontal gyrus increases post-treatment; activation in left inferior, middle, and medial frontal gyri and parahippocampal gyrus in AD post-treatment comparable to HC; (2) target detection: bilateral cingulate gyrus activation in AD post-treatment comparable to HC
McGeown WJ	2008	Mild AD = 11 HC = 9	Rivastigmine	6 mg bid	20 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	1.5T, EPI, block design, semantic association working memory (n-back)	(1) Semantic association: increased activation in bilateral middle frontal, paracentral gyri, parahippocampal, and fusiform gyri in AD prior vs post-treatment; increased activation in right inferior frontal and left anterior cingulate cortex post-treatment in AD vs HC; (2) working memory: increased activation in right frontal, precentral gyrus in AD prior vs post-treatment, and increased activation in right middle frontal, postcentral, and supramarginal gyri post-treatment in AD vs HC; decreased activation in left middle frontal, precentral, cingulate gyrus, insula, and thalamus, and decreased activation in left posterior cingulate and angular gyrus post-treatment in AD vs HC
Bokde AL	2009	Mild AD = 5	Galantamine	4 mg bid 1st month, 8 mg bid 2nd month, 12 mg bid 3rd month	3 mo	2 Scans: baseline and at end of treatment	1.5T, EPI, block design, visual attention (face/location matching) tasks	(1) Location-matching task: decrease activation in dorsal visual pathway after treatment; (2) face-matching task: no differences in activation after treatment
Petrella JR	2009	MCI = 13 (6 treated)	Donepezil	Dose unknown	24 wk	3 Scans: baseline, 12 and 24 wk	1.5T, EPI, event-related design, visual delayed face recognition task	(1) Untreated: decreased activation in dorsolateral prefrontal; (2) treated: increased activation in ventrolateral prefrontal cortex; (3) significant donepezil-related but not placebo-related change in the left inferior frontal gyrus
Venneri A	2009	Mild AD = 26 HC = 9	ChEIs on AD	Standard care; maximum dosage for >2 mo	20 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	1.5T, EPI, block design, semantic association, and n-back working memory task	(1) AD responders = 9, nonresponders = 17; (2) AD responders: restoration of brain function in the same regions used by HC during tasks; (3) nonresponders: activation patterns differed more from HC

(Continues)

TABLE 1 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	fMRI experiment	Main fMRI findings on treatment effect
McGeown WJ	2010	AD = 12 HC = 9	Donepezil on AD	Standard care; stable dose 10 mg/d	20 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	1.5T, EPI, block design, semantic association, and an n-back working memory task	(1) More pronounced difference in AD post-treatment from HC; (2) deactivation in task-relevant areas at retest; (3) increased behavioral scores at retest correlated with higher activation levels in non-task-relevant areas
Thiyagesh SN	2010	AD = 10 HC = 11	Donepezil on AD	5 mg/d	23 wk	2 Scans: baseline and 23 wk (AD) or 37 wk (HC)	1.5T, EPI, block design, visuospatial perception task	(1) AD: increased activation in left precuneus, cuneus, supramarginal gyrus and right parietotemporal cortex, inferior parietal lobule; (2) increased activation in left precuneus correlated with improved function
Goveas JS	2011	Mild AD = 14 HC = 18	Donepezil on AD	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	2 Scans: baseline and at end of treatment (in AD only)	3.0T, EPI, resting phase	(1) Improvement in MMSE correlated with FC changes in left parahippocampus, DLPFC, and inferior frontal gyrus; (2) improvement in ADAS-cog correlated with hippocampal FC changes in left DLPFC and middle frontal gyrus
Lorenzi M	2011	Moderate-to-severe AD = 15 (7 treated)	Memantine	5 mg/d, increasing by 5 mg/d to a final dose of 20 mg/d at 6 mo	6 mo	2 Scans: baseline and at end of treatment	3.0T, sequence unknown, resting phase	Increase activation in right precuneus and calcarine gyrus within default mode network post-treatment
Miettinen PS	2011	Mild AD = 20	Rivastigmine	Single dose: 3 mg, chronic dose: 1.5 mg bid	4 wk	3 Scans: placebo and single dose and at end of 4 wk	1.5T, EPI, block design, face recognition task	(1) Greater activity in prefrontal areas in both dosages than in placebo; (2) better-preserved cognition with less enhanced prefrontal activity in treated
Song X	2011	Mild AD = 12	ChEIs	Standard care	26 wk	2 Scans: baseline and at end of treatment	4.0T, spiral, mixed block-event design, semantic discrimination and episodic retrieval tasks	(1) Improvement in global cognition and memory in more than 75% of patients post-treatment; (2) increased fMRI activation in the left dorsal lateral prefrontal lobe; (3) increased deactivation in post cingulate gyrus and left parietal operculum cortex; (4) the number of voxels with increased activation correlated with fMRI task performance
Li W	2012	Mild AD = 12	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	2 Scans: baseline and at end of treatment	3.0T, EPI, resting phase	(1) Enhanced FC in the parahippocampal, temporal, parietal, and prefrontal cortices; (2) CBF increased in the middle and posterior cingulate cortex in AD post-treatment; (3) the change of FC associated with CBF and with ADAS-cog change

(Continues)

TABLE 1 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	fMRI experiment	Main fMRI findings on treatment effect
McLaren DG	2012	Mild AD = 24	Memantine with stable dose donepezil 10 mg/d >6 mo	12 Pts had both for 24 wk; 12 Pts first had donepezil for 12 wk then both, for 12 wk	24 wk	2 Scans: baseline and at end of treatment	3.0T, EPI, block design, visual face-name paired encoding task	(1) Correlations between changes in memory accuracy and fMRI activity in the angular gyrus, parahippocampal gyrus, inferior frontal gyrus, and cerebellum; (2) correlations between changes in test-free recall and fMRI activation in inferior parietal lobule, precuneus, hippocampus, and parahippocampal gyrus
Zaidel L	2012	Mild AD = 11	Donepezil	5 mg/d for 4 wk, 10 mg/d for 4 wk	8 wk	2 Scans: baseline and at end of treatment	1.5T, EPI, resting phase	FC increased in bilateral dorsolateral prefrontal cortices after treatment
Dhanjal NS	2013	Mild AD = 9	Donepezil	5 mg/d for 2 wk, 10 mg/d for 4 wk	6 wk	3 Scans: 2 at baseline for test-retest variability, 1 at end of treatment	3.0T, EPI, block design, auditory sentence encoding, and retrieval tasks	(1) Auditory: no significant response of right Heschl's gyrus after treatment; (2) auditory verbal memory encoding: increased activation in left pars triangularis and anterior ventral temporal lobe after treatment
Pa J	2013	MCI = 26 (13 treated)	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	3 Scans: baseline, 4 wk, and end of treatment	3.0T, EPI, block design, delayed memory recognition (face/scene) task	(1) Left fusiform face area has FC with hippocampus and inferior frontal junction; (2) treated group showed larger increases in network connectivity over time compared to placebo group
Risacher SL	2013	MCI = 18 HC = 20	Donepezil	5 mg/d for 4 wk, 10 mg/d until the end of study	~3 mo	2 Scans: baseline and at end of treatment	1.5T, sequence unknown, event-related design, verbal episodic encoding task	(1) Increased activation in right medial temporal lobe (hippocampus and parahippocampal gyrus) and middle frontal gyrus post-treatment; (2) Increased deactivation of medial parietal lobe; (3) the fMRI change was associated with cognitive performance
Solé-Padullés C	2013	AD = 15 (8 treated)	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	2 Scans: baseline and at end of treatment	3.0T, sequence unknown, block design, visual scenes encoding task and resting phases	(1) Resting: higher connectivity in default mode network (right parahippocampal gyrus) post-treatment compared to untreated; (2) task: treated group exhibited stable brain activity, while untreated showed increased activation in left middle temporal gyrus and bilateral precuneus at follow-up compared to baseline

(Continues)

TABLE 1 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	fMRI experiment	Main fMRI findings on treatment effect
Dhanjal NS	2014	Mild AD = 9	Donepezil	5 mg/d for 2 wk, 10 mg/d for 4 wk	6 wk	3 Scans: 2 at baseline for test-retest variability, 1 at end of treatment	3.0T, EPI, block design, auditory sentence encodings, and retrieval tasks	(1) Increased activation in left lateral posterior parietal and lateral frontal cortex after treatment, greater in low-performance compared to high-performance sentences; (2) greater activation in left parahippocampal gyri and anterior ventral temporal lobe with more accurate recall at baseline, but not after treatment
Wang L	2014	Mild AD = 46 (25 treated including 16 APOE-ε4 carriers)	ChEIs	Standard care	4-78 mo	1 scan after enrollment	3.0T, gradient spin-echo sequence, resting phase	Greater FC of dorsal attention, control, and salience network for APOE-ε4 carriers post-treatment
Miettinen PS	2015	Mild AD = 18	Rivastigmine	Single dose: 3 mg, chronic dose: 1.5 mg bid	4 wk	3 Scans: placebo, single dose, and at end of 4 wk	1.5T, EPI, block design, face recognition task	Changes in MMSE and fMRI post-treatment (1) positively correlated in right prefrontal cortex; (2) negatively correlated in left prefrontal cortex and fusiform gyrus; (3) a greater signal intensity in right vs left fusiform gyrus predicted MMSE increase post-treatment
Blautzik J	2016	AD = 13 HC = 11	AD = 6 for 12-mo galantamine; AD = 7 for 6-mo placebo + 6-mo galantamine	8 mg/d for 4 wk, 16 mg/d for 4 wk, and then 24 mg/d	12 mo	3 Scans: baseline and at end of treatment (12 mo) for all, AD only at 6 mo	3.0T, EPI, resting phase	(1) Increased FC in posterior cingulate cortex and precuneus following 12-mo galantamine; (2) greater FC in posterior cingulate cortex and precuneus in AD than in HC; (3) greater FC in anteromedial temporal lobes with galantamine than with galantamine + placebo
Bokde AL	2016	Amnesic MCI = 12 (5 treated)	Rivastigmine	3 mg/d in month 1, 6 mg/d in month 2, 9 mg/d from 3rd month forward	1 y	3 Scans: baseline, and after 3 and 6 mo post-treatment	1.5T, EPI, block design, visual attention (face/location matching) tasks	(1) Face-matching task: higher activation of visual areas after 3 mo treatment, but no differences compared to baseline at 6 mo; (2) location-matching task: higher activation along the dorsal visual pathway both 3 and 6 mo post-treatment
Griffanti L	2016	AD = 18	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	2 Scans: baseline and at end of treatment	3.0T, EPI, resting phase	(1) There were 10 responders; (2) FC increase in orbitofrontal network, correlated with MoCA post-treatment

