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

Hui Guo1,2,3 | Lukas Grajauskas1,2 | Baraa Habash1,4 | Ryan CN D’Arcy1,2,4,5 | Xiaowei Song1,2,4,5

1SFU ImageTech Laboratory, Surrey Memorial Hospital, Surrey, BC, Canada
2Health Sciences and Innovation, Surrey Memorial Hospital, Fraser Health, Surrey, BC, Canada
3Department of Diagnostic Imaging, Tianjin Medical University General Hospital, Tianjin, China
4Department of Engineering Science, Simon Fraser University, Burnaby, BC, Canada
5Department of Computing Science, Simon Fraser University, Burnaby, BC, Canada

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 (fMRI) 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.1-3 Alongside the impact to the individual, AD has greatly challenged global socioeconomic systems due to its high prevalence and costs.4-7 Pathogenesis of AD is complex and heterogeneously presented in individuals,8 for example, extracellular deposition of amyloid-β 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.9,10 Mechanisms underlying AD neuropathological changes can involve both combined environmental and genetic effects.11

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Over the last 3 decades, β-amyloid has been the centre of a great deal of clinical trials for new drug development, but to date, none have proven successful.\textsuperscript{8,12} Drug development has also targeted the Tau pathology with unproven effect.\textsuperscript{12,13} 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.\textsuperscript{14} 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.\textsuperscript{15-17}

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.\textsuperscript{14} During synaptic transmission, acetylcholine is released into the synaptic cleft to activate receptors on the postsynaptic 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.\textsuperscript{18} 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.\textsuperscript{19,20}

Advances of functional magnetic resonance imaging (fMRI) 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,\textsuperscript{21,22} based on the paramagnetic differences between oxygenated and deoxygenated hemoglobin, which allows the detection of activated brain areas as their oxygen demand increases.\textsuperscript{21,22} 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.\textsuperscript{23} The latter measures spontaneous low-frequency fluctuations in the BOLD signal without an explicit task to investigate the status of brain functional connection.\textsuperscript{24} 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.\textsuperscript{25}

Perfusion-weighted imaging (PWI) represents another important functional MRI modality. PWI is used for noninvasively assessing cerebral hemodynamics (cerebral blood flow [CBF] and volume),\textsuperscript{26} 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).\textsuperscript{26,27} 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,\textsuperscript{28} in which radio frequency pulses are optimized to label inflowing blood water, allowing the measurement of arterial blood flow.\textsuperscript{29} The former 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.\textsuperscript{30} Based on the magnetic resonance properties of the hydrogen proton, MRS can be used to quantify levels of neurometabolites in the living brain.\textsuperscript{23,31,32} 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),

\begin{tikzpicture}[scale=0.8]
\begin{scope}
\node[draw,rectangle,align=left] (pubmed) at (0,0) {PUBMED database};
\node[draw,rectangle,align=left] (initial) at (0,-1) {Initial set of studies found 1796};
\node[draw,rectangle,align=left] (first_filter) at (0,-2) {Filter for “Human”};
\node[draw,rectangle,align=left] (second_filter) at (0,-3) {Filter for “English”};
\node[draw,rectangle,align=left] (full_text_filter) at (0,-4) {Filter for “full text”};
\node[draw,rectangle,align=left] (original_filter) at (0,-5) {Filter for “original research”};
\node[draw,rectangle,align=left] (exclude) at (0,-6) {Title and abstracts reading to exclude non-MRI & non-pharmacologic, etc.};
\node[draw,rectangle,align=left] (bold-fmri) at (3,-7) {BOLD-fMRI = 38};
\node[draw,rectangle,align=left] (pwi) at (3,-8) {PWI = 4};
\node[draw,rectangle,align=left] (mrs) at (3,-9) {MRS = 14};
\end{scope}
\draw[->] (pubmed) -- (initial);
\draw[->] (initial) -- (first_filter);
\draw[->] (first_filter) -- (second_filter);
\draw[->] (second_filter) -- (full_text_filter);
\draw[->] (full_text_filter) -- (original_filter);
\draw[->] (original_filter) -- (exclude);
\draw[->] (exclude) -- (bold-fmri);
\draw[->] (exclude) -- (pwi);
\draw[->] (exclude) -- (mrs);
\end{tikzpicture}

\textbf{FIGURE 1} Flowchart showing the literature search process
| 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 gyrus, fusiform gyrus, posterior cingulate, hippocampus, and left anterior parahippocampal gyrus. |

(Continues)
| 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 gyrus, 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 an 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 |
| 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)
| 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 | 12 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)
| 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 encoding, and retrieval tasks | (1) Increased activation in left lateral posterior parietal and lateral frontal cortex aftertreatment, 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 | | 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 anterior cingulate temporal lobes with galantamine than with galantamine + placebo |
| Bokde AL     | 2016 | Amnestic 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; DLPFC, 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.
and at high field may also include myo-inositol (mI), lipid, lactate, glutamate (Glu), glutamine (Gln), and γ-aminobutyric acid.\textsuperscript{23,30-32} 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

| First author     | Year | Medication | Donepezil | Galantamine | Rivastigmine | ChEI$^a$ | 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-Padullé 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.
$^a$Can be any ChEI (ie, the original studies did not name it).
glutamatergic abnormalities in the AD that can occur long ahead of clinical manifestation). 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.

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

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

CHEI, cholinesterase inhibitors.

*Number of studies. Some studies used more than 1 tasks.

b Can be any ChEI (ie, the original studies did not report it).
### 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) | ChEIs on AD | Donepezil: 5-10; galantamine: 24; rivastigmine: 4.5, reminyl: 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 compared 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 bl; (2) CBF decreased in AD relative to HC during task at bl; (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.
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. 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 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. The same group 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. Goekoop et al 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 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 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 studied MCI patients performing a spatial navigation task and showed an increased activation in multiple regions after 7-day galantamine treatment.

Shanks et al 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 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. Later, McGeown et al 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. In a retrospective analysis, Venneri et al divided the patients into drug responders and nonresponders and observed activation changes only in the former group.

Further, Petrella et al 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 studied 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 examined the effect of 3-6 months of rivastigmine treatment on MCI and reported an increased activation. Thiagesh et al 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 showed that mild AD patients improved their hippocampal-functional connectivity after 3-month donepezil treatment, correlated with global cognition assessment. Lorenzi et al showed an increased activation in the right precuneus and calcarine gyrus in moderate AD patients after 6-month memantine treatment. Similarly, Zaidel et al showed increased activation in the bilateral dorsolateral prefrontal cortex after 8 weeks of donepezil treatment.

Miettinen et al reported a greater prefrontal fMRI activation during face recognition post a single dose or 4-week rivastigmine treatment in mild AD. Miettinen et al 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 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 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 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 mm³), left parietal lobe (25 × 25 × 30 mm³); 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 each medial frontal, right parietal, and left 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 cm³ 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 | Memantine | 5 mg/d for 4 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 mm³ 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)
| 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 mm³, 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 cm³ 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 mm³ 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 mm³ 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 mm³ 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 |
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; 26 wk 4.0 cm³ 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 mm³ 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.
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.69

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 al70 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.70

Jessen et al71 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 al72 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 al73 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.73

More recent studies have acquired MRS at 3.0T for improved signal-to-noise ratio.70 Henigsberg et al74 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 al75 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 al76 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.76

At 3.0T, Gordon et al77 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.77 Moon et al78 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.78

| TABLE 7 Medications in each study that used proton magnetic resonance spectroscopy (MRS) and MRS imaging |
| --- |
| First author | Year | Medication |
| | | Donepezil | Galantamine | Rivastigmine | ChEI * | 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.
*Can be any ChEI (ie, the original studies did not report it).
A few studies showed changes in glutamate rather than NAA. Glodzik et al.\(^7\) 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.\(^7\) Bartha et al.\(^8\) 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.\(^8\) The same group\(^9\) 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.\(^9\)

### 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.\(^8\) 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.\(^8\)
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 1997/2002,85,86 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,23 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),52,54,63-67 and that the brain functional responses were often correlated with cognition.52,66,67

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,38,39,45,47 auditory working memory tasks increased activation of the anterior ventral temporal cortex, pars triangularis, and left hippocampus,60,61 while these also included the left dorsolateral prefrontal cortex and superior frontal cortex.41 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.40,48,55,59 Semantic association task was associated with variable results in several brain regions.44-47

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

4.3 Effect of AD medications on brain circulation

The PWI studies under review all used PCASL.67-69 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 or CBF stabilization.

### 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. 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; some also suggested a change of Im/Cr in the occipital and prefrontal lobe. A small number of studies showed decreased NAA in the hippocampus, posterior cingulate gyrus, or dorsolateral prefrontal cortex. A few studies suggested a positive treatment effect based on the change of Glu or Glu/Cr in the hippocampus, while other studies failed to show such a change. Several studies suggested the clinical meaningfulness of the brain metabolite changes.

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

### 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, herbs, xanomeline, and metformin.

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

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

Using PCASL-PWI, Koenig et al 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.

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### CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

### ORCID

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