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Review

Determinants of approved acetylcholinesterase inhibitor response outcomes in Alzheimer's disease: relevance for precision medicine in neurodegenerative diseases

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ABSTRACT

Acetylcholinesterase inhibitors (ChEI) are the global standard of care for the symptomatic treatment of Alzheimer's disease (AD) and show significant positive effects in neurodegenerative diseases with cognitive and behavioral symptoms. Although experimental and large-scale clinical evidence indicates the potential long-term

List of Abbreviations: [^{18}F]-FDG, [^{18}F]-fluorodeoxyglucose; α7 nAChR, α7 nicotinic acetylcholine receptor subunit; Aβ, amyloid-β; Aβ42, 42-amino acid-long amyloid-β peptide; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; ADAM-17, a disintegrin and metalloproteinase 17; ADD, AD patients with dementia; ADME, absorption, distribution, metabolism, and excretion profiles; AI, artificial intelligence; APOE, apolipoprotein E; APOE ε4, ε4 allele of the APOE gene;; APP, amyloid precursor protein; BChE, butyrylcholinesterase; BF, basal forebrain; BOLD, blood oxygenation level-dependent signal; BPSD, behavioral psychological symptoms of dementia; BRB, blood retinal barrier; CBF, cerebral blood flow; ChAT, choline acetyltransferase; ChEI, acetylcholinesterase inhibitors; CPIC, Clinical Pharmacogenetics Implementation Consortium; CSF, cerebrospinal fluid; CYP, cytochrome P450 superfamily; CYP2D6, subunit 2D6 of the cytochrome P450; CYP3A4, subunit 3A4 of the cytochrome P450; DLB, dementia with Lewy bodies; DMEs, drug-metabolizing enzymes; DMT, disease-modifying therapy; DTF, directed transfer function; DTI, diffusion tensor imaging; EEG, electroencephalography; ESR1, estrogen receptor α gene; FDA, U.S. Food and Drug Administration; FTLD, frontotemporal lobar degeneration; fMRI, functional magnetic resonance imaging; FUS, Fused in Sarcoma protein; GM, gray matter; GSK3, glycogen synthase kinase-3; GWAS, genome-wide association studies; HER, electronic health record; IPL, retinal inner plexiform layer; Jak2, janus kinase-2 tyrosine kinase; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy; LOAD, late-onset AD; MCI, mild cognitive impairment; MCI-AD, MCI participants converting to AD dementia; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NBM, nucleus basalis of Meynert; NF-κB, nuclear factor κB; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PDD, Parkinson's disease with dementia; PET, positron emission tomography; PHB, primary human brain cultures; PKC, protein kinase C; PON-1, paraoxonase-1; QSP, quantitative systems pharmacology; RCTs, randomized controlled trials; rsEEG, resting-state electroencephalography; sAPPα, soluble α form of APP; SNPs, single-nucleotide polymorphism; VGKCh, voltage-gated potassium channel; VGNaCh, voltage-gated sodium channel; WM, white matter; WT, wild-type variant.

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efficacy of ChEI, primary outcomes are generally heterogeneous across outpatient clinics and regional healthcare systems. Sub-optimal dosing or slow tapering, heterogeneous guidelines about the timing for therapy initiation (prodromal versus dementia stages), healthcare providers' ambivalence to treatment, lack of disease awareness, delayed medical consultation, prescription of ChEI in non-AD cognitive disorders, contribute to the negative outcomes. We present an evidence-based overview of determinants, spanning genetic, molecular, and large-scale networks, involved in the response to ChEI in patients with AD and other neurodegenerative diseases. A comprehensive understanding of cerebral and retinal cholinergic system dysfunctions along with ChEI response predictors in AD is crucial since disease-modifying therapies will frequently be prescribed in combination with ChEI. Therapeutic algorithms tailored to genetic, biological, clinical (endo)phenotypes, and disease stages will help leverage inter-drug synergy and attain optimal combined response outcomes, in line with the precision medicine model.

1. Introduction

The cholinergic circuitry of the brain is a structural, neurochemical, and functional subcortical-cortical network progressively disrupted in Alzheimer's disease (AD), including the early preclinical stages of the pathophysiological continuum (Liu et al., 2015; Mesulam, 2012). Cross-disciplinary and translational evidence coupled with in-human neuropathological findings demonstrate that the basal forebrain (BF) – specifically in Ch4 neurons within the nucleus basalis of Meynert (NBM) – represents the most significant supplier of cholinergic innervation to different cortical structures (Fig. 1) (Liu et al., 2015; Mesulam, 2013). Limbic and paralimbic neuclei represent the exclusive source of cholinergic projections to BF Ch4 neurons, which, in turn, widely project to the cerebral cortex (Francis et al., 1999; Liu et al., 2015; Mesulam, 2012), including the extra-thalamic ascending reticular activating system, the limbic system, entorhinal and prefrontal neocortex neurons. Single BF cholinergic neurons can project to all hippocampal layers, indicating the pivotal biological role of BF integrity in physiological functions of the limbic system (Ballinger et al., 2016; Francis et al., 1999; Liu et al., 2015; Mesulam, 2012).

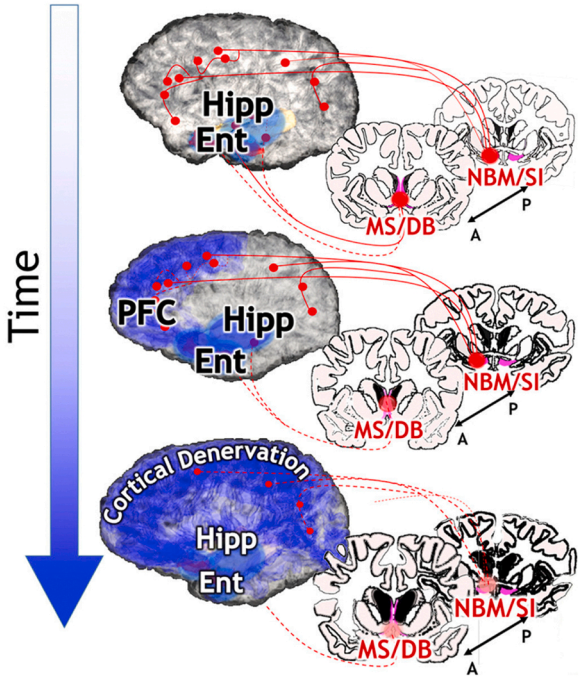

Fig. 1. The loss of cholinergic homeostasis in Alzheimer's disease: neuroanatomical substrates of a selective degenerative process. The cholinergic nuclei of the basal forebrain represent one of the first brain structures damaged in AD, followed by the progressive decay of the entire cholinergic circuitry linked to AD-related cognitive decline (i.e., basal forebrain and its cortical projections to the hippocampus and entorhinal cortex). The shift toward blue color indicates the growing neurodegeneration process affecting brain areas. *Abbreviations*: DB, the diagonal band nuclei; Ent, entorhinal cortex; Hipp, hippocampus; MS, medial septal nucleus; NB, nucleus basalis; NBM, Nucleus Basalis of Meynert; PFC, prefrontal cortex; SI, substantia innominata. Ballinger EC, et al. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. Neuron. 2016 Sep 21;91(6):1199–1218. https://doi.org/10.1016/j.neuron.2016.09.006. Copyright © 2016, Elsevier Inc.
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The loss of cholinergic homeostasis within the subcortical-cortical circuitry is associated with impaired high-order brain functions, such as learning, attention, sensory processing, memory, goal-driven behavior, mood-affective regulation, and the sleep-wake cycle (Ballinger et al., 2016; Geula and Mesulam, 1999; Li et al., 2022a; Machado et al., 2020). In addition, strict regulation of cholinergic signaling is essential for proper retinal functioning.

Animal models of AD and aging demonstrate that Ch4 neurons have a higher vulnerability to neurodegeneration and bioenergetic failure than other subcortical structures primarily affected by AD pathophysiology. This partially relates to their bio-energetic and electrophysiological properties, including the limited resources for biological adaption (Ballinger et al., 2016; Hampel et al., 2019; Li et al., 2022a)

This consistent evidence underlies the "Cholinergic Hypothesis of AD" (see also Fig. 2) (DeKosky et al., 2002; Ikonomovic et al., 2007; Poirel et al., 2018) and led to the development of symptomatic drugs modulating (and raising) the synaptic levels of acetylcholine (ACh) – namely acetylcholinesterase inhibitors (ChEI). Currently, three ChEI drugs – donepezil, rivastigmine, and galantamine – are approved (see also Table 1) and widely prescribed for symptomatic treatment of mild-to-moderate AD dementia. Clinical trials reports support the early experimental evidence that ChEI treatment can help mitigating both cognitive impairment and neuropsychiatric symptoms (namely, behavioral psychological symptoms of dementia [BPSD]) of AD (Cumbo and Ligori, 2014; Geda et al., 2013; Jelic and Winblad, 2016; Machado et al., 2020).

Despite such compelling biological and neuropharmacological data, primary and secondary therapeutic outcomes reported in daily clinical practice are inconsistent across different outpatient speciality clinics and healthcare systems (Maneno et al., 2006; Wang and Zhang, 2019), depicting ChEI efficacy as relatively short-term (6–9 months) and somewhat modest.

Potential explanations for such discrepancies concern multidimensional factors, such as sub-optimal dosing or slow tapering, unclear and heterogeneous guidelines about the timing for initiating the therapy (prodromal versus dementia stages), overall healthcare provider's ambivalence to treatment, lack of disease awareness and delayed seek for medical help, and misdiagnosis with consequent prescription of ChEI in non-AD diseases. These results from clinical practice contrast with evidence from both randomized placebo-controlled and open-label clinical trials with a 12- or 24-month follow-up, indicating a long and persistent meaningful clinical effect. In addition, longitudinal studies suggest that consistent administration of ChEI in the therapeutic dose range, alongside more prolonged drug exposure, is associated with increased survival, delayed home-nursing institutionalization (Bond et al., 2012; Feldman et al., 2009; Hansen et al., 2008; Tricco et al.,