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; bid, twice a day; ChEI, cholinesterase inhibitors; DLPPFC, dorsolateral prefrontal cortex; EPI, echo planar imaging; FC, functional connectivity; HC, healthy control; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.



**TABLE 2** Medications in each study that used blood oxygen level-dependent functional magnetic resonance imaging

First author	Year	Medication						
		Donepezil	Galantamine	Rivastigmine	ChEI <sup>a</sup>	Memantine	ChEI + Memantine	Other Meds
Rombouts SA	2002			✓				
Goekoop R	2004		✓					
Saykin AJ	2004	✓						
Kircher TT	2005	✓						
Goekoop R	2006		✓					
Grön G	2006		✓					
Shanks MF	2007		✓					
Bentley P	2008							✓
McGeown WJ	2008			✓				
Bentley P	2009							✓
Bokde AL	2009		✓					
Petrella JR	2009	✓						
Venneri A	2009				✓			
McGeown WJ	2010	✓						
Thiyagesh SN	2010	✓						
Goveas JS	2011	✓						
Lorenzi M	2011					✓		
Miettinen PS	2011			✓				
Song X	2011				✓			
Bakker A	2012							✓
Li W	2012	✓						
McLaren DG	2012						✓	
Zaidel L	2012	✓						
Dhanjal NS	2013	✓						
Pa J	2013	✓						
Risacher SL	2013	✓						
Solé-Padullés C	2013	✓						
Dhanjal NS	2014	✓						
Haller S	2014							✓
Wang L	2014				✓			
Zhang J	2014							✓
Bakker A	2015							✓
Miettinen PS	2015			✓				
Zhang J	2015							✓
Blautzik J	2016		✓					
Bokde AL	2016			✓				
Griffanti L	2016	✓						
Zhang J	2016							✓
Total number of studies		14	6	5	3	1	1	8

ChEI, cholinesterase inhibitors.

Other Meds: physostigmine, levetiracetam, caffeine, or Chinese herbal medicine.

<sup>a</sup>Can be any ChEI (ie, the original studies did not name it).

and at high field may also include myo-inositol (mI), lipid, lactate, glutamate (Glu), glutamine (Gln), and  $\gamma$ -aminobutyric acid.<sup>23,30-32</sup> MRS can be very useful in studying AD, as MRS acquisition does not require the patients to perform any task.

Given the ability of these MRI technologies in detecting blood oxygen, blood flow, and brain metabolite changes, they provide unique ways to noninvasively investigate the effect of medication treatment (in addition to detecting AD-related cholinergic and



**TABLE 3** Number of studies grouped by medication and blood oxygen level-dependent functional magnetic resonance imaging experimental condition

Experimental condition	N <sup>a</sup>	Medication						
		Donepezil	Galantamine	Rivastigmine	ChEI <sup>b</sup>	Memantine	ChEI + Memantine	Other Meds
Task phase	37	11	7	7	4		1	7
Auditory working memory	3	3						
Episodic memorial encoding	1							1
Episodic memory retrieval	1				1			
Face encoding	4	1	1	1				1
Face recognition	5	2	1	2				
Face-name paired encoding	1						1	
Forced-choice recognition	2							2
Scenes encoding	1	1						
Semantic association	4	1	1	1	1			
Semantic discrimination	1				1			
Spatial navigation	1		1					
Target detection	1		1					
Verbal episodic encoding	1	1						
Visual attention	2		1	1				
Visual judgments	1							1
Visual n-back working memory	7	1	1	2	1			2
Visuospatial perception	1	1						
Resting phase	9	5	1		1	1		1
Total number of studies		16	8	7	5	1	1	8

ChEI, cholinesterase inhibitors.

<sup>a</sup>Number of studies. Some studies used more than 1 tasks.

<sup>b</sup>Can be any ChEI (ie, the original studies did not report it).

glutamatergic abnormalities in the AD that can occur long ahead of clinical manifestation).<sup>33-35</sup>

Here, we review current findings and discuss the future role of these functional MRI modalities, for example, BOLD-fMRI, PWI, and MRS, in studying the treatment effects of various medications on AD and MCI. For this purpose, we surveyed the literature and summarized the information. Our focus is the medications that have been approved by FDA to treat AD and MCI (ie, ChEIs and memantine), rather than trials for developing new drugs. Studies that reported use of other on-shelf medications primarily for treating other conditions (eg, epilepsy, diabetes) on AD-associated comorbidities were also briefly discussed.

## 2 | METHODS

### 2.1 | Search terms

We searched MEDLINE, which represents the most well-known biomedical research database, with comprehensive coverage of biomedical publications of more than 5600 journals.<sup>36</sup> During the initial search, we used terms that combined the following 3 sets of phrases or key words. Set-1: "Alzheimer's" or "AD" or "mild cognitive impairment" or "MCI" or "dementia". Set-2: "therapeutic" or

"therapy" or "medication" or "treatment" or "pharmacological" or "memantine" or "donepezil" or "galantamine" or "rivastigmine" or "cholinesterase inhibitors" or "cholinesterase inhibition" or "ChEI" or "cholinergic". Set-3: "functional MRI" or "fMRI" or "functional magnetic resonance imaging" or "BOLD" or "cortical activation" or "functional connectivity" or "MRS" or "MRS imaging" or "Magnetic resonance spectroscopy" or "MR spectroscopy" or "perfusion MRI" or "Perfusion Weighted Imaging" or "PWI" or "Cerebral Blood Flow" or "CBF" or "Cerebral Blood Volume" or "CBV" or "Hemodynamic." This initial search yielded 1796 articles (Figure 1).

### 2.2 | Inclusion and exclusion criteria

Articles were further eliminated by restricting inclusion to studies that investigated human subjects, were published in the English language, and had a full-text, using Set-4: "Humans" and Set-5: "English," and a subset of 1084 articles was resulted. After such compilation, review and opinion papers were further discarded. Through title and abstract review of articles that reported original research studies, those that used only non-MR imaging techniques such as single-photon emission computed tomography, positron emission tomography, electroencephalography, and magnetoencephalography, and those that used nonpharmacological treatments

**TABLE 4** Studies that used perfusion-weighted imaging (PWI) with FDA-approved medications

First author	Year	Sample	Medication	Dose	Treatment duration	MRI scan	PWI experiment	Main PWI findings on treatment effect
Li W	2012	Mild AD = 12	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk	12 wk	2 Scans: baseline and at end of treatment	3.0T, PCASL, resting phase, absolute CBF	(1) CBF increased in MCC and PCC in AD post-treatment; (2) baseline and treatment-induced changes in CBF in MCC and PCC correlated with changes in ADAS-cog; (3) FC enhanced in medial cholinergic pathway network in parahippocampal, temporal, parietal, and prefrontal cortices; (4) changes of FC in medial prefrontal lobe associated with CBF in MCC and PCC and with ADAS-cog change
Chaudhary S	2013	Early AD = 25 (bl), 15 (fl) HC = 20 (bl), 11 (fl)	ChEIs on AD	Donepezil: 5-10; galantamine: 24; rivastigmine: 4.5, reminyli: 24 (mg/d)	6 mo	2 Scans: baseline and at end of treatment	3.0T, PCASL, resting phase, absolute CBF, arterial transit time	(1) Baseline: hypoperfusion in AD compares to HC (lateral temporal lobe gray matter, posterior cingulate, anterior cingulate); (2) increased perfusion post-treatment in most cortical regions investigated, and in posterior cingulate and prefrontal white matter
Janik R	2016	Mild AD = 35 (bl), 26 (6 mo), 11 (12 mo); HC = 29 (bl), 14 (6 mo), 3 (12 mo)	ChEIs on AD	Dosage as guidelines recommend	12 mo	3 Scans: baseline, 6 mo, 12 mo	3.0T, PCASL, resting phase, block design visual task, CBF, arterial transit time	(1) No gray matter atrophy nor resting perfusion difference between AD and HC at bi; (2) CBF decreased in AD relative to HC during task at bi; (3) further reduced CBF during task at fl, which stabilized at 12 mo; (4) higher MMSE scores associated with higher perfusion responses to task

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; bl, baseline; CBF, cerebral blood flow; ChEI, cholinesterase inhibitors; FC, functional connectivity; fl, follow-up; HC, healthy control; MCC, middle cingulate cortex; MMSE, Mini-Mental State Examination; PCASL, pseudo-continuous arterial spin labeling; PCC, posterior cingulate cortex.

