Review article

Overview of the cholinergic contribution to gait, balance and falls in Parkinson's disease

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ABSTRACT

Mobility deficits, including gait disturbance, balance impairments and falls, are common features of Parkinson's disease (PD) that negatively impact quality of life. Mobility deficits respond poorly to dopaminergic medications, indicating a role for additional neurotransmitters. Due to the critical role of cortical input to gait and balance, acetylcholine—an essential neurotransmitter system for attention—has become an area of interest for mobility. This review aimed to identify the role of cholinergic function on gait, balance, and falls in PD using three techniques; pharmacological, imaging, and electrophysiological. Studies supported the role of the cholinergic system for mobility in PD, with the most promising evidence indicating a role in falls. Imaging studies demonstrated involvement of anterior cholinergic (basal forebrain) systems in gait, and posterior (brainstem) systems in balance. However, this review identified a small number of studies which used varying protocols, making comparisons difficult. Further studies are warranted, measuring comprehensive gait and balance characteristics as well as gold standard falls detection to further quantify the relationship between ACh and mobility in PD.

1. Introduction

Gait disturbances, difficulty with balance, and falls are prominent features of Parkinson's disease (PD) that lead to reduced quality of life, increased healthcare costs and caregiver burden [1,2]. Mobility deficits in people with PD are particularly problematic because they show limited improvement, and in some instances worsen, with treatments such as levodopa [3] and deep brain stimulation [4]. This clinical observation and mounting research make it increasingly clear that neurotransmitter systems besides the dopaminergic system play a role in regulation of gait and balance in PD.

One neurotransmitter system that may be particularly important for control of mobility is acetylcholine (ACh), which is reduced in people with PD compared to age-matched, healthy controls [5,6]. Beyond subcortical cholinergic systems in the striatum, thalamus and cerebellum critical to mobility, ACh is primarily associated with alertness and cognition, specifically executive function and sustained attention [7]. The ACh system is of particular interest in PD because of the prominence of cognitive impairments from early in the disease course,

which mainly impacts frontal lobe executive function and attention mechanisms [8]. Executive function and attention are important not only for cognitive functioning but also for mobility, as cognitive control of gait and balance is essential for safe mobilization [9,10]. Gait and balance are complex sensorimotor tasks from which a number of comprehensive characteristics are measured. Due to the high number of characteristics, previous literature has sought to comprise characteristics onto domains of gait (e.g. pace, variability, asymmetry and trunk movement), and domains of balance (e.g. sway and jerkiness, anteroposterior and mediolateral sway) [11,12] in order to simplify interpretation. Specific gait and balance domains, such as pace, variability and dynamic balance, may be more dependent on cortical control than others, such as gait asymmetry or sway [9]. Thus, it is hypothesized that ACh deficiencies contribute to mobility deficits via executive function and attentional mechanisms.

There are a number of sources of ACh in the brain. First, the basal forebrain nuclei, which contains the medial septal nucleus, diagonal band of Broca, nucleus basalis of Meynert (nbM) and substantia innominata, see Fig. 1. The basal forebrain cholinergic nuclei project to
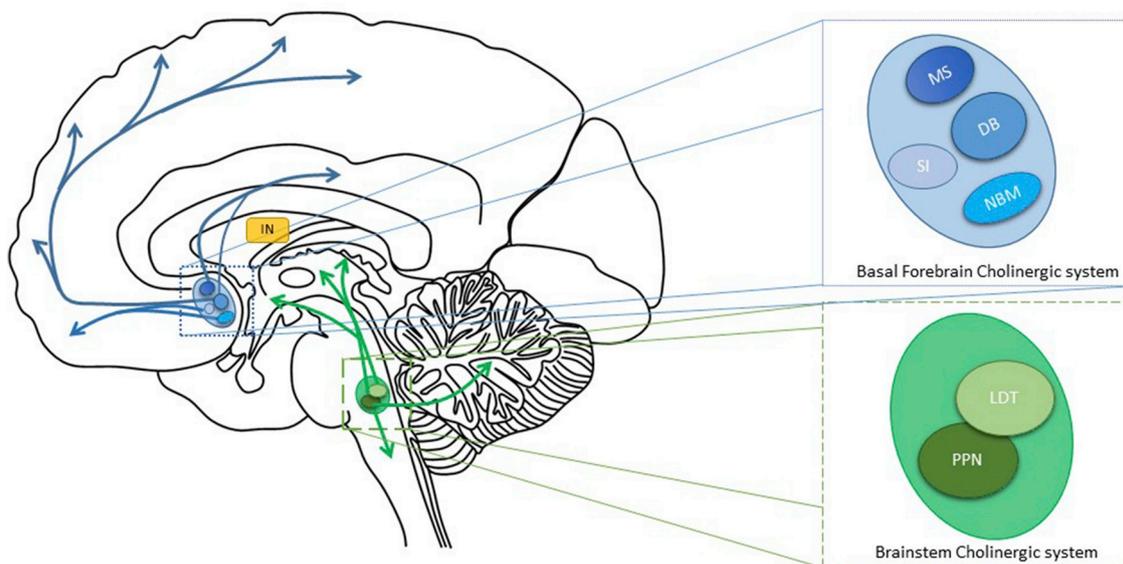

Fig. 1. Cholinergic projections of the central nervous system. Blue: basal forebrain cholinergic system which contains the medial septal nucleus (MS), the diagonal band of Broca (DB), nucleus basalis of meynert (NBM) and the substantia innominate (SI). The basal forebrain nuclei project to the prefrontal cortex, thalamus and striatum. Green: the brainstem cholinergic system contains the pedunculopontine nucleus (PPN) and the laterodorsal tegmental nucleus (LDT) which project to the thalamus, brainstem and cerebellum. IN = cholinergic striatal interneurons. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the cerebral cortex (including prefrontal cortex), thalamus and striatum. Second, located in the brainstem and composed of two nuclei; the pedunculopontine nucleus (PPN) and the laterodorsal tegmental nucleus (LDT), which project to the thalamus, brainstem, basal forebrain and cerebellum (Fig. 1) [13,14]. Third, cholinergic interneurons make up 1–2% of striatal cells that modulate dopaminergic and GABAergic pathways [15] (Fig. 1). The cholinergic systems degenerate in PD, with basal forebrain degeneration producing cortical cholinergic denervation and brainstem degeneration producing thalamic cholinergic denervation [16–20].