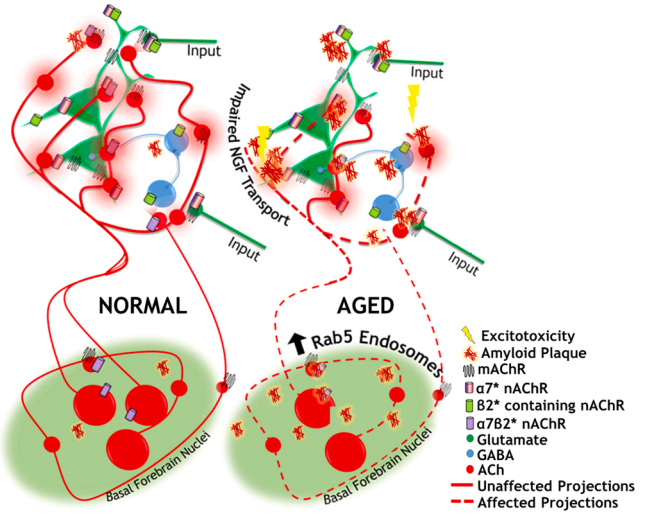

Fig. 2. The molecular dynamics behind the loss of cholinergic homeostasis in Alzheimer's disease**.** Understanding the cellular and ultrastructural dynamics of the cholinergic homeostasis is pivotal to fine tune strategies for pharmacological modulation of ACh -mediated cognitive functions, including learning, memory storage, and retrieval (Francis et al., 1999). Filling this knowledge gap goes along the importance of uncovering multi-scale compensatory mechanisms of the cholinergic system in preclinical AD (Francis et al., 1999). In AD, remodeling of the cholinergic system – including axonal projections and cortical/subcortical receptor changes – is hypothesized to reflect the degree of synaptic disruption and to "correlate" with the magnitude of the pathophysiological changes. Muscarinic (M) and nicotinic receptors are not equally affected at different spatial and temporal stages of the disease (Giacobini, 1992, 1990). Animal models of aging/AD show that M1 receptors serve to memory and learning physiological processes, which are impaired in AD, with a stage-dependent fashion (Giacobini, 1992, 1990). The clinical data on the first generation of M1 agonists has been largely inconsistent, either because of poor cognitive outcomes or side effects, often involving the cardiovascular system (Giacobini, 1992, 1990). A promising extension of the concept of selective allosteric M1 receptor modulation is the recent development of muscarinic agonists targeting the sigma-1 receptor, such as AF710B (Fisher et al., 2016). In animal models, these compounds result in lower synaptic loss, Aβ and tau pathology markers, alongside better cognitive outcomes (Fisher et al., 2016). In contrast to studies of M receptors, nicotinic receptor binding is reduced in AD brain tissue (Hall et al., 2016). Neuropathological studies and in-vivo PET imaging studies confirmed the severe loss of cortical nicotinic receptors in AD (DeSarno et al., 1988; Kadir et al., 2006), supporting the use of selective nicotinic agonists. Of particular interest have been α7 nicotinic receptors (α7 nAChR), which are highly expressed in brain regions involved in cognitive processes and are particularly vulnerable to AD pathology (Parri et al., 2011). So far, results are inconclusive for clinical, symptomatic recommendation in AD. * secondary targets might not contribute to the clinical benefits. *Abbreviations*: Aβ, amyloid-β; α7 nAChR, α7 nicotinic acetylcholine receptor subunit; ACh, acetylcholine; AD, Alzheimer's disease; M1, M1 muscarinic acetylcholine receptor; PET, positron emission tomography. Ballinger EC, et al. Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline. Neuron. 2016 Sep 21;91(6):1199–1218. https://doi.org/10.1016/j.neuron.2016.09.006. Copyright © 2016, Elsevier Inc.
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2018), decreased mortality rates (Bond et al., 2012; Feldman et al., 2009; Hansen et al., 2008; Tricco et al., 2018), and (Deardorff and Grossberg, 2016; Hampel et al., 2018; Jelic and Winblad, 2016; Wattmo et al., 2015) the possibility of a slower loss of key functional abilities when treatment is started timely (Hampel et al., 2018; Jelic and Winblad, 2016; Wattmo et al., 2015, 2011a).

1.1. Potential healthcare caveats and knowledge gaps

Although a considerable number of variables - such as the treatment duration and medication cost coverage - contribute to general uncertainty about their overall meaningfulness, treatment of AD with ChEI appears to be a resource-effective strategy (Bond et al., 2012; Pouryamout et al., 2012).

The traditional diagnostic workup of AD, based on syndromic phenotypes and not assisted by validated biological signatures, i.e., (biomarkers)-guided diagnostic and therapeutic decision-making, may lead to erroneous prescriptions of ChEI (Hampel et al., 2021a).

Patients with established vascular dementia have a low likelihood of ChEI efficacy, coupled with potential paradoxical worsening as well as cognitive and behavioral features.

Individuals with AD pathophysiology in comorbidity with moderate-to-severe chronic cerebrovascular brain damage – a frequent, age-related, clinical-radiological phenotype – exhibit mixed outcomes under treatment with ChEI (Erkinjuntti et al., 2004; Rockwood et al., 2013; Román and Kalaria, 2006).

The intake of ChEI in too advanced clinical stages of AD dementia, i.e., moderate-to-severe AD, is associated with more negligible effect and a higher risk of adverse events than in milder stages (Richter et al., 2018). Such a stage-related discrepancy can be explained through experimental, clinical, and in-silico computational models of AD, indicating a negligible possibility of recovering homeostasis when cholinergic BF neurons and ascendent projections are severely damaged (Mesulam, 2013; Richter et al., 2018).

By contrast, evidence suggests that a residual cholinergic input may be present in severe AD and/or may be mediated through spared cholinergic pathways of the thalamus and basal ganglia (Davis et al., 1999). Hence, a biological rationale for ChEI therapy in AD advanced late stage is backed by evidence of active subcortical structures and circuitries (Deardorff and Grossberg, 2016).

Although data on prescription of ChEI in prodromal (mild cognitive impairment [MCI]) stages of AD are not systematic and largely lack in-vivo assessment of AD pathophysiology, a broad range of studies –including randomized, protocol harmonized, prospective longitudinal, and biomarker-based observational studies – suggest a potentially more remarkable and extended improvement of AD long-term outcomes, if ChEI are started in prodromal stages of the disease (Atri et al., 2008; Gillette-Guyonnet et al., 2011; Petersen et al., 2018; Russ and Morling, 2012).

Concerning BPSD and their response to ChEI, there is still remarkable heterogeneity in data derived from mono-centric studies, multi-centric trials, and systematic reviews of the literature (Hampel et al., 2018; Lanctôt et al., 2017; Pinto et al., 2011). Older and recent meta-analyses and systematic reviews of the literature indicate that all the three approved ChEI may have either significant beneficial effects (Hampel et al., 2018; Herrmann, 2005; Lanctôt et al., 2017; Pinto et al., 2011) or negligible impact on different BPSD, either alone or combined (Dou et al., 2018). The lack of consensus on diagnostic frameworks for some neuropsychiatric symptoms (e.g., depression and the apathetic syndrome), the unavailability of validated tools for behavioral outcome/endpoint assessment, the heterogeneity in neuropsychiatric symptom scales used, alongside the contribution of neurochemical systems other than the cholinergic one account for the considerable discrepancy in literature (Gibson et al., 2022; Lanctôt et al., 2017; Miller et al., 2021; Pinto et al., 2011).

1.2. The redefinition of AD according to a clinical-biological construct

The Alzheimer's conceptual framework has recently evolved toward a clinical-biological construct, creating momentum for a deeper understanding of AD neurochemical changes and the biological determinants of the response to ChEI. In the last 10 years, the definition of AD has been re-considered and transformed along a clinical-biological continuum, as captured in the ATN biomarker-based classification system (see also Fig. 3) (Hampel et al., 2021a).

Biomarker-guided drug development pipelines have increasingly

facilitated drug R&D, including compounds with putative disease-modifying therapy (DMT) effect by targeting AD pathophysiological hallmarks, including tau and amyloid-β (Aβ) pathways, neuronal-axonal damage, cellular senescence, oxidative stress, and neuroinflammation. A first compound with DMT potential was approved in June 2021 by the U. S. Food and Drug Administration (FDA), while other drugs have achieved late-stage clinical development. According to the trials design and expected regulatory processes, DMT will be prescribed alongside symptomatic treatments such as ChEI (Nagata et al., 2022). Mapping out biological determinants of cholinergic pharmacological modulation and therapeutic response will optimize the combined (or, perhaps, synergistic) effect of ChEI plus one or more DMT hitting AD pathophysiological alterations. Moreover, a comprehensive understanding of the cholinergic system-enhancing strategies will open up opportunities for combination of pharmacological approaches with developing non-invasive brain stimulation (Nagata et al., 2022).

A systematic, multi-disciplinary blueprint for AD holds the potential to supply consistent evidence and related clinical guidance on the use of ChEI in other neurodegenerative diseases, such as the traditionally defined alpha synucleinopathies (i.e., dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), TDP-43 pathology, pure tauhopathies (see sections below dedicated to non-AD degenerative diseases).

In the present review, we propose a cross-disciplinary state-of-the-art overview of the established and putative biological determinants of ChEI therapy response. This intellectual endeavor aims to devise clinical insights to harmonize and optimize current ChEI prescription practices and set the stage for the upcoming biological treatments for AD.

2. The cholinergic system changes across the Alzheimer's continuum and in cognitively normal aging

There is compelling evidence that BF cholinergic neurons are highly affected by AD-related molecular pathways, including Aβ and tau proteinopathies, neuroinflammation and neurodegeneration (Hampel et al., 2021a).

Neuropathological studies conducted in AD patients and cognitively normal older adults show that Aβ accumulation in neocortical and subcortical structures, the earliest pathophysiological alteration in the AD biological continuum, is associated with accelerated loss of cholinergic fibers in the entorhinal cortex and inferior temporal gyrus (Beach et al., 1997; Cohen et al., 1988; Liu et al., 2015). Moreover, ChAT downregulation correlates with the rate of Aβ aggregates (Beach et al., 2000; Liu et al., 2015; Potter et al., 2011).

Tau neurofibrillary tangles and threads are tightly associated with AD clinical progression, with both Aβ-dependent and independent tau-mediated neurotoxic pathways (Hampel et al., 2021a). In dementia and prodromal stages of AD, most Ch4 neurons contain a substantial number of tau aggregates (Hanna Al-Shaikh et al., 2020; Liu et al., 2015; Mesulam et al., 2004). Although a causative role has not yet been ascertained, studies suggest that neurofibrillary degeneration in the NBM may be detrimental to axonal integrity (Hanna Al-Shaikh et al., 2020). When coupling these findings with the clinical evidence of age-related neurofibrillary tangles accumulation in cognitively healthy

Table 1
Key pharmacological features of approved ChEI.

Substance	Systematic name	Half-life period	Max. plasma concentration	Metabolism	Protein binding	Dosage (start/ maximum)	Mechanims of action	Potential action on muscarinic/ nicotinic receptors
Donepezil	(*RS*)− 1-Benzyl-4-[(5,6-dimethoxyindan-1-on-2-yl) methyl]piperidin	70 h	3–4 h	CYP450	95%	5/10 mg	*Primary target* Reversible noncompetitive inhibitor of AChE *Secondary targets** Agonist of the sigma-1 receptors (Ramakrishnan et al., 2014) Inhibitor of VGNaCh and VGKCh (at high doses) (Yu and Hu, 2005) Modulator of NMDA receptors (reduction of excitotoxicity) (Moriguchi et al., 2005) Inhibitor of inflammatory pathways (Kim et al., 2017)	Stimulation of α4bβ2 and α7 nicotinic receptors (Shen et al., 2010; Takada et al., 2003)
Rivastigmine	(*S*)-{3-[α-(Dimethylamino) ethyl]phenyl}-N-ethyl-N-methylcarbamat	1 h	1 h	Cholinesterase-mediated hydrolysis	40%	3/12 mg	*Primary target* Pseudo-irreversible noncompetitive inhibitor of AChE and BChE *Secondary targets** None described	None described
Galantamine	(4a*S*,6 *R*,8a*S*)− 3-Methoxy-11- methyl-4a,5,9,10,11,12-hexahydroxy-6*H*- benzofuro [3a,3,2-*e*,*f*]benzazepin-6-ol	8–10 h	4,4 h (hard capsules)	CYP2D6, CYP3A4	18%	8/24 mg	*Primary target* Reversible competitive inhibitor of AChE *Secondary targets** None described	Positive allosteric modulator (PAM) of nicotinic receptors (Albuquerque et al., 2001)

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; BChE, butyrylcholinesterase; ChEI, acetylcholinesterase inhibitors; CYP, cytochrome P450 superfamily; CYP2D6, subunit 2D6 of the cytochrome P450; CYP3A4, subunit 3A4 of the cytochrome P450; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; VGKCh, voltage-gated potassium channel; VGNaCh, voltage-gated sodium channel.