**TABLE 5** Medications in each study that used perfusion-weighted imaging (PWI)

First author	Year	Medication		
		Donepezil	ChEI <sup>a</sup>	Other Meds
Li W	2012	✓		
Chaudhary S	2013		✓	
Janik R	2016		✓	
Koenig AM	2017			✓
Total number of studies		1	2	1

ChEI, cholinesterase inhibitors.

Other Meds: metformin.

<sup>a</sup>Can be any ChEI (ie, the original studies did not report it).

such as acupuncture or cognitive training were further discarded. To ensure a complete inclusion, a consultation of other reviews was conducted, for example, for BOLD-fMRI.<sup>37</sup> These processes yielded a final subset of 55 articles remaining to be further reviewed (Figure 1), arranged based on the functional MRI methods used, that is, BOLD (n = 38), PWI (n = 4), and MRS (n = 14).

### 3 | RESULTS

#### 3.1 | BOLD-fMRI studies

Studies investigating the effects of pharmacological treatments in AD and MCI using BOLD-fMRI were summarized in Tables 1-3, with individual studies described in Table 1.

Rombouts et al<sup>38</sup> reported the first fMRI study on AD treatment in human subjects. Patients with mild AD performed face-encoding and n-back tasks. An increase in fMRI activation in the fusiform gyrus and frontal cortices was found with a single-dose rivastigmine administration.<sup>38</sup> The same group<sup>39</sup> scanned 28 MCI patients at baseline, after a single dose of galantamine, and after 5 days of galantamine treatments. An increased activation was found during face-encoding task after 5 days in the anterior cingulate, left prefrontal, and occipital gyri, and in the posterior hippocampus, while during the working memory task there was increased fMRI activation in the right precuneus and right middle frontal gyrus.<sup>39</sup> Goekoop et al<sup>40</sup> further reported different activation intensities in the hippocampus and posterior cingulate gyrus between MCI and AD during face recognition in response to galantamine treatment.

Saykin et al<sup>41</sup> used an auditory n-back task and showed enhanced frontal lobe fMRI activation in MCI treated with donepezil, which was correlated with baseline hippocampal volume. Kircher et al<sup>42</sup> showed an increase in fMRI activation in the right fusiform gyrus in AD during a face-encoding task after 10 weeks of donepezil treatment. Grön et al<sup>43</sup> studied MCI patients performing a spatial navigation task and showed an increased activation in multiple regions after 7-day galantamine treatment.

Shanks et al<sup>44</sup> reported that in AD, galantamine increased fMRI activation in the left inferior, middle, and medial frontal, and parahippocampal gyri during a semantic association task, and in the bilateral

cingulate gyrus during a target detection task. In their subsequent study, McGeown et al<sup>45</sup> used rivastigmine and reported an increased fMRI activation in the bilateral middle frontal, paracentral, parahippocampal, and fusiform gyri during a semantic association task, and in the right frontal and right precentral gyri during a working memory task. Decreased activation was found in the left middle frontal, precentral, and cingulate gyri, insula, and thalamus during the working memory task.<sup>45</sup> Later, McGeown et al,<sup>46</sup> evaluated the effects of 20-week donepezil treatment applying the same fMRI tasks, but found decreased fMRI activation, whereas increased deactivation was found in task-irrelevant areas.<sup>45,46</sup> In a retrospective analysis, Venneri et al<sup>47</sup> divided the patients into drug responders and nonresponders and observed activation changes only in the former group.

Further, Petrella et al<sup>48</sup> reported a multicenter double-blind placebo-controlled trial on donepezil in MCI and showed an increased activation in the left inferior frontal gyrus during face recognition. Bokde et al<sup>49</sup> studied 5 mild AD subjects and on the effect of 3-month galantamine treatment using a visual attention task and showed a decreased activation in bilateral dorsal visual pathways during location-matching task. Later, Bokde et al<sup>50</sup> examined the effect of 3-6 months of rivastigmine treatment on MCI and reported an increased activation. Thiyagesh et al<sup>51</sup> showed fMRI activation changes in the left precuneus during visuospatial processing in AD after 23-week donepezil treatment.

While the earlier studies were conducted at 1.5T, since 2011 investigations have mostly used a higher MRI field, for example, 3.0T, while an increasing number of studies have targeted brain functional connectivity at resting phase without an explicit task.

Goveas et al<sup>52</sup> showed that mild AD patients improved their hippocampal-functional connectivity after 3-month donepezil treatment, correlated with global cognition assessment. Lorenzi et al<sup>53</sup> showed an increased activation in the right precuneus and calcarine gyrus in moderate AD patients after 6-month memantine treatment. Similarly, Zaidel et al<sup>54</sup> showed increased activation in the bilateral dorsolateral prefrontal cortex after 8 weeks of donepezil treatment.

Miettinen et al<sup>55</sup> reported a greater prefrontal fMRI activation during face recognition post a single dose or 4-week rivastigmine treatment in mild AD. Miettinen et al<sup>56</sup> subsequently reported that fMRI changes in the prefrontal cortex and fusiform gyrus in mild AD after rivastigmine treatment were correlated with cognition and that a greater level of baseline fMRI activation in the right (vs left) fusiform gyrus predicted cognitive improvement. Song et al<sup>57</sup> found an increased fMRI activation in the left dorsal lateral prefrontal lobe and increased deactivation in the posterior cingulate gyrus and left parietal operculum cortex in mild AD after ChEI treatment using semantic discrimination and episodic retrieval tasks at 4.0T. Using 3.0T, McLaren et al<sup>58</sup> reported a change in fMRI activation during a memory-encoding task in mild AD after a combined donepezil-memantine treatment.

A number of studies also employed resting-phase BOLD-fMRI techniques. Pa et al<sup>59</sup> reported a double-blind placebo-controlled study examining donepezil treatment in MCI and showed a greater functional connectivity between the left fusiform, hippocampus, and

**TABLE 6** Studies that used proton magnetic resonance spectroscopy (MRS) and MRS Imaging with FDA-approved medications

First author	Year	Sample	Medication	Dose	Treatment duration	MRS scan	MRS experiment	Main MRS findings on treatment effect
Krishnan KR	2003	AD = 51 (treated = 28)	Donepezil	5 mg/d for 4 wk, 10 mg/d for 20 wk	24 wk	6 Scans: baseline, every 6 wk until 24 wk, 1 after 6 wk of washout	1.5T, MRS imaging PRESS, short TE; subcortical and cortical gray matter, periventricular matter, and white matter; NAA and ml	Mean normalized NAA concentration was higher in treated group, but not at endpoint
Jessen F	2006	Mild-to-moderate AD = 17	Donepezil	5 mg/d for 4 wk, 10 mg/d for 8 wk (except for 3 remained 5 mg)	12 wk	2 Scans: baseline and at end of treatment	1.5T, single voxel, PRESS, long TE; 2 VOIs: left medial temporal lobe (35 × 25 × 20 mm <sup>3</sup> ), left parietal lobe (25 × 25 × 30 mm <sup>3</sup> ); NAA, Cho, Cr, and ratio to Cr	(1) Changes of NAA and NAA//Cr in parietal VOI correlated with ADAS-cog after treatment; (2) lower baseline NAA/Cr in the parietal VOI was associated with greater increase in ADAS-cog
Modrego PJ	2006	AD = 34 (treated = 24)	Rivastigmine	12 mg/d (stabilized within 2 mo)	4 mo	2 Scans: AD (baseline and 4 mo), control (baseline and 1 mo)	1.5T, single voxel, PRESS, short TE; 3 VOIs on medial frontal, right parietal, and medial occipital lobes; NAA, Cr, Cho and ml and to Cr	(1) Treated AD: NAA/Cr in frontal cortex and ml/Cr in occipital cortex increased, but not significant after correcting for confounders; (2) only in frontal cortex the changes in metabolite ratios correlated with clinical scales; (3) untreated AD: no significant difference in metabolite levels or ratios to Cr between the 2 scans
Bartha R	2008	AD = 10 HC = 5	Donepezil on AD	5 mg/d for 4 wk, 10 mg/d for 12 wk	16 wk	2 Scans: AD: baseline and end of treatment, HC: baseline and 1-y follow-up	4.0T, single voxel, LASER, short TE; one 2.7–5.2 cm <sup>3</sup> VOI in right hippocampus; NAA, Glu, ml, Cr, Cho and metabolite ratios	(1) AD: Decreased levels of NAA, Cho, NAA/Cr, Cho/Cr, and ml/Cr post-treatment; (2) HC: increased ml/Cho ratio at 1-y follow-up; (3) decrease of Cho and ml/Cr may indicate a positive treatment effect
Glodzik L	2008	Treated: 3 AD, 4 MCI, 3 oHC Untreated: 3 oHC, 3 yHC	Memantine	5 mg/d for 4 <sup>+</sup> wk, 10 mg bid for 20 wk	24 wk	2 Scans: baseline and at end of treatment	3.0T, MRS imaging, PRESS, short TE; 2 VOIs: 70 × 90 × 20 mm <sup>3</sup> on each hippocampus; NAA/Cr, Glu/Cr	(1) Left hippocampus Glu/Cr was lower in treated than in untreated group; (2) no group or over time difference in NAA/Cr

(Continues)