Three main techniques assess the central cholinergic system: pharmacological, imaging, and electrophysiological. First, pharmacological studies use acetylcholinesterase (AChE) inhibitors to increase the available amount of central ACh. AChE inhibitors such as donepezil or rivastigmine increase ACh concentration within cholinergic synapses by inhibiting the cholinesterase enzyme [21,22]. Second, molecular imaging, such as single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) targeting cholinergic markers, has enabled study of the cholinergic system in PD. Imaging targets include markers of cholinergic activity, which can be both presynaptic (VAChT and AChE) and postsynaptic ($\alpha_4\beta_2$ nicotinic acetylcholine receptors [nAChR] and muscarinic acetylcholine receptors [mAChRs]) [18]. Third, transcranial magnetic stimulation (TMS) measures short latency afferent inhibition (SAI), an electrophysiological technique used to investigate cortical cholinergic activity [23,24]. Evidence for the cholinergic contribution to SAI is demonstrated by muscarinic antagonists, which significantly decrease SAI in healthy adults (Di Lazzaro et al., 2000). Additionally, patients with Alzheimer's disease, which is known to impair cholinergic function, have significantly worse SAI than otherwise healthy controls [25].

Due to recent interest in the relationship between the cholinergic system and mobility, we sought to review the role of cholinergic function in gait, balance, and falls in people with PD. This review will focus on the three different measurement techniques – pharmacological, imaging and electrophysiological – to collate current evidence for the role of the cholinergic system in gait, balance, and falls in PD. We hypothesize that these three techniques will support the role of the cholinergic system for mobility in PD.

2. Methods

2.1. Search strategy

Three databases were used for the search: Medline, Scopus, and PsychInfo. For each of the databases used, separate searches were performed for the three focuses of the review: pharmacological, imaging, and electrophysiology techniques. The search terms used are shown in Table 1.

The search was limited to full journal articles written in the English language published from February 1990 to March 2018. Three master databases were produced for each focus of the review, duplicates were deleted and an initial title screen was performed (RM, DM and TM). After the initial title screen, abstracts were reviewed by the three reviewers (RM, DM and TM). Full review of the text was completed when it remained unclear from the abstract whether the paper was suitable for inclusion.

2.2. Inclusion and exclusion criteria

Articles were included if (1) they assessed cholinergic function via pharmacological, imaging or electrophysiological techniques in people with PD, and (2) they associated cholinergic function with mobility, inclusive of comprehensive objective measures of balance and gait as well as falls (including falls status), in PD.

2.3. Data extraction

Three separate extraction forms were used for each focus of the review. Information from the forms were then transferred to the review table. Information extracted included participant groups, participant characteristics, mobility assessed (including individual variables of balance and gait), analysis tools, medication status and key findings.

3. Results

3.1. Search yield

The search strategy generated a total of 2106 papers. After

Table 1
Structured review search terms.