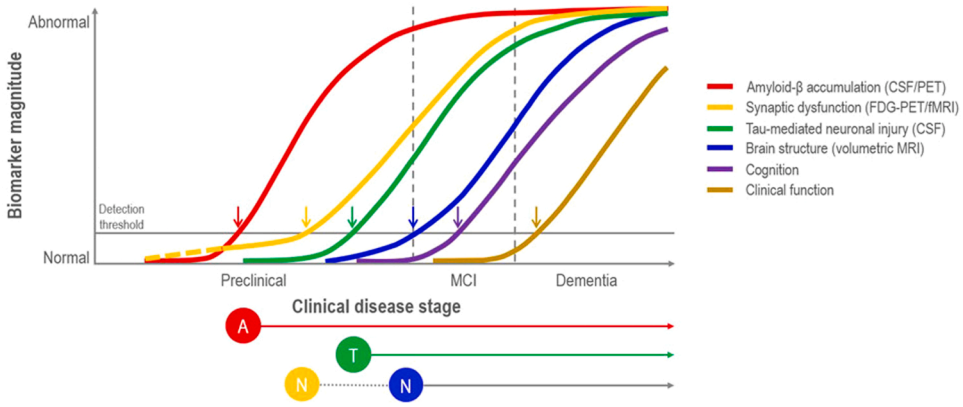

Fig. 3. Hypothetical biomarker evidence-driven model of Alzheimer's disease pathophysiology. The hypothetical model of dynamic biomarkers of AD is expanded to explicate the preclinical phase. Aβ is identified by CSF Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by [^{18}F]-FDG-PET or fMRI, with a dashed yellow line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho- tau, and brain structure is documented by structural MRI. Biomarkers changes from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Neurofilament light chain and neurogranin are newer and potentially more accurate markers of neuronal injury. *Abbreviations*: [^{18}F]-FDG, [^{18}F]-fluorodeoxyglucose; [^{18}F]-FDG-PET, [^{18}F]-fluorodeoxyglucose-positron emission tomography; Aβ, amyloid-β; Aβ42, 42-amino acid-long amyloid-β peptide; CSF, cerebrospinal fluid; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography. *Note*: from (Hampel et al., 2021b). Hampel H, et al. The Amyloid-β Pathway in Alzheimer's Disease. Mol Psychiatry. 2021 Oct;26(10):5481–5503. https://doi.org/10.1038/s41380–021–01249–0. Copyright © 2021, The Author(s).

older individuals (Moloney et al., 2021; Reas, 2017), it is conceivable to argue that neurofibrillary degeneration of cholinergic neurons in the NBM is an early biological event of the aging-AD continuum.

2.1. *The interplay between AD pathophysiology and the cholinergic homeostasis: in-vivo imaging studies*

Qualitative and semi-automatic quantitative data in molecular and structural neuroimaging confirm post-mortem findings reporting an age-related BF volumes reduction before the clinical onset of AD. In addition, a correlation of cortical Aβ load with rates of BF atrophy has been consistently reported (Grothe et al., 2016; Kerbler et al., 2015; Teipel et al., 2018) in different study cohorts.

BF atrophy is associated with cognitive decline (Grothe et al., 2010) as well as regional cortical degeneration (Teipel et al., 2011) and glucose hypometabolism (Grothe et al., 2016) that links to the cognitive deficits in a domain-specific manner. Additionally, BF atrophy covaries with the degree of Aβ pathway and tau pathophysiology expression/burden in both cognitively healthy and MCI individuals and AD dementia patients (Fernández-Cabello et al., 2020; Grothe et al., 2014; Kerbler et al., 2015; Vergallo et al., 2021).

Studies conducted on cognitively healthy individuals at risk for AD or early stages MCI individuals indicate that degeneration of the BF may be as early or even preceding entorhinal and hippocampal atrophy and that the Aβ/tau cerebral levels mediate such an effect (Brueggen et al., 2015; Fernández-Cabello et al., 2020). BF volumetric loss may be part of a vicious cycle driving the cortical spread of AD pathology and memory impairment (Schmitz et al., 2016). Clinical relevance of BF atrophy is supported by preliminary evidence that BF volumes perform significantly better than hippocampal volumes as an up-to-three-year predictor of decaying cognitive trajectories in ChEI-treated AD dementia patients (Teipel et al., 2018).

Studies using tractography diffusion tensor imaging (DTI), a technique suitable for assessing WM connections macro- and microstructural features, showed an association of the structural decay of the NBM in biologically characterized AD with loss of NBM-originating WM projections(Schumacher et al., 2021a). This study also reported a stronger correlation of NBM-WM fiber tracts with cognitive outcomes than NBM degeneration rates alone. Another tractography DTI study, conducted in two independent cohorts with available AD pathophysiology biomarkers, showed that cholinergic WM pathways are altered already in cognitively healthy individuals and worsens with relatively predictable pattern in prodromal MCI and dementia stages of the AD continuum (Nemy et al., 2022).

Among the functional neuroimaging techniques, the traditional eyes-closed resting-state electroencephalography (rsEEG) holds the unique property to capture the effects of AD on the neurophysiologic oscillatory thalamocortical mechanisms < 40 Hz underlying the (dys)functions of cholinergic systems in arousing cerebral cortex (i.e., the balance between neural hyperexcitability and hyper synchronization) to regulate the vigilance tone and selective attention in wakefulness.

Clinical evidence shows that rsEEG rhythms may be sensitive to the effects of AD pathophysiology on cholinergic ascending systems impinging on thalamocortical and cortical circuits (Babiloni et al., 2020a, 2020b; Pfurtscheller and Lopes da Silva, 1999; Rossini et al., 2020).

Finally, in-vivo evidence of an interaction between BF integrity and neuroinflammation, potentially triggered/facilitated by the accumulation of Aβ and tau species, has recently been proposed upon a data-driven pathophysiological model, in line with experimental findings (Teipel et al., 2022).

2.2. *Putative neural substrates of ChEI effects on cognitive dysfunction in AD*

The comprehensive understanding of the neural pathways of ChEI effects in AD is not fully accomplished yet. The benefit of the cholinergic stimulation in AD can occur through different neural substrates and cognitive-behavioral networks; 6–8 weeks of exposure to donepezil showed improved verbal memory (Dhanjal et al., 2013), possibly due to enhanced attention (Ollat et al., 2007; Vila-Castelar et al., 2019). By contrast, a 24–26 week intake of either donepezil or rivastigmine reported significant benefits on single or multiple domains, spanning episodic memory (Farlow et al., 2010; Grossberg et al., 2010; Salloway et al., 2008), psychomotor speed, attention (Salloway et al., 2008), visual-spatial motor abilities (Saumier et al., 2007) and lexical-semantic functioning (Saumier et al., 2007), language, and praxis (Farlow et al., 2010; Grossberg et al., 2010). Rivastigmine administered for 48 weeks also showed beneficial effects on episodic memory and world recognition (Alva et al., 2014; Wattmo et al., 2011a). A recent trial reported that muscarinic M1 receptor agonist in add-on to stable doses of donepezil can improve attention and episodic memory after 4-week combined treatment (Nathan et al., 2022).

Functional MRI studies conducted in AD dementia patients showed

that stable doses of ChEI can partially recover episodic memory by different mechanism and neuroanatomical substrates, including the modulation of the encoding-related activity in: (1) sensory cortical areas (avoiding an excessive activation interfering with the involvement of the cortical semantic systems) (Dhanjal et al., 2013), and (2) the prefrontal cortex controlling working memory and attention circuits (Miettinen et al., 2011), and (3) inferior parietal lobule, precuneus, hippocampus, and parahippocampal gyrus (McLaren et al., 2012). Emerging paradigms in neuroscience, capable of integrating multi-modal biological and imaging markers, will offer viable research blueprints to investigate the ChEI effects from the molecular up to the large-scale network level (see the Section 4.2).

2.3. The cholinergic-monoaminergic systems interplay in AD cognitive and behavioral deficits

Translational studies indicate that the dopaminergic and cholinergic systems operate dynamically to regulate motion, vigilance, incentive-motivated behaviors, and cognitive functions (Amalric et al., 2021). Failure to keep this balance is associated with neurological and psychiatric disorders (Aosaki et al., 2010). Cortical dopaminergic projections are involved in cognitive and behavioral functions (Ott and Nieder, 2019), as also indicated by the association of spatial working memory impairment and dopamine depletion within the medial prefrontal cortex (Surmeier, 2007). Disruption of the dopaminergic system alongside the loss of the modulatory effect that the cholinergic system exerts on the former is documented in AD, including its early clinical stages (Koch et al., 2014; Nobili et al., 2017). The cholinergic-dopaminergic systems interaction is suggested by evidence about the loss of cholinergic neurons in AD and is associated with downstream disruption of the dopaminergic neurotransmission and subsequent onset of psychiatric symptoms (Lyketsos et al., 2011; Martorana and Koch, 2014). In addition, high-doses of anticholinergic drugs – particularly mAChR antagonists – can induce psychosis (Terry, Jr, 2008). The molecular mechanisms underlying the physiological and pathophysiological cholinergic-dopaminergic system interaction still remain elusive. The *nucleus accumbens* is innervated by the cholinergic latero-dorsal tegmental and pedunculopontine nuclei, which in turn innervates the NBM. ACh released in the *nucleus accumbens* is hypothesized to regulate dopamine release through M4 autoreceptors (Hampel et al., 2018; Mesulam, 2013). Moreover, local ACh-release from cholinergic nicotinic receptor-expressing interneurons tunes DA-release in the striatum (Bohnen et al., 2022; Mercuri et al., 2021). Authoritative neuropathological studies suggest that mental, mood-affective, and/or behavioral disorders may mainly depend on neurodegenerative processes within neuromodulatory subcortical noradrenergic and serotoninergic nuclei, including the locus coeruleus, dorsal raphe nucleus, and the hypothalamic nuclei (Gibson et al., 2022; Lanctôt et al., 2017; Miller et al., 2021; Pinto et al., 2011). The loss of NBM cholinergic neurons and related ascending projections is associated with an imbalance of both serotonergic and noradrenergic ascending projections (Bohnen et al., 2022; Lanctôt et al., 2017). Co-occurring monoaminergic alterations are observed in experimental models of AD-like dementia with BPSD, such as psychosis, agitation, disinhibition, and aggression (Albin et al., 2022; Bohnen et al., 2022; Lanctôt et al., 2017; Pinto et al., 2011). Such a complex neurochemical landscape, characterized by elegant bidirectional regulatory feedback loops and molecular cross-talks, may partially explain heterogenous data about the efficacy of ChEI in relieving the BPSD in AD (for a more extensive overview of ChEI in PD and DLB, see the dedicated section below).