TABLE 6 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRS scan	MRS experiment	Main MRS findings on treatment effect
Modrego PJ	2010	Mild-to-moderate AD = 63	Donepezil (n = 32), memantine (n = 31)	Donepezil: 5 mg/d for 4 wk, 10 mg/d for 20 wk, memantine 20 mg/d for 24 wk	24 wk	2 Scans: baseline and at end of treatment	1.5T, single voxel, PRESS, short TE; 6 VOIs: 20 × 20 × 20 mm <sup>3</sup> , bilateral prefrontal and temporal lobes, PCG, and left medial occipital lobe; NAA, ml, Cr, Cho, NAA/Cr, ml/Cr, Cho/Cr	(1) Increased PCG NAA/Cr and Cho/Cr; increased left medial occipital lobe and right prefrontal ml/Cr, decreased left prefrontal NAA/Cr after donepezil treatment; (2) no metabolite changes with memantine treatment; (3) no differences in clinical scales or metabolite levels between donepezil and memantine groups, more patients worsened than improved in ADAS-cog score in both group; (4) increased NAA/Cr related with improved ADAS-cog in PCG
Penner J	2010	AD = 10	Galantamine	8 mg/d for 4 wk, 16 mg/d for 12 wk	16 wk	2 Scans: baseline and at end of treatment	4.0T, single voxel, LASER, short TE; 2.8–4.7 cm <sup>3</sup> right hippocampus; NAA, Glu, Cr, Cho, ml, and ratios	(1) Glu, Glu/Cr, and Glu/NAA increased after treatment; (2) changes in Glu (ΔGlu) correlated with ΔNAA; (3) ΔGlu and ΔGlu/Cr correlated with ΔMMSE scores
Ashford JW	2011	Mild-to-moderate AD = 10 (4 treated)	Memantine	5 mg/d, with increments 5 mg/wk to reach 10 mg bid at the week 3	1 y	2 Scans: baseline and at end of treatment (average of 54 wk)	3.0T, single voxel, PRESS, short TE; 20 × 20 × 20 mm <sup>3</sup> in left cerebral cortex, inferior parietal, posterior cingulate, and occipital; NAA/Cr, Cho/Cr, ml/Cr	(1) No NAA/Cr differences between treatment and placebo groups at either baseline or post-treatment; (2) changes in NAA/Cr correlated with changes in ADAS-cog; (3) baseline NAA/Cr correlated with age and verbal fluency
Henigsbeg N	2011	Mild-to-moderate AD = 12	Donepezil	10 mg/d	26 wk	2 Scans: baseline and at end of treatment	3.0T, long TE; 1 VOI 25 × 25 × 25 mm <sup>3</sup> in right dorsolateral prefrontal cortical region; NAA/Cr	(1) A significant increase in NAA/Cr post-treatment; (2) less reduction in ml/Cr in patients with a decreased ADAS-cog post-treatment
Gordon ML	2012	Mild-to-moderate AD = 11 HC = 28	ChEIs, Memantine on AD	24 wk of ChEI only, and 24 wk of ChEI and memantine (20 mg/d) combined	48 wk	3 Scans for AD: baseline, 24 wk, and 48 wk. 1 scan for HC: baseline	3.0T, single voxel, PRESS, short TE; 1 VOI: 20 × 20 × 27 mm <sup>3</sup> in precuneus and posterior cingulate region; NAA, ml, Cho, Cr, NAA/Cr, ml/Cr, Cho/Cr, NAA/Cho, NAA/ml	(1) Higher ml/Cr and lower NAA, NAA/Cr, NAA/Cho, and NAA/ml in AD than in HC at baseline; (2) baseline NAA/Cr, ml/Cr, and NAA/ml correlated with cognitive/functional testing scores; (3) when memantine was added to a ChEI, there was an increase in ml and a decrease in NAA/ml, but no other change in metabolites or cognition

(Continues)

TABLE 6 (Continued)

First author	Year	Sample	Medication	Dose	Treatment duration	MRS scan	MRS experiment	Main MRS findings on treatment effect
Song X	2012	Mild AD = 16 HC = 20	ChEIs on AD	Standard care following guidelines	26 wk	2 Scans: baseline and at end of treatment	4.0T, LASER, short TE; 2 6.4 cm <sup>3</sup> VOIs in medial PCG and in left DLPFC regions: NAA, Cr, Glu	(1) Higher level of Cr in AD than in HC in PCG but not in DLPFC; (2) lower level of Glu/Cr in DLPFC and lower level of NAA/Cr in both VOIs in AD than in HC regardless of treatment; (3) 84% accuracy in classification of early AD and HC using baseline and follow-up NAA, Glu, and Cr
Moon CM	2016	AD = 11 HC = 10	Donepezil on AD	10 mg/d	24 wk	2 Scans: baseline (for all) and at end of treatment (in AD only)	3.0T, single voxel, PRESS, short TE; VOI: 12 × 25 × 15 mm <sup>3</sup> in left hippocampus; NAA, Cr, Cho, ml, and ratios/Cr	(1) Decreased NAA/Cr and increased ml/Cr in AD than in HC at baseline; (2) decreased NAA/Cr in AD post-treatment than in HC; (3) AD showed increased NAA/Cr and decreased ml/Cr and Cho/Cr post-treatment than baseline

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; bid, twice a day; ChEI, cholinesterase inhibitors; Cho, choline; Cr, creatine; DLPFC, dorsolateral prefrontal cortex; Glu, glutamate; HC, healthy control; LASER, localization by adiabatic selective refocusing; MCI, mild cognitive impairment; ml, myo-inositol; MMSE, Mini-Mental State Examination; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; oHC, old healthy control; PCG, posterior cingulate gyrus; PRESS, point-resolved spectroscopy; TE, time of echo; VOI, voxel of interest; yHC, young healthy control.

the inferior frontal junction during a delayed memory recognition task. Dhanjal et al studied mild AD, MCI, and health control (HC) using auditory encoding<sup>60</sup> and retrieval<sup>61</sup> and showed that donepezil was effective in AD with an increased fMRI activation in the left anterior ventral temporal cortex and pars triangularis during encoding,<sup>60</sup> and in the left lateral posterior parietal cortex and lateral frontal cortex during retrieval.<sup>61</sup> Risacher et al<sup>62</sup> evaluated the effect of donepezil treatment on MCI using an encoding task; the 1.5T study showed increased activations in the right (para)hippocampal and middle frontal areas.

Solé-Padullés et al<sup>63</sup> acquired the fMRI data at 3.0T at both resting and task phases (encoding visual scenes) with donepezil treatment in AD and reported a higher connectivity in the right parahippocampal gyrus at rest and stable activation, vs baseline during the task.

Wang et al<sup>64</sup> studied very mild and mild AD participants with different genetic risks (eg, Apolipoprotein allele) under ChEI treatment and examined connectivity changes of 5 resting-phase networks: default mode, control, dorsal attention, salience, and sensory-motor. A greater level of connectivity was shown in the control, dorsal attention, salience networks for treated compared to untreated APOE-ε4 carriers.<sup>64</sup> More recently, Blautzik et al<sup>65</sup> showed that 12 months of galantamine treatment in mild-to-moderate AD affected functional connectivity: It was increased in the posterior cingulate cortex and the precuneus, and stable in the anteromedial temporal lobes. Griffanti et al<sup>66</sup> showed that after donepezil treatment for 12 weeks, mild-to-moderate AD patients increased functional connectivity in the orbitofrontal network, correlated to cognitive testing scores.

Another resting-state study by Li et al<sup>67</sup> used both BOLD and PWI fMRI and reported increased network connectivity in the parahippocampal, temporal, parietal and prefrontal cortices in AD after 12-week donepezil treatment, and changes in functional connectivity and regional CBF in the medial prefrontal lobe were correlated.

### 3.2 | Perfusion-weighted imaging (PWI) studies

There have been only a small number of PWI studies investigating the effects of pharmacological treatments in AD and MCI. These were summarized in Tables 4 and 5, with individual studies described in Table 4.

The study by Li et al<sup>67</sup> used pseudo-continuous arterial spin labeling-PWI (PCASL-PWI), based on the arterial spin labeling technique, and found an enhancement of the regional CBF in the middle and posterior cingulate cortex in AD after donepezil treatment (also see above with BOLD-fMRI).<sup>67</sup>

Chaudhary et al<sup>68</sup> reported ChEI treatment-elicited increases in CBF in the lateral temporal lobe, posterior and anterior cingulate gyrus (including white matter), and prefrontal regions, independent of the regional volume of brain tissues.

A subsequent study by Janik et al<sup>69</sup> investigated changes of CBF and fMRI activation in mild AD during both rest and task phases using PCASL-PWI. Without treatment, AD patients showed a



**TABLE 7** Medications in each study that used proton magnetic resonance spectroscopy (MRS) and MRS imaging

First author	Year	Medication						
		Donepezil	Galantamine	Rivastigmine	ChEI <sup>a</sup>	Memantine	ChEI + Memantine	Other Meds
Satlin A	1997							✓
Frederick Bd	2002							✓
Krishnan KR	2003	✓						
Jessen F	2006	✓						
Modrego PJ	2006			✓				
Bartha R	2008	✓						
Glodzik L	2008					✓		
Modrego PJ.	2010	✓				✓		
Penner J	2010		✓					
Ashford JW	2011					✓		
Henigsberg N	2011	✓						
Gordon ML	2012						✓	
Song X	2012				✓			
Moon CM	2016	✓						
Total number of studies		6	1	1	1	3	1	2

ChEI, cholinesterase inhibitors.