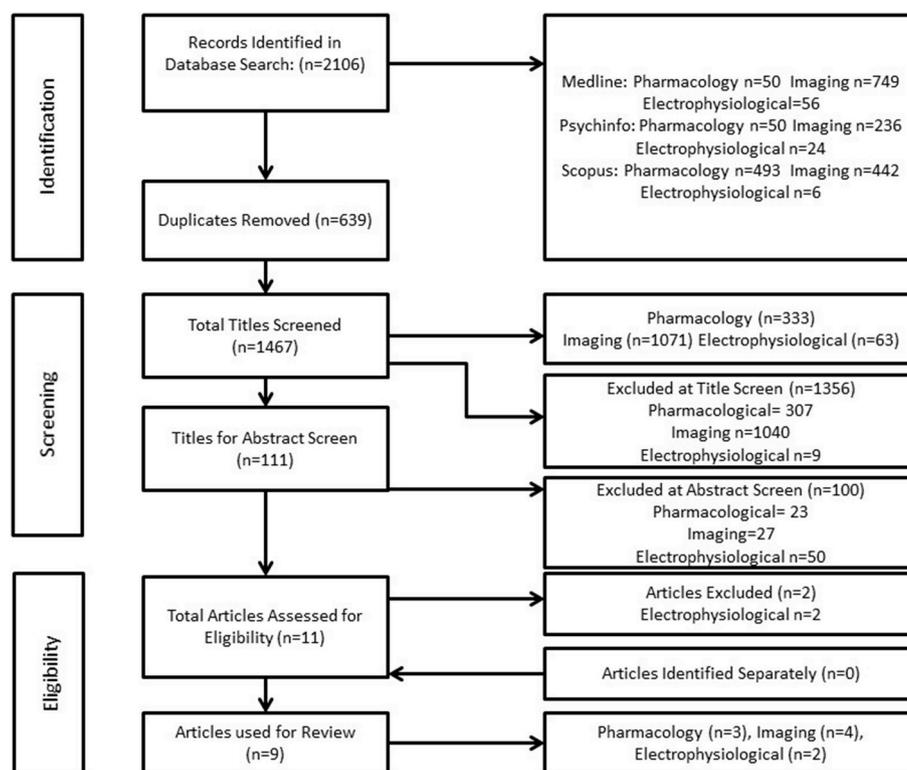|		Medline	PsychInfo	Scopus
Mobility and Cohort (for all three searches)	Mobility	**MESH:** Gait, locomotion, walking, postural balance, fall **Keyword Search:** Gait OR locomotion OR walking OR symmetry OR asymmetry OR frequency OR variability OR speed OR velocity OR stance OR step OR swing OR stride OR double limb, OR balance OR sway OR postural control, OR fall	**MESH:** Gait, locomotion, walking, postural balance, fall **Keyword Search:** Gait OR locomotion OR walking OR symmetry OR asymmetry OR frequency OR variability OR speed OR velocity OR stance OR step OR swing OR stride OR double limb, OR balance OR sway OR postural control, OR fall	**Keyword Search:** Gait OR locomotion OR walking OR symmetry OR asymmetry OR frequency OR variability OR speed OR velocity OR stance OR step OR swing OR stride OR double limb, OR balance OR sway OR postural control, OR fall
	Cohort	**MESH:** Parkinson's disease **Keyword Search:** Parkinson* OR Parkinson disease OR Parkinson's disease OR Idiopathic Parkinson's disease	**MESH:** Parkinson's disease **Keyword Search:** Parkinson* OR Parkinson disease OR Parkinson's disease OR Idiopathic Parkinson's disease	**Keyword Search:** Parkinson* OR Parkinson disease OR Parkinson's disease OR Idiopathic Parkinson's disease
Measurement	Pharmacological	**MESH:** Cholinesterase inhibitors **Keyword Search:** Cholinesterase inhibitors OR Anticholinesterase drugs OR Anticholinesterases OR Anticholinesterase Agents OR Anti-cholinesterasers OR Acetylcholinesterase inhibitors OR Rivastigmine OR Exelon OR Donepezil OR Aricept OR Galantamine OR Galanthamine OR Reminyl OR Nivalin OR Razadyne	**MESH:** Cholinesterase inhibitors **Keyword Search:** Cholinesterase inhibitors OR Anticholinesterase drugs OR Anticholinesterases OR Anticholinesterase Agents OR Anti-cholinesterasers OR Acetylcholinesterase inhibitors OR Rivastigmine OR Exelon OR Donepezil OR Aricept OR Galantamine OR Galanthamine OR Reminyl OR Nivalin OR Razadyne	**Keyword Search:** Cholinesterase inhibitors OR Anticholinesterase drugs OR Anticholinesterases OR Anticholinesterase Agents OR Anti-cholinesterasers OR Acetylcholinesterase inhibitors OR Rivastigmine OR Exelon OR Donepezil OR Aricept OR Galantamine OR Galanthamine OR Reminyl OR Nivalin OR Razadyne
	Imaging	**MESH:** positron-emission tomography, 'Tomography, Emission-Computed, Single-Photon', magnetic resonance imaging, functional magnetic resonance imaging **Keyword search:** PET OR SPECT OR vesicular acetylcholine transporter PET ligand OR pedunculopontine nucleus (PPN) OR nucleus basalis of meynart (NbM) OR [123I]IBVM OR [18F]FEOBV OR [18F]Fluoroethoxy-Benzovesamicol OR [18F]Fluoroethoxybenzovesamicol OR [11C]MP4A OR [11C]PMP OR [123I]5IA OR [18F]2FA 2-[18F]fluoro-3-(2(S) azetidinylmethoxy)pyridine (2FA) OR [11C]nicotine, [11C]N-methyl-4-piperidyl benzilate OR [11C]NMPB, 3-quinuclidinyl-4-iodobenzilate (QNB) OR [123I]QNB OR [123I]-(R,R)-I-QNB	**MESH:** positron-emission tomography, 'Tomography, Emission-Computed, Single-Photon', magnetic resonance imaging, functional magnetic resonance imaging **Keyword search:** PET OR SPECT OR vesicular acetylcholine transporter PET ligand OR pedunculopontine nucleus (PPN) OR nucleus basalis of meynart (NbM) OR [123I]IBVM OR [18F]FEOBV OR [18F]Fluoroethoxy-Benzovesamicol OR [18F]Fluoroethoxybenzovesamicol OR [11C]MP4A OR [11C]PMP OR [123I]5IA OR [18F]2FA 2-[18F]fluoro-3-(2(S) azetidinylmethoxy)pyridine (2FA) OR [11C]nicotine, [11C]N-methyl-4-piperidyl benzilate OR [11C]NMPB, 3-quinuclidinyl-4-iodobenzilate (QNB) OR [123I]QNB OR [123I]-(R,R)-I-QNB	**Keyword search:** PET OR SPECT OR vesicular acetylcholine transporter PET ligand OR pedunculopontine nucleus (PPN) OR nucleus basalis of meynart (NbM) OR [123I]IBVM OR [18F]FEOBV OR [18F]Fluoroethoxy-Benzovesamicol OR [18F]Fluoroethoxybenzovesamicol OR [11C]MP4A OR [11C]PMP OR [123I]5IA OR [18F]2FA 2-[18F]fluoro-3-(2(S) azetidinylmethoxy)pyridine (2FA) OR [11C]nicotine, [11C]N-methyl-4-piperidyl benzilate OR [11C]NMPB, 3-quinuclidinyl-4-iodobenzilate (QNB) OR [123I]QNB OR [123I]-(R,R)-I-QNB
	SAI	**Keyword Search:** Short-Latency Afferent Inhibition OR Short Latency Afferent Inhibition OR SAI OR Cholinergic	**Keyword Search:** Short-Latency Afferent Inhibition OR Short Latency Afferent Inhibition OR SAI OR Cholinergic	**Keyword Search:** Short-Latency Afferent Inhibition OR Short Latency Afferent Inhibition OR SAI OR Cholinergic

Fig. 2. PRISMA diagram of search yield used for structured review.

duplicates, a total of 1467 papers were yielded from the search. The total number of papers were split into three arms of the search: pharmacology studies (333), imaging studies (1071) and electrophysiological techniques (63). After an abstract screen, 11 papers were eligible for data extraction (n = 3 for pharmacology studies, n = 4 for imaging studies and n = 4 for electrophysiological techniques). Two papers did not meet inclusion criteria and were excluded; thus, a total of nine papers were included in this review. The search yield and all parameters are demonstrated in Fig. 2. All articles were published in the English language, and publication dates ranged from 2009 to 2016.