3. Genetic factors involved in the cholinergic homeostasis

3.1. Common LOAD genetic risk factors and cholinergic system

According to large-scale genome-wide association studies (GWAS) and functional annotation data, neither causal (autosomal dominant or recessive) genetic mutations nor genetic susceptibility factors stand out for an association with the cholinergic system decay in late-onset AD (LOAD). However, cross-dictionary evidence indicates that a few genetic risk factors for LOAD, as well as genes coding for proteins and pathways involved in the cholinergic homeostasis, are likely to influence biological predictors of AD and drug treatment outcomes.

3.2. Apolipoprotein E

The apolipoprotein E (*APOE*) *ε4* allele is the most significant genetic risk factor for LOAD (Corder et al., 1993; Poirier et al., 1993). *APOE* has three major allelic variants, *APOE ε2*, *APOE ε3*, and *APOE ε4*, with the *ε3* allele being the most common (~75%) and *ε2* allele the least common (~7%) (Liu et al., 2013).

Age-related memory performance in *APOE ε4* carriers may diverge from performance of non-carriers before the age of 60 years despite normal clinical status, as the presence of *APOE ε4* correlates with steeper clinical trajectories and earlier functional and cognitive decline (Caselli et al., 2009; Liu et al., 2013). Homozygosity for the *APOE ε4* allele increases the risk of developing LOAD by 3- to 15-fold in a dose-dependent manner (Liu et al., 2013).

The positive association of the *APOE ε4* allele with AD pathophysiological hallmarks, including the Aβ pathway and tau pathology, is established by clinical and translational studies (Hampel et al., 2021b; Shi et al., 2017; Sperling et al., 2020; Verghese et al., 2011). A consistent association of the cholinergic system with the *APOE ε4* allele in aging/AD has not been reported. Preliminary in-vitro and animal neuropathological studies indicate a potential detrimental subcellular effect of *APOE ε4* allele on the BF cholinergic homeostasis (Duan et al., 2014; Dubelaar et al., 2004; Salehi et al., 1998).

An experimental brain aging model reports that *APOE ε4* allele is associated with deficits in the cholinergic hippocampal compensatory sprouting and remodeling response that is hypothesized to cancel out age-related decay of cholinergic deafferentation (Bott et al., 2016). However, these findings are inconsistent since previous reports indicate no direct biological association between *APOE* genotypes and the cholinergic system in AD (Miranda et al., 2015; Waring et al., 2015).

In terms of ChEI therapy response rates, few and non-systematic studies have addressed the existence of a potential *APOE*-wise effect. Results are primarily inconsistent and challenging to compare because of several study design and statistical approach issues.

Consistent findings indicate that the long-term clinical response to donepezil and rivastigmine in mild-to-moderate AD dementia patients is likely to be influenced by the *APOE ε4* allele. Studies with different designs, outcome measures, follow-up, but consistent for utilization of stable doses of donepezil/rivastigmine, point out a significant negative effect of the *ε4* allele on memory and attention scores, global cognition measures, and functional outcomes (Bizzarro et al., 2005; Choi et al., 2008; Farlow et al., 2004; Waring et al., 2015; Xiao et al., 2016). Moreover, a six-month treatment study reports a higher response of *APOE ε4* non-carriers than carriers after exposure to one of the three approved ChEI (Wattmo et al., 2011b).

All the above-mentioned studies have been performed in clinically characterized, but not biomarker-based, AD cohorts. It is plausible to speculate that an *APOE*-wise difference in ChEI treatment outcomes may be found if explicitly addressed in the AD clinical-biological continuum. Such a difference could be mediated by AD neurobiological and pathophysiological changes, which have a tight connection to the *APOE ε4* allele, as also suggested by anti-Aβ passive immunotherapy trials (Tolar et al., 2020).

In summary, the impact of the *APOE ε4* allele on the Aβ/tau pathways coupled with the established biological link between the latter and BF cholinergic neurons, allows inferring that the *APOE ε4* allele may influence short- and long-term clinical trajectories of individuals treated with future combinatorial ChEI-DMT therapeutic approaches.

3.3. Cholinergic system gene polymorphisms and treatment response

The three "traditional" genes encoding for the cholinergic system enzymes – namely acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and choline acetyltransferase (ChAT) – have been extensively studied, reporting single-nucleotide polymorphism (SNPs) in *AChE* (chromosome 7q22.1), *BCHE* (chromosome 3q26.1-q26.2), and *ChAT* (chromosome 10q11.2) genes across the general population and AD patients. While there is currently no consolidated evidence suggesting the association of these three cholinergic genes with increased risk for AD (AlzGene, n.d.), a highly-quoted study indicates that the polymorphism at *rs2177369* – with G/G over the G/A+A/A genotypes – may represent a risk factor for AD (Scacchi et al., 2009).

In addition, there are several studies investigating whether AD patients carrying some of these SNPs may exhibit different treatment response rates to donepezil and rivastigmine therapy (Harold et al., 2006; Lee et al., 2015; Scacchi et al., 2009; Yoon et al., 2015). Inconsistent results have been reported, with studies showing no differences in drug response between SNPs carrier and non-carriers and others presenting divergent longitudinal outcomes (Scacchi et al., 2009; Yoon et al., 2015).

Paraoxonase-1 (PON-1) is a protein with esterase activity and displays various biological properties, including a potent ChEI effect (Bacchetti et al., 2015; Reichert et al., 2020). The Q allozyme (Gln-192) and R allozyme (Arg-192) exhibit low and high paraoxon-hydrolyzing activity, respectively (Bacchetti et al., 2015; Reichert et al., 2020).

The influence of the *PON-1 Q192R* polymorphism on the responsiveness to treatment with ChEI, in particular, donepezil and rivastigmine in AD patients, is acknowledged: individuals carrying the *R* allele are more likely to respond to treatment rather than those *QQ* homozygous (Bacchetti et al., 2015; Pola et al., 2005; Reichert et al., 2020). This result could depend on the fact that mutations accountable for the *Q192R* SNP lead to the biosynthesis of PON-1 proteins with divergent hydrolyzing activity rates (higher for the *R* allele, lower for the *Q* allele). Given the PON-1 intrinsic anti-AChE properties, it is conceivable that its overactivity might amplify the ChEI effects (Pola et al., 2005; Salazar et al., 2021).

A SNP study coupled with haplotype analysis shows the association of *rs2177370* and *rs3793790* polymorphisms, located in the introns of the ChAT-encoding gene, with ChEI therapeutic outcomes (Yoon et al., 2015). In particular, two different haplotypes are associated with divergent ACh synthesis rates hypothesized to affect downstream ChEI response (Yoon et al., 2015). One study reports significantly different, albeit with small effect size, longitudinal changes in Mini-Mental State Examination (MMSE) scores (the primary outcome measure in ChEI efficacy assessment) according to the presence or not of the *ChAT C* allele (Harold et al., 2006).

Another longitudinal study, although not showing *ChAT A* allele effect on ChEI response at 3-month follow-up, disclosed a significant difference after 6-month stable dose therapy (Lee et al., 2015). The authors argued that ChAT biological dynamics, including time-dependent and drug-induced gene expression modulation, may account for different outcomes across evaluation time-points.

Unlike these significant differences, one study did not show any genetic effect on ChEI response when investigating SNPs in the two cholinergic system genes within a Northern Italy cohort of AD patients (Scacchi et al., 2009).

The gene *CHRNA7* (chromosome 15q14) – encoding the α7 nicotinic acetylcholine receptor (α7 nAChR) subunit – is characterized by some polymorphisms that are potential neuroprotective factors for late-life cognitive decline and AD (Barabash et al., 2009; Braga et al., 2015; Carson et al., 2008; Weng et al., 2013). *CHRNA7* SNPs *rs1514246*, *rs2337506*, *rs8027814* are associated with an overall lower risk of AD and better prognosis in MCI individuals, i.e., lower conversion rates to dementia (Barabash et al., 2009; Carson et al., 2008).

Although GWAS studies do not point out these SNPs (Lambert et al., 2013), experimental models of aging and AD and clinical case reports indicate a potential association between *CHRNA7* expression, cholinergic homeostasis, and ChEI response. The *CHRFAM7A* (fusion gene containing *CHRNA7* partial duplication)− 2-bp deletion is also associated with a lower risk of AD dementia and overall age-related cognitive decline.

In addition, galantamine displays a positive allosteric effect on α7 nAChR with a downstream boost of the cholinergic transmission (Texidó et al., 2005). In a study genotyping nine haplotype-tagging SNPs of *CHRNA7*, Weng and colleagues (2013) reported the first significant association between *CHRNA7* polymorphisms and better ChEI therapy response in a cohort of mild-to-moderate AD patients treated with stable doses of donepezil or rivastigmine (Weng et al., 2013). Of note, AD female patients, carrying the *rs8024987* SNP (i.e., GG+GC versus CC) with a GG haplotype and taking stable doses of donepezil, were 11 times more likely to be treatment responders than female non-carriers.

Such findings were confirmed by another workgroup reporting a significant association between the SNP *rs6494223* of *CHRNA7* (*T* allele) and a better response to treatment with ChEI in patients with mild AD (MMSE $\geq$ 20) (Braga et al., 2015).

A study performed in an Italian cohort of 169 CE patients did not observe any association of SNPs *rs6494223* and *rs8024987* of the *CHRNA7* gene with ChEI-related clinical response. However, *rs6494223* exhibits a consistent trend toward significance increased by meta-analysis with previous studies (Clarelli et al., 2016).

3.4. Drug-metabolizing enzymes and genetics

Meta-analyses, systematic reviews of the literature, and recent studies conducted according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines indicate that genetically-driven polymorphisms account for different expression levels and activity rates of critical molecular pathways related to ChEI pharmacokinetics (Gaedigk et al., 2017; Koopmans et al., 2021; Teh and Bertilsson, 2012).

Subunits 2D6 and 3A4 of the cytochrome P450 (CYP) superfamily are established phase I drug-metabolizing enzymes (DMEs) of several psychotropic drugs, including donepezil, galantamine, and rivastigmine (Koopmans et al., 2021; Lu et al., 2020, 2016; Ortner et al., 2020a; Xiao et al., 2016). *CYP2D6* (chromosome 22q13.1), the only functional gene in the CYP2D subfamily of the human genome, includes nine exons and is in close proximity to two nonfunctional pseudogenes (Gaedigk et al., 2017; Koopmans et al., 2021; Ortner et al., 2020a). Presently, more than 90 allelic variants have been disclosed for *CYP2D6* (for more extensive reading, see Sim and colleagues (Sim and Ingelman-Sundberg, 2013)), with several *CYP2D6* SNPs likely to affect ChEI pharmacokinetics through gain or loss of function (Koopmans et al., 2021; Lu et al., 2020, 2016; Ortner et al., 2020b, 2020a; Xiao et al., 2016).