Other Meds: xanomeline.

<sup>a</sup>Can be any ChEI (ie, the original studies did not report it).

significantly lower CBF and BOLD signal intensity than HC. After 6 months of ChEI treatment, a further CBF decline was seen in the occipital lobe during visual stimulation, whereas the CBF response was stabilized after 12 months of treatment.<sup>69</sup>

### 3.3 | Proton MRS and MRS imaging studies

Studies investigating the effects of pharmacological treatments in AD and MCI using proton MRS or MRS imaging were summarized in Tables 6 and 7, with individual studies described in Table 6.

Krishnan et al<sup>70</sup> reported the first randomized, placebo-controlled trial on medication treatment-induced changes in MRS imaging in relation to hippocampal volume changes at 1.5T. A slightly higher level of NAA level was found in donepezil-treated AD than placebo, associated with a higher mean Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog) score and a less significant hippocampal volume reduction at the end of treatment.<sup>70</sup>

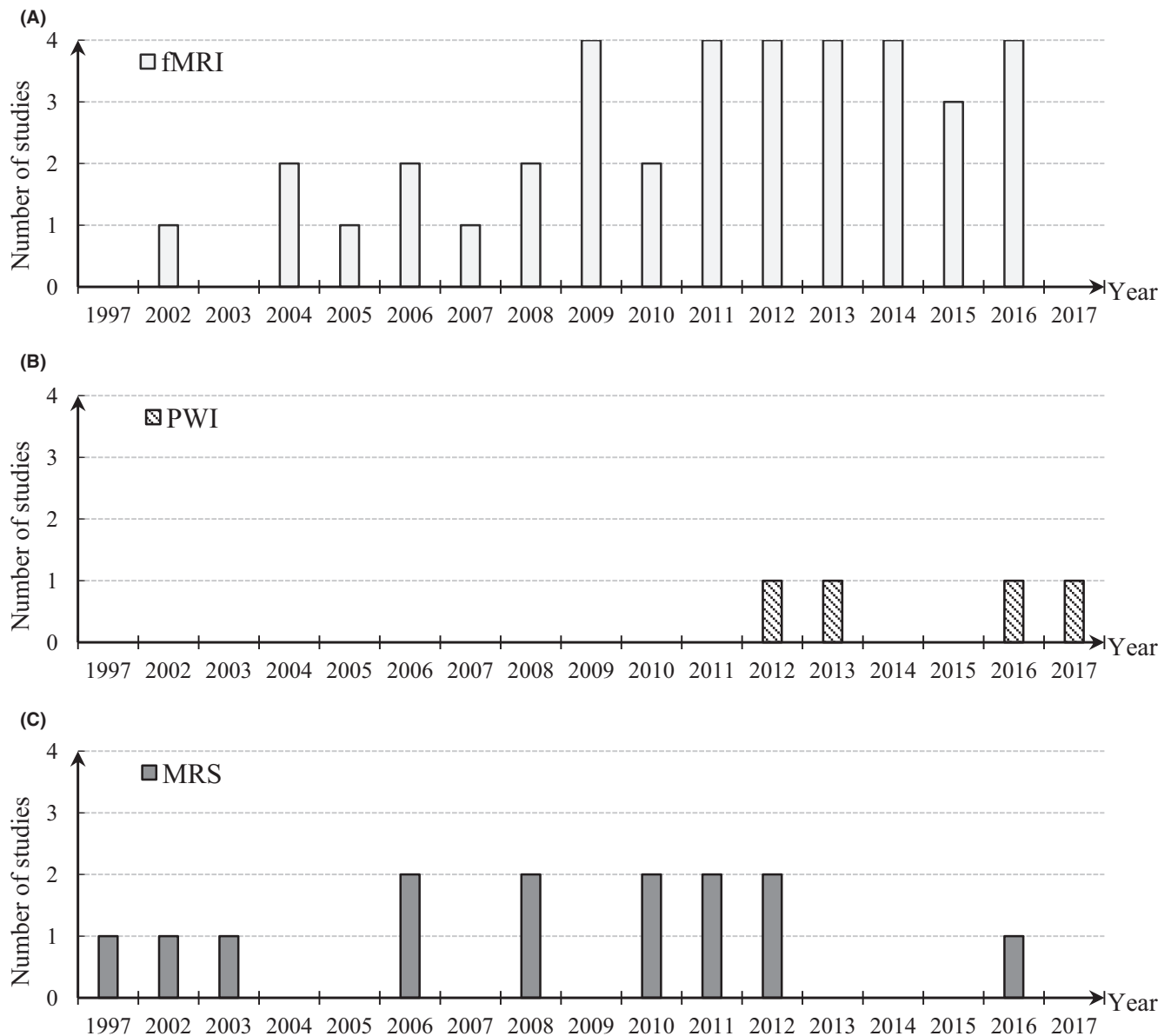
Jessen et al<sup>71</sup> reported a significant increase in both NAA and NAA/Cr in the voxel of interest (VOI) in the left parietal lobe, after 3 months of donepezil treatment in mild-moderate AD, which was correlated with the ADAS-cog score. Modrego et al<sup>72</sup> showed that rivastigmine had a modest effect on AD, in preventing the reduction of NAA/Cr in the medial frontal cortex VOI (but not in the right parietal or medial occipital VOIs), whereas the treatment did not seem to affect ml/Cr in any of the brain regions. Modrego et al<sup>73</sup> further investigated the effect of either donepezil or memantine in treating mild-to-moderate AD using 6 VOIs covering several major

cortical and subcortical structures. They showed that the 2 drugs had a similar moderate effect size in terms of spectroscopic (NAA/Cr) and clinical (ADAS-cog) responses, while these measures were correlated.<sup>73</sup>

More recent studies have acquired MRS at 3.0T for improved signal-to-noise ratio.<sup>30</sup> Henigsberg et al<sup>74</sup> reported an increase of NAA/Cr in the left dorsal lateral prefrontal cortex in 10 out of 12 mild-moderate AD patients postdonepezil treatment. Ashford et al<sup>75</sup> conducted a pilot study investigating brain metabolite response to memantine treatment in 10 mild-moderate AD patients, but failed to detect a treatment-induced change in NAA/Cr in the right dorsal lateral prefrontal cortex VOI, nor a change in ADAS-cog. A 4.0T study by Song et al<sup>76</sup> on mild AD patients undergoing standard ChEI treatment showed a higher level of Cr (than HC) in the posterior cingulate VOI, but not in the dorsolateral prefrontal VOI. A lower level of NAA/Cr and Glu/Cr was also seen in AD regardless of treatment.<sup>76</sup>

At 3.0T, Gordon et al<sup>77</sup> placed a VOI in the precuneus-posterior cingulate area in studying brain metabolite changes in response to a combined ChEI (either donepezil or galantamine) and memantine treatment in mild-moderate AD. An increase in ml and a decrease in NAA/ml were found after 48 weeks of treatment.<sup>77</sup> Moon et al<sup>78</sup> used voxel-based morphometry and MRS to investigate alterations of brain structure and hippocampal metabolites in AD with donepezil treatment. They showed simultaneous increases in NAA/Cr and decreases in ml/Cr and Cho/Cr, and increased hippocampal, precuneus, fusiform, and caudate volumes in treated AD, compared to baseline.<sup>78</sup>





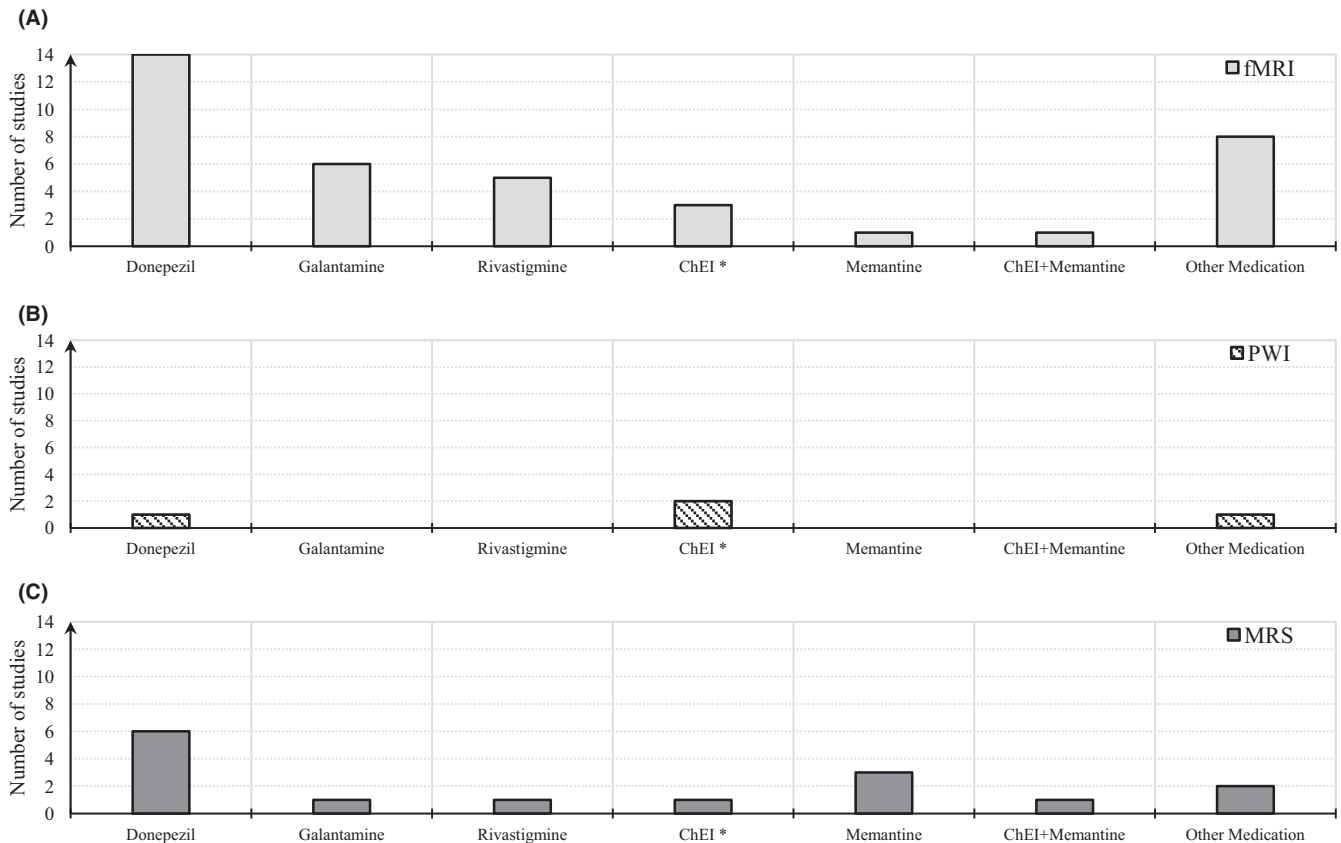
**FIGURE 2** Number of studies using different functional magnetic resonance imaging (MRI) technologies by year. A, Blood oxygen level-dependent fMRI (BOLD-fMRI); B, perfusion-weighted imaging (PWI); C, proton magnetic resonance spectroscopy (MRS) and MRS imaging