3.2. Pharmacological studies

The results of the three phase 2 clinical trials [26–28] assessing pharmacological intervention in relation to gait, balance and falls are presented in Table 2. All three studies used AChE inhibitors, either donepezil or rivastigmine. All were randomised, double-blind studies, with two randomised placebo-controlled parallel group trials [27,28], and one crossover trial [26]. One study assessed gait [27], measuring characteristics of gait speed (m/s) and step time variability (s). This study identified that those receiving AChE significantly increased gait speed and reduced step time variability under both single and dual-task conditions (gait assessment whilst completing a concurrent cognitive or motor task) compared to the control group. Two studies assessed balance, one using the Berg Balance Scale [26] and the other study using the controlled leaning balance score [27]. The Berg Balance Score did not change (Chung et al., 2010) but the controlled leaning balance score improved [27] with ACh supplementation. All three of pharmacological studies assessed number of falls [26–28] before and after intervention, and all identified a reduced number of falls when taking either donepezil or rivastigmine. Thus, three RCT's show a benefit of ACh enhancement via AChE inhibitors on gait, balance, or falls. However, interpretation is limited due to the differences in outcome measures used.

3.3. Imaging studies

Four PET studies assessing the cholinergic system were all from the same laboratory, as shown in Table 3 [5,16,17,29]. All used ^{1}C-methylpiperidin-4-yl propionate (^{11}C-PMP PET) as a radioligand for presynaptic AChE. Two of the four studies assessed the relationship between AChE levels and gait speed [5,29]. One study of a total of 101 participants assessed both neocortical and thalamic AChE and found neither were significantly associated with gait speed [5] but in the 31 subjects with low neocortical AChE, the relationship between cholinergic function and gait speed approached significance. In contrast, the second study in 125 subjects showed that gait speed was slower in those with nigrostriatal dopaminergic and basal forebrain cholinergic denervation [29]. One study of the relationship between cholinergic activity and balance ([17] identified that decreased thalamic cholinergic innervation, not cortical cholinergic or striatal dopaminergic deficits, was associated with increased center of pressure sway speed (indicating impaired balance) when controlling for cognitive and motor impairments. Two of the four studies assessed falls using the Unified Parkinson's disease Rating Scale (UPDRS) part II [16] and self-reported falls history [5]. PD fallers had significantly reduced cortical and thalamic AChE, but PD non-fallers only had reduced cortical AChE compared to controls [16]. The second study split PD subjects into groups by AChE activity (low combined neocortical and thalamic, low isolated neocortical, or low isolated thalamic) [5] and identified that PD fallers had lower thalamic AChE compared to non-fallers.

In summary, four PET studies consistently show that balance problems and falls history are linked to reduced thalamic, but not cortical, ACh levels whereas gait abnormalities relate to cortical ACh in people with PD. Thus, ACh may play a role in both balance and gait, but in different brain networks.

3.4. Short-latency afferent inhibition (SAI)

Table 4 presents the results of the two studies using SAI to assess

Table 2
Main characteristics of the studies observing gait, balance, and falls in relation to pharmacological studies.

Study	Participant Characteristics	Study Type	Medication	Mobility Measured	Analysis Tool	Main Study Findings
Chung et al., 2010	Number: 19 Gender: 15M & 4F Age: 68.3 ± 10.8 Years since diagnosis: 10 ± 5.6 Med: NR	Randomised, crossover, double-blind study	*Treatment phase:* Donepezil, 5 mg for 3 weeks, increased to 10 mg for 3 weeks. 3-week washout period before placebo phase. *Placebo Phase:* aesthetically identical medication	Balance: Balance scale score Falls: Number of falls and near falls	Balance: Berg Balance Scale Falls: Falls postcards	Balance: No significant change on Berg Balance Scale score. Falls: During treatment phase, subjects fell significantly less than during placebo phase. Those who fell most frequently at baseline showed greatest reduction in falls.
Henderson et al., 2016	*Treatment group:* Number: 65 Gender: 35M & 30F Age: 71 (54–90) Years since diagnosis: 8 (5–13) Med: NR *Placebo group:* Number: 65 Gender: 46M & 19F Age: 69 (46–88) Years since diagnosis: 9 (5–13) Med: NR	Randomised, double-blind, placebo-controlled, phase 2 trial	*Treatment group:* 3 mg Rivastigmine (1.5 mg 2 × per day), titrated up in 3 mg increments every 4 weeks to maximum of 12 mg per day from week 13 onwards. Placebo: placebo tablet titrated as with treatment group.	Gait: gait speed (m/s), step time variability (s) Balance: Controlled leaning balance score Falls: rate of falls per month	Gait: Triaxial accelerometer (DynaPort Hybrid, McRoberts, Netherlands), 22 m flat covered walkway under three conditions: 1) single task, 2) simple dual task and 3) complex dual task Balance: Controlled leaning balance test Falls: monthly falls diaries. Posted monthly, telephoned once per month for additional information.	Gait: Gait speed increased in treatment group. Step time variability was 28% and 21% lower in single and dual task conditions respectively in the treatment group. Balance: Treatment group had significantly better scores on controlled leaning balance test. Falls: Treatment group had 45% falls reduction.
Li et al., 2015	*Treatment group:* Number: 41 Gender: 30M & 11F Age: 67.5 (52.7–71.1) Years since diagnosis: 5.3 (2.4–7.1) Med: NR *Placebo group:* Number: 40 Gender: 21M & 19F Age: 66.9 (53.8–70.3) Years since diagnosis: 5.5 (2.6–8.0)	Randomised, double-blind, placebo controlled trial	Treatment group: 3 mg Rivastigmine for 12 months Placebo group: NR	Falls: Number of falls per person in years, Incidence of falls (number)	Falls: Weekly Telephone Follow-up calls	Falls: Number and incidence of falls were significantly reduced in the treatment arm compared to placebo arm.