In general, pharmacogenetic studies of CYP2D6 indicate the existence of four activity-based phenotypes, spanning poor, intermediate, normal, and rapid metabolizers (Bradford, 2002).

A significantly higher frequency of AD patients with the *G* allele of the SNP *rs1080985* (C-1584→G) in the *CYP2D6* gene is observed in stable-dose donepezil non-responders than responders due to the poor metabolizer phenotype (Pilotto et al., 2009). CYP2D6 displays variability in allele frequencies, diplotypes, and predicts phenotype across different ethnicities, including Caucasians, Africans, and Asians populations (Gaedigk et al., 2017; Koopmans et al., 2021; Teh and Bertilsson, 2012). Numbers of rapid metabolizers across global populations show high heterogeneity, specifically 20–30% in East-African populations and only 2–3% in the European area, which also accounts for the lowest number of poor metabolizers (the highest is observed in Asian populations) (Gaedigk et al., 2017; Koopmans et al., 2021; Teh and Bertilsson, 2012).

Most of the inter-ethnic genetic differences are associated with variations in DMEs and transporters and are likely to impact a broad set of

therapeutic outcomes in neurology and psychiatry healthcare, including ChEI (Koopmans et al., 2021; Lu et al., 2020, 2016; Ortner et al., 2020b, 2020a; Xiao et al., 2016).

Overall, these results suggest that pre-emptive pharmacogenetic investigation for polymorphisms of ChEI DMEs genes may inform the daily practice to stratify individuals by rates of successful treatment outcomes or predict a high risk of little response/or risk for adverse events, thus optimizing multi-dimensional healthcare resources.

3.5. *The cerebrovascular - cholinergic system interplay and ChEI effect: qualifying biomarkers*

There is no univocal clinical explanation for the mixed outcomes of ChEI in patients with AD-vascular co-pathology; however, both experimental and in-human studies suggest the existence of a cholinergic - vascular systems interplay that may account for the interindividual variability in pharmacological responses (Román and Kalaria, 2006).

In humans, the pharmacological enhancement of the cholinergic firing from the NBM is associated with increased cerebral blood flow (CBF) in several areas involved in high-order cognitive and behavioral functions as indicated by previous clinical trials using perfusion and functional imaging (Nazmuddin et al., 2021; Nobili et al., 2002; Rodriguez et al., 2004; Shimizu et al., 2006). Mouse models point out a cholinergic-mediated regulation of the CBF through the NBM, and the perivascular postganglionic sympathetic nerve innervation (Van Beek and Claassen, 2011).

This body of evidence coupled with more recent clinical imaging data (see subsections below) suggests that part of the natural history of the cholinergic dysfunction in aging and AD may lie in chronic, cumulative ischemic microinsults of the BF cholinergic parenchyma (Moghekar et al., 2012; Román and Kalaria, 2006; Ter Telgte et al., 2018).

A selective structural vulnerability of the BF to suboptimal perfusion and downstream ischemic damage is assumed to depend on the finely-tuned regional bloodstream. Tightly regulated perfusion ensures time-sensitive and dynamic switches in tissue oxygen supply to accommodate the cholinergic neurons high bioenergetic demand (Román and Kalaria, 2006).

Magnetic resonance imaging (MRI)-based studies, using different perfusion-weighted sequences and, in some cases, arterial-spin labeling approaches, reported a ChEI-associated enhancement of the regional CBF, mainly encompassing cingulate and prefrontal cortical areas alongside a few middle temporal structures in AD dementia patients (Chaudhary et al., 2013; Janik et al., 2016; Li et al., 2012). These results were controlled for regional gray matter (GM) volumes. Moreover, some studies indicated that blood perfusion changes also occurred in white matter (WM) fibers; whether these findings represent an actual biological signal or methodological artifact is disputable.

Tractography DTI studies show a significant association of the loss of NBM structure with NBM-cortical WM connections and WM hypointensities (Nemy et al., 2020). The latter is an established surrogate marker of small vessel disease, an age-related condition with high comorbidity in AD. Spontaneous cerebral microbleeds and parenchymal microinfarctions (namely, lacunes) represent small vessel disease typical radiological features, which impact long-term cognitive outcomes and the overall AD prognosis (Habes et al., 2018; Ter Telgte et al., 2018; Wardlaw et al., 2013).

To date, only one study highlighted a match between perfusion and functional MRI (fMRI) data, with the latter based on the blood oxygenation level-dependent (BOLD) signal (Janik et al., 2016).

Rs-EEG rhythms were used to probe abnormalities in the function of cholinergic systems in AD patients with and without vascular lesions burden. As compared with the age-matched old persons with intact cognition, prodromal AD (or MCI-AD) show topographically widespread alpha "spectral coherence" - as a linear measure of "interrelatedness" of rsEEG activity between electrode pairs - in relation to the cerebrovascular impairment in cholinergic tracts from BF to cerebral cortex, as revealed by MRIs (Babiloni et al., 2010).

4. State-of-the-art in Parkinson's disease dementia and dementia with Lewy Bodies: roadmap to ChEI precision pharmacology

The co-occurrence of several neuropathologies in the same individual is a common finding at brain autopsy. In addition, at least 30% of dementia cases occur without significant AD (co-)pathology, raising the question if ChEI treatment is recommended in some of the non-AD pathologies as well. For some alpha-synuclein-related diseases, such as PDD and DLB, there is strong evidence that the neuronal demise characterizing cognitive alteration is not only confined to the dopaminergic system but numerous Lewy bodies rich of alpha-synuclein accumulated outside of the *substantia nigra* and being differently distributed in neurons and dendrites from neocortical and paralimbic regions.

Neuropathological studies reported an impairment of the cholinergic innervation which is associated with cognitive and neuropsychiatric symptoms in these diseases (Bohnen et al., 2003; Perry et al., 1985; Tiraboschi et al., 2000). There is a prominent loss of cholinergic neurons in the NBM (Whitehouse et al., 1983) which is associated with the loss of cholinergic markers in the NBM and cerebral cortex and is related to cognitive disturbances (Perry et al., 1985, 1987). Recent evidence indicates that NBM might be altered up to an extent similar to what occurs in AD (Alexandris et al., 2020) and the same has been suggested also in PDD (Wilson et al., 2021). Of note, the reduction of midfrontal ChAT activity was found to be markedly reduced in PD and DLB, being more extensive compared with AD and controls. Thus, patients with PDD have a greater cholinergic deficit than those with AD, and the extent of the deficit correlates with the severity of cognitive symptoms (Bohnen et al., 2003; Tiraboschi et al., 2000). Interestingly, in PD, NBM alterations have been put in relation to specific symptoms, such as, for instance, delusion and hallucination (Sakai et al., 2019), even though such observations are mainly anecdotal, lacking large systematic studies. Moreover, the disruption of NBM cholinergic neurons in PDD is associated with the loss of serotonergic and noradrenergic ascending projections (Bohnen et al., 2022; Lanctôt et al., 2017). Animal models of PD show that co-existing monoaminergic alterations are associated with BPSD, including psychomotor agitation, hallucinations, and other psychotic symptoms (Albin et al., 2022; Bohnen et al., 2022; Lanctôt et al., 2017; Pinto et al., 2011).

Structural brain MRI studies corroborate traditional neuropathological studies, showing that PDD but not PD have lower GM volume and mean diffusivity of NBM (Schulz et al., 2018). Atrophy of cholinergic BF in PD developing cognitive impairment was found by morphometric MRI analysis (Ray et al., 2018). Finally, NBM volume in patients with MCI-DLB is significantly reduced compared with age-matched controls and similar to what observed in MCI-AD patients (Schumacher et al., 2021b).

At the clinical-pharmacological level, a therapeutic intervention using the ChEI galantamine, rivastigmine, and donepezil has been largely used to ameliorate cognitive performances (e.g. attention, and memory) as well as behavioral symptoms at least in the early phase of PD and PDD (Aarsland et al., 2004).

Randomized clinical trials investigating donepezil in PDD patients showed a significant, albeit mild, improvement in cognition (Dubois et al., 2012). A similar rate of therapeutic effect was found in trials assessing rivastigmine, where also a moderate improvement of neuropsychiatric symptoms was reported (Emre et al., 2004). This drug has been reported to produce performance-related normalization in the left frontal cortex activity as studied with functional MRI (Possin et al., 2013). Moreover, a positron emission tomography (PET) study has demonstrated that prefrontal and parietal association areas may be relevant structures for the pharmacological response to ChEI in patients with PDD (Lee et al., 2008). In line with clinical and trail-based, rivastigmine was approved by FDA for use in PDD patients.

Concerning the effects of ChEI in DLB, donepezil-induced improvement in cognition has been shown by several single- and multi-centric studies (Ikeda et al., 2015; Mori et al., 2015). The largest trial performed by McKeith and colleagues (McKeith et al., 2000), assessed rivastigmine effects during 20 weeks and reported failure to significantly improve cognition. Suh a negative result counteracted those found from previous smaller studies (Rozzini et al., 2007). Interestingly, a significant improvement of sleep disturbances by rivastigmine in DLB was shown by other analyses (Grace et al., 2000; Maclean et al., 2001).

The investigation of ChEI in DLB has mostly been performed without considering the frequent co-occurrence of AD pathological features, such as Aβ aggregates and plaques (Apaydin et al., 2002; Braak et al., 2003; Leech et al., 2001). Recent in-vivo neuroimaging studies report that, in DLB spectrum, the BF volume is associated with widespread cognitive dysfunction whereas the rate of Aβ predicts faster progression (Yoo et al., 2022, 2020). In line with these findings, of particular interest is the observation that 12 patients with DLB and treated with ChEI had significantly less parenchymal Aβ deposition (Ballard et al., 2007). Moreover, in DLB, homozygosity for the reduced-activity K-variant and/or heterozygosity for the atypical variant of *BCHE* have a slower rate of cognitive decline than those with the wild-type variant and show better response to rivastigmine (O'Brien et al., 2003).

This body of evidence support biomarker-driven clinical research to understand whether the early and long-lasting ChEI administration in DLB, (including the form with Aβ pathology), is associated with a delay of disease cognitive and functional progression.

4.1. Preliminary evidence in the frontotemporal lobar degeneration spectrum

In contrast to PDD and DLB, there is little evidence for the frontotemporal lobar degeneration (FTLD) spectrum, so that ChEI treatment is not recommended for the clinically defined conditions of frontotemporal dementia or primary progressive aphasia (Li et al., 2015). However, FTLD does not represent a homogeneous pathology but encompasses several pathologies, including aggregates of tau, TDP-43, and, less commonly, Fused in Sarcoma (FUS) protein (Borroni et al., 2019). Stratification of ChEI response according to underlying pathology in FTLD is currently unpractical due to the lack of specific biomarkers. The recently defined entity of limbic predominant TDP-43 pathology (LATE-NC) (Nelson et al., 2019) may indicate a link between FTD-TDP-43 and AD, if it does not represent a separate pathological entity. Recent evidence suggests a similar degree of cholinergic BF atrophy in LATE-NC as in AD (Teipel and Grothe, 2022); however, the clinical relevance of this finding is currently unclear.