A few studies showed changes in glutamate rather than NAA. Glodzik et al<sup>79</sup> investigated memantine effect on AD, MCI, and younger and older HC subjects using MRS imaging, and reported a significantly reduced rate of Glu/Cr increase in the left hippocampus in the treated subjects, compared to nontreated subjects; a change in Glu/Cr was not found in the right hippocampus, nor in NAA/Cr on either side.<sup>79</sup> Bartha et al<sup>80</sup> conducted a MRS study at 4.0T and reported a decrease in the level of NAA, Cho, and ml/Cr in the right hippocampal VOI in AD after donepezil treatment; however, the level of Glu remained relatively stable over the 16-week treatment duration, which was interpreted as a positive medication effect.<sup>80</sup> The same group<sup>81</sup> further tested the effect of galantamine in treating AD, and were able to identify an increase in Glu in the right hippocampal VOI, following 4-month treatment, while a change in NAA was not found.<sup>81</sup>

## 4 | DISCUSSION

### 4.1 | Trends of research publications

This review suggests that BOLD-fMRI has been preferably used in studying pharmacological effects on AD. After the first publication in 2002, the number of BOLD-fMRI studies on ChEI/memantine increased since 2009, and stabilized onwards until 2016 (Figures 2A and 3A). Most of the studies were on ChEI, while only 2 involved memantine (Table 2). Most recent studies have targeted nonpharmacologic alternatives, for example, exercise or cognitive training, on MCI/AD in 2017.<sup>82,83</sup> There have been only 3 PWI studies investigating medication effect on AD: All were after 2012, 1 combined BOLD and PWI, and none on memantine, while the most recent one was on other intervention, that is, the insulin sensitizer metformin<sup>84</sup>



**FIGURE 3** Number of studies investigating various medications using different functional magnetic resonance imaging (MRI) technologies. A, Blood oxygen level-dependent fMRI (BOLD-fMRI); B, perfusion-weighted imaging (PWI); C, proton magnetic resonance spectroscopy (MRS) and MRS imaging. ChEI, cholinesterase inhibitors; \*Can be a ChEI of any type (ie, the original studies did not report the exact name); other medications: physostigmine (n = 2), levetiracetam (n = 2), caffeine (n = 1), Chinese herbal medicine (n = 3), xanomeline (n = 2), or metformin (n = 1)

(Table 5; Figures 2B and 3B). The first MRS paper on AD treatment with the approved therapies was published in 2003. The number of MRS papers has remained scarce, although MRS was already used by a group of researchers in 1997/2002,<sup>85,86</sup> in studying xanomeline (Table 7; Figures 2C and 3C). Among the 3 ChEIs with a name reported in the original studies, donepezil was studied more. Memantine was typically studied using MRS (Figure 3), related to its role on moderate AD.

## 4.2 | Effect of AD medications on brain functional activation

The BOLD-fMRI studies under review used the same EPI—echo planar imaging sequence,<sup>23</sup> but were conducted under different treatment conditions (eg, medication, dosage, duration) and experimental designs (eg, tasks).

The resting-phase studies consistently suggested that each treatment resulted in increased activation in multiple brain regions (posterior cingulate cortex, parahippocampus, dorsolateral frontal cortex, middle cingulate, precuneus, anterior hippocampus, middle frontal, and precentral gyri, insular cortex and the thalamus) and increased functional connectivity in multiple networks (eg, the default mode, dorsal

attention, control and salience networks),<sup>52,54,63-67</sup> and that the brain functional responses were often correlated with cognition.<sup>52,66,67</sup>

The task-phase studies revealed different patterns of brain activation post-treatment, often depending on the fMRI tasks being used (Table 3). Visual working memory tasks increased activation in the bilateral inferior, middle, and superior frontal gyrus, and right precuneus;<sup>38,39,45,47</sup> auditory working memory tasks increased activation of the anterior ventral temporal cortex, pars triangularis, and left hippocampus,<sup>60,61</sup> while these also included the left dorsolateral prefrontal cortex and superior frontal cortex.<sup>41</sup> Face recognition task was associated with an increase in the bilateral prefrontal cortex, left fusiform, left posterior cingulate cortex, bilateral temporal lobes, left parietal lobe, and right parahippocampus.<sup>40,48,55,59</sup> Semantic association task was associated with variable results in several brain regions.<sup>44-47</sup>

The 2 studies on memantine and combined ChEI and memantine treatments both suggested a positive effect.<sup>53,58</sup>

## 4.3 | Effect of AD medications on brain circulation

The PWI studies under review all used PCASL.<sup>67-69</sup> The studies consistently suggested a treatment-induced positive effect: a CBF increase in multiple brain regions (lateral temporal lobe, cingulate,

and the white matter of posterior cingulate and prefrontal) that was clinically meaningful<sup>67,68</sup> or CBF stabilization.<sup>69</sup>

#### 4.4 | Effect of AD medications on brain metabolites

The MRS studies under review used several popular sequences for VOI selection, for example, PRESS and LASER.<sup>30</sup> They all examined changes in NAA (surrogate neuronal marker) in response to treatment, while high-field studies also examined Glu (excitatory neurotransmitter and involvement in glucose metabolism).

Magnetic resonance spectroscopic findings have varied markedly, presumably related to the differences in medication and treatment duration being applied, and brain location being examined. Most studies suggested a positive ChEI treatment effect based on increased NAA or NAA/Cr in the posterior cingulate gyrus, hippocampus, and prefrontal lobe;<sup>70-74,81</sup> some also suggested a change of Im/Cr in the occipital and prefrontal lobe.<sup>72,73</sup> A small number of studies showed decreased NAA in the hippocampus, posterior cingulate gyrus, or dorsolateral prefrontal cortex.<sup>76,78,80</sup> A few studies suggested a positive treatment effect based on the change of Glu or Glu/Cr in the hippocampus,<sup>81</sup> while other studies failed to show such a change.<sup>76,80</sup> Several studies suggested the clinical meaningfulness of the brain metabolite changes.<sup>71-73,81</sup>

Studies have not suggested a significant change in the level of NAA/Cr or Glu/Cr post memantine treatment,<sup>73,75,79</sup> likely reflecting a disease-condition influence, while the efficacy of combining ChEI-memantine was also unclear.<sup>77</sup>

#### 4.5 | Effect of other medications

Tables 1-7 and Figures 1-3 have also included the studies investigating other medications that are beyond the FDA-approved ones but are sometimes used as supplementary treatments, for example, physostigmine, levetiracetam, caffeine, herbs, xanomeline, and metformin.

Using BOLD-fMRI, Bentley et al<sup>87,88</sup> showed that single-dose physostigmine modulated AD patients' visual and attentional responses and help with memory. Bakker et al<sup>89,90</sup> showed that levetiracetam helped reduce hippocampal hyperactivity and improve medial temporal lobe network in MCI. Haller et al<sup>91</sup> reported that caffeine administration enhanced brain response in MCI. Zhang et al<sup>92-94</sup> reported the effect of Chinese medicine in treating MCI at both resting and task phases.

Using MRS, Satlin et al<sup>85</sup> showed decreased Cho/Cr in parietal lobe, while Frederick et al<sup>86</sup> showed improved acetylcholine synthesis, with xanomeline treatment.

Using PCASL-PWI, Koenig et al<sup>84</sup> showed an orbitofrontal cerebral blood flow increase in MCI and AD with metformin treatment.

#### 4.6 | Strengths, challenges, and future of the functional MRI technologies on AD therapy

Functional MRI technologies can provide valuable information indicating brain function, circulation, and metabolite changes in response to

AD medication treatment. As these brain changes can be sensitively detected, the technologies allow for more focused study by taking advantage of smaller relatively sample sizes, improving efficiency. The quantitative PWI and MRS methods have enabled noninvasive collection of and objective data that are easy to compare and repeat over time, benefiting long-term evaluation of intervention efficacy.