NR = not reported.

Table 3
Main characteristics of the studies observing gait, balance, and falls and imaging techniques.

Study	Participant Characteristics	Imaging Technique	Mobility Measured	Analysis Tool	Main Study Findings
Bohnen et al., 2009	*PD fallers:* Number: 17 Gender: NR Age: 72.5 ± 9.3 Years since diagnosis: 8.8 ± 4.3 Med: NR *PD non-fallers:* Number: 27 Gender: NR Age: 66.6 ± 9.1 Years since diagnosis: 6.0 ± 3.9 Med: NR *Control:* Number: 15 Gender: 7 M & 8F Age: 64.4 ± 9.6 (50–81)	MRI and PET (PMP & DTBZ)	Falls: Fall status	Falls: UPDRS, Part II, Question 13 (score of 0 is non-faller, score of > 1 classified as faller)	Falls: Significantly reduced cortical AChE hydrolysis rates seen in PD fallers followed by PD non-fallers compared to control subjects.
Bohnen et al., 2012	*PD:* Number: 101 Gender: 76 M & 25F Age: 65.3 ± 7.2 (50–84) Years since diagnosis: 5.9 ± 3.9 (0.5–19) Med: Off *Control:* Number: 29 Gender: 16 M & 13F Age: 66.8 ± 10.9 (50–84)	MRI and PET (PMP & DTBZ). Patients classified as low (n = 31) or normal neocortical (n = 70) AChE and low (n = 18) or normal (n = 83) thalamic AChE.	Gait: Speed Falls: Fall History	Gait: Time to walk 8.5 m Falls: Fall history self-reported clinically	Gait: Gait speed difference near significance between low and normal neocortical AChE groups. No gait speed difference between low and normal thalamic AChE groups. Falls: Increased history of falls in the low thalamic AChE group (18% of subjects).
Bohnen et al., 2013	*PD DA+:* Number: 87 Gender: 61 M & 26F Age: 64.2 ± 7.1 Med: OFF *PD DA+/Ach+:* Number: 38 Gender: 34 M & 4F Age: 68.7 ± 7.0 Med: OFF *Controls"* Number: 32 Gender: 18 M & 14F Age: 66.0 ± 10.6	MRI and PET (PMP & DTBZ)	Gait: Speed	Gait: Time to walk 8.5 m	Gait: The group with DA+/Ach + had significantly slower gait speed. No association with gait speed and low PPN ACh levels.
Muller et al., 2013	*PD:* Number: 124 Gender: 32F & 92 M Age: 65.5 ± 7.4 Motor disease duration: 6.0 ± 4.2 Med: OFF *Control:* Number: 25 Gender: 10F & 15 M Age: 66.8 ± 10.1	PET, ^{11}C-methylpiperidin-4-yl propionate AChE positron emission tomography (^{11}C-PMP)	Balance: Center of Pressure (COP) speed and COP RMS	Balance: EquiTest balance platform (NeuroCom, a division of Natus) sensory organisation test	Balance: Increased postural sway associated with lower thalamic AChE activity No association of neocortical cholinergic innervation with postural sensory integration

ACh = acetylcholine, AChE = Acetylcholinesterase, DTBZ = [(11)C] dihydrotetrabenazine, MRI = Magnetic Resonance Imaging, NR = not reported, PET = Positron Emission Tomography, PMP = 1C-methylpiperidin-4-yl propionate, PPN = pedunculopontine nucleus, RMS = root mean square.

cortical cholinergic activity and relate this to gait and falls [30,31]. Both studies were cross-sectional, included subjects who were ON levodopa medication and used the GAITRite electronic walkway to assess spatiotemporal gait characteristics. Rochester et al., used the interstimulus intervals of N20 + 0 to N20 + 4, in increments of one millisecond, whereas Pelosin et al., used the interstimulus intervals of N20-2 to N20 + 8, in increments of two milliseconds. SAI was calculated as the grand mean of the percentage of the unconditioned trial for each interstimulus interval. Rochester et al. included a PD group regardless of fall status, whereas Pelosin et al., only assessed a PD faller group. Both groups found SAI to be significantly worse in the PD group compared to controls. Gait speed (m/s) was reported in both investigations, though Rocehster et al., also reported stride length (m), stride time (s), step width (cm), as well as the variability (SD) of these variables. Rochester et al., found that both slower single-task gait speed and shorter step length were significantly correlated with worse SAI in PD only. In contrast, Pelosin et al., reported the dual-task cost, defined as dual-task gait speed minus single-task gait speed, with increased dual-task through to reflect a greater need for cortical control of walking. They identified a significant correlation between increased dual-task cost of gait speed and worse SAI. One study assessed the number of falls in six months prior to participation [31] and demonstrated worse SAI in both the PD faller and older adult faller groups than the older adult non-faller group, indicating that cortical cholinergic activity may play a role in falls, regardless of PD status.

Thus, two small SAI studies show that lower ACh levels are associated with reduced gait speed, stride length and increased dual-task cost, as well as falls in people with PD. However, no studies to date have evaluated the relationship between SAI and balance.