5. Challenges and perspectives

5.1. Sexual dimorphism in the cholinergic system and ChEI response: the quest of sex-stratified outcomes for optimal ChEI therapeutic scheme

In the perspective of observational studies investigating the long-term effect of ChEI and the preservation of the cholinergic homeostasis, the presence of sex-biased ChEI response outcome measures shall be carefully considered.

Clinical data on ChEI sex-biased response profiles are poorly systematic, not extensive, and relatively conflicting with each other; such data stem from single-center prospective/outpatient clinical registry-based retrospective studies. A systematic review of the literature, spanning 1996–2016, has addressed all the randomized controlled trial (RCTs) involving the three currently approved ChEI (Canevelli et al., 2017). The study aimed to break down treatment outcomes and understand the possible presence of sex-based differences in pharmacological features, including efficacy, safety, and tolerability. From over 1200 RCTs, it turned out that neither safety nor tolerability data were available concerning sex (Canevelli et al., 2017). The meta-analytic samples do not match the epidemiological data: for instance, the mean percentage of females is 63.8% (range 52.2–84%), resulting slightly lower than the sex distribution of AD in the whole population. Once the analysis is narrowed down on the 48 RCTs, only two studies (Greenberg et al., 2000; Winblad et al., 2001) – both investigating the potential impact of sex on donepezil treatment efficacy (but differing in terms of study design) – have been performed, reporting no significant dissimilarities across sexes (Canevelli et al., 2017).

Stable doses of rivastigmine were associated with slower MCI-to dementia conversion rates in females but not in males compared with individuals with no treatment (Ferris et al., 2009). Another study confirmed a more substantial therapeutic effect of donepezil and rivastigmine in females than males (Wattmo et al., 2014).

A monocentric three-year study reported a higher response in males than females after a six-month treatment with one of the three approved ChEI (Wattmo et al., 2011b). Another study also showed slower clinical progression of AD in males versus females (Doody et al., 2010).

To date, only one study has explored whether sex and the estrogen receptor α gene (*ESR1*) variants may affect the response to donepezil and rivastigmine. A significant difference was observed in donepezil response with females showing better longitudinal cognitive outcomes (Scacchi et al., 2014). This sex-based result is partially interpretable through primate and rodent models data, thus suggesting sexual dimorphism. Estrogens could significantly influence the chronobiology of cholinergic enzymes, i.e., sex-biased turn-over rates of ChEI and BChE have been described (Alves-Amaral et al., 2010; Franconi and Campesi, 2014; Wang et al., 2000). This, in turn, may modulate the bioavailability of ChEI and the downstream synaptic effect (Wang et al., 2000). Higher bioavailability of ChEI in females may also be indirect because of testosterone putative inhibitory effect on the brain ChEI access (Wang et al., 2001).

Investigating sex-biased differences in human neurobiology of aging and AD precision medicine should not be constrained to the traditional paradigm of adjusting regression models for sex.

This approach is insufficient to untangle the intra- and inter-individual variability and phenotypic overlap between male and female brains. The study of sexual dysmorphism in brain diseases and neurodegeneration calls for holistic, system-scaled, preclinical-to-clinical inspection of hormonally-driven molecular differences and careful evaluation of arising sex-wise differences in biological readouts and treatment outcomes. In the case of ChEI, it is conceivable that a comprehensive reconstruction of response kinetics and neurobiological dynamics has not yet occurred.

Sexual dimorphism in the cholinergic system exists in the first place. This is a critical conceptual passage since the higher vulnerability of females, especially those in hormonal transition to menopause than males, has been established by large-scale epidemiological projections, clinical multi-modal biomarker studies, post-mortem studies, experimental models of aging, and AD (Babapour Mofrad and van der Flier, 2019; Cavedo et al., 2018; Counts et al., 2011; Ferretti et al., 2018; Hohman et al., 2018; Vergallo et al., 2019). Such an apparent female predisposition to AD is not affected by age itself, thus reinforcing the hypothesis that the hormonal factors linked to menopause may play a critical role. A thorough argumentation about genetic, molecular, metabolic, and neuroendocrinological aspects accounting for brain sexual dysmorphism and sex-biased susceptibility of AD pathophysiology goes beyond the scope of the present endeavor (see recent elegant review articles for more information on this matter) (Christensen and Pike, 2015; Ferretti et al., 2018).

From an anatomical standpoint, a recent allometric-based U.K. Biobank study emphasizes that the brainstem volume is greater in adult males than females, whereas the hippocampus is larger in females (Williams et al., 2021) – in line with previous findings (Malykhin et al., 2017; Nordenskjöld et al., 2015).

In general, there is a sex-based difference in hippocampal volume in either adolescence or adulthood/aging (Lotze et al., 2019; Tan et al.,

2016). By contrast, another study shows a hippocampal total volume-controlled inter-sex difference in the hippocampus (males higher than females), prominently in the fimbria and parasubiculum (van Eijk et al., 2020).

No clinical studies investigating sexual dysmorphism in the function of the brainstem cholinergic system in adult, aging, and AD individuals are currently available.

Experimental (rodent/mouse) aging models indicate that cholinergic neurons are more abundant but smaller in females than males, and their maturation occurs earlier (Mitsushima, 2011; Rhodes and Rubin, 1999; Wang et al., 2000). Both animal and in-vitro models of the hippocampal cholinergic circuitry show lower activity levels in females than males alongside higher vulnerability in the former group to block muscarinic receptors (Berger-Sweeney et al., 1995; Gur and Gur, 2002; Hall et al., 2017). The same line of research suggests that an estrogen-mediated trophic action or estrogen-nerve growth factor (NGF) axis may account for such inter-sex differences (Giacobini et al., 2022). Considering this extensive evidence, it is conceivable that harmonized protocols for assessing sexual dimorphism should be set up to circumvent current approaches.

5.2. *The need for a multi-scale approach and intervening earlier in the AD course to leverage molecular and large-scale network compensatory/homeostatic dynamics*

Post-mortem and in-vivo human studies demonstrate that individuals exhibiting AD-related pathophysiology alongside normal cognition or subtle, incipient decline may have active compensatory mechanisms that ensure "synaptic" and functional resilience (Hampel et al., 2019). Remodeling and plasticity-based mechanisms are hypothesized to support compensatory cortical-subcortical dynamics that sustain proper cholinergic transmission and biological network activity, necessary for memory, attention, and learning.

In cognitively healthy or early MCI individuals with AD pathology, a regional hyper-regulated ChAT activity has been reported (particularly, in both frontal cortex and hippocampus), as well as a remodeling of BF cholinergic cortical projections (cholinergic axonal sprouting in hippocampi) (DeKosky et al., 2002; Ikonomovic et al., 2007; Poirel et al., 2018). The degree of these pathomechanistic alterations matches the BF cholinergic neurons depletion rate (DeKosky et al., 2002; Ikonomovic et al., 2007; Poirel et al., 2018).

Functional and structural imaging techniques capture different spatial and temporal coordinates of ChEI effect on brain homeostasis and multi-scale organization in cerebral regions critical/vulnerable to AD pathophysiology (Péran et al., 2021), even in subjects with no or prodromal symptoms. Neuroimaging surrogate outcomes may be used to supplying partially different biological information at short- and long-term in clinical trials exploring the synergy between ChEI and DMT.

For instance, although systematic data in preclinical AD and cognitively healthy older adults at genetic/clinical risk are required to better understand the biological trajectories of the cholinergic system, it is established that the BF atrophy precedes and predicts both entorhinal AD pathology and memory impairment. In addition, the prognostic performance is considerable (80% accuracy in discriminating cognitive non-decliners and decliners) (Teipel et al., 2018).

5.2.1. *Structural MRI studies*

A double-blind, RCT study conducted in clinically identified MCI individuals reported an association between one-year treatment with stable and high-dose of donepezil and lower rates of hippocampal atrophy, compared with placebo (Dubois et al., 2015). A subsequent study in the same cohort, but with three-year clinical follow-up, showed reduced AD-regions cortical thickness in the treatment arm individuals compared with placebo controls (Cavedo et al., 2016).

Eventually, the same work group observed a significant association of donepezil with smaller rates of atrophy in the BF and NBM, specifically compared with untreated participants (Cavedo et al., 2017).

5.2.2. *Functional MRI studies*

Studies based on fMRI with different task designs, data pre- post-processing pipelines, and heterogeneous follow-up and study sample size indicate that ChEI may exert/facilitate/sustain a modulatory action on traditionally defined cholinergic memory and attention networks.

Most of these analyses report that ChEI exposure in untreated AD dementia patients or MCI of the AD clinical-biological type is associated with improved functional connectivity measures that reflect network segregation, integration, and other large-scale dynamics pivotal for cognitive performance across different domains (Bokde et al., 2016, 2009; Goekoop et al., 2006, 2004; Goveas et al., 2011; Kircher et al., 2005; McGeown et al., 2010; Petrella et al., 2009; Rombouts et al., 2002; Saykin et al., 2004; Shanks et al., 2007; Thiyagesh et al., 2010).

Regarding attention and learning, a few studies report that intrinsic and functional connectivity activity patterns in the prefrontal cortex – a brain area engaged in attention mechanisms – are reduced in AD and are partially restored after exposure to ChEI, thus suggesting a "cognitively pleiotropic" effect of ChEI, as it is expected from the cholinergic neural substrates of attention, learning, and memory (Bentley et al., 2008; Goekoop et al., 2004).

Recent fMRI studies also suggest a ChEI-related network modulatory effects in the MCI condition, considered the transition toward dementia within the AD continuum, and hypothesized to have active compensatory mechanisms ensuring overall cognitive and functional activities (Bokde et al., 2009; Goekoop et al., 2006; Petrella et al., 2009; Ray et al., 2015). Studies in MCI individuals showed the preservation of the BF among MCI individuals correlates with a shift of memory recall from the fornix-hippocampal tract to the parahippocampal cingulum tract. A recent fMRI study conducted in treated AD dementia patients versus placebo control patients shows increased cerebellar network connectivity (mean connectivity) after galantamine administration, indicating a potential normalizing effect of galantamine on the cerebellar circuitry in AD patients (Klaassens et al., 2019). Such findings suggest an association between cholinergic activity and cerebellar connections, which have recently been argued to play a role in cognition (Guo et al., 2016).

A fMRI, double-blind, randomized, crossover design study demonstrates that cognitively healthy adults taking donepezil have lower functional connectivity indexes in the right executive control network and different connectivity patterns in the cingulate cortex and parahippocampal regions compared with age-matched individuals enrolled in the placebo arm.

A fMRI-EEG co-registration study coupled with the network metrics approach shows that donepezil induces specific network reorganization patterns not particularly influenced by common stressful conditions in AD, such as sleep deprivation (Wirsich et al., 2018).