However, interpretation of task-based data can be limited by the choice of experimental paradigm. Ability to attend to task can also bias resulting activation. Even so, data acquisition with BOLD-fMRI, PWI, and MRS can also be completed without a task performance, particularly beneficial in the study of AD.

Another caveat of functional MRI is related to unsatisfactory signal-to-noise ratio with functional imaging data, which can affect the complexity of data processing and accuracy of analysis results, especially regarding quantification. With this aspect, high MRI field strengths have great advantages.

In addition, caution should be taken to result interpretation by taking into account details in the study design. Even when using the same imaging technologies, variations can occur in field strength, medication dose, treatment duration, sample size, and analysis methods, leading to possible variability in the result.

In the future, multiple modalities of functional MRI technology can be combined to integrate different aspects of brain responses, allowing us to achieve a more comprehensive interpretation of the pharmacological effects of treatment on AD.

## 5 | CONCLUSION

Functional MRI techniques have provided valuable information over the past few decades, in helping researchers and neuroscientists understand the treatment effect of AD medications. This information is critical to developing patient-centered novel/better approaches that aim to potentially prevent and cure the disease.

### ACKNOWLEDGEMENTS

We would like to gratefully acknowledge China's Scholarship Council for providing Scholarship Award to H. Guo; Canada's National Science and Engineering Research Council for providing funding to L. Grajauskas in the form of an Alexander Graham Bell graduate research fellowship; and operating grants from Canadian Institutes of Health Research #CSE-125739 and Surrey Hospital and Outpatient Centre Foundation (#FHREB2015-030) to X. Song.

### CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

### ORCID

Xiaowei Song  <http://orcid.org/0000-0001-9589-2520>

## REFERENCES

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
2. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13:614-629.
3. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269.
4. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2016;12:459-509.
5. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9:63-75.
6. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366:2112-2117.
7. Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. 2017;13:1-7.
8. Harrison JR, Owen MJ. Alzheimer's disease: the amyloid hypothesis on trial. *Br J Psychiatry*. 2016;208:1-3.
9. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256:184-185.
10. Perl DP. Neuropathology of Alzheimer's disease. *Mt Sinai J Med*. 2010;77:32-42.
11. Reitz C, Mayeux R. Alzheimer's disease: epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem Pharmacol*. 2014;88:640-651.
12. Schneider LS, Mangialasche F, Andreasen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med*. 2014;275:251-283.
13. Bakota L, Brandt R. Tau biology and tau-directed therapies for Alzheimer's disease. *Drugs*. 2016;76:301-313.
14. Babic T. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry*. 1999;67:558.
15. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. *Clin Med (Lond)*. 2016;16:247-253.
16. Galimberti D, Scarpini E. Treatment of Alzheimer's disease: symptomatic and disease-modifying approaches. *Curr Aging Sci*. 2010;3:46-56.
17. Folch J, Busquets O, Ettcheto M, et al. Memantine for the treatment of dementia: a review on its current and future applications. *J Alzheimers Dis*. 2018;62:1223-1240.
18. Muir JL. Acetylcholine, aging, and Alzheimer's disease. *Pharmacol Biochem Behav*. 1997;56:687-696.
19. Molino I, Colucci L, Fasanaro AM, Traini E, Amenta F. Efficacy of memantine, donepezil, or their association in moderate-severe Alzheimer's disease: a review of clinical trials. *ScientificWorldJournal*. 2013;2013:925702.
20. Tan CC, Yu JT, Wang HF, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2014;41:615-631.
21. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*. 1990;14:68-78.
22. Ogawa S, Menon RS, Tank DW, et al. Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J*. 1993;64:803-812.
23. Holdsworth SJ, Bammer R. Magnetic resonance imaging techniques: fMRI, DWI, and PWI. *Semin Neurol*. 2008;28:395-406.
24. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol*. 2010;20:519-534.
25. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol*. 2013;34:1866-1872.
26. McGehee BE, Pollock JM, Maldjian JA. Brain perfusion imaging: how does it work and what should I use? *J Magn Reson Imaging*. 2012;36:1257-1272.
27. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. *J Cereb Blood Flow Metab*. 1999;19:701-735.
28. Chen W, Song X, Beyea S, D'Arcy R, Zhang Y, Rockwood K. Advances in perfusion magnetic resonance imaging in Alzheimer's disease. *Alzheimers Dement*. 2011;7:185-196.
29. Liu TT, Brown GG. Measurement of cerebral perfusion with arterial spin labeling: part 1. Methods. *J Int Neuropsychol Soc*. 2007;13:517-525.
30. Zhang N, Song X, Bartha R, et al. Advances in high-field magnetic resonance spectroscopy in Alzheimer's disease. *Curr Alzheimer Res*. 2014;11:367-388.
31. Novotny EJ Jr, Fulbright RK, Pearl PL, Gibson KM, Rothman DL. Magnetic resonance spectroscopy of neurotransmitters in human brain. *Ann Neurol*. 2003;54:S25-S31.
32. Zhu H, Barker PB. MR spectroscopy and spectroscopic imaging of the brain. *Methods Mol Biol*. 2011;711:203-226.
33. Wierenga CE, Bondi MW. Use of functional magnetic resonance imaging in the early identification of Alzheimer's disease. *Neuropsychol Rev*. 2007;17:127-143.
34. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2:a006213.
35. Jack CR Jr, Marjanska M, Wengenack TM, et al. Magnetic resonance imaging of Alzheimer's pathology in the brains of living transgenic mice: a new tool in Alzheimer's disease research. *Neuroscientist*. 2007;13:38-48.
36. [https://www.nlm.nih.gov/pubs/factsheets/dif\\_med\\_pub.html](https://www.nlm.nih.gov/pubs/factsheets/dif_med_pub.html). Accessed September 08, 2017.
37. Canu E, Sarasso E, Filippi M, Agosta F. Effects of pharmacological and nonpharmacological treatments on brain functional magnetic resonance imaging in Alzheimer's disease and mild cognitive impairment: a critical review. *Alzheimers Res Ther*. 2018;10:21.
38. Rombouts SA, Barkhof F, Van Meel CS, Scheltens P. Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002;73:665-671.
39. Goekoop R, Rombouts SA, Jonker C, et al. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. *NeuroImage*. 2004;23:1450-1459.
40. Goekoop R, Scheltens P, Barkhof F, Rombouts SA. Cholinergic challenge in Alzheimer patients and mild cognitive impairment differentially affects hippocampal activation—a pharmacological fMRI study. *Brain*. 2006;129:141-157.
41. Saykin AJ, Wishart HA, Rabin LA, et al. Cholinergic enhancement of frontal lobe activity in mild cognitive impairment. *Brain*. 2004;127:1574-1583.
42. Kircher TT, Erb M, Grodd W, Leube DT. Cortical activation during cholinesterase-inhibitor treatment in Alzheimer disease: preliminary findings from a pharmaco-fMRI study. *Am J Geriatr Psychiatry*. 2005;13:1006-1013.
43. Grön G, Brandenburg I, Wunderlich AP, Riepe MW. Inhibition of hippocampal function in mild cognitive impairment: targeting the cholinergic hypothesis. *Neurobiol Aging*. 2006;27:78-87.
44. Shanks MF, McGeown WJ, Forbes-McKay KE, Waiter GD, Ries M, Venneri A. Regional brain activity after prolonged cholinergic