Table 4

Main characteristics of the studies observing gait, balance, and falls and electrophysiological techniques.

Study	Study Type	Participant Characteristics	Method	Mobility Measured	Analysis Tool	Main Study Findings
Rochester et al., 2012	Cross Sectional	*PD:* Number: 22 Gender: 16 M & 6F Age: 70.2(9.7) Months since diagnosis: 19.8(8.6) Med: ON *Control:* Number: 22 Gender: 9 M & 13F Age: 67.4(8.4)	TMS: SAI from N20 to N20 + 4	Gait: gait speed (m/s), stride length (m), stride time (s) and step width (cm), variability of gait speed, stride length, stride time and step width described as the standard deviation	Gait: GAITRite electronic walkway	Gait: SAI was significantly correlated with gait speed and stride length in PD only. SAI was a significant independent predictor of gait speed in PD only. SAI remained a significant predictor when adjusting for age, cognition, depression, and disease severity.
Pelosin et al., 2016	Cross Sectional	*PD Fallers (PD-F):* Number: 33 Gender: 17 M & F16 Age: 72.6(4.4) Years since diagnosis: NR Med: ON *Older Adult Fallers (OA-F):* Number: 17 Gender: 7 M & 10F Age: 73.4(4.2) *Older Adult Non-Fallers (OA-NF):* Number: 14 Gender: 9 M & 5F Age: 72.1(4.9)	TMS: SAI from N20-2 to N20 + 8, by 2's.	Gait: gait speed (m/s) and DTC of gait speed. Falls: number of falls in 6 months prior to study.	Gait: GAITRite electronic walkway Clinical Assessments: MOCA, and UPDRS-III	Gait: During single task alking, gait speed was significantly lower in both PD-F and OA-F compared to OA-NF with no difference between PD-F and OA-F. During dual task walking, gait speed was significantly lower in PD-F than in both OA-F and OA-NF and in OA-F than in OA- NF. SAI was significantly worse in PD-F compared to both OA-F and OA-NF. SAI was significantly worse in OA-F compared to OA-NF. SAI significantly correlated with dual task change in gait speed. SAI was a significant independent predictor of dual task change in gait speed. SAI remain a significant predictor when adjusting for age and cognition.

DTC = dual task cost, NR = not reported, SAI = short-latency afferent inhibition.

4. Discussion

This structured review aimed to provide an overview of the role of the cholinergic system in gait, balance, and falls in people with PD. We reviewed pharmacological, imaging, and electrophysiological techniques to improve understanding of this central neural transmitter system on mobility in PD. Evidence from all three measurement techniques appear to support the hypothesis that ACh plays a role in gait, balance, and falls in people with PD. Although evidence to date is promising, it is limited due to a small number of studies with varying assessments of balance, gait and falls.

4.1. The cholinergic system and gait

This review showed significant associations between cholinergic activity and gait. Gait speed was the most commonly assessed gait characteristic and was strongly associated with ACh levels (both PET and SAI), supporting the hypothesis for a cholinergic role in gait. However, comprehensive gait characteristics, beyond gait speed, improve utility due to the sensitive and specific nature of discrete gait characteristics [9]. For example, step length and step time variability were associated with cholinergic function. Step length is thought to be a characteristic of gait highly dependent on cognition [9] as demonstrated by improvement in step length when using attentional cues [32] and its sensitivity to cognitive decline in PD [33]. Although this result is unsurprising, step length was only assessed in one study so further work is needed to validate these findings.

In contrast to gait speed, step time variability, assessed in two studies, was not related to cholinergic function as measured by SAI, although it was improved with rivastigmine [27,30]. The response to

rivastigmine suggests a cholinergic role in gait variability, which was previously demonstrated to be cortically controlled in PD but not in older adults [9]. The reason for these contradictory findings may be twofold. First, different gait measurement techniques were used with body worn sensors having increased sensitivity to characteristics of variability compared to the electronic walkway [34]. Second, the SAI study was in an incident cohort of PD [30] whereas the pharmacological study by Henderson et al., was in a more advanced PD cohort. The differences in cohorts suggest dopaminergic and cholinergic loss may mirror findings in older adults in which gait variability, in mild disease, does not appear to be mediated by cognition [9]. Thus, in an early PD cohort, dopaminergic and cholinergic loss may not have reached a threshold at which attention is needed to compensate for deficits in gait variability.

The findings for gait speed, step length and gait variability support the notion that gait requires higher cognitive function, namely executive function and attention, for safe and purposeful mobility [35]. The gait-cognition relationship can be assessed via dual-task paradigms in which concurrent cognitive tasks are performed whilst walking [36]. Decline in gait performance under dual-task compared to single-task conditions are thought to reflect impaired automaticity of gait control and/or an increase in the need to use cognitive processes, such as attention, to control gait [35]. In light of this, one reviewed article identified an association between cholinergic activity and dual-task gait, further indicating the role of attention under challenging gait conditions.

Poorer performance on gait was only associated with neocortical ACh, but not thalamic ACh levels, suggesting that the basal forebrain, but not brainstem, cholinergic system contributes to cholinergic control of gait. This finding complements evidence of higher cognitive control

for gait characteristics and the underpinning role of attention for gait in PD [9,11]. A small number of studies in this review identified better performance on executive function and attention assessments correlated with poorer gait with lower ACh levels, thus, suggesting an indirect role for ACh on gait via cognition [5,27,30]. However, more comprehensive assessments of gait, balance and cognition in association with ACh are required to further understand the extent to which ACh affects mobility both indirectly and directly via attentional contributions and sensorimotor control of gait and balance.

4.2. The cholinergic system and balance

Evidence from this review supported the role of ACh in balance deficits in PD, with two of three studies identifying an association. However, there were some contradictory results, which are most likely due to the different balance outcome measures used across studies. Balance improved when measured by the controlled leaning balance scale in those taking rivastigmine [27] and poorer balance was noted in those with lower thalamic AChE when using an objective measure of postural sway [17]. In contrast, there was no improvement in the Berg Balance Scale when taking donepezil [26,37]. This was the only study that did not use an objective measure of postural sway and it is likely that the Berg Balance scale is not sensitive enough to detect subtle changes in balance in the PD cohorts for these studies. Although other subjective paper-based outcome measures are more sensitive to milder deficits in PD [38], discrete changes in balance are difficult to measure with such scales [39].

As measured by PET studies, poorer balance was associated only with thalamic ACh but not neocortical ACh, which implies the brainstem cholinergic system has greater influence for static balance than the basal forebrain system. In support of this, stereology techniques identified those with PD and impaired balance have fewer cholinergic neurons in the PPN compared to those without balance deficits [40]. Furthermore, the PPN has a critical role in regulation of Rapid Eye Movement (REM) in humans with REM sleep disorder, a common feature of PD, and may be associated with balance deficits. Recent studies have identified critical links between those with REM sleep disorder and poorer postural stability, using quantitative gait and balance measures [41,42]. Evidence suggests direct targeting of the PPN to treat balance deficits; however, deep brain stimulation of the PPN has so far shown mixed clinical improvements in balance [43]; therefore alternative therapies to improve activity of the brainstem cholinergic system are indicated.

4.3. The cholinergic system and falls

The most promising evidence that emerged from this review supported the association between reduced ACh activity and increased incidence of falls. All three pharmacological studies found a reduction in fall rates when patients took either donepezil or rivastigmine. All three studies used the gold standard outcome measure of self-report falls diaries [44], further validating these findings. The imaging work from this review revealed reduced thalamic AChE was associated with PD fallers, and although those with low neocortical AChE had a higher incidence of falls, this was not significant [5]. Previous work has identified the 'dual-hit hypothesis' which describes dual dopaminergic and cholinergic loss [45] in PD. Studies in rodents demonstrate that dual dopaminergic and cholinergic loss results in a significant increase in falls, when using an agility course that reflects balance capabilities in humans. Furthermore, an increase in falls was correlated with poorer performance on an attention task [45]. The authors hypothesize that attentional control can no longer compensate for striatal impairments in rodents. In PD, cognitive reserve may compensate for gait and balance deficits, but when cognitive reserve is diminished, gait and dynamic balance may no longer be compensated for by attentional control, leading to an increased falls risk (see Fig. 3). Interestingly, SAI was

reduced in older adult fallers compared to older adult non-fallers [31], suggesting reduced ACh, likely from the brainstem, increases falls risk unrelated to PD. However, SAI was significantly worse in PD fallers compared to older adult fallers in the same article [31]. This further demonstrates the dual-hit hypothesis in PD, in which dual dopaminergic and cholinergic loss further increases falls risk.

The above results suggest a critical role of the brainstem cholinergic system as a neural correlate for falls in PD, but it is likely that underlying cognitive deficits associated with neocortical ACh from the basal forebrain play a role that further exacerbates falls in PD. Studies in humans suggest that the role of attention in falls may be important later in disease. In an incident cohort of PD, discrete gait characteristics predicted future falls risk but not cognition [46,47]. However, in more advanced disease, an intervention that incorporated cognitive challenges, a virtual reality paradigm combined with treadmill training, was shown to reduce falls compared to treadmill training alone [48]. Thus, in later disease, when ACh levels are further reduced, training to increase attentional resources may override dopaminergic loss. This indicates that attention could mediate the impact of gait and balance deficits on falls risk (see Fig. 4). In accordance with Fig. 4, reduced cholinergic activity may be a consequence of anticholinergic medications in addition to PD pathology. Anticholinergic drugs are commonly used in PD to treat both motor symptoms and non-motor symptoms. In turn, such medications have demonstrated increased falls risk and reduced physical function [49,50].

One caveat to our findings is that the imaging studies from this review utilized clinical self-reported falls measures, which limits the scope of interpretation around falls. The use of the gold-standard falls diaries to classify recurrent fallers and faller phenotype [51–53] would help to determine the association of neocortical and thalamic ACh with detailed fall characteristics. In addition, there were no electrophysiological studies assessing SAI between PD fallers and PD non-fallers, and therefore future work using this technique would further validate the role of ACh in falls in this population.

4.4. Future implications

The recent evidence for the role of ACh in gait, balance, and falls has future therapeutic implications for PD. One of the main challenges is the variety of protocols used to assess gait, balance and falls; however this is unsurprising due to the small number of current publications. To further collate evidence of ACh for mobility deficits in PD, future research should use standardized, validated protocols assessing comprehensive measures of gait and balance. The use of current gait and balance models would allow for comprehensive variables and reduce heterogeneity allowing for replication and validation of research [11,12,54]. Pharmacological studies show promising results for improving mobility in PD; however, side effects of AChE inhibitors are burdensome and especially problematic in the older adult population [27]. Furthermore, current AChE inhibitors have limited brain uptake and therefore limited efficacy. Thus, other treatment options to increase cholinergic function need to be sought. Exercise may provide a non-pharmacological alternative therapy based upon evidence from animal studies in which exercise interventions increased ACh production [55,56]. In humans, exercise interventions that include cognitive components have demonstrated beneficial effects on mobility and falls [48], but to the best of our knowledge such interventions have not been related specifically to ACh. Other techniques to improve cholinergic output such as deep brain stimulation of the NbM [57,58] and non-invasive vagus nerve stimulation [59] are in the early stages of investigation, and so far, demonstrate mixed results.

4.5. Limitations

Limitations to this review include the lack of use of a quality assessment tool to assess quality of individual articles; however, due to
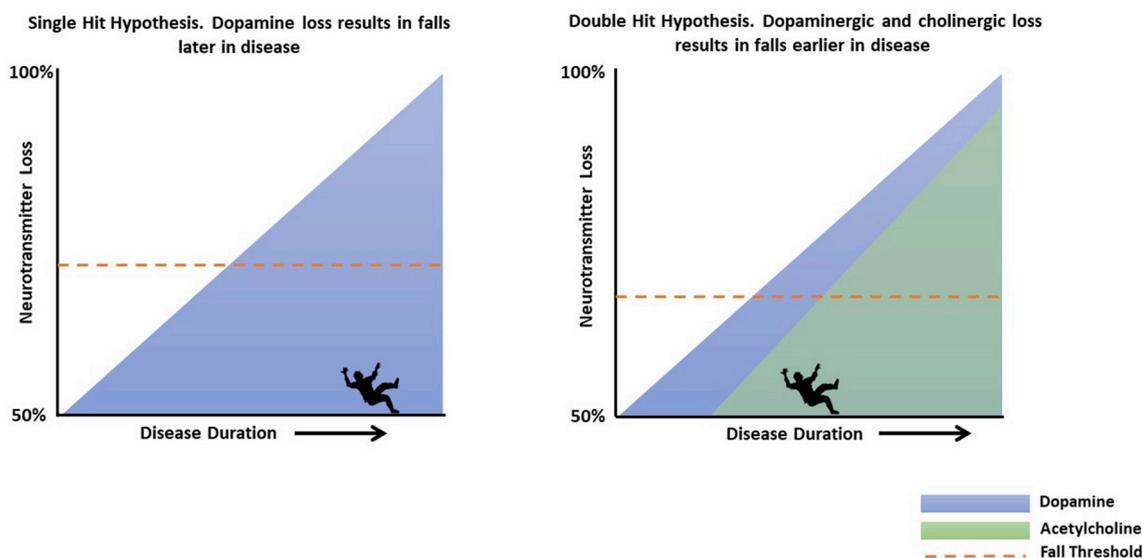
Fig. 3. Single and double hit hypothesis of dopaminergic and cholinergic loss for falls risk in Parkinson's disease. **Single hit hypothesis**; mainly loss of dopamine with minimal, age-related loss of acetylcholine. **Double hit hypothesis**; loss of both dopamine and acetylcholine. Dotted red line indicates the decreased fall threshold with both dopaminergic and cholinergic loss causing falls to occur earlier in disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
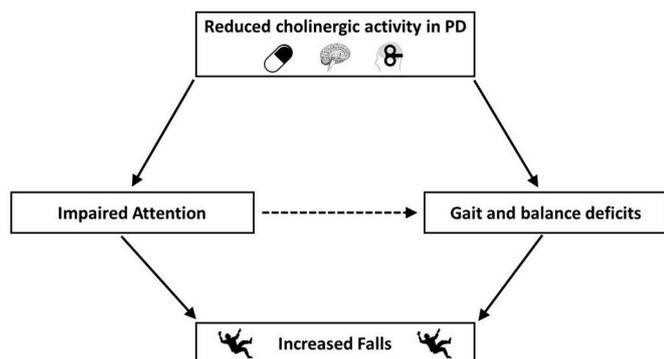

Fig. 4. Reduced cholinergic activity in PD causes deficit in attention (direct relationship) and gait and balance (direct relationship). Impaired attention, gait and balance then lead to an increased falls risk (direct relationship). It is proposed that reduced cholinergic activity leads to poorer attention which indirectly affects gait and balance leading to increased falls risk (dashed line).

the small number and the variability of study designs included in this review, we did not see this as appropriate. In addition, we chose to focus on gait, balance, and falls in PD and not other motor symptoms such as Freezing of Gait; this would be of interest for future studies. Finally, we have to acknowledge that imaging and electrophysiological techniques bias measurement for cortical over subcortical neural networks and therefore the role of subcortical circuits in mobility may be underrepresented in our findings. Although 11C-PMP PET provides a precise index of AChE activity in brain regions with a low AChE concentration (i.e., cortex), estimates of AChE activity in areas of high activity (i.e, cerebellum, basal ganglia) are poorer. This is due to the combination of a relatively high hydrolysis rate of 11C-PMP by AChE and high concentration of AChE resulting in the uptake of the tracer being limited by delivery to the tissue, resulting in low sensitivity to change [60]. Thus, papers were implicitly limited to examining group differences in cholinergic innervation of areas with relatively low AChE concentration. For SAI, as TMS is a cortical assessment, the outcome measure is cortical in nature. This does not rule out subcortical input on MEP response, including the striatal cholinergic interneurons. For example, Nardone et al. (2008) identified worse SAI in subcortical ischemic vascular disease (SIVD) but findings are difficult to interpret as

the authors were not able to rule out concurrent AD pathology from their SIVD group, confounding TMS results [61]. Ultimately, the direct role of subcortical neural input on motor output following cortical stimulation with TMS remains unknown [62–64].

5. Conclusions

This review aimed to synthesize current evidence for the role of cholinergic function in gait, balance, and falls in people with PD. Current evidence from pharmacological, imaging, and electrophysiological studies support the role of ACh for mobility in PD. Given the prevalence of mobility problems in PD and their poor response to current treatment, an improved understanding of how ACh influences mobility in PD has the potential to inform future interventions with the aim to improve patient quality of life and reduce caregiver burden. To better inform future work, comprehensive measurements of balance, gait, falls and cognition are required in order to extract both the direct and indirect effects of ACh on mobility in PD.

Conflicts of interest

FH has a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology-this potential institutional and individual conflict has been reviewed and managed by OHSU.

Acknowledgements

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