5.2.3. *EEG studies*

The sensitivity of rsEEG biomarkers to the dysfunctions and partial recovery of cholinergic systems was demonstrated in rsEEG studies performed in AD patients taking ChEI, enhancing the cholinergic tone. In relation to untreated ADD patients, those receiving ChEI showed the following beneficial effects: (1) decreased widespread rsEEG delta and/or theta rhythms after 3–12 months of therapy with tacrine (Alhainen and Riekkinen, 1993; Shigeta et al., 1993), rivastigmine (Shigeta et al., 1993), and donepezil (Balkan et al., 2003; Kogan et al., 2007, 2001); (2) decreased widespread rsEEG delta and/or theta rhythms after 5 days and 1–2 weeks (Adler and Brassen, 2001; Brassen and Adler, 2003) of therapy with rivastigmine; (3) partial protection against the reduction in posterior rsEEG alpha rhythms after 1 year of therapy with donepezil (Babiloni et al., 2006); (4) decreased the ratio of the widespread rsEEG alpha-theta rhythms after a single dose of tetrahydroaminoacridine as a predictor of the clinical status at 7-week follow-up (Alhainen et al., 1991); (5) decreased rsEEG theta power density after 1 week of therapy

with rivastigmine as a predictor of the chronic treatment response at 6-month follow-up (Adler et al., 2004).

5.2.4. Preliminary experimental data on cholinergic system-AD pathophysiology cross-talks

Albeit preliminary (due to limitations including small sample size, uncorrected p-values, short-term follow-up, and unavailability of independent validation cohort), the multi-modal MRI results indicate that short-term exposure to ChEI may modulate brain activity at different scales, including regional neuroplasticity and large-scale functional organization.

The underlying putative biological effects cannot be comprehensively explained at the clinical level because of the lack of validated biomarkers of cholinergic integrity/disruption. However, experimental evidence at the cellular subcompartment and ultrastructural level allows to infer that remodeling mechanisms – based on cholinergic/AD proteinopathies cross-talks – may explain a potential ChEI-mediated mitigating effect on the Aβ pathway.

Pharmacological manipulation studies, conducted with enhancers of the cholinergic firing, indicate the existence of biological cross-talks between the related neurochemical system and molecular pathways linked to AD pathophysiology. ChEI and muscarinic agonists can influence the amyloid precursor protein (APP) metabolism and promote non-amyloidogenic pathways over the amyloidogenic one (Giacobini et al., 2022; Nitsch et al., 1992; Pakaski et al., 2001). In particular, activation of M1 and M3 muscarinic receptors – either directly or through presynaptic M2 receptor disruption – upregulates the a disintegrin and metalloproteinase 17 (ADAM-17) α-secretase (Giacobini et al., 2022; Nitsch et al., 1992). M1 agonists may act as functional activators of protein kinase C (PKC) signaling which, in turn, promotes a metabolic shift towards the α-secretase-mediated protective effect (Cisse et al., 2011; Welt et al., 2015).

Mice carrying three transgenes encoding familial AD mutations (3xTg-AD), exhibit a significant association of the magnitude of decrease in α7 nAChR expression with rates of both Aβ deposition and cognitive impairments (Oddo et al., 2005).

A recent study carried out in primary human brain (PHB) cultures and, then, matched with 3xTg-AD and human post-mortem brain tissues highlights that rivastigmine dose-dependent upregulates the levels of ADAM-9, -10, and -17 with downstream raise of α-secretase activity (Ray et al., 2020). Co-treatment with an α-secretase suppressor removes the rivastigmine-induced elevation of the soluble α form of APP (sAPPα) (Ray et al., 2020).

Aβ bioreactive molecules, such as oligomers, can bind to nicotinic receptors and exert either an antagonist or agonist effect, according to the aggregation species concentration (Puzzo et al., 2008). Moreover, pharmacological tuning of the α7 nAChR activity slows down Aβ-induced toxicity through indirect downregulation of glycogen synthase kinase-3 (GSK3), an enzyme aberrantly regulated in AD and a molecular orchestrator of tau hyperphosphorylation (Chu et al., 2017). Also, the coupling of M1 to PKC may lead to a downregulation of detrimental cell processes occurring in AD, such as GSK3-mediated toxicity.

Activation of the α7 nAChR is associated with anti-inflammatory pathways also through downregulation of the nuclear factor κB (NF-κB) via the janus kinase-2 (Jak2) tyrosine kinase, a pathway aberrantly overexpressed in neurodegeneration models (Kalkman and Feuerbach, 2016).

5.2.5. AD-related cholinergic system dysfunctions in the ocular-retinal system

Experimental evidence indicates that cholinergic interneurons and ACh play a crucial role in proper neuroanatomical development and functioning of visual neurophysiology, including temporal progression of retinogenesis (Trujillo-Gonzalez et al., 2019), retinal layer-specific angiogenesis and blood retinal barrier (BRB) integrity (Weiner et al., 2019), corneal homeostasis (Faiq et al., 2019), and modulation of the intrinsic ocular motility, cortical/subcortical visual information processing (Beelke and Sannita, 2002; Levitt and Lund, 1997; Müller et al., 2003).

Moreover, strict regulation of cholinergic signaling is essential for proper retinal functioning. In the context of AD, growing experimental and clinical evidence from histological, biochemical, and imaging data suggest that the pathogenic hallmarks of AD are also reflected in neurosensory retina (Du et al., 2022; Dumitrascu et al., 2021; Hart et al., 2016; Koronyo et al., 2017, 2012; Mirzaei et al., 2020; Santangelo et al., 2020).

Despite having profound studies on the role of ACh and cholinergic neurotransmission system in the AD brain, their roles in AD retina is extremely limited. However, as AD retinopathy appears to promote degeneration of most retinal neuronal cell types (Asanad et al., 2019; Koronyo et al., 2017; Shi et al., 2020b; Xu et al., 2022), including amacrine cells, attenuated cholinergic signaling is expected along with visual dysfunctions, as seen in AD (Frost et al., 2017; Watts et al., 2010). Independent AD animal model-based studies suggest that ACh signaling has crucial retinoprotective roles during AD progression and that loss of retinal cholinergic signaling could have profound negative roles in the AD retina (Chang et al., 2020; Espírito-Santo et al., 2021; Watts et al., 2010).

In human AD, one study suggested that higher number of inclusion bodies found within the retinal inner plexiform layer (IPL), which includes the amacrine cell projections, were mostly observed in elderly PET-Aβ positive individuals compared with PET-Aβ negative individuals and cognitively normal older adults (Snyder et al., 2016). Increased IPL volume was also more pronounced in the PET-Aβ positive individuals versus PET-Aβ negative group, which possibly reflected early inflammatory processes associated with cholinergic disruption and possibly concurrent Aβ accumulation in the retina (Alber et al., 2020).

Changes in the oculomotor system in the Edinger–Westphal nucleus and subsequent degeneration of the NBM resulting in cholinergic deficit are possibly associated with the changes in the pupillary system. Therefore, changes in pupil response to light in AD patients could be because of the central cholinergic depletion, as also indicated by correlation studies between AD biomarkers in MCI and dementia and cognitively normal individuals (Bittner et al., 2014; Frost et al., 2017; Granholm et al., 2003; Prettyman et al., 1997; Scinto et al., 1994).

ChEI studies in animal models of aging and AD supply indirect evidence on the putative role of the cholinergic system in AD. Galantamine can promote retinal vasoprotection and increased ocular blood flow in rodent models of glaucoma (Almasieh et al., 2013). As vasculopathy is a critical pathogenic event in the AD retina (Shi et al., 2022, 2020a) (reviewed in (Shi et al., 2021)) and galantamine has vasoprotective effects in glaucoma, this drug may also have similar effects on promoting cholinergic activity in the AD retina. It is further conceivable that will have implications of protecting against visual dysfunctions in AD (Vit et al., 2021a, 2021b). Furthermore, since donepezil facilitates the visual signal detection by promoting contrast sensitivity, this may suggest that ChEI might improve visual perception in patients with AD (Boucart et al., 2015).

5.3. A systems-wise outlook to future ChEI pharmacological investigation

The three approved ChEI were developed prior to the validation of contemporary in-silico approaches. Combining computational and traditional experimental-clinical pharmacological workstreams could allow to quantify absorption, distribution, metabolism, and excretion (ADME) profiles alongside key physiological properties, including blood brain barrier penetration rates (Herrera-Acevedo et al., 2021; Li et al., 2022b; Rehman et al., 2022; Şahin, 2022).

In-silico and in-vivo approaches complement each other and can act in synergy for drug design investigations. Quantitative systems pharmacology (QSP)-based modelling approaches have already been

hypothesized and preliminarily applied to AD since they can supply critical data about genetic-determined drug response, drug-induced immune reactions, drug-drug interactions, and drugs-multi targets interaction (Geerts et al., 2017a, 2017b). Such information could significantly inform combined therapeutic approaches for AD, such as ChEI and anti-Aβ or anti-tau treatments. The clinical and pharmacological perspective of QSP lies in the notion of exploiting multi-targets and stage-specific treatments that can be tailored to the individuals genetic-biological profile, overcoming the limitation inherent in the traditional "one-drug-one-target" model.

Moreover, as machine and deep learning techniques continue to develop, clinical decision-making, from differential diagnosis, to early prediction, and treatment target choices become more accurate (Barnes et al., 2020; Richards et al., 2019). Based on electronic health record (HER) datasets, artificial intelligence (AI)-based algorithms could identify individuals heading toward AD-related decline and facilitate ChEI early treatment initiation (Barnes et al., 2020; Liu et al., 2022). Hence, AI-guided clinical decision-making could slow down cognitive impairment (Barnes et al., 2020; Liu et al., 2022).