- enhancement in early Alzheimer's disease. *Magn Reson Imaging*. 2007;25:848-859.
45. McGeown WJ, Shanks MF, Venneri A. Prolonged cholinergic enrichment influences regional cortical activation in early Alzheimer's disease. *Neuropsychiatr Dis Treat*. 2008;4:465-476.
  46. McGeown WJ, Shanks MF, Forbes-McKay KE, et al. Established donepezil treatment modulates task relevant regional brain activation in early Alzheimer's disease. *Curr Alzheimer Res*. 2010;7:415-427.
  47. Venneri A, McGeown WJ, Shanks MF. Responders to ChEI treatment of Alzheimer's disease show restitution of normal regional cortical activation. *Curr Alzheimer Res*. 2009;6:97-111.
  48. Petrella JR, Prince SE, Krishnan S, Husn H, Kelley L, Doraiswamy PM. Effects of donepezil on cortical activation in mild cognitive impairment: a pilot double-blind placebo-controlled trial using functional MR imaging. *AJNR Am J Neuroradiol*. 2009;30:411-416.
  49. Bokde AL, Karmann M, Teipel SJ, et al. Decreased activation along the dorsal visual pathway after a 3-month treatment with galantamine in mild Alzheimer disease: a functional magnetic resonance imaging study. *J Clin Psychopharmacol*. 2009;29:147-156.
  50. Bokde AL, Cavado E, Lopez-Bayo P, et al. Effects of rivastigmine on visual attention in subjects with amnesic mild cognitive impairment: a serial functional MRI activation pilot-study. *Psychiatry Res*. 2016;249:84-90.
  51. Thiyaresh SN, Farrow TF, Parks RW, et al. Treatment effects of therapeutic cholinesterase inhibitors on visuospatial processing in Alzheimer's disease: a longitudinal functional MRI study. *Dement Geriatr Cogn Disord*. 2010;29:176-188.
  52. Goveas JS, Xie C, Ward BD, et al. Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. *J Magn Reson Imaging*. 2011;34:764-773.
  53. Lorenzi M, Beltramello A, Mercuri NB, et al. Effect of memantine on resting state default mode network activity in Alzheimer's disease. *Drugs Aging*. 2011;28:205-217.
  54. Zaidel L, Allen G, Cullum CM, et al. Donepezil effects on hippocampal and prefrontal functional connectivity in Alzheimer's disease: preliminary report. *J Alzheimers Dis*. 2012;31:S221-S226.
  55. Miettinen PS, Pihlajamäki M, Jauhiainen AM, et al. Effect of cholinergic stimulation in early Alzheimer's disease – functional imaging during a recognition memory task. *Curr Alzheimer Res*. 2011;8:753-764.
  56. Miettinen PS, Jauhiainen AM, Tarkka IM, et al. Long-term response to cholinesterase inhibitor treatment in related to functional MRI response in Alzheimer's Disease. *Dement Geriatr Cogn Disord*. 2015;40:243-255.
  57. Song X, D'Arcy RCN, Fisk J, Darvesh S, Beyea S, Rockwood K. Correlations of prefrontal cortical activation and cognitive performance with therapeutic cholinesterase inhibitor treatment: a high-field functional magnetic resonance imaging study. *Alzheimers Dement*. 2011;7:S377.
  58. McLaren DG, Sreenivasan A, Diamond EL, et al. Tracking cognitive change over 24 weeks with longitudinal functional magnetic resonance imaging in Alzheimer's disease. *Neurodegener Dis*. 2012;9:176-186.
  59. Pa J, Berry AS, Compagnone M, et al. Cholinergic enhancement of functional networks in older adults with mild cognitive impairment. *Ann Neurol*. 2013;73:762-773.
  60. Dhanjal NS, Warren JE, Patel MC, Wise RJ. Auditory cortical function during verbal episodic memory encoding in Alzheimer's disease. *Ann Neurol*. 2013;73:294-302.
  61. Dhanjal NS, Wise RJ. Frontoparietal cognitive control of verbal memory recall in Alzheimer's disease. *Ann Neurol*. 2014;76:241-251.
  62. Risacher S, Wang Y, Wishart HA, et al. Cholinergic enhancement of brain activation in mild cognitive impairment during episodic memory encoding. *Front Psychiatry*. 2013;4:105.
  63. Solé-Padullés C, Bartrés-Faz D, Lladó A, et al. Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memory encoding in Alzheimer's disease. *J Clin Psychopharmacol*. 2013;33:199-205.
  64. Wang L, Day J, Roe CM, et al. The effect of APOE ε4 allele on cholinesterase inhibitors in patients with Alzheimer disease: evaluation of the feasibility of resting state functional connectivity magnetic resonance imaging. *Alzheimer Dis Assoc Disord*. 2014;28:122-127.
  65. Blautzik J, Keeser D, Paolini M, et al. Functional connectivity increase in the default-mode network of patients with Alzheimer's disease after long-term treatment with Galantamine. *Eur Neuropsychopharmacol*. 2016;26:602-613.
  66. Griffanti L, Wilcock GK, Voets N, et al. Donepezil enhances frontal functional connectivity in Alzheimer's Disease: a pilot study. *Dement Geriatr Cogn Dis Extra*. 2016;6:518-528.
  67. Li W, Antuono PG, Xie C, et al. Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathways associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. *NeuroImage*. 2012;60:1083-1091.
  68. Chaudhary S, Scouten A, Schwindt G, et al. Hemodynamic effects of cholinesterase inhibition in mild Alzheimer's disease. *J Magn Reson Imaging*. 2013;38:26-35.
  69. Janik R, Thomason LA, Chaudhary S, et al. Attenuation of functional hyperemia to visual stimulation in mild Alzheimer's disease and its sensitivity to cholinesterase inhibition. *Biochim Biophys Acta*. 2016;1862:957-965.
  70. Krishnan KR, Charles HC, Doraiswamy PM, et al. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *Am J Psychiatry*. 2003;160:2003-2011.
  71. Jessen F, Traeber F, Freymann K, Maier W, Schild HH, Block W. Treatment monitoring and response prediction with proton MR spectroscopy in AD. *Neurology*. 2006;67:528-530.
  72. Modrego PJ, Pina MA, Fayed N, Díaz M. Changes in metabolite ratios after treatment with rivastigmine in Alzheimer's disease: a nonrandomised controlled trial with magnetic resonance spectroscopy. *CNS Drugs*. 2006;20:867-877.
  73. Modrego PJ, Fayed N, Errea JM, Rios C, Pina MA, Sarasa M. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. *Eur J Neurol*. 2010;17:405-412.
  74. Henigsberg N, Kalember P, Hrabac P, et al. 1-H MRS changes in dorsolateral prefrontal cortex after donepezil treatment in patients with mild to moderate Alzheimer's disease. *Coll Antropol*. 2011;35: S159-S162.
  75. Ashford JW, Adamson M, Beale T, et al. MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia. *J Alzheimers Dis*. 2011;26:S331-S336.
  76. Song X, Zhang N, D'Arcy R, et al. Increased creatine in the posterior cingulate cortex in early Alzheimer's disease: a high-field MR spectroscopy study. The 12th International Conference on Alzheimer's Disease. *Alzheimers Dement*. 2012;8:S350-S351.
  77. Gordon ML, Kingsley PB, Goldberg TE, et al. An open-label exploratory study with memantine: correlation between proton magnetic resonance spectroscopy and cognition in patients with mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Dis Extra*. 2012; 2:312-320.
  78. Moon CM, Kim BC, Jeong GW. Effects of donepezil on brain morphometric and metabolic changes in patients with Alzheimer's disease: a DARTEL-based VBM and (1)H-MRS. *Magn Reson Imaging*. 2016;34:1008-1016.
  79. Glodzik L, King KG, Gonen O, Liu S, De Santi S, de Leon MJ. Memantine decreases hippocampal glutamate levels: a magnetic resonance spectroscopy study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1005-1012.



80. Bartha R, Smith M, Rupsingh R, Rylett J, Wells JL, Borrie MJ. High field  $^1\text{H}$  MRS of the hippocampus after donepezil treatment in Alzheimer disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:786-793.
81. Penner J, Rupsingh R, Smith M, Wells JL, Borrie MJ, Bartha R. Increased glutamate in the hippocampus after galantamine treatment for Alzheimer disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:104-110.
82. Chirles TJ, Reiter K, Weiss LR, Alfini AJ, Nielson KA, Smith JC. Exercise training and functional connectivity changes in mild cognitive impairment and healthy elders. *J Alzheimers Dis*. 2017;57:845-856.
83. Ochmann S, Dyrba M, Grothe MJ, et al. Does functional connectivity provide a marker for cognitive rehabilitation effects in Alzheimer's disease? An interventional study *J Alzheimers Dis*. 2017;57:1303-1313.
84. Koenig AM, Mechanic-Hamilton D, Xie SX, et al. Effects of the insulin sensitizer metformin in Alzheimer disease: pilot data from a randomized placebo-controlled crossover study. *Alzheimer Dis Assoc Disord*. 2017;31:107-113.
85. Satlin A, Bodick N, Offen WW, Renshaw PF. Brain proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) in Alzheimer's disease: changes after treatment with xanomeline, an M1 selective cholinergic agonist. *Am J Psychiatry*. 1997;154:1459-1461.
86. Frederick BD, Satlin A, Wald LL, Hennen J, Bodick N, Renshaw PF. Brain proton magnetic resonance spectroscopy in Alzheimer disease: changes after treatment with xanomeline. *Am J Geriatr Psychiatry*. 2002;10:81-88.
87. Bentley P, Driver J, Dolan RJ. Cholinesterase Inhibition modulates visual and attentional brain responses in Alzheimer's disease and health. *Brain*. 2008;131:409-424.
88. Bentley P, Driver J, Dolan RJ. Modulation of fusiform cortex activity by cholinesterase inhibition predicts effects on subsequent memory. *Brain*. 2009;132:2356-2371.
89. Bakker A, Krauss GL, Albert MS, et al. Reduction of hippocampal hyperactivity improves cognition in amnesic mild cognitive impairment. *Neuron*. 2012;74:467-474.
90. Bakker A, Albert MS, Krauss G, Speck CL, Gallagher M. Response of the medial temporal lobe network in amnesic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. *Neuroimage Clin*. 2015;7:688-698.
91. Haller S, Montandon ML, Rodriguez C, et al. Acute caffeine administration effect on brain activation patterns in mild cognitive impairment. *J Alzheimers Dis*. 2014;41:101-112.
92. Zhang J, Wang Z, Xu S, et al. The effects of CCRC on cognition and brain activity in aMCI patients: a pilot placebo controlled BOLD fMRI study. *Curr Alzheimer Res*. 2014;11:484-493.
93. Zhang J, Xu K, Wei D, et al. The effects of bushen capsule on episodic memory in amnesic mild cognitive impairment patients: a pilot placebo controlled fMRI study. *J Alzheimers Dis*. 2015;46:665-676.
94. Zhang J, Liu Z, Zhang H, et al. A two-year treatment of amnesic mild cognitive impairment using a compound Chinese medicine: a placebo controlled randomized trial. *Sci Rep*. 2016;6:28982.

**How to cite this article:** Guo H, Grajauskas L, Habash B, D'Arcy RCN, Song X. Functional MRI technologies in the study of medication treatment effect on Alzheimer's disease. *Aging Med*. 2018;1:75-95. <https://doi.org/10.1002/agm2.12017>