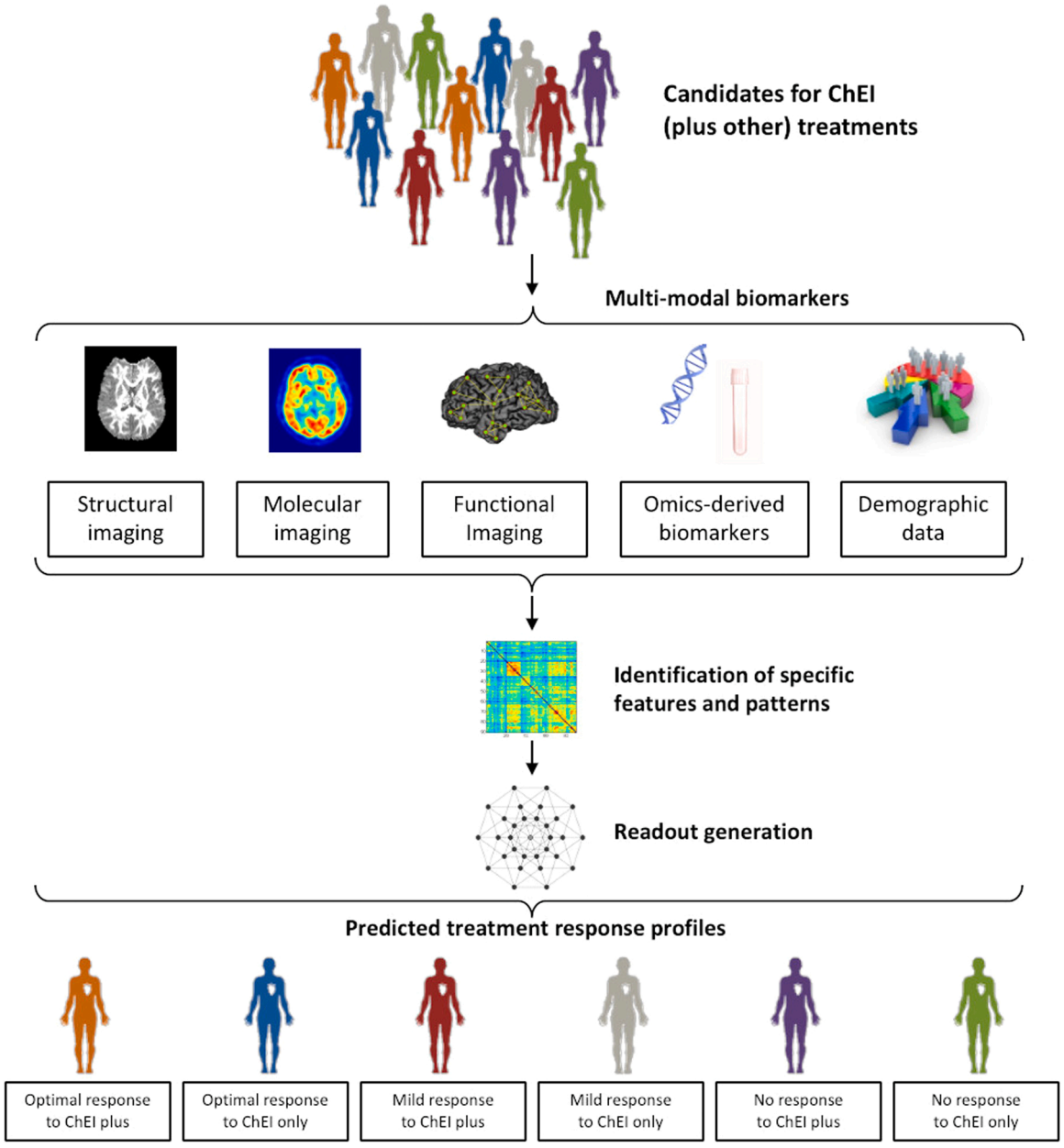

Fig. 4. Schematic representation of a potential precision medicine-oriented workflow. Individuals with incipient symptoms of suspected neurodegenerative nature would be assessed with multi-modal biomarkers to comprehensively investigate their clinical-biological-genetic features and match them with profiles of expected treatment response derived from clinical research. Multi-modal biomarker assessment of individuals with clinical indication to ChEI, either alone or in combination with drugs with putative biological and DMT effect, will allow to characterize intermediate endophenotypes at different biological scales. Artificial intelligence algorithms will be used to combine multimodal data, extrapolate shared features, and classify training and test (i.e., unseen) single subjects on the basis of the cluster (i.e., pattern of homogenous features) they belong (or are closer) to. Diagnostic and therapeutic decision-making will be consolidated upon analysis output. *Abbreviations*: ChEI, acetylcholinesterase inhibitors; DMT, disease-modifying therapy. J Alzheimers Dis. 2015 Sep 24;48 Suppl 1:S171-S191. https://doi.org/10.3233/JAD-150202. Copyright © 2015, IOS Press.
(a) Adapted and used from Lista S, et al. Evolving Evidence for the Value of Neuroimaging Methods and Biological Markers in Subjects Categorized with Subjective Cognitive Decline. (b) Reprinted with permission from IOS Press.

6. Discussion

The knowledge of cholinergic homeostasis, its structural-functional decline within the aging-AD (and other neurodegenerative diseases) continuum – including compensatory mechanisms during preclinical stages of diseases – is sufficient to support further clinical pharmacological research on ChEI.

A comprehensive understanding of the early molecular dynamics involving the cerebral and retinal cholinergic system and its interaction with other neurobiological substrates and downstream pathophysiological changes characterizing AD is essential to foster the implementation of standardized ChEI-cholinergic biomarkers co-development programs.

A system-scaled workflow encompassing multiple biological layers is suitable for precision medicine-oriented strategies (Fig. 4). Most of the previous studies investigating genetic determinants (e.g., *APOE*, DMEs polymorphisms), ChEI response, as well as related short- and long-term multi-dimensional outcomes did not ascertain the presence of AD biology, which has unique spatial and temporal dynamics (Busche and Hyman, 2020; Hampel et al., 2021a).

In addition, several studies did not take into account concomitant brain pathophysiological changes and shared pathologies that impact psychotropic drug responses and prognostic trajectories (Ter Telgte et al., 2018; Wardlaw et al., 2013). In the case of cerebral small vessel disease (and idiopathic cerebral amyloid angiopathy), acknowledged as a critical vascular contributor to cognitive decline and dementia, it would be recommendable not excluding these co-pathologies for sake of gaining further knowledge, but take them into account when modelling outcomes.

Moreover, the molecular and cellular mechanisms underlying the putative interrelation among the cholinergic system, AD pathophysiology, and aging processes are poorly understood in both animal models and humans. Despite robust data generated by elegant experimental studies, the reconstruction of the subcellular and ultrastructural landscape and dynamics of the cholinergic synapse in aging and AD is still fragmented. QSP approaches can help deepening our understanding of the molecular dynamics occurring within the BF during early preclinical stages of AD, such as cholinergic inter-receptor co-activation mechanisms, cholinergic-glutamate cross-regulation (Gasiorowska et al., 2021), intracellular signaling of Aβ-dependent cholinergic excitotoxicity (Chen and Mobley, 2019; Francis et al., 1999), NGF-cholinergic receptor combined homeostasis (Cuello, 2019), among others, to increase the long-term potential of ChEI-pathway targeting therapies.

To follow, it is paramount to assess whether some specific genetic polymorphisms influence the efficacy and safety of ChEI in a broad set of potential clinical-biological individual scenarios. A modeling approach capable of accounting for the complexity of AD pathophysiology and the elegant regulation of the cholinergic system is compelling.

Coupling GWAS data with experimental functional annotation data and hybrid in-vivo clinical approaches, including neuroimaging-omics, are expected to map out genetic-driven cholinergic structural and functional endophenotypes. Such a research endeavor holds the potential to facilitate the identification of biological clusters at different time-related and disease risk-wise rates of cholinergic disruption (Huang et al., 2017; Meng et al., 2020).

The late-stage clinical validation of multi-modal biomarkers – such as AD bodily fluid biomarkers and molecular imaging, BF volume and functional connectivity measures – reveals that integrative cholinergic-aging-disease data patterns may be identified through AI-based multivariate analysis coupled with expert human observation to build up plausible theoretical models. Such a paradigm can facilitate a revaluation of ChEI, from proof-of-mechanism, trials enrolment to dose-stratification, until efficacy and safety monitoring. Moreover, accessible high-throughput technologies could enable a real-world and daily practice screening of individuals likely to experience adverse events and/or poor ChEI therapeutic outcomes.

For instance, patients may be stratified by DMEs profiles from poor to rapid metabolizers, while already available CPIC guidelines may walk clinicians through the best optimal therapeutic algorithms.

Such biology-centered paradigm could help overcome a few current hurdles: 1) understand whether ChEI have biologically modulatory properties and long-term effects, 2) quantify the clinical advantage in administering ChEI in prodromal stages, 3) evaluation of sex-stratified short- and long-term multi-dimensional outcomes, 4) identify biological clusters associated with prediction of optimal ChEI-DMT synergy, 5) stratification of ChEI effects according to underlying~~a~~ pathology rather than clinical symptomatology profiles. The latter point requires a further development of biomarker beyond Aβ and tau.

There is consolidated evidence that neurofibrillary aggregates and Aβ species accumulate in manifold "cholinergic circuitry hubs", including NBM, the entorhinal cortex, amygdala, and hippocampus. Hence, boosting the synergy between drugs with different mechanism-of-action(s) represents the most suitable way forward. In particular, a combination approach capable of targeting the cholinergic-AD pathophysiological mechanisms interplay – instead of each single component – could be developed along blueprints deriving from biomarker-guided, multi-target cancer treatments.

Eventually, the accurate definition of target populations (biological clusters) seems relevant for optimizing the combinatorial or even synergistic effect of ChEI with emerging biomarker-guided, pathway-based targeted therapies (e.g., anti-Aβ, anti-tau, NGF pathway modulators) and avoiding that non-biologically informed prescription of ChEI exerts a mask effect on compounds with disease-modifying effects.

A holistic approach to the individual and patient, spanning thorough genetic assessment and extensive multi-dimensional clinical and biomarker investigation, will constitute the next-generation medical practice, in line with the precision medicine paradigm.

CRediT authorship contribution statement

Simone Lista: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Andrea Vergallo**: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Stefan J. Teipel, Pablo Lemercier, Filippo Sean Giorgi, Audrey Gabelle, Francesco Garaci, Nicola B. Mercuri, Claudio Babiloni, Bhakta Prasad Gaire, Yosef Koronyo, Maya Koronyo-Hamaoui**: Writing – original draft, Writing – review & editing. **Harald Hampel**: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Robert Nisticò**: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Conflict of Interest

SL declares no competing financial interests related to the present article. This work was conceptualized and initiated during his previous position at Sorbonne University (Paris, France) and it reflects only and exclusively his own opinion and academic expertise on the matter. AV declares no competing financial interests related to the present article, and his contribution to this article reflects only and exclusively his own academic expertise on the matter. This work was conceptualized and initiated during his previous academic position at Sorbonne University, Paris, France. AV was an employee of Eisai Inc. [Nov 2019 - June 2021]. AV does not receive any fees or honoraria since November 2019. Before November 2019 he had received lecture honoraria from Roche, MagQu LLC, and Servier. YK, and MKH are co-founding members and consultants of NeuroVision Imaging, Inc., Sacramento, CA, USA. HH is an employee of Eisai Inc. The present article has been initiated and prepared as part of his academic position at Sorbonne University, Paris, France, and reflects entirely and exclusively his own opinion. He serves as Senior Associate Editor for the Journal Alzheimer's & Dementia and does not receive any fees or honoraria since May 2019. He is inventor of

11 patents and has received no royalties: In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Patent Number: 8916388; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Patent Number: 8298784; Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20120196300; In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100062463; In Vitro Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100035286; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Publication Number: 20090263822; In Vitro Method for The Diagnosis of Neurodegenerative Diseases Patent Number: 7547553; CSF Diagnostic in Vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases Publication Number: 20080206797; In Vitro Method for The Diagnosis of Neurodegenerative Diseases Publication Number: 20080199966; Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20080131921; Method for diagnosis of dementias and neuroinflammatory diseases based on an increased level of procalcitonin in cerebrospinal fluid: Publication number: United States Patent 10921330. SJT, PL, FSG, AG, FG, NBM, CB, BPG, and RN declare that they have no conflict of interest.